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Synthetic Study toward the Total Synthesis of Taxezopidines A and B

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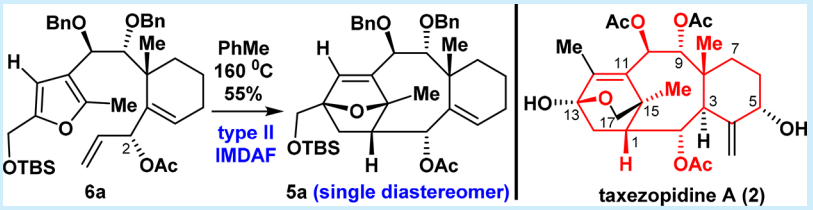
Supporting Information



ABSTRACT: A concise synthetic approach to construct the [6,8,6]-tricyclic core of taxezopidines A and B, which contains a synthetically challenging bridged bicyclo[5.3.1]undecane ring system bearing most of the desired functionalized groups and stereocenters, has been established. This approach features a diastereoselective type II intramolecular Diels−Alder furan reaction. The stereochemistry of the acetoxy group at the allylic position of the dienophile alkene group, such as in **6a**, was found to be critical for achieving the desired highly diastereoselective outcome.

Taxol (**1**, Figure 1) is a widely used anticancer drug with some harmful side effects.[1] Taxezopidines, which are a series of bioactive taxane-type diterpenoid natural products, have been isolated from seeds of the Japanese yew (*Taxus cuspidata Sieb.* et Zucc.) and characterized by Kobayashi et al.[2] Taxezopidine A (**2**) is the first taxoid isolated from yew trees bearing a hemiketal ring comprising C11−C13, C15, and C17,[2a] while taxezopidine B (**3**) is the first taxoid bearing a double bond between C3 and C4.[2b] Similar to Taxol (**1**), the structures of taxezopidines A and B contain several synthetically challenging features found in numerous oxygenated terpenoid natural products,[3] such as a highly strained and distorted [6,8,6]-tricyclic bridged framework containing 8−9 stereogenic centers, including an all-carbon quaternary stereocenter at C8. Unlike Taxol, taxezopidine A (**2**) contains an all-carbon quaternary stereocenter at C15 and an oxabicyclo[2.2.2]octane moiety with a cagelike backbone conformation, which pose further considerable synthetic challenges. In addition to their structural complexity, taxezopidines markedly inhibit the Ca^{2+}-induced depolymerization of microtubules.[2] However, the relative scarcity of taxezopidine natural sources has impeded a more systematic evaluation of their biological activity. Therefore, the development of an efficient synthesis for the construction of these complex molecules and Taxol analogues is highly desirable.

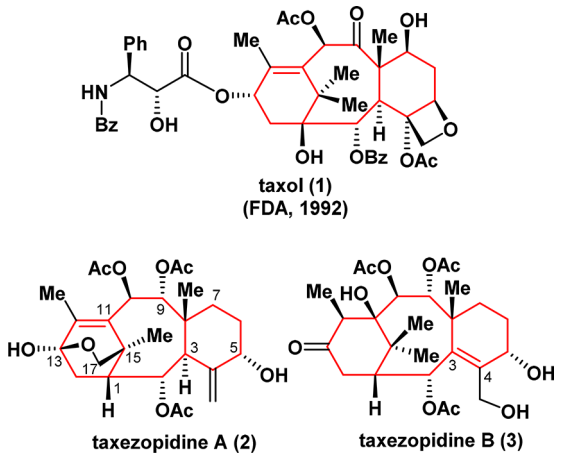


Figure 1. Structures of Taxol and taxezopidines A and B.

