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First Enantiocontrolled Formal Synthesis of (+)-Neovibsanin B, A Neurotrophic Diterpenoid

Tomoyuki Esumi,* Takehiro Mori, Ming Zhao, Masao Toyota, and Yoshiyasu Fukuyama*

Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro-cho, Tokushima 770-8514, Japan

fukuyama@ph.bunri-u.ac.jp

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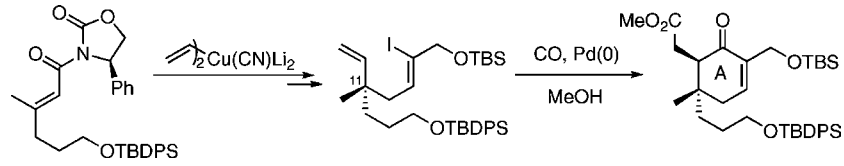
ABSTRACT



An enantiocontrolled formal synthesis of (+)-neovibsanin B has been achieved by a sequence that applies an asymmetric 1,4-addition of $(H_2C{=}CH)_2Cu(CN)Li_2$ to trisubstituted α,β-carboxylic acid derivative 1 to induce the chirality at the C-11 all-carbon quaternary center. Together with a modified Negishi cyclic carbopalladation-carbonylative esterification tandem reaction for constructing the A-ring, the synthesis was completed.

Neovibsanins A and B, vibsane-type diterpenoids, which were isolated from the leaves of *Viburnum awabuki* by Fukuyama et al.,[1] have attracted considerable synthetic attention because of their challenging structures combined with interesting neurotrophic activity. They have been found to significantly promote the neurite outgrowth of NGF-mediated PC12 cells,[2] and thus have shown potential as drugs for the treatment of neurodegenerative diseases such as Alzheimer's disease.[3] Recently, Nishizawa et al.[4] achieved the total synthesis of (±)-neovibsanin B by utilizing an intramolecular Diels−Alder reaction to construct the A-ring system and a chelation-controlled diastereoselective alkylation at C-4 as two key steps, and the resultant synthetic (±)-neovibsanin B was shown to exhibit neurite outgrowth-promoting activity in NGF-mediated PC12 cells comparable to that of natural (+)-neovibsanin B. On the other hand, Williams et al.[5] reported a synthesis of (±)-4,5-bis-*epi*-neovibsanins A and B, which were also shown to accelerate neurite outgrowth in NGF-mediated PC12 cells (Figure 1).

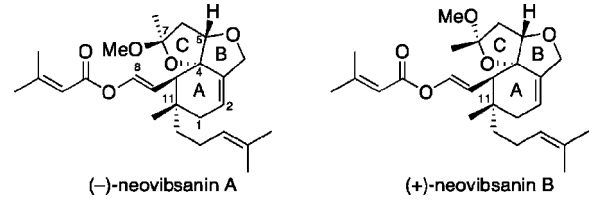


Figure 1. Structures of neovibsanins A and B.

However, no enantioselective synthetic study on neovibsanins has been published. Herein, we wish to demonstrate the first enantiocontrolled formal synthesis of (+)-neovibsanin B

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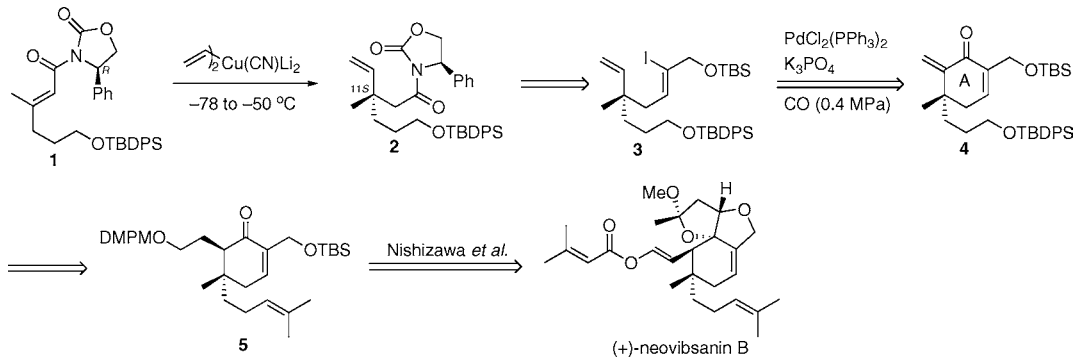
Scheme 1. Synthetic Plan of (+)-Neovibsanin B



based on an asymmetric 1,4-addition, which was previously developed by us,[6] and a modified Negishi cyclic carbopalladation-carbonylative esterification tandem reaction.[7]

