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Synthesis and neurite outgrowth promoting activity of vibsanin B derivatives

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ABSTRACT

Intramolecular hetero-DA reaction and unexpected retro-aldol like ring opening reaction were performed. As a result, six derivatives with different skeletons of vibsane-type diterpenoids were synthesized from vibsanin B within three steps. Moreover, compounds **2**, **3**, and **6** enhanced the neurite outgrowth of NGF-mediated PC12 cells.

Vibsane-type diterpenoids are uniquely natural products and they have been only found exclusively in a few species of *Viburnum* (Caprifoliaceae), such as *V. awabuki*,[1] *V. odoratissimum*,[2] *V. suspensum*,[3] *V. sieboldii*,[4] and *V. chingii*.[5] Until now, more than 80 vibsane-type diterpenoids have been reported.[6] According to the carbon skeletons, these diterpenoids are further classified into three subtypes: 11-membered ring type, 7-membered ring type, and the rearranged type, with vibsanin B, vibsanin C, and neovibsanin A as the represented examples, respectively.

In recent years, vibsane-type diterpenoids have attracted increasing attention because of the unique structures and broad spectrum of activities.[5,6] Among them, vibsanin B, a plant growth inhibitor, was first isolated from the leaf of *V. awabuki* by Kawazu.[7] It has a unique 11-membered ring skeleton, three chiral centers, five unsaturated double bonds, and three michael acceptor fragments. The absolute configuration of vibsanin B was determined based on chemical correlation with vibsanin C by X-ray crystallographic analysis of its derivative.[8] Fukuyama et al. reported the bio-mimic transformations of vibsanin B, vibsanin C, neovibsanin A and B under thermal, photochemical, and lewis acids conditions (Fig. 1). Moreover, neovibsanin A and B were reported to show the neurite outgrowth promoting activity.[9]

In our continued research aimed at discovering structurally interesting and bioactive terpenoids from *Viburnum* species,[5,11] vibsanin B was found to be a typically abundant constituent. Based on the reported biogenetic hypothesis, vibsanin B was considered as the crucial precursor of 7-membered ring type and the rearranged type diterpenoids. Attracted by the unique structures and inspired by the neurite outgrowth promoting activity of vibsane-type diterpenoids, we hope to explore the reactivity of vibsanin B and to discover bioactive compounds from the derivatives of vibsanin B by modification. In this Letter, we report some new vibsane-type diterpenoids with various skeletons from vibsanin B through high-yielding intramolecular hetero-DA (IMHDA) reaction, retro-aldol ring opening reaction, and stereospecific reductive cyclization reaction. NGF-mediated PC12 cell model is chosen to evaluate their activities.

Although the absolute configuration of vibsanin B has been determined by chemical correlation with vibsanin C, there was no report about the configuration determined by vibsanin B itself or its derivatives with the same skeleton. During the modification of vibsanin B, **1a**, the derivative with the *t*-butyldiphenylsilyl (TBDPS) group at C-18, gave a crystal from MeOH (see Supporting information). Consequently, the relative configuration of vibsanin B was first directly determined by single crystal X-ray diffraction (Fig. 2).

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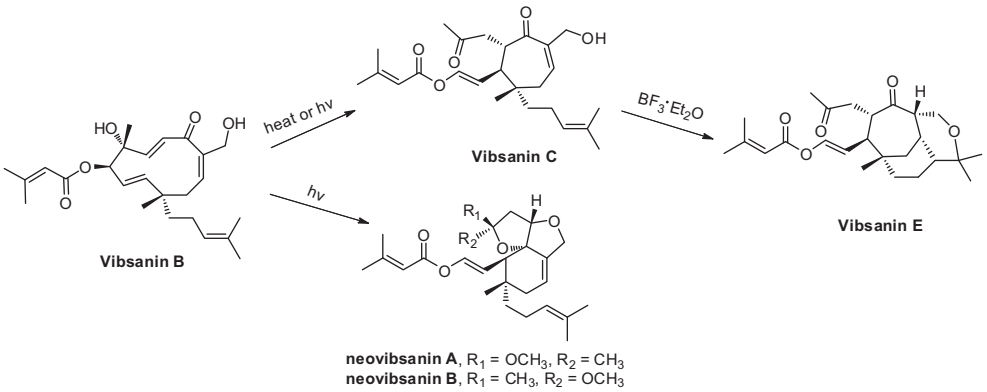