Owing to its unusual structural motifs and promising pharmacological properties, Taxol (**1**) has attracted considerable attention from synthetic chemists, which has resulted in seven total syntheses[4] and three formal syntheses.[5] However, no synthetic studies or total syntheses of taxezopidines A and B have been reported. As part of our continuing efforts toward the synthesis of biologically active natural products,[6] we herein report a concise synthetic approach to the construction of the core of taxezopidines A and B, which contains a [6,8,6]-tricyclic bridged ring system, using a type II intramolecular Diels−Alder furan (IMDAF) reaction.

Figure 2 shows the bond disconnections of taxezopidines A (**2**) and B (**3**) used to develop the concise synthetic strategy employed in this study. Taxezopidines A (**2**) and B (**3**) were

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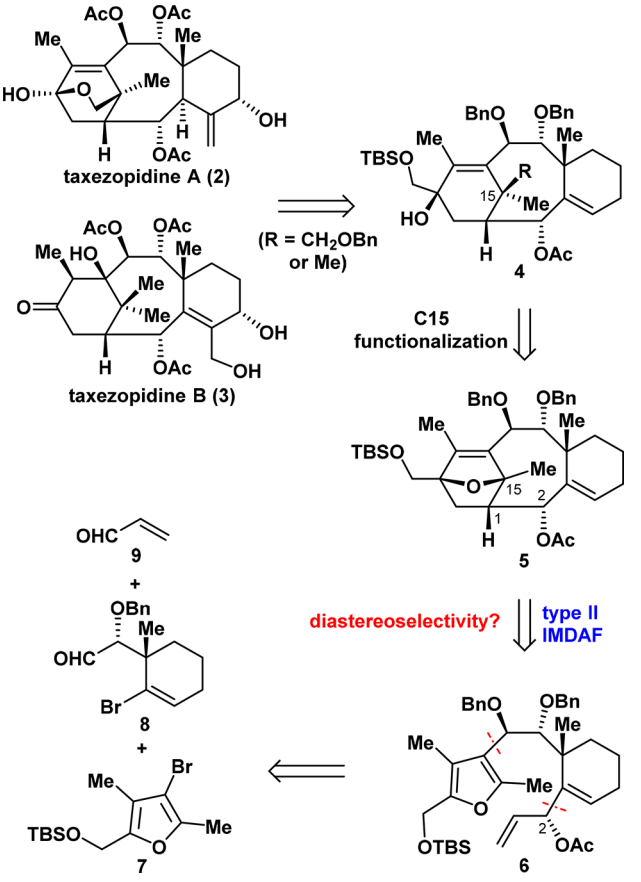


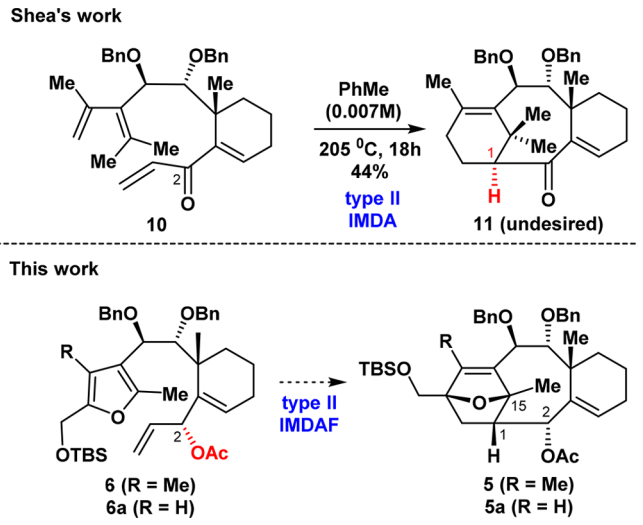
Figure 2. Retrosynthetic analysis of taxezopidines A and B.

envisioned to be generated from tricyclic core **4** (R = CH_2OBn or Me) through a series of functional group transformations. Compound **4** could be synthesized through chemoselective alkylation or methylation at the allylic C15 position in **5**.[7] This approach could be used to obtain structurally diverse analogues at C15 for structure−activity relationship (SAR) studies. Furthermore, compound **5**, containing a bridgehead double bond, could be synthesized diastereoselectively from **6** through a type-II IMDAF reaction. Finally, compound **6** could be prepared from readily available bromofuran **7**, known aldehyde **8**,[9] and acrolein (**9**) through successive 1,2-additions.