Our synthetic plan of (+)-neovibsanin B is outlined in Scheme 1. To achieve its synthesis in an enantiocontrolled fashion, the enantioselective construction of the chiral all carbon quaternary center at C-11 was a requirement. We decided to employ the asymmetric 1,4-addition reaction of $(H_2C{=}CH)_2Cu(CN)Li_2$ to the trisubstituted α,β-carboxylic acid derivative **1** of (*R*)-4-phenyl-2-oxazolidinone[6] to prepare (11*S*)-**2**. According to our previous report,[8] removal of the chiral auxiliary of (11*S*)-**2** followed by the alkynylation and selective iodination would lead to iodoalkene, (11*S*)-**3**. Previously we reported that the modified Negishi palladium(0)-catalyzed carbonylative cyclization[7] of (±)-**3** smoothly proceeded to give rise to the cyclohexen-1-one derivative, (±)-**4**.[8] Therefore, (11*S*)-**4** would be prepared from (11*S*)-**3** by employing the same reaction (Scheme 2). After C1 extension from the *exo*-methylene group by a 1,4-addition reaction, simple functional group manipulation would lead to Nishizawa's intermediate, (11*S*)-**5** in optical active form.

Negishi's iodomethylation[9] of 4-pentyn-1-ol gave the alkenyl iodide **6**, which was followed by the silylation of the hydroxy group with TBDPSCl. Subsequent palladium(0)-catalyzed carbonylation-amidation of **6** with (*R*)-4-phenyl-2-oxazolidinone afforded the trisubstituted α,β-carboxylic acid derivative **1** in 68% yield. The asymmetric 1,4-addition reaction of $(H_2C{=}CH)_2Cu(CN)Li_2$ to **1** gave rise to **2** as a diastereomeric mixture of 95 (11*S*):5 (11*R*) in good yield, and each diastereomer was readily separated by column chromatography over silica gel. The optically pure (11*S*)-isomer of **2** was used for the subsequent reaction. Removal of the oxazolidinone in **2** with 30% aqueous H_2O_2/LiOH[10] followed by esterification with EtOH yielded the ester, which was then reduced with $LiAlH_4$ to the alcohol **7** in 87% yield over three steps. PCC oxidation of **7**, followed by Corey-Fuchs dibromoolefination,[11] provided 1,1-dibromoolefin **8** in 89% yield. The stereoselective conversion of **8** into the cyclization precursor (2*Z*)-**3** was achieved by the following sequence. Treatment of **8** with *n*-BuLi generated the alkynyl anion, which was trapped in situ with formaldehyde, giving rise to the alkynyl alcohol. Regio- and stereoselective hydrostannylation[12] of its alkyne moiety with tributyltin hydride in the presence of AIBN exclusively afforded (2*Z*,11*S*)-**3** after protecting the hydroxyl group as a TBS group in 83% yield over four steps. Then, carbonylative cyclization of (2*Z*)-**3** in the presence of 10 mol % of

Scheme 2. Synthesis of (11*S*)-**4**

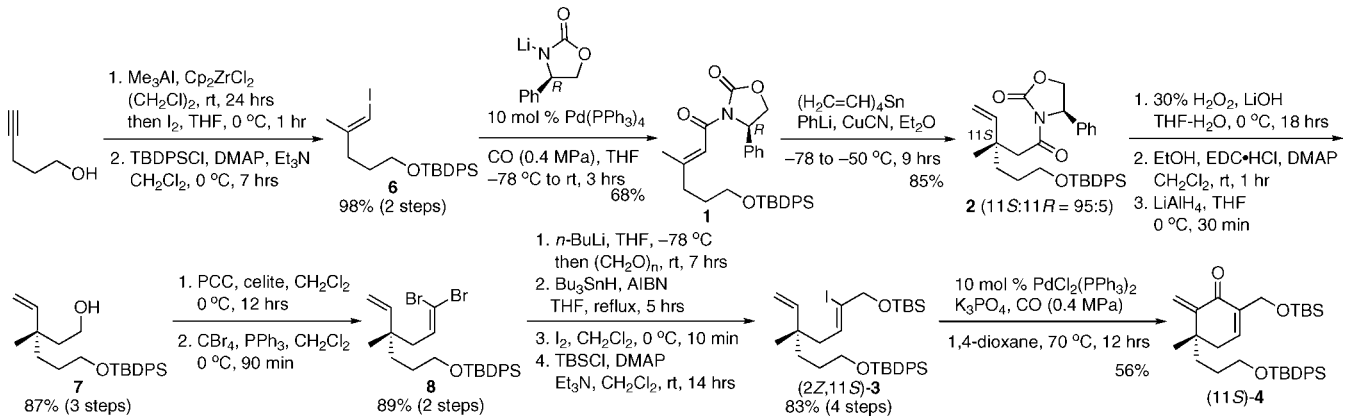
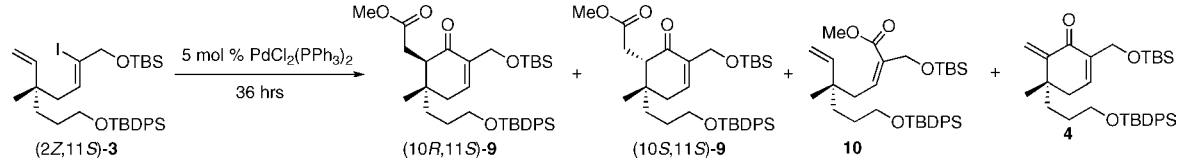


