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Authors: Yusuke Imamura, Shun Yoshioka, Masanori Nagatomo, and Masayuki Inoue

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Total Synthesis of 1-Hydroxytaxinine

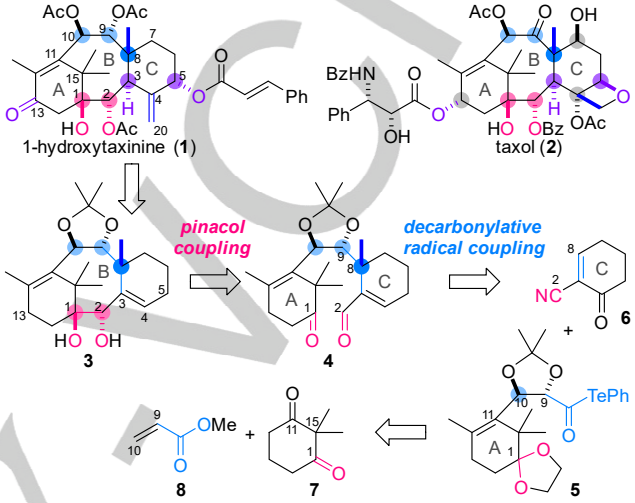
Yusuke Imamura[+], Shun Yoshioka[+], Masanori Nagatomo, and Masayuki Inoue*

Dedication ((optional))

Abstract: 1-Hydroxytaxinine (**1**) is a cytotoxic taxane diterpenoid. Its central 8-membered B-ring possesses four oxygen-functionalized centers (C1, 2, 9, and 10) and two quaternary carbons (C8 and 15), and is fused with 6-membered A- and C-rings. The densely functionalized and intricately fused structure of **1** makes it a highly challenging synthetic target. We developed an efficient radical-based strategy for assembling **1** from A- and C-ring fragments. A-ring **5** bearing the α-alkoxyacyl telluride moiety underwent intermolecular coupling with C-ring **6** via a Et_3B/O_2-promoted decarbonylative radical formation. After construction of the C8-quaternary stereocenters, a pinacol coupling reaction of **4** using a low-valent titanium reagent formed the B-ring of **3** with stereoselective installation of the C1,2-diol system. Subsequent manipulations at the A- and C-rings furnished **1** in 26 total steps.

1-Hydroxytaxinine (**1**, Scheme 1), isolated from stems of the Japanese yew, *Taxus cuspidata*,[1] is cytotoxic to murine leukemia L1210 cells and human epidermoid carcinoma KB cells (IC_{50} = 4.6 and 6.9 μg/mL, respectively). This natural product belongs to a family of taxane diterpenoids containing more than 400 congeners.[2] Many compounds in this family have biologically important properties, and taxol (**2**),[3] one of the most bioactive congeners, is used clinically to treat various cancers.[4]

As exemplified by the structures of **1** and **2**, taxane diterpenoids share a 6/8/6-membered carbon framework (ABC-ring system) and differ in their substitution patterns of oxygen functionalities. Compound **1** has six oxygen-substituted carbons (C1, 2, 5, 9, 10, and 13). The presence of two quaternary carbons (C8, 15) and two olefins (C4, 11) in this densely oxygenated skeleton further heightens the synthetic challenge of **1**. Whereas **2** has been chemically constructed by 10 research groups,[5,6] the total synthesis of **1** was only reported in a dissertation from Kishi's group in 1998.[7] In this report, Ni(II)/Cr(II)-mediated coupling[8] was applied for the construction of the 8-membered B-ring and **1** was synthesized in 38 steps (longest linear sequence). Herein, we describe a new radical-based strategy for the total synthesis of **1**. A combination of intermolecular and intramolecular radical coupling reactions permitted us to efficiently annulate the B-ring from A- and C-ring fragments.



Scheme 1. Structures of 1-hydroxytaxinine (**1**) and taxol (**2**) and synthetic plan for **1**.

