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Stereoselective synthesis of an advanced taxusin intermediate: an application of the type 2 intramolecular Diels–Alder reaction☆

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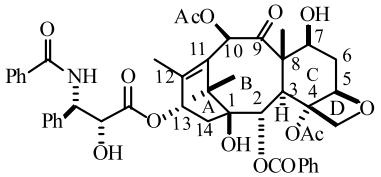
Abstract—Stereoselective synthesis of an advanced taxusin intermediate is described. The key step is the successful application of the type 2 intramolecular Diels–Alder (IMDA) reaction for the assembly of the tricyclic core of this natural product.

Taxol (**1**) is one of the most powerful, naturally occurring antitumor agents, and is widely used in the treatment of breast, ovarian and lung cancers.[1] Although, it has no known curative properties Taxusin (**2**) has also attracted much attention in recent years, due its close structural relationship with taxol.[2] Several total syntheses of **2** have appeared[3] (Fig. 1). The type 2 intramolecular Diels–Alder (IMDA) reaction provides one of the few direct methods for the synthesis of bridged bicyclic rings, incorporating a bridgehead double bond present both in taxol and **2**.[4] Despite this advantage, successful application of this strategy for the synthesis of taxane natural products has not appeared.

We report the synthesis of an advanced taxusin intermediate **3**. The reaction employs a type 2 (IMDA) reaction and features a masked diene strategy. A significant challenge to the successful implementation of this approach is stereochemical control of the cycloaddition step. At the very least the reaction must relate the two remote stereogenic centers at C-1 and C-8 to achieve the natural product stereochemistry.

Computational studies in this laboratory suggested that the hybridization at C-3 exerts an important influence on the stereochemical outcome of this cycloaddition.[5] Earlier efforts incorporating a sp^2 carbon at C-3 resulted in formation of the C-1 epi-taxane skeleton.[6] The Diels–Alder precursor utilized here incorporates a sp^3 carbon at C-3 and *trans* stereochemistry at the BC ring junction. On the basis of our computational studies[5] and results from others[7] we anticipated that this substitution would result in a strong preference for the α-approach of the dienophile to assemble the AB rings and establish the natural stereochemistry between C-1 and the stereocenters at carbons 8, 9, and 10. In addition, the synthesis employs a bromocyclopropane as a diene surrogate in the steps leading to the key Diels–Alder reaction. Its use provides a solution to the chemoselectivity problem associated with 2-metallo-1,3-butadienes. The antithetic sequence for the synthesis of an advanced intermediate **3** (Scheme 1) is detailed below.



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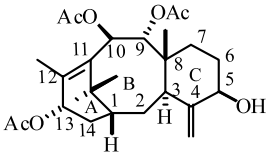

2

Figure 1.