Figure 1. Chemical transformation of vibsanin B into other vibsane-type diterpenoids reported by Fukuyama et al.[10]

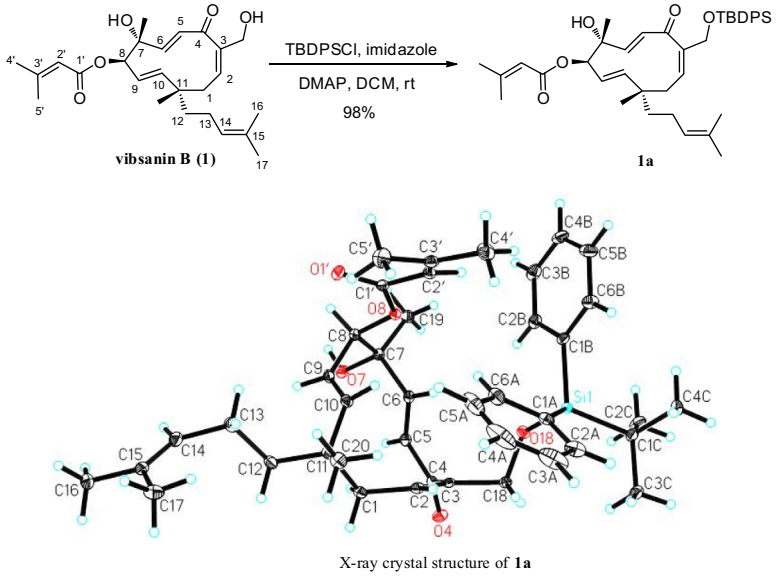


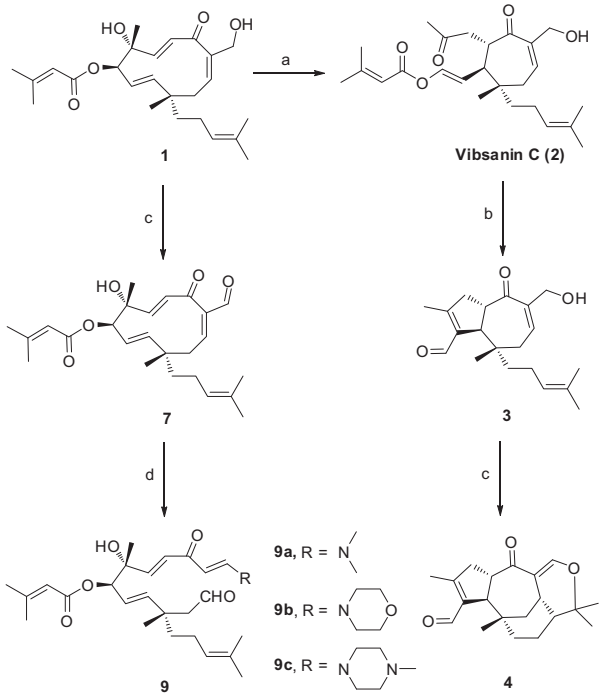
Figure 2. Synthesis and X-ray crystal structure of **1a**.

Our synthesis protocol started from vibsanin B (**1**) (Scheme 1). Six different kinds of skeletons were obtained within three simple steps from **1**. These different skeletons included vibsanin C (**2**)[8] (7-membered ring system), compound **3**[8] (5/7-ring system), compound **4** (5/7/6/6-ring system), vibsanin E-type (**8a** and **8b**), ring opening product **9**, and furanvibsane-type (**10** and **11**). Moreover, new routes from vibsanin B to vibsanin E-type and furanvibsane-type diterpenoids were also achieved in 2–3 steps.