Table 1. Negishi's Pd(0)-Catalyzed Cyclic Carbopalladation-Carbonylative Tandem Reaction of (2*Z*,11*S*)-**3**



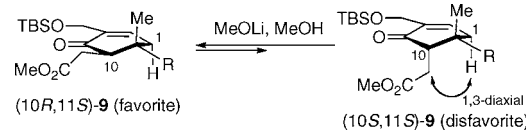
entry	base (1.5 equiv)	solvent	MeOH (equiv)	CO (MPa)	temp. (°C)	**9** (10*R*:10*S*)[a]	**10**	**4**	**3** (%)
1	Et_3N	MeCN/PhH (1:1)	4	4	100	11 (1.1:1)	0	6	52
2	Et_3N	MeCN/PhH (1:1)	**48**	4	100	54 (2.4:1)	10	2	0
3	Et_3N	MeCN/PhH (1:1)	48	**8**	100	41 (2.3:1)	9	12	0
4	Et_3N	MeCN/PhH (1:1)	48	4	**60**	49 (2.7:1)	13	0	21
5	Et_3N	MeCN/PhH (1:1)	**24**	4	60	**69 (2.6:1)**	14	0	0
6	Et_3N	**1,4-dioxane**	4	4	100	0	0	0	90
7	Et_3N	**MeOH**	–	4	100	6 (1.4:1)	13	4	52
8	**K_3PO_4**	MeCN/PhH (1:1)	4	4	100	16 (1.4:1)	18	0	3
9	**i-Pr_2NEt**	MeCN/PhH (1:1)	4	4	100	0	0	0	85
10	**DABCO**	MeCN/PhH (1:1)	4	4	100	24 (1.6:1)	0	9	0

[a] Ratio was determined by ^{1}H NMR spectroscopy in $CDCl_3$ (300 MHz).

$PdCl_2(PPh_3)_2$ under a carbon monoxide atmosphere (0.4 MPa) smoothly proceeded to give rise to the desired cyclohexenone derivative (11*S*)-**4** in 56% yield. In order to produce (10*R*,11*S*)-**5** from (11*S*)-**4**, we tried the C1-extension from the *exo*-methylene moiety of (11*S*)-**4** by using 1,4-addition reaction of a CN^- species. However, all these attempts were fruitless due to the poor electrophilicity of the conjugated *exo*-methylene moiety, which was diminished by the additional conjugated endocyclic olefin. This result prompted us to explore alternative routes to the key intermediate **5** with an extended C1 unit.

In principle, compound **3** could be obtained by Negishi palladium(0)-catalyzed cyclic carbopalladation-carbonylative tandem reaction in the presence of MeOH.[7b] The desired product **9**, which has a methyl ester group, would be directly formed instead of the *exo*-methylene type compound **4**. Thus, we examined this reaction. First, the reaction was performed using 5 mol % $PdCl_2(PPh_3)_2$ and Et_3N (1.5 equiv) in MeCN/PhH (1:1) containing 4 equiv of MeOH at 100 °C in an autoclave, which gave rise to the desired diastereomeric mixture of **9** in 11% yield along with ca. 50% of the starting material containing a small amount of **4** (6%) (Table 1, entry 1). On the other hand, the addition of an excess amount (48 equiv) of MeOH to this reaction system dramatically increased the yield of **9** to 54%, contaminated with 10% of the noncyclic ester **10** (entry 2). The use of high pressure (8 MPa) was found to be ineffective at suppressing the generation of **10** (entry 3), but low temperature (60 °C) was able to decrease the generation of **4** (entry 4). After several trials, we were pleased to find that the following reaction conditions of 24 equiv of MeOH, 4 MPa CO and a temperature of 60 °C, led to the formation of **9** alone in ca. 70% yield as a diastereomeric mixture (10*R*:10*S* = 2.6:1) (entry 5). Each diastereomer of **9** was readily separated by silica gel column chromatography to give (10*R*,11*S*)-**9** and (10*S*,11*S*)-**9**. Furthermore, treatment of the undesired isomer, (10*S*,11*S*)-**9** with MeOLi in MeOH gave the equilibrating diastereomers (10*R*,11*S*)-**9** and (10*S*,11*S*)-**9** in a ratio of 1.5:1. Thus, repeating this operation enabled the conversion of the undesired isomer (10*S*,11*S*)-**9** to the desired isomer (10*R*,11*S*)-**9**. This was due to the 1,3-diaxial interaction between the side chain at the C10 position and the proton at the C1 position as depicted in Scheme 3.