Keywords: stereoselective synthesis; type 2 (IMDA); advanced taxusin intermediate; bromocyclopropane.
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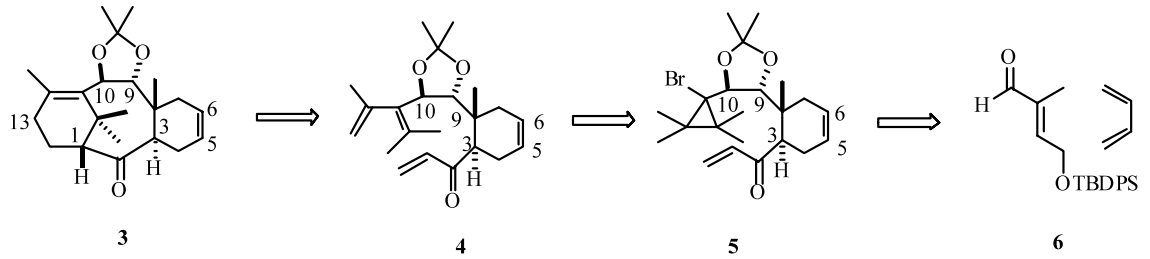
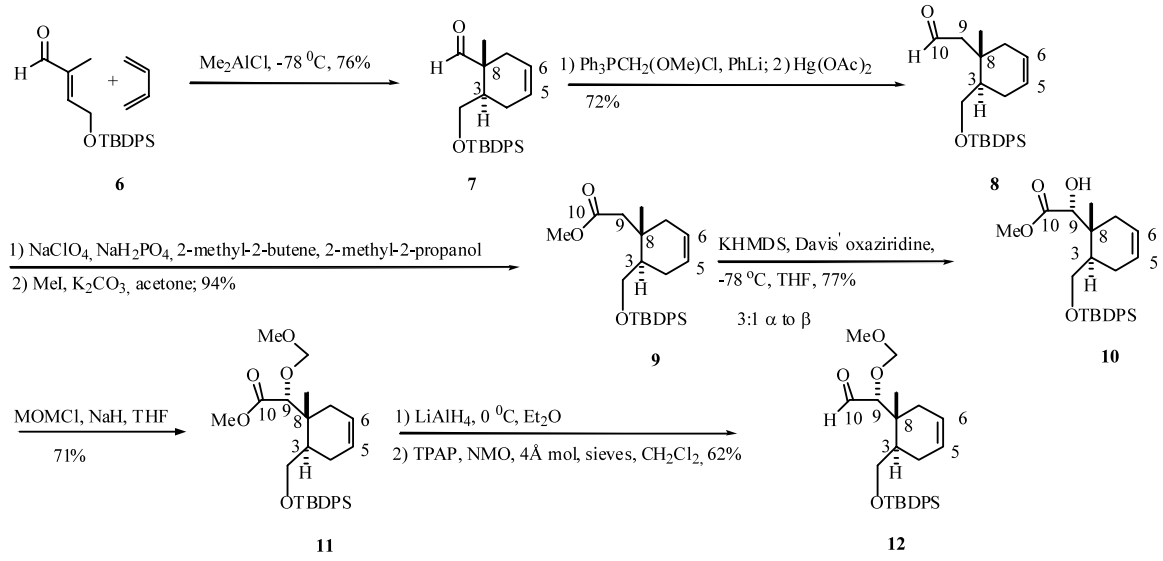


Scheme 1.

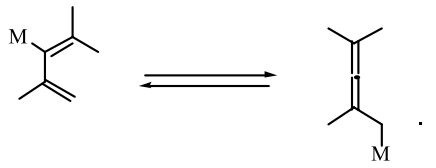


Scheme 2.

The C-ring substituent pattern, incorporating the C-(5)–C-(6) unsaturation in **3**, could be most expediently prepared by a Lewis acid-catalyzed intermolecular Diels–Alder reaction of aldehyde **6** and butadiene.[8] The reaction provides cycloadduct **7** with *trans* stereochemistry at C3–C8 (taxane numbering). Treatment of methoxymethylene-triphenylphosphorane with PhLi in ether followed by addition of **7** led to, after hydrolysis, a one carbon homologation to give **8**. The aldehyde was converted in two straightforward steps to the ester **9**. The next challenge was the introduction of an α-hydroxy group at C-(**9**). This task was achieved by a Davis' oxaziridine protocol[9] which favored the α-hydroxy ester **10** in a 3:1 ratio. The alcohol was subsequently protected as the MOM ether **11**. This was then reduced with $LiAlH_4$ in ether to give a primary alcohol which on oxidation with TPAP gave aldehyde **12**.[10] In effect, only six laboratory steps are required to advance from **6** to **12** (Scheme 2).

The next hurdle was the stereoselective incorporation of the diene carbons to intermediate **12**. We,[6] and others,[11] have found the 2-metallo-1,3-butadiene derivative to be a useful reagent for the introduction of the diene fragment in a single step. However, the reaction is often complicated by side products arising from the metallo-allenyl species as indicated in Figure 2. In some cases formation of the allenyl side product could be minimized by addition of $CeCl_3$ to the organolithium reagent before aldehyde addition but this was not a general solution.[6] However, the product ratio of diene to allene depended on many factors, including solvent, aldehyde substrate, and metal additives.

We pursued a more general solution to this problem which utilizes the organometallic reagent generated from dibromo-2,2,3,3-tetramethylcyclopropane **13**.[12] Its addition to aldehydes, followed by cyclopropyl ring opening[13] gives the desired dienic alcohol. In the event, treatment of **13** at low temperature with *n*-butyllithium followed by addition of aldehyde **12** in THF led to a 5:1mixture of the cyclopropyl alcohol **14** and its epimer. Column chromatography on silica gel gave a clean separation of **14** from its epimer. The structure of **14** was confirmed by X-ray diffraction (Fig. 3(a)). Direct protection of the alcohol at C-10 resulted in complica-



Dienyl-Allenyl equilibrium of metallo diene

Figure 2.