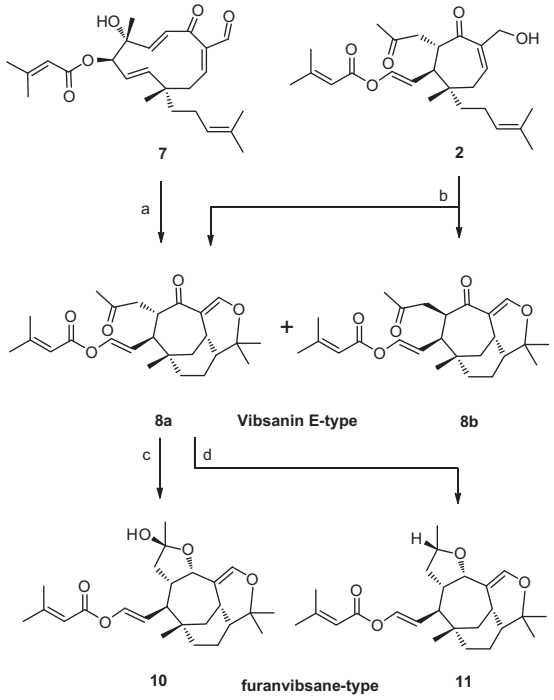
The 7-membered ring product **2** was obtained by heating **1** in boiling toluene for 24 h through a gram-scale oxy-cope rearrangement[8] in 88% yield. Hydrolysis and following aldol condensation of compound **2** in 2 N NaOH methanol solution[8] afforded compound **3** in 60% yield. Surprisingly, IMHDA reaction was carried out by treating compound **3** with IBX (2.5 equiv) in DCM-DMSO (5:1) at room temperature to give compound **4** with 82% yield in gram-scale. The relative configuration of compound **4** was determined by single crystal X-ray diffraction (Fig. 3) (see Supporting information). The primary bioassay of compounds **1**, **2**, **3**, and **4** showed that compound **3** had neurite outgrowth promoting activity. Therefore, 3,3-dimethylpropenoic ester was introduced to C-8 of **3** to produce **6** in four steps (Scheme 2)[12] for further bioactive investigation.

Unlike reported method,[13] an IMHDA reaction mediated by IBX was introduced to form vibsanin E-type compounds **8a** and **8b** from **2**. Differed from **2**, treating **1** with the same reaction condition produced **7**, instead of a hetero-DA product. The different chemical behaviors between compounds **1** and **2** might ascribe to the different ring strains between **1** (11-membered ring) and **2** (7-membered ring). Furthermore, compound **8a** was obtained by heating **7** in xylene for 12 h. We concluded that compound **7** was firstly transformed into an oxy-cope rearrangement intermediate which further underwent a [4+2] cyclization to yield compound **8a**. Stereospecific reductive cyclization of compound **8a** with $NaCNBH_3$ (4.5 equiv) in AcOH at room temperature gave vibsanin E-type compound **11** in 90% yield as the only product. When DCM-*i*PrOH (1:1) substituted AcOH was used as solvent, the intermediate compound **10** was obtained in 83% yield based on the recycling of starting material (brsm) (Scheme 3). The absolute configurations of **10** and **11** could be determined by chemical correlation with vibsanin C and 2D-NMR. To our surprise, reductive amination of compound **7** afforded unexpected ring opening products, compounds **9a**–**9c** through retro-aldol like reaction in high yield (80–94%). The plausible reaction mechanism was proposed as shown in Scheme 4. We supposed that compound **7** firstly converted into H_2O adduct **t1** and then **t1** reacted with dimethylamine to form imine **t2** which finally underwent a retro-aldol like reaction to give compound **9a**.

All compounds were subjected to evaluate their neurite outgrowth promoting activities (Fig. 4). Among them, compound **6**



Scheme 1. Synthesis of vibsane-type diterpenoid derivatives. Reagents and conditions: (a) Toluene (0.1 M), reflux, 88%; (b) 2*N* NaOH, MeOH, rt, 60%; (c) IBX (2.5 equiv), DCM-DMSO, rt, 82% for **4**, 95% for **7**; (d) $NaBH(OAc)_3$ (2 equiv), secondary amine (2 equiv), DCM, rt.