Radical reactions are compatible with diverse oxygen functionalities and applicable to the formation of sterically hindered C–C bonds, thereby serving as methods to forge the complex architectures of highly oxygenated terpenoids.[9] In this context, we developed a series of powerful coupling reactions of α-alkoxy carbon radicals.[10,11] Our continued interest in these reactions motivated us to devise an efficient radical-based convergent route to **1** from chiral **5** and achiral **6** (Scheme 1).[12] A-ring **5** and C-ring **6** were designed to have an acetonide-protected C9,10-diol and C2-nitrile groups as stereocontrolling and reactivity-enhancing elements, respectively. Decarbonylative radical formation from α-alkoxyacyl telluride **5** would generate the corresponding C9-α-alkoxy radical,[13] which would stereoselectively add to 2-cyano-2-cyclohexen-1-one (**6**) to link the C8–C9 bond. After construction of the C8-quaternary carbon, pinacol coupling of ketoaldehyde **4** was to be applied for both cyclization of the 8-membered B-ring and installation of the C1,2-stereocenters of **3**.[14] Subsequent adjustment of the C3-, C4-, C5-, and C13-functional groups at the A- and C-rings would transform **3** to target **1**. Retrosynthetically, the key radical precursor **5** was further simplified into methyl acrylate (**8**) and 2,2-dimethylcyclohexane-1,3-dione (**7**), which has the preinstalled C15-quaternary carbon. Hence, **1** was to be assembled from three commercially available components **6**, **7**, and **8**.

[*] Y. Imamura,[+] Dr. D. Yoshioka,[+] Dr. M. Nagatomo, and Prof. Dr. M. Inoue
Graduate School of Pharmaceutical Sciences
The University of Tokyo
7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033 (Japan)
E-mail: inoue@mol.u-tokyo.ac.jp
[+] These authors contributed equally to this work
Supporting information and the ORCID identification number(s) for the author(s)of this article can be found under: https://doi.org/10.1002/anie.XXXXX.

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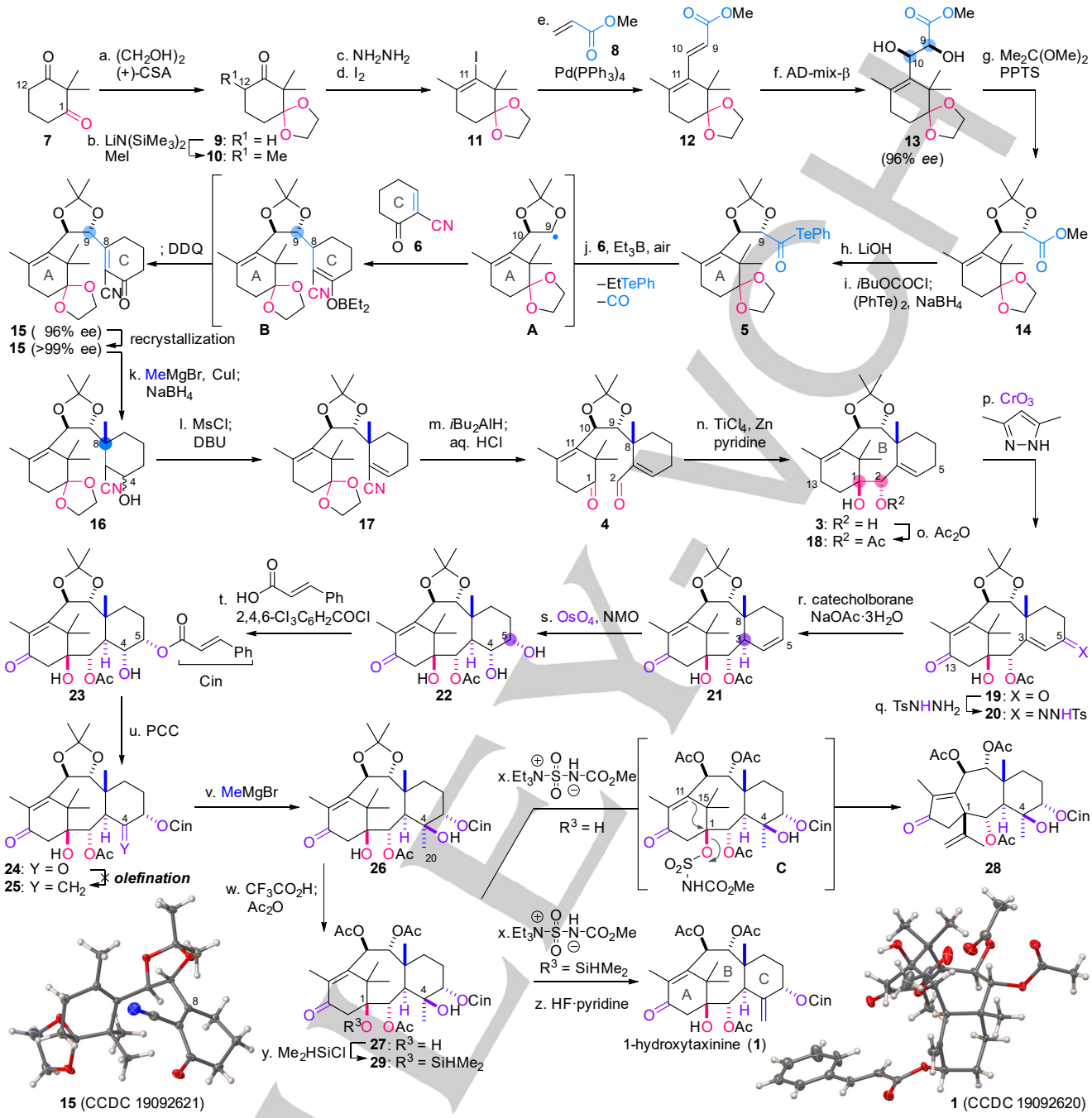