The key step in our proposed synthesis was the type-II IMDA reaction, which is a powerful synthetic tool first developed by Shea et al. in 1978[8a] for the direct construction of synthetically challenging bridged cyclohexene bicyclic skeletons. The reaction has subsequently been used to construct a number of complex natural products.[8d−h] In 1994, Shea et al. attempted to construct the taxane core structure through the type-II IMDA reaction of compound **10**.[9] Unfortunately, the reaction afforded tricyclic core **11** with the undesired stereochemistry at C1 in 44% yield (Scheme 1).

We speculated that using a type-II IMDAF reaction in our strategy, as well as taking advantage of the conformationally preorganized feature[10] of substrate **6**, would proceed differently to the IMDA reaction of **10**. In our previous study on type II intramolecular [5 + 2] cycloaddition reactions,[11] the acetoxy group at the allylic position of the dienophile alkene group was found to be crucial for high diastereoselectivity (>20:1 dr). Therefore, it was anticipated that the C2 acetoxy group in **6** could control the diastereoselectivity of the reaction

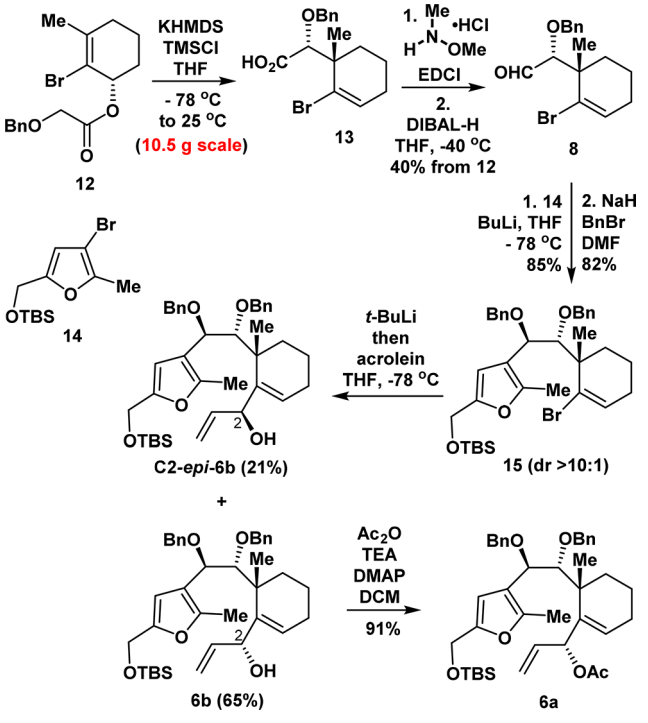
Scheme 1. Diastereoselectivity in Shea's Work and This Work



to afford the desired stereochemistry at C1 in **5** (Scheme 1). However, the presence of four substituents on the furan ring system of **6** would result in increased strain, which has rarely been reported in substrates for IMDAF reactions,[12] making this reaction particularly challenging. To achieve the proposed synthetic transformation, compound **6a** (R = H) was selected as a test substrate to assess the cyclization tendency of this IMDAF reaction.

