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Synthesis of Novel C2−C3′N-Linked Macrocyclic Taxoids by Means of Highly Regioselective Heck Macrocyclization

Xudong Geng, Michael L. Miller, Songnian Lin, and Iwao Ojima*

Department of Chemistry, State University of New York at Stony Brook, Stony Brook, New York 11794-3400

iojima@notes.cc.sunysb.edu

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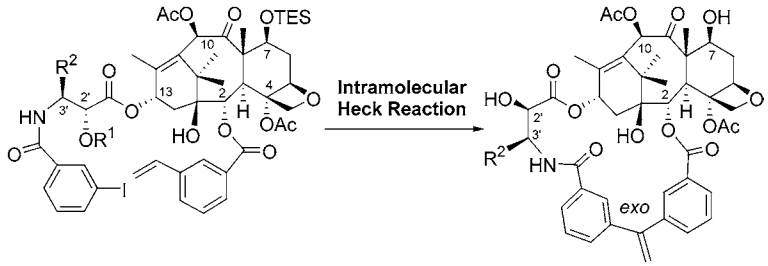
ABSTRACT



Novel C2−C3′N-linked macrocyclic taxoids are synthesized using intramolecular Heck reaction in the key step. Macrocyclization proceeds with high regioselectivity in good yield. Taxoids bearing an olefin moiety at C2 and an iodide at C3′N give *exo*-products exclusively. However, the *endo*-products are formed with up to 100% regioselectivity just by switching the positions of the olefin and the iodide moieties. Some of these macrocyclic taxoids are significantly cytotoxic.

The Heck reaction was introduced to organic chemists in the late 1960s,[1] but only the past decade or so has witnessed the rapid development and wide applications of this powerful and flexible C−C bond-forming reaction.[2] Now, the Heck reaction has become one of the most useful synthetic tools with its excellent functional group tolerance and highly successful stereoselective processes. The asymmetric intramolecular Heck reaction has recently been extensively studied because of its ability to efficiently construct congested quaternary carbon centers.[2a,3] Such capability has led to its various applications in the key steps in the assembly of many complex molecules.[2a−d,3b,4]

In the course of our study on the bioactive conformation of paclitaxel and its congeners,[5] we became interested in constructing C2−C3′N-linked macrocyclic taxoids to mimic the tubulin-bound docetaxel conformation proposed by Nogales et al.,[6] which is close to that found in its X-ray crystallographic analysis.[7] Accordingly, we reported previously the synthesis of a series of such macrocyclic taxoids using ring-closing metathesis (RCM) as the key reaction.[8] However, we found that RCM reactions using the Grubbs

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catalyst[9] were rather sensitive to the substitution pattern in the proximity of the terminal olefin, e.g., certain allylic substitutions substantially slowed or inhibited ring closing to form macrocyclic taxoids.[5d] Consequently, we decided to explore an alternative approach, i.e., intramolecular Heck reaction.

The intramolecular Heck reaction has two modes of ring-closing, i.e., *exo*- and *endo*-cyclization. Small size ring (5, 6, 7) formation usually favors *exo*-cyclization[2a,b,f,4,10] since the corresponding *endo*-cyclization is sterically very demanding. *endo*-Cyclization requires that the olefin bond moves into the loop of the substrate and generates an energetically favorable substituted alkene product. Thus, a large size ring (~20) formation with a flexible tether generally favors *endo*-cyclization.[2c,10a,11,12] To the best of our knowledge, only a limited number of examples of macrocyclization by intramolecular Heck reaction have appeared in the literature.[11−14] We report here efficient and highly regioselective intramolecular Heck macrocyclizations to construct novel C2−C3′N-linked macrocyclic taxoids that have shown significant cytotoxicity.

We first designed taxoid substrates **1a** and **2a**, bearing 2-methylprop-1-enyl or phenyl at the C3′ position as shown in Figure 1A. *exo*-Cyclization or *endo*-cyclization of these