Scheme 2. Total synthesis of 1-hydroxytaxinine. Reagents and conditions: a) $(CH_2OH)_2$, (+)-10-camphorsulfonic acid (CSA), toluene, 50 °C, 67%; b) $LiN(SiMe_3)_2$, MeI, THF, –78 °C to RT, 98%; c) $NH_2NH_2{\cdot}H_2O$, Et_3N, EtOH, 100 °C, 76%; d) I_2, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), Et_2O, RT, 72%; e) **8**, Et_3N, $Pd(PPh_3)_4$ (3 mol%), DMF, 80 °C, 94%; f) AD-mix-β (2 equiv), methanesulfonamide ($MsNH_2$), H_2O, *t*BuOH, RT; g) 2,2-dimethoxypropane, pyridinium *p*-toluenesulfonate (PPTS), CH_2Cl_2, RT, 41% (2 steps, 96% ee); h) LiOH·H_2O, THF, H_2O, RT; i) *i*BuOCOCl, *N*-methylmorpholine (NMM), THF; $(PhTe)_2$, $NaBH_4$, THF, MeOH, 0 °C to RT, 91% (2 steps). j) **6** (2 equiv), Et_3B (3 equiv), air, benzene, 50 °C; 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ), 2,6-lutidine, 50 °C, **15** (96% ee): 65%; recrystallization (hexane, EtOAc, 60 °C), **15** (>99% ee): 76%; k) MeMgBr, CuI, Me_2S, toluene, –20 °C; $NaBH_4$, EtOH, RT; l) methanesulfonyl chloride (MsCl), Et_3N, benzene, RT; 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 100 °C, **17**:C8-*epi*-**17** = 7:1; m) *i*Bu_2AlH, hexane, –20 °C; 1 M aq. HCl, RT, 61% (3 steps); n) $TiCl_4$ (4 equiv), Zn (10 equiv), pyridine, THF, 50 °C; o) Ac_2O, *N*,*N*-dimethyl-4-aminopyridine (DMAP), pyridine, CH_2Cl_2, RT, **18**: 45% (2 steps), C2-*epi*-**3**: 6% (2 steps); p) CrO_3, 3,5-dimethylpyrazole (3,5-DMP), CH_2Cl_2, RT, 55%; q) *p*-toluenesulfonyl hydrazide ($TsNHNH_2$), AcOH, RT, 94%; r) catecholborane, THF, 0 °C; $NaOAc{\cdot}3H_2O$, $CHCl_3$, 85 °C, **21**: 47%, C3-*epi*-**21**: 21%; s) OsO_4 (10 mol%), *N*-methylmorpholine *N*-oxide (NMO), acetone, H_2O, RT, 76%; t) cinnamic acid, 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene, RT; u) pyridinium chlorochromate (PCC), MS4A, CH_2Cl_2, RT, 76% (2 steps); v) MeMgBr, THF, –60 °C to –30 °C, 12% recovered **24**; w) CF_3CO_2H, MeOH, 50 °C; Ac_2O, DMAP, pyridine, CH_2Cl_2, RT, 34% (2 steps); x) $Et_3NSO_2NCO_2Me$, toluene, 120 °C, **28**: 16%, **1**: 13%; y) Me_2HSiCl, imidazole, DMF, 0 °C, 89%; z) HF·pyridine, THF, RT, 56% (2 steps from **29**).