Our synthesis began with the preparation of aldehyde **8** using a previously reported procedure with modifications (Scheme 2).[9] Subsequent 1,2-addition of the lithium reagent resulting from the reaction of BuLi with **14**[13] to **8** (5.0 g scale), followed by treatment with NaH and BnBr, gave **15** in 70% overall yield (>10:1 dr). Next, 1,2-addition of the lithium

Scheme 2. Synthesis of 6a



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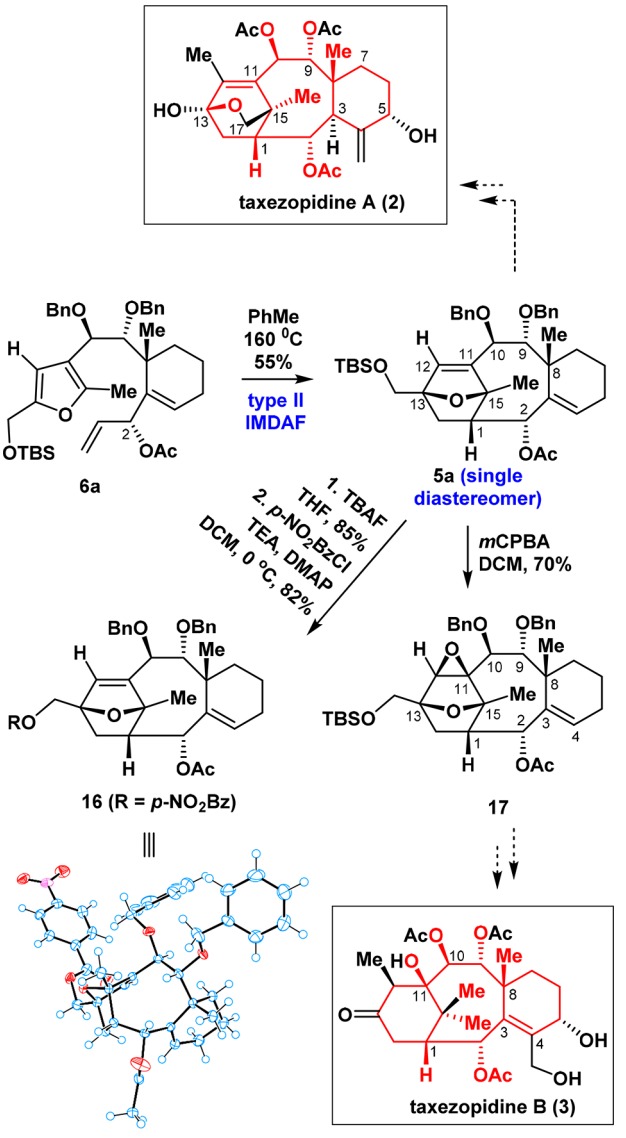
reagent resulting from the reaction of *t*-BuLi with bromide **15** to acrolein gave **6b** as the major product (**6b**/**C2-*epi*-6b** = 3.1:1, 2.1 g scale), followed by acylation of the secondary hydroxyl group in **6b** to afford desired precursor **6a** in 60% overall yield.

With **6a** in hand, we proceeded to investigate the proposed type-II IMDAF reaction for the synthesis of **5a**. Pleasingly, the type-II IMDAF reaction of **6a** in PhMe with heating gave **5a** containing the [6,8,6]-tricyclic core as a single diastereomer in 55% yield. The structure of **5a** with the desired functional groups, including a bridgehead double bond at C11−C12 and the correct relative stereochemistry at C1, C2, C8, C9, C10, C13, and C15 of taxezopidine A (as highlighted in red), was unambiguously confirmed by X-ray crystallographic analysis of derivative **16** (Scheme 3). Substrate-controlled stereoselective epoxidation of **5a** with *m*-CPBA in CH_2Cl_2 provided desired epoxide **17** in 70% yield. The structure of **17** was determined using two-dimensional NMR spectroscopy, which contained the desired double bond at C3−C4 and other functional groups, including the desired stereochemistry at C1, C2, C8, C9, C10, and C11 of taxezopidine B (as highlighted in red),