Scheme 3. Equilibrium between (10*R*,11*S*)-**9** and (10*S*,11*S*)-**9**



With (10*R*,11*S*)-**9** in hand, we focused on the last few steps for the synthesis of Nishizawa's intermediate **5** (Scheme 4). Treatment of (10*R*,11*S*)-**9** with *n*-Bu_4NF containing acetic acid gave **11**, and the resultant hydroxy group was oxidized by Swern oxidation to its aldehyde, which was subjected to

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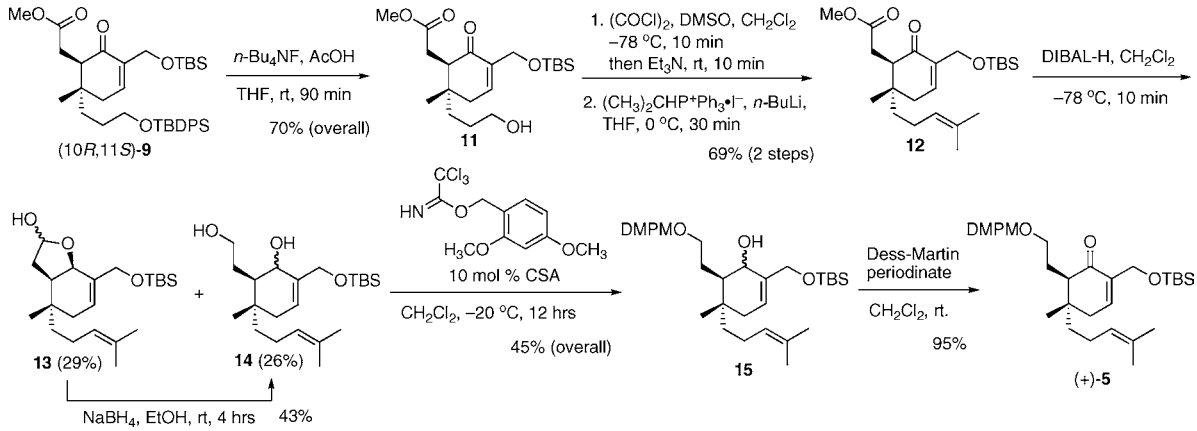
Scheme 4. Completion of Enantiocontrolled Formal Synthesis of (+)-Neovibsanin B



Wittig olefination to give the dimethyl olefin **12** in 69% yield over two steps. Reduction of **12** with DIBAL-H provided the cyclic hemiacetal **13** and diol **14** in 29 and 26% yields, respectively. The cyclic hemiacetal **13** was transformed to **14** by reduction with $NaBH_4$. Unfortunately, the selective protection of the primary alcohol in **14** using the reaction conditions, 2,4- DMPMCl and Bu_2SnO, utilized by Nishizawa et al.[4,13] did not succeed in our hands. However, when **14** was reacted with freshly prepared 2,4-DMPM-trichloroacetoimidate[14] in the presence of 10 mol % CSA, the desired 2,4-DMPM-ether **15** was obtained in 45% yield. Finally Dess−Martin oxidation[15] of **15** afforded the Nishizawa's intermediate **5** as an optically active form ($[\alpha]_D^{22}$ +20.1 (*c* 1.05, MeOH)) in 95% yield. The spectroscopic data (MS, IR, ^{1}H NMR, ^{13}C NMR) of our synthetic **5** were identical to those of Nishizawa's intermediate.[4]

In conclusion, the first enantiocontrolled formal synthesis of (+)-neovibsanin B was accomplished in 1.1% overall yield over 20 steps. Our formal synthesis of (+)-neovibsanin B not only demonstrates a useful application of the asymmetric 1,4-addition of the trisubstituted α,β-carboxylic acid derivative **1**, but also emphasizes the potential use of the Negishi's cyclic carbopalladation-carbonylative esterification tandem reaction for constructing the neovibsanin skeleton. Work is now in progress to achieve total synthesis of (+)-neovibsanin B.

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

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