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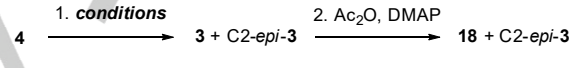
A-ring fragment **5** was prepared from **7** and **8** in nine steps (Scheme 2). One of the two carbonyl groups of **7** was protected as the dioxolane of **9** using ethylene glycol and camphorsulfonic acid (CSA). The remaining ketone of **9** was α-methylated with $LiN(SiMe_3)_2$ and MeI, and transformed to the vinyl iodide of **11** through generation of the corresponding hydrazone and its treatment with I_2 in the presence of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN).[15] The Pd(0)-catalyzed Heck reaction between **11** and **8** extended the carbon chain at C11, leading to the α,β,γ,δ-unsaturated ester **12**.[16] The less substituted C9-olefin of diene **12** was regio- and enantioselectively dihydroxylated by employing AD-mix-β to provide **13** (96% ee).[17,18] After acetonide protection of the resulting vicinal diol **13**, methyl ester **14** was saponified with aqueous LiOH. The activated ester was formed using *i*BuOCOCl and *N*-methylmorpholine (NMM) and changed in situ into an α-alkoxyacyl telluride of **5** by attack of the TePh anion generated from $NaBH_4$ and $(PhTe)_2$.[13]

Next, the adduct **15** was produced by radical coupling between A-ring **5** and C-ring **6**, and subsequent oxidative C8-olefin regeneration. Specifically, treatment of **5** and **6** (2 equiv) with Et_3B (3 equiv) in benzene at 50 °C under air effected the formation of the C8–C9 bond,[19] and 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) was introduced to the reaction mixture to provide **15** as a single C9-isomer in 65% yield.[20] In this reaction, an ethyl radical generated from Et_3B/O_2 promotes homolytic cleavage of the C–Te bond to afford an acyl radical, which undergoes the spontaneous release of carbon monoxide to form α-alkoxy radical **A** and loses the C9-stereochemical information.[21] The acetonide-protected 1,2-diol of **A** redefines the correct C9-stereochemistry upon 1,4-radical addition,[13b] as enone **6** only approaches from the opposite side of the bulky C10-substituent of **A**. Subsequently, Et_3B captures the resultant radical intermediate to form boron enolate **B**, and subsequent DDQ-oxidation furnishes enone **15**. Thus-obtained **15** (96% ee) was recrystallized to afford enantiopure **15**, and its absolute structure was determined by X-ray crystallographic analysis.[22]

Prior to construction of the substrate **4** for another key radical reaction, the C8-quaternary center was stereoselectively installed from **15** through nucleophilic 1,4-addition of MeMgBr in the presence of CuI and Me_2S in toluene (d.r. = 7:1).[23,24] The following $NaBH_4$-reduction of the C4-ketone in one pot gave rise to alcohol **16**. The X-ray structure of **15** suggests that the bulky A-ring structure would block the bottom face of the C8-double bond and the desired C8-stereochemistry would be established by the favorable top face addition of the nucleophile. The secondary alcohol of **16** was then sequentially treated with methanesulfonyl chloride (MsCl) and Et_3N, and with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), resulting in the formation of α,β-unsaturated nitrile **17** by elimination of the mesylate. Nitrile **17** was reduced to the corresponding imine with diisobutylaluminum hydride, and the following acidic work-up simultaneously hydrolyzed the C2-imine and C1-acetal to produce the requisite ketoaldehyde **4**. It is important to note that the C2-nitrile group has multiple roles in this route: it enhances the reactivity of two 1,4-acceptors **6** and **15** as an electron-withdrawing group, and serves as a precursor of the C2-aldehyde of **4**.