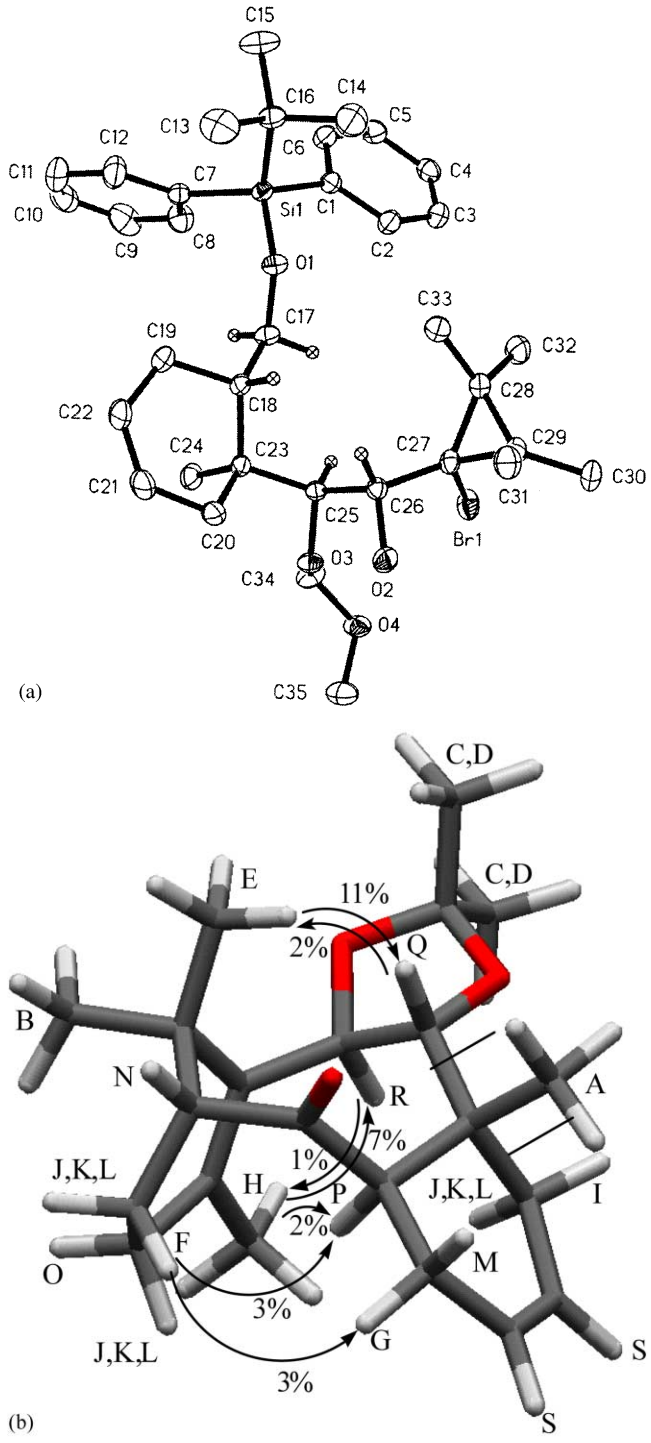


Figure 3. (a) ORTEP of compound **14**. Thermal ellipsoids depicted at the 50% probability level (selected hydrogen atoms omitted for clarity). (b) NOE of cycloadduct **3**.

tions during installation of the dienophile. The following deprotection–protection sequence was undertaken. The hydrolysis of **14** with MeOH–TsOH gave the triol **15**. The C-9, and C-10 hydroxy groups present in **15** were protected as an acetonide which, resulted in primary alcohol **16**. Oxidation of the primary alcohol using TPAP to **17**, followed by vinyl Grignard addition and subsequent reoxidation with Dess–Martin reagent[14] gave enone **5** which accomplished the synthesis of the dienophile fragment. Heating this enone in DMSO in the presence of collidine gave the Diels–Alder precursor **4**, which on heating in toluene for four days gave the desired cycloadduct **3** along with 10% of the tentatively assigned epimer at C1 (Scheme 3).