Scheme 3. Synthesis of vibsane-type diterpenoid derivatives. Reagents and conditions: (a) Xylene (0.1 M), reflux, 61%; (b) IBX (2.5 equiv), DCM-DMSO, rt, (**8a**:**8b** = 6:1), 82%; (c) $NaBH_3CN$ (10 equiv), DCM-*i*PrOH, rt, 83% brsm; (d) $NaBH_3CN$ (4.5 equiv), AcOH, rt, 90%.

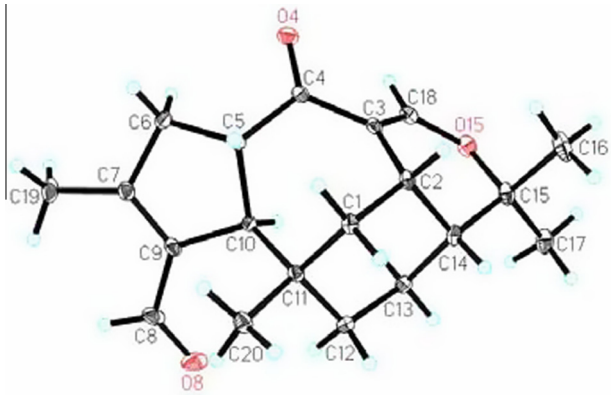
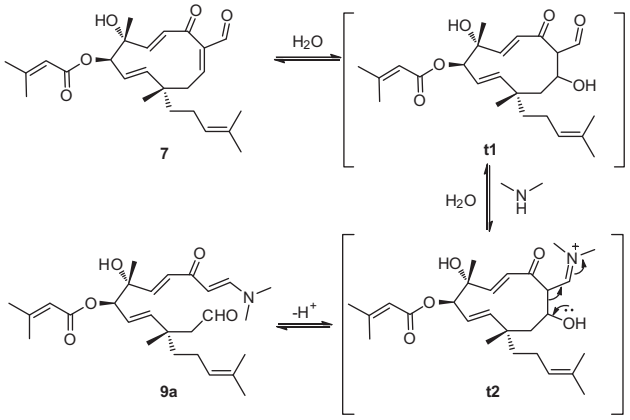


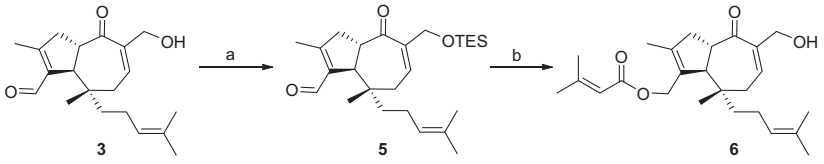
Figure 3. X-ray crystal structure of **4**.



Scheme 4. Hypothetic mechanism of ring opening reaction of **7**.

exhibited moderate activity of neurite outgrowth promoting. The neurite grew up with a measurable length after 72 h, compared to blank control and negative (Fig. 4f). It is worth mentioning that the synthesis of compounds **2** and **3** was reported by Fukuyama et al.,[8,10] but their bio-activities were out of discussion. According to the bio-assay results, compounds **2** and **3** showed higher activity than that of blank and negative control (Fig. 4). Compounds **4**, **8a**, **8b**, **10**, and **11** exhibited very weak activity. While compounds **1**, **7**, and **9a**–**9c** seemed to be negative of neurite outgrowth-promoting activity.

In summary, the synthesis route presented here provides a series of vibsane-type diterpenoids with multiple skeletons (**2**–**4** and **8**–**11**) derived from vibsanin B (**1**) within few steps. The relative



Scheme 2. Synthesis of vibsane-type diterpenoid derivatives. Reagents and conditions: (a) i. TESCl (2 equiv), TEA (3 equiv), DCM, rt; ii. $NaBH_4$ (1 equiv), DCM-*i*PrOH, rt, 95% in 2 steps; (b) (i). 3,3-dimethylpropenoic acid (1.2 equiv), DCC (2 equiv), DMAP (0.5 equiv), DCM, 0 °C to rt; (ii). AcOH, THF–H_2O, rt, 88% in 2 steps.