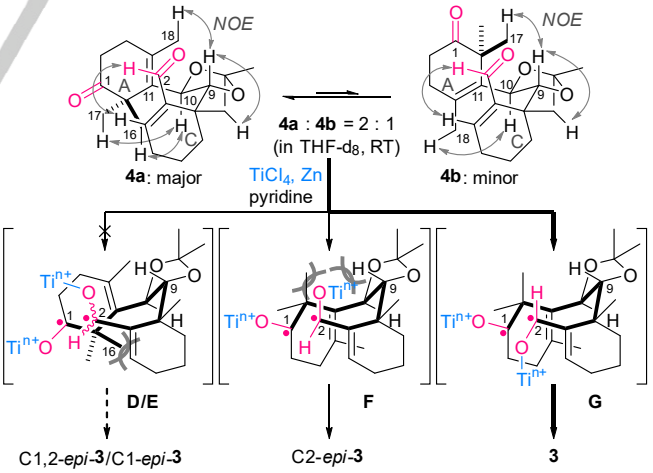
The stage was set for exploring the pinacol coupling reactions for stereoselective cyclization of the 8-membered B-ring (Table 1).[25] Whereas application of SmI_2 at room temperature did not generate the cyclized compound (entry 1),[26] the same conditions at 50 °C allowed for the formation of tricycle **3** with the desired C1,2-stereochemistry (entry 2). After acetylation, however, **18** was isolated in variable yields (0%-33%) due to competing reduction of the C2-aldehyde of **4** to a primary alcohol. Because of the low yield and reproducibility, we turned our attention to other low-valent metal reagents. When **4** was subjected to $VCl_3(THF)_3$[27] (entry 3) or $NbCl_3(DME)$[28] (entry 4), no reaction occurred, indicating their inadequacy for single-electron reduction of **4**. Considerable experimentations and optimizations revealed that the low-valent titanium reproducibly provided the desired tricycle **3** (entry 5).[29] Treatment of **4** with $TiCl_4$ (4 equiv) and Zn (10 equiv) at 50 °C in THF in the presence of pyridine resulted in the formation of **3** and C2-*epi*-**3** as the major and minor components, respectively.[30] Upon acetylation of the diastereomeric mixture with Ac_2O and DMAP, the secondary C2-OH of **3** was acetylated chemoselectively over the tertiary C1-OH to give **18** (45%) along with the unreacted C2-*epi*-**3** (6%). The three-dimensional structure of **18** was unambiguously confirmed by X-ray crystallographic analysis (Figure S4).[22] Thus, all four oxygen functionalities on the 8-membered B-ring (C1, 2, 9, and 10) were successfully installed at this stage.

Table 1. Investigation of pinacol coupling reactions of **4**.



entry	conditions	results[a]
1	SmI_2 (10 equiv), THF, RT	**18** (0%)
2	SmI_2 (10 equiv), THF, 50 °C	**18** (0-33%)
3	$VCl_3(THF)_3$ (5 equiv), Zn, CH_2Cl_2, RT	No reaction
4	$NbCl_3(DME)$ (10 equiv), THF, RT	No reaction
5	$TiCl_4$ (4 equiv), Zn (10 equiv), pyridine, THF, 50 °C	**18** (45%) C2-*epi*-**3** (6%)

[a] yield over 2 steps.



Scheme 3. Two stable conformers of ketoaldehyde **4** in THF-d_8 and rationale for the C1,2-stereoselectivity of the pinacol coupling reaction.

The C1,2-stereochemical outcome of the intramolecular radical coupling can be explained by steric interactions of the four titanium-coordinated radical intermediates **D**, **E**, **F**, and **G** that lead to C1,2-*epi*-**3**, C1-*epi*-**3**, C2-*epi*-**3**, and **3**, respectively (Scheme 3). As the C16-H becomes proximal to the C-ring, **D**

and **E** are significantly disfavored compared with **F** and **G**. **G** is considered to be energetically more favorable than **F** due to steric repulsion of the pseudo-axial C2O-functionality, ultimately resulting in the generation of **3** as the major isomer. On the other hand, the temperature dependency of the cyclization efficiency (e.g., entries 1 and 2, Table 1) would originate from the hindered rotation of the C10–C11 bond. Namely, detailed NMR analysis of **4** at room temperature in THF-d_8 revealed that it exists as a 2 : 1 mixture of conformers **4a** and **4b** because of the high rotational barrier around the C10–C11 bond (Scheme 3).[31] The relative orientations between the A- and C-rings of **4a** and **4b** match those of **D**/**E** and **F**/**G**, respectively. As only **4b** would lead to productive cyclization via the intermediacy of **F**/**G**, a higher temperature would be required to facilitate the conformational change from **4a** to **4b**.

The last stage of the total synthesis involved carefully optimized functional group transformations at the C3, C4, C5, and C13 positions from the 6/8/6-membered ring system **18** (Scheme 2). First, the C5- and C13-allylic methylenes of **18** were simultaneously oxidized using CrO_3 and 3,5-dimethylpyrazole to produce bis-enone **19**.[32] The C5-enone of **19** was then used as a handle for introducing the C3-hydrogen and C5-olefin. Thus, the addition of *p*-toluenesulfonyl hydrazide and AcOH changed the less hindered C5-carbonyl group of diketone **19** into the corresponding sulfonyl hydrazone of **20**, which was subjected to catecholborane and NaOAc.[33] As a result, 1,2-reduction of hydrazone **20** occurred from the more exposed top face and induced the elimination of a *p*-tolylsulfinate. The following allylic diazene rearrangement transferred the C3-hydrogen from the bottom face and shifted the olefin location, giving rise to the selective formation of **21** (47%) along with its epimer C3-*epi*-**21** (21%).

