



Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis and neurite outgrowth promoting activity of vibsantin B derivatives

Li-Dong Shao^{a,b}, Jun Xu^{a,b}, Xiu Gao^{a,b}, Juan He^a, Yu Zhao^a, Li-Yan Peng^a, Huai-Rong Luo^a, Chengfeng Xia^{a,*}, Qin-Shi Zhao^{a,*}

^a State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences, Kunming 650201, Yunnan, People's Republic of China

^b University of Chinese Academy of Sciences, Beijing 10049, People's Republic of China

ARTICLE INFO

Article history:

Received 13 February 2014

Revised 13 April 2014

Accepted 17 April 2014

Available online xxxxx

Keywords:

Intramolecular hetero-DA reaction
Retro-aldol like ring opening reaction
Vibsantin B
Neurite outgrowth promoting

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 vibsantin B within three steps. Moreover, compounds **2**, **3**, and **6** enhanced the neurite outgrowth of NGF-mediated PC12 cells.

© 2014 Elsevier Ltd. All rights reserved.

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 vibsantin B, vibsantin C, and neovibsantin 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, vibsantin 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 vibsantin B was determined based on chemical correlation with vibsantin C by X-ray crystallographic analysis of its derivative.⁸ Fukuyama et al. reported the bio-mimic transformations of vibsantin B, vibsantin C, neovibsantin A and B under thermal, photochemical, and lewis acids conditions

(Fig. 1). Moreover, neovibsantin 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} vibsantin B was found to be a typically abundant constituent. Based on the reported biogenetic hypothesis, vibsantin 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 vibsantin B and to discover bioactive compounds from the derivatives of vibsantin B by modification. In this Letter, we report some new vibsane-type diterpenoids with various skeletons from vibsantin 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 vibsantin B has been determined by chemical correlation with vibsantin C, there was no report about the configuration determined by vibsantin B itself or its derivatives with the same skeleton. During the modification of vibsantin 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 vibsantin B was first directly determined by single crystal X-ray diffraction (Fig. 2).

* Corresponding authors. Tel./fax: +86 871 65223354 (C.X.); tel.: +86 871 65223058; fax: +86 871 65215783 (Q.-S.Z.).

E-mail addresses: xiachengfeng@mail.kib.ac.cn (C. Xia), qinshizhao@mail.kib.ac.cn (Q.-S. Zhao).

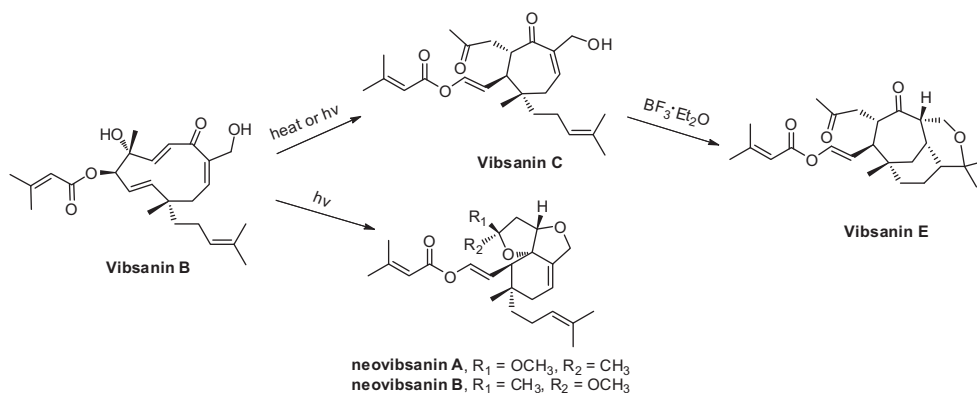


Figure 1. Chemical transformation of vibsananin B into other vibsane-type diterpenoids reported by Fukuyama et al.¹⁰

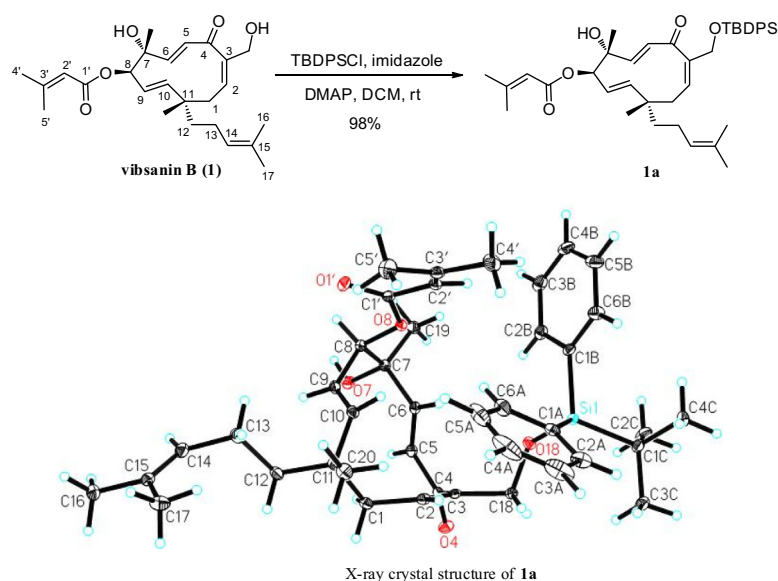


Figure 2. Synthesis and X-ray crystal structure of **1a**.

Our synthesis protocol started from vibsananin B (**1**) (Scheme 1). Six different kinds of skeletons were obtained within three simple steps from **1**. These different skeletons included vibsananin C (**2**)⁸ (7-membered ring system), compound **3**⁸ (5/7-ring system), compound **4** (5/7/6/6-ring system), vibsananin E-type (**8a** and **8b**), ring opening product **9**, and furanvibsane-type (**10** and **11**). Moreover, new routes from vibsananin B to vibsananin 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 rearrangement⁸ in 88% yield. Hydrolysis and following aldol condensation of compound **2** in 2 N NaOH methanol solution⁸ 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 vibsananin 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 NaCNBH₃ (4.5 equiv) in AcOH at room temperature gave vibsananin E-type compound **11** in 90% yield as the only product. When DCM–iPrOH (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 vibsananin 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 H₂O 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**

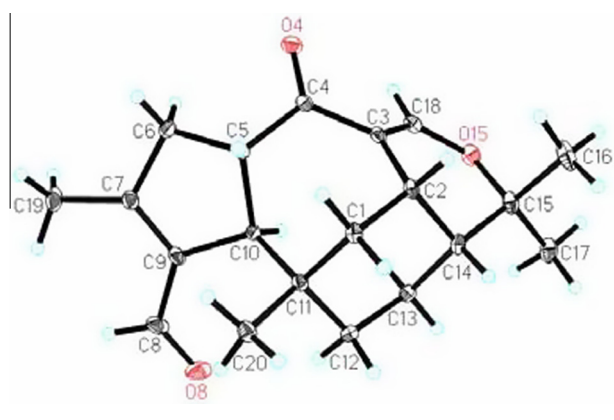
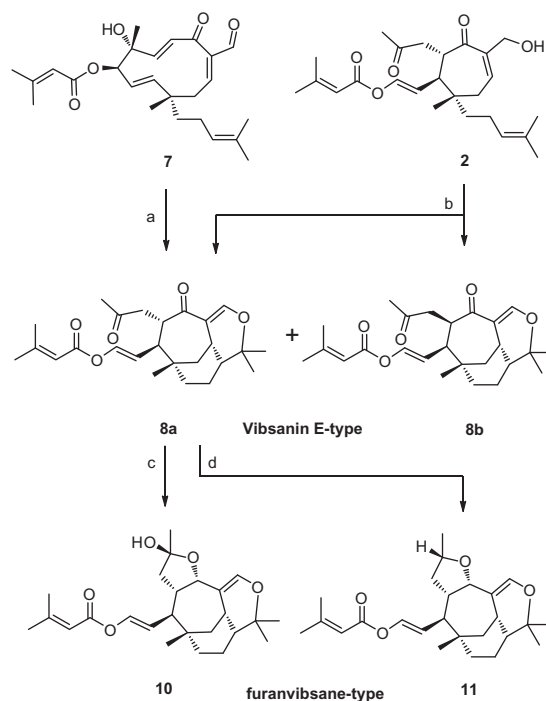
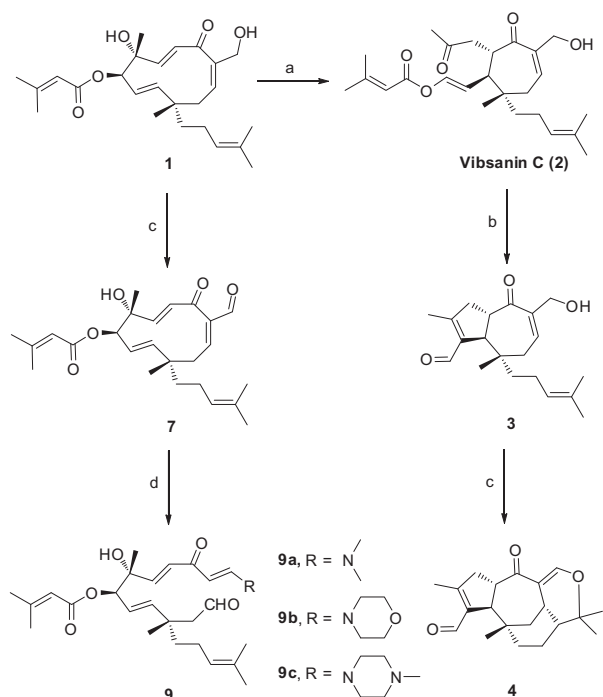
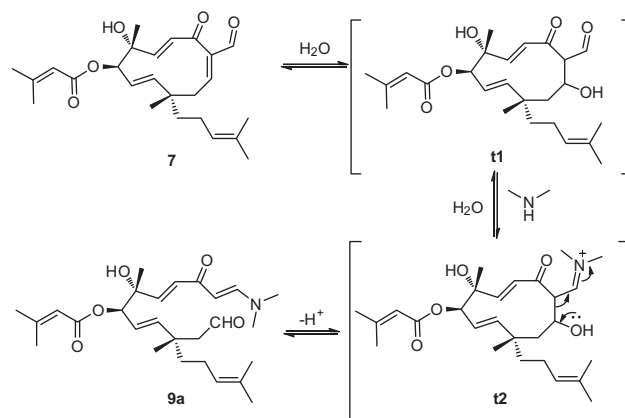


Figure 3. X-ray crystal structure of **4**.

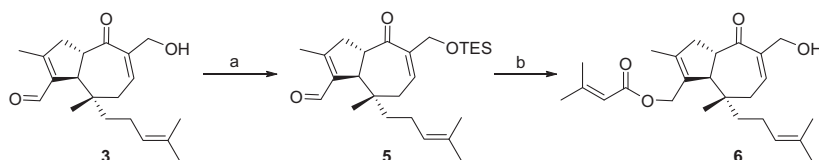


Scheme 4. Hypothetic mechanism of ring opening reaction of **7**.

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. NaBH₄ (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-H₂O, rt, 88% in 2 steps.

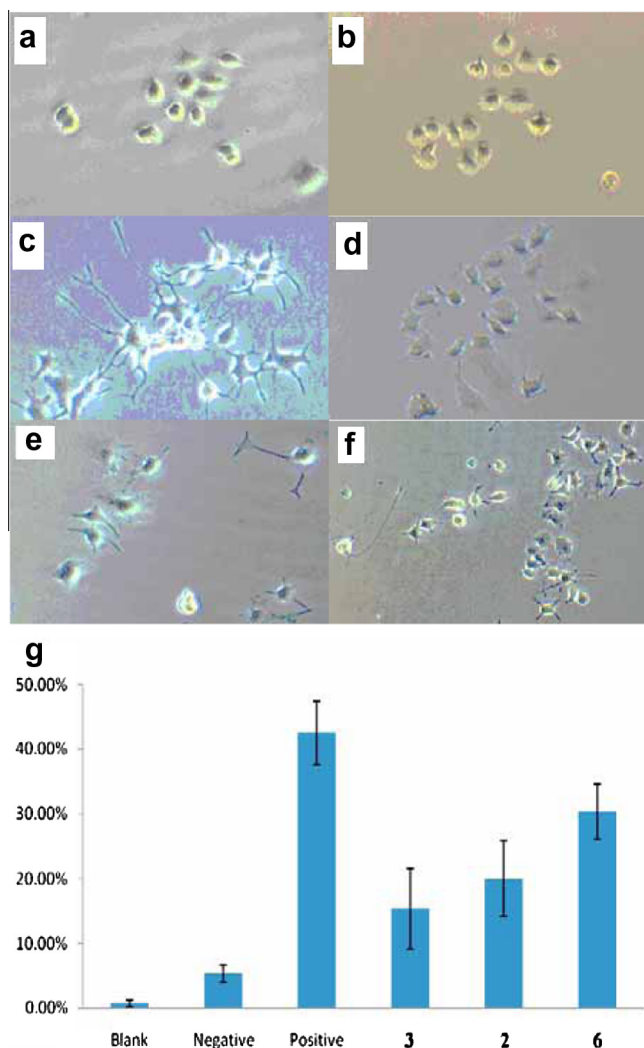


Figure 4. Neurite outgrowth-promoting activities of compounds **3**, **2**, and **6**. (a) Morphology of PC12 cells in the blank group. (b) Morphology of PC12 cells in the negative group (5 ng/mL NGF in PC12 cell). (c) Morphology of PC12 cells in the positive group (50 ng/mL NGF in PC12 cell). (d) Morphology 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 vibsantin 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

This work was financially supported by the National Natural Science Foundation (Grant Nos. 81102347, U0932602, 90813004, and 21272242), Yunnan High-End Technology Professionals Introduction Program (2010CI117), and the National Basic Research Program (973 Program No. 2011CB915503) of China.

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>.

References and notes

- (a) Fukuyama, Y.; Minami, H.; Yamamoto, I.; Kodama, M.; Kawazu, K. *Chem. Pharm. Bull.* **1998**, *46*, 545–547; (b) Duh, C.-Y.; El-Gamal, A. A. H.; Wang, S.-K. *Tetrahedron Lett.* **2003**, *44*, 9321–9322; (c) Fukuyama, Y.; Minami, H.; Takeuchi, K.; Kodama, M.; Kawazu, K. *Tetrahedron Lett.* **1996**, *37*, 6767–6770.
- (a) Shen, Y.-C.; Prakash, C. V. S.