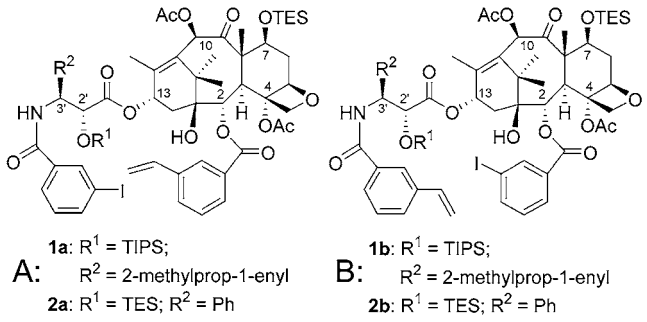


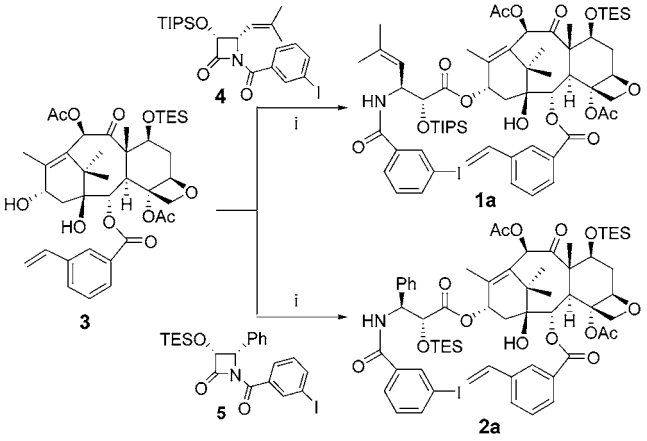
Figure 1. Taxoid substrates **1** and **2**.

substrates would give the corresponding 19- or 20-membered macrocyclic taxoids.

The taxoids **1a** and **2a** were synthesized through the Ojima−Holton β-lactam ring-opening coupling reaction with properly modified baccatins (Scheme 1).[15]

Enantiopure β-lactams were prepared through a highly efficient chiral enolate-imine cyclocondensation.[5d,15,16] β-Lactam **4** was prepared by acylation of the corresponding *N*-*H*-β-lactam.[8,17] Modified baccatin **3**[8] was coupled with β-lactam **4** in the presence of LiHMDS to afford **1a** in high yield. For the synthesis of **2a**, 3-TESO-β-lactam **5**, prepared following the procedure we reported previously,[18] was employed since we[19] and others[14] had found that *N*-benzoyl-4-phenyl β-lactams bearing a large silyl group (TIPS or TBS) at C3 were difficult to couple with baccatins. The coupling of β-lactam **5** with baccatin **3** proceeded smoothly to afford **2a** in excellent yield.

Scheme 1. Preparation of Taxoid Substrates **1a** and **2a**[a]



[a] (i) LiHMDS (1.5 equiv), **4** or **5** (1.5−2.0 equiv), THF, −40 °C, 0.5 h. **1a** 81%; **2a** 88%.

As Scheme 2 shows, the reaction of **1a** was carried out in acetonitrile with a catalytic amount of $Pd(PPh_3)_4$ and excess triethylamine at 55 °C overnight. The reaction gave only *exo*-cyclization product **6** in 65% isolated yield, which is substantially higher than those achieved in most of the reported macrocyclic intramolecular Heck reactions.[11−13] Then, the deprotection of **6** with HF-pyridine afforded macrocyclic taxoid **7-*exo*** in 74% yield. Taxoid **2a** was subjected to the same conditions but failed to give any cyclized product. However, the use of triphenylarsine, a weaker σ-donor ligand,[20] in place of triphenylphosphine solved the problem. Thus, the reaction of **2a** using $Pd_2(dba)_3$ as the Pd source and $AsPh_3$ as the ligand afforded *exo*-

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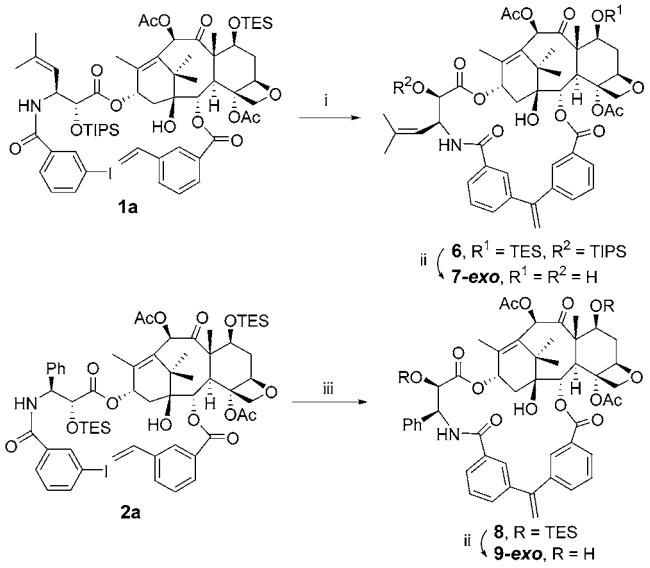
Scheme 2. Heck Macrocyclization of Taxoids **1a** and **2a**[a]