Dihydroxylation of the disubstituted C5-olefin of diene **21** using catalytic OsO_4 and stoichiometric *N*-methylmorpholine *N*-oxide (NMO) proceeded stereoselectively from the bottom side to generate **22** presumably because the top side approach of the osmium reagent would cause a severe 1,3-diaxial interaction with the C8-methyl group. The less hindered C5-OH of diol **22** was in turn converted to the cinnamoyl ester of **23** using the Yamaguchi reagent system,[34] and the remaining C4-OH of **23** was oxidized to the C4-ketone of **24** with pyridinium chlorochromate (PCC). Olefination of **24**, however, did not give **25** under a variety of conditions using Wittig, Peterson, Takai, or Tebbe reagent. The shielded and base-sensitive nature of the β-acetoxy C4-ketone of **24** would be responsible for the failure of this simple transformation.

To overcome this problem, we adopted a stepwise methylation/dehydration approach to build the C4-olefin. Nucleophilic addition of MeMgBr to C4-ketone **24** chemo- and stereoselectively furnished **26** without affecting the C13-carbonyl, C2- and C5-acyloxy groups. Before the dehydration, the acetonide group of C9,10-OHs was exchanged for the two Ac groups by sequential treatment with CF_3CO_2H/MeOH and Ac_2O in one pot. Burgess reagent ($Et_3NSO_2NCO_2Me$) indeed promoted the elimination of C4-OH of **27**,[35,36] leading to 1-hydroxytaxinine (**1**), albeit in low yield (13%). The major byproduct turned out to be 5/7/6-membered **28** (16%), the skeleton of which is found in abeotaxane diterpenoids.[2] Apparently, activation of the C1-bridgehead hydroxy group (**27**→**C**) induces the C11-migration from C15 to C1 through the Wagner–Meerwein rearrangement (**C**→**28**).[37] To impede this side reaction, we temporarily protected the sterically encumbered C1-OH of **27** with its dimethylsilyl group in the presence of Me_2HSiCl and imidazole,[38,39] and **29** was treated with Burgess reagent and subsequently with HF·pyridine. This alternative protocol enabled the formation of the targeted 1-hydroxytaxinine (**1**) in 56% yield over 2 steps from **29** without forming **28**. The X-ray structure in Scheme 2 shows the structural integrity of the synthesized **1**,[22] which was further validated by the matched physical data (^{1}H NMR, ^{13}C NMR, IR, $[\alpha]_D$ and HRMS) of **1** with those reported previously.[1,40]

In summary, we achieved an asymmetric total synthesis of 1-hydroxytaxinine (**1**) in 26 total steps from 2,2-dimethylcyclohexane-1,3-dione (**7**). The two powerful radical reactions annulated the B-ring from the judiciously designed A- and C-ring substrates and streamlined the overall synthetic sequence. Because of their flexibility and robustness, the strategy and tactics developed here would potentially be applicable to the synthesis of highly oxygenated taxane diterpenoids, including taxol (**2**).

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Conflict of interest

The authors declare no conflict of interest.

Keywords: Natural products • Tellurium • Terpenoids • Total synthesis • Radical reactions

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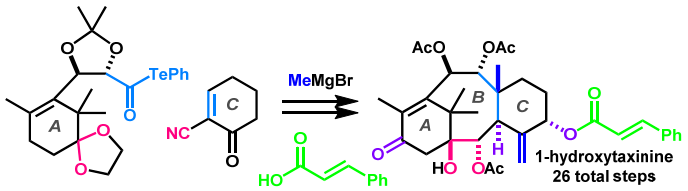

*Yusuke Imamura, Shun Yoshioka, Masanori Nagatomo, and Masayuki Inoue**

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Total Synthesis of 1-Hydroxytaxinine

1-Hydroxytaxinine, a cytotoxic taxane diterpenoid, possesses a highly oxygenated 6/8/6-membered ring (ABC-ring) system. Decarbonylative intermolecular radical coupling and low-valent titanium-promoted intramolecular radical cyclization were employed as the two key reactions to annulate the B-ring from A- and C-ring fragments. Subsequent manipulations at the A- and C-rings furnished 1-hydroxytaxinine in 26 total steps.