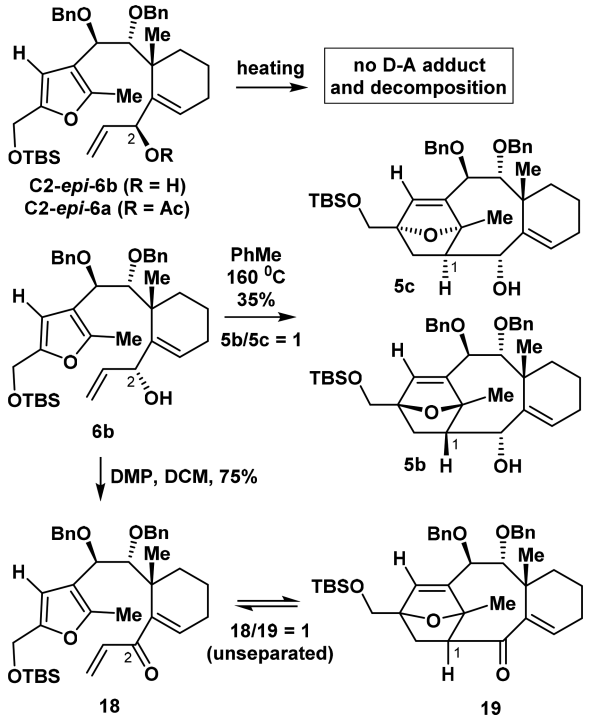
Scheme 3. Syntheses of 5a and 17



which was the first taxoid containing a double bond at C3−C4. Notably, in previous studies, generating the C2 hydroxyl group diastereoselectively through reduction of the corresponding ketone was problematic.[14] In contrast, the current work allowed efficient, direct construction of the C2 hydroxyl group.

Interestingly, we found that heating **6b**, bearing a free alcohol at C2, in PhMe afforded desired product **5b** and undesired epimer **5c** (**5b**/**5c** = 1:1) in 35% combined yield (Scheme 4). Surprisingly, when compound **6b** underwent

Scheme 4. Syntheses of 5b, 5c, and 19



oxidations with Dess−Martin periodinane (DMP) at room temperature, compound **18** and its DA cycloadduct **19** were obtained (**18**/**19** = 1:1). However, after many attempts (see the Supporting Information for details), **18** and **19** could not be separated, showing that the type-II IMDAF reaction of **18** was reversible. The relative stereochemistry at C1 in **19** was too difficult to determine, owing to **18** and **19** being inseparable. Based on these results, we concluded that the stereochemistry of the acetoxy group at the allylic position of the dienophile alkene group, such as in **6a**, was critical for the desired highly diastereoselective outcome of this type II IMDAF reaction.

Additionally, we have also tested a type-II IMDAF reaction of the compounds **C2-*epi*-6b** and **C2-*epi*-6a** which possessed an incorrect configuration of the C2 hydroxyl group (Scheme 4). To our surprise, when the two compounds were treated under the same conditions, we could not isolate any DA cycloadduct; only decomposition of the starting materials resulted. Therefore, we speculated that the correct configuration of the C2 hydroxyl group is essential for the type-II IMDAF reaction.

In summary, a concise synthetic approach to construct the [6,8,6]-tricyclic core of taxezopidines A (**2**) and B (**3**), which contains a synthetically challenging bridged bicyclo[5.3.1]-undecane ring system, has been developed. This approach features a diastereoselective type-II IMDAF reaction. Seven of

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the nine stereocenters in **2** and six of the eight stereocenters in **3** bearing the desired functional groups have been installed in compounds **5a** and **17**, respectively. Therefore, **5a** and **17** are potential advanced intermediates for the preparation of taxezopidines A and B. Efforts to further streamline this sequence and apply it to the total synthesis of **2** and **3** are underway in our laboratory. An investigation into the biological activities of this oxa[6,8,6] core is also underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02571.

Detailed experimental procedures, ^{1}H NMR and ^{13}C NMR spectra, as well as X-ray data information (PDF)

Accession Codes

CCDC 1861400 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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§Y.-J.H. and J.-H.F. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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