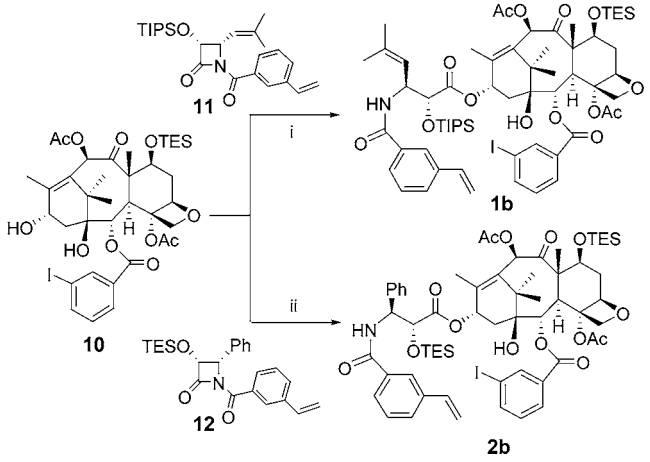


[a] (i) $Pd(PPh_3)_4$ (0.07 equiv), Et_3N, CH_3CN, 55 °C, overnight, 65%; (ii) HF-pyridine, pyridine, CH_3CN, overnight, 74%, (iii) $Pd_2(dba)_3$ (0.05 equiv), $AsPh_3$ (0.2 equiv), Et_3N, CH_3CN, 55 °C, 1 d, then (ii). 56% for two steps.

product **8** exclusively (Scheme 2). Removal of silyl protecting groups by HF-pyridine gave **9-*exo*** in 56% yield for two steps.

Since the observed exclusive *exo*-cyclization was unexpected, we switched the positions of iodide and olefin moieties in **1a** and **2a** to examine a possible effect of this change on the regioselectivity. Thus, taxoid substrates **1b** and **2b** (Figure 1B) were synthesized in a manner similar to that for **1a** and **2b** (Scheme 3). Baccatin **10** was prepared using the same protocol as that for **3**[8,16] and coupled with *β*-lactams **11** and **12** to give **1b** and **2b**, respectively, in good yields.

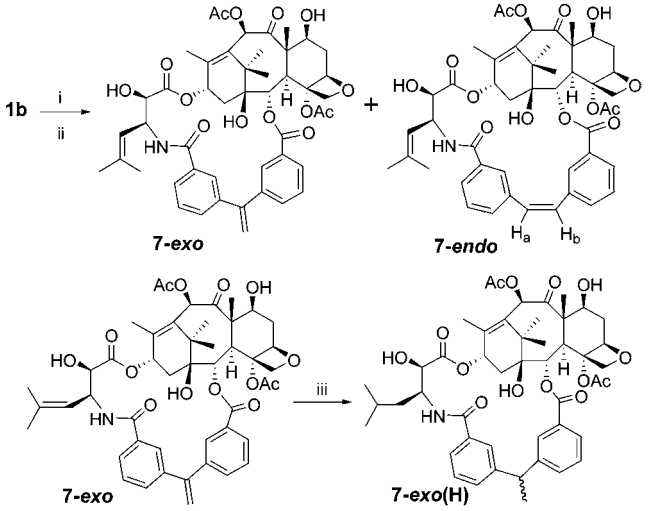
Scheme 3. Preparation of Taxoids **1b** and **2b**[a]



[a] (i) LiHMDS (1.5 equiv), **11** or **12** (1.5−1.8 equiv), THF, −40 °C, 35 min. **1b** 78%; **2b** 77%.

Macrocyclization of **1b** was carried out using the same conditions as those employed for **1a** (cat. = $Pd(PPh_3)_4$), which gave a mixture of *exo*- and *endo*-products (*exo*:*endo* = 3:1) in 68% isolated yield (Scheme 4). Thus, the formation

Scheme 4. Heck Macrocyclization of Taxoid **1b**[a]

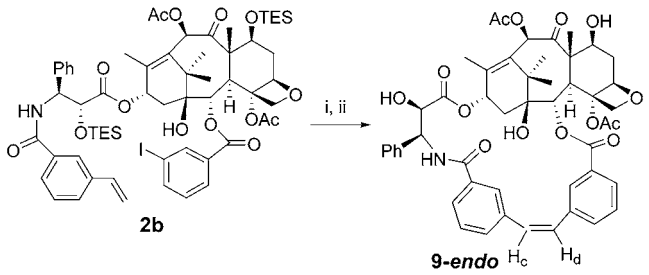


[a] (i) $Pd(PPh_3)_4$ (0.07 equiv), Et_3N, CH_3CN, 50 °C, overnight, 68% (*exo*:*endo* = 3:1); (ii) HF-pyridine, pyridine, CH_3CN, overnight. **7-*exo*** 56%; **7-*endo*** 19%. (iii) Pd/C, H_2, EtOAc, 18 h, 83%.

of the *endo*-product was observed. Deprotection with HF-pyridine and HPLC separation afforded macrocyclic taxoids **7-*exo*** (56%) and **7-*endo*** (19%). For **7-*endo***, only the *Z*-isomer was formed on the basis of NMR analysis (J_{HaHb} = 9.0 Hz). Taxoid **7-*exo*** was hydrogenated over Pd/C to afford **7-*exo*(H)** (3.5:1 diastereomer mixture) (Scheme 4).