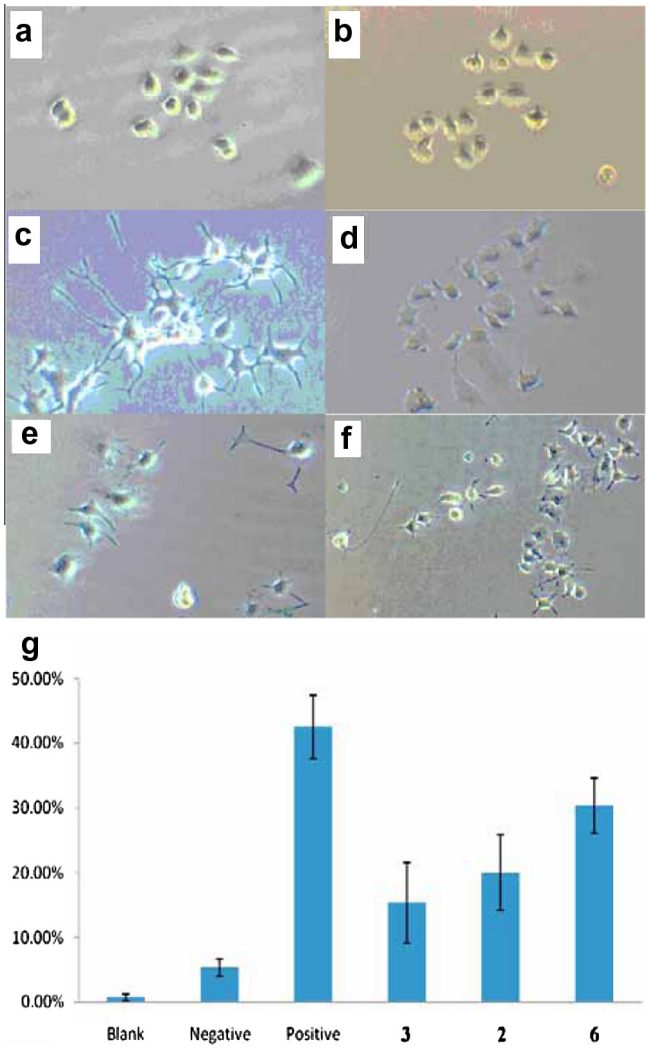


Figure 4. Neurite outgrowth-promoting activities of compounds **3**, **2**, and **6**. (a) Morphology of PC12 cells in the blank group. (b) Morphology of PC12 cells in the negative group (5 ng/mL NGF in PC12 cell). (c) Morphology of PC12 cells in the positive group (50 ng/mL NGF in PC12 cell). (d) Morphology of PC12 cells in 10 μM compound **3** with 5 ng/mL NGF. (e) Morphology of PC12 cells in 10 μM compound **2** with 5 ng/mL NGF. (f) Morphology of PC12 cells in 10 μM compound **6** with 5 ng/mL NGF. (g) A differentiation percentage of 10 μM compounds **3**, **2**, and **6** with 5 ng/mL NGF in PC12 cells after 72 h.

configuration of vibsanin B was firstly determined by X-Ray diffraction of its C-18 derivative **1a**. Some interesting reactions like high-yielding IMHDA reaction, retro-aldol ring opening reaction, and stereospecific reductive cyclization reaction were introduced. Furthermore, some conversions including **1** to **7**, **2** to **8**, and **3** to **4**, could be well performed in gram scale. New vibsane-type diterpenoids with neurite outgrowth promoting activity were obtained. Compound **6** showed potential neurotrophic activity in bio-assay. Most importantly, some compounds like **5**, the precursor of compound **6**, can be used as a starting material for further modification and optimization and will be developed and benefited for further drug discovery.

Acknowledgments

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Supplementary data

Supplementary data (experiments procedures and characterization data of all compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.04.061.

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