The characterization of the major product was accomplished by analysis of the ^{1}H, ^{13}C, COSY, and NOE NMR spectra. Importantly, the stereochemistry of **3** was determined by difference NOE experiments. Analysis of the NOE results was added by MM2* calculated structures of the lowest energy conformation of the two diasteriomeric cycloadducts. The critical NOE's are shown in Figure 3(b). Most useful were the methyl groups E and H on the bridge and the vinyl linkages, respectively. In cycloadduct **3** (natural taxane stereochemistry) the gem-dimethyl bridge (methyls B and E) is on the α-face of the molecule and *syn* to the angular methyl(A), while the vinyl methyl(H) is situated on the β-face of the molecule and anti to angular methyl(A). These relationships are reversed for the non-natural cycloadduct (epimer at C-1). Experimentally methyl E exhibits a strong NOE to methine proton Q and vinyl methyl H exhibits a strong NOE to methine proton R. Finally, proton F on the A-ring exhibits a strong NOE to protons P and G on the C-ring. The NOE enhancements correlated with those anticipated from analysis of the lowest energy conformation of cycloadduct **3**. The NOE's anticipated for C1-epimer of **3** were not observed. These results establish that the major product from the cycloaddition has the relative configuration of C-1 and C-8,9, and 10 corresponding to that of taxusin.

In conclusion, a highly functionalized taxane ring system containing oxygenation at C-9 and C-10 and unsaturation in ring C has been synthesized. The tricyclic skeleton was assembled utilizing the type 2 intramolecular Diels–Alder reaction. Methodology has also been developed to employ a highly functionalized bromocyclopropane as a diene surrogate.

Supplementary material available. Detailed experimental procedures and spectroscopic data for compounds **3**–**17** are available online through ScienceDirect.

Acknowledgements

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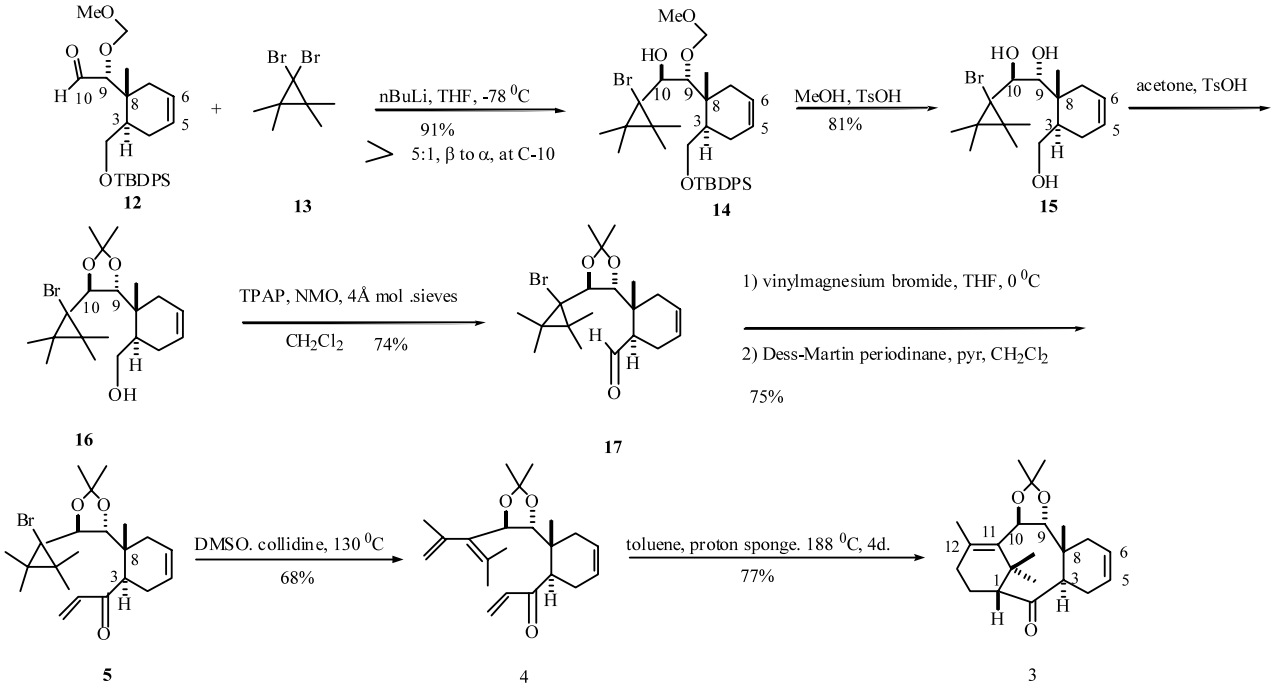

Scheme 3.

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