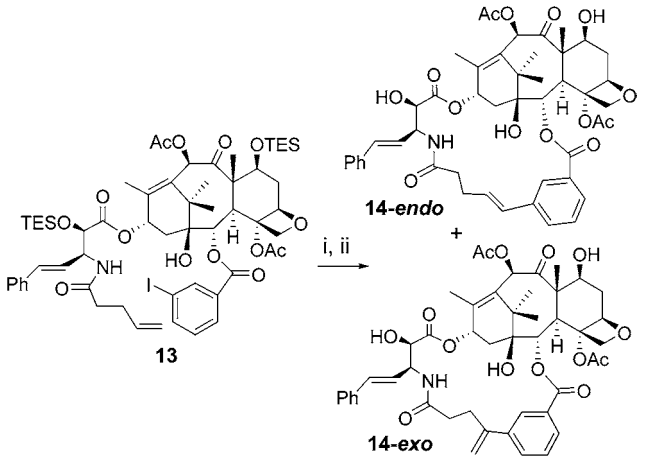
Next, the Heck macrocyclization of **2b** was examined. Unlike its regioisomer **2a**, this taxoid underwent macrocyclization smoothly under the "standard conditions", i.e., using $Pd(PPh_3)_4$ as the catalyst, to afford the corresponding *endo*-product exclusively. Deprotection with HF-pyridine gave macrocylic taxoid **9-*endo*** in 87% yield for two steps (Scheme 5). Again, only the *Z*-isomer was formed on the basis of NMR analysis (J_{HcHd} = 10.2 Hz).

Scheme 5. Heck Macrocyclization of Taxoid **2b**[a]



[a] (i) $Pd(PPh_3)_4$ (0.07 equiv), Et_3N, CH_3CN, 50 °C, 11 h; (ii) HF-pyridine, pyridine, CH_3CN, overnight. 87% for two steps.

Scheme 6. Heck Macrocyclization of Taxoid **13**[a]



[a] (i) $Pd(PPh_3)_4$ (0.1 equiv), Et_3N, CH_3CN, 70 °C, 1 d; (ii) HF-pyridine, pyridine, CH_3CN, overnight. 67% for two steps: **14-*endo*:14-*exo*** = 3:1 (HPLC).

We have also found that the Heck macrocyclization can be applied to unactivated olefin systems. As Scheme 6 shows, the reaction of taxoid **13**, prepared in a manner similar to those of taxoids **1** and **2**, proceeded under the standard conditions to give macrocyclic taxoids **14** (*exo*:*endo* = 1:3) in 67% yield after deprotection. Two regioisomers were separated by HPLC. It should be noted that the cinnamyl group at C3′ was intact during the reaction. To the best of our knowledge, only a few examples have been reported of the macrocyclization by intramolecular Heck reactions involving unactivated olefin.[11,12] However, we have demonstrated here that the intramolecular Heck reaction serves as a highly efficient method for constructing macrocyclic compounds.

The observed regioselectivity in these intramolecular Heck reactions may well be predictable by estimating the relative energies of the *endo*- or *exo*-ring-closing transition states or the Pd(II)I-olefin intermediate complexes, which should be influenced by the unique tetracyclic taxane skeleton. Accordingly, extensive molecular modeling studies on the transition state/intermediate of this process have been performed using the Spartan program (sybyl and PM3), which are found to be able to accommodate the observed switching between *exo*-cyclization and *endo*-cyclization, depending on the relative positions of the iodide and ethenyl moieties. However, the geometry of Pd needs optimization in some cases. Thus, further studies are currently underway in these laboratories, and the results will be reported in due course.

Biological Activity of Macrocyclic Taxoids. Some of these macrocyclic taxoids, especially the *exo*-isomers, were found to be significantly cytotoxic against the LCC6-WT human breast cancer cell line, with IC_{50} values of 0.071 μM for **7-*exo*** and 0.067 μM for **9-*exo*** (paclitaxel 0.004 μM), despite their rigidity. Interestingly, **7-*exo*(H)** (IC_{50} 0.060 μM) exhibited potency even higher than that of **7-*exo***. These macrocyclic taxoids are considerably more potent than most of the previously reported macrocyclic taxoids synthesized using RCM.[5d,8,14,21] The cytotoxicity of **9-*endo*** (IC_{50} 0.530 μM) was substantially weaker than that of **9-*exo***. Also, **14-*endo*** (IC_{50} 4.5 μM) was less potent than **14-*exo*** (IC_{50} 0.79 μM). Obviously, taxoids **14** are much less potent than taxoids **7** and **9**, which can be ascribed to the increased flexibility of the molecule as a result of the lack of a benzene moiety. Further SAR studies on macrocyclic taxoids are actively underway in these laboratories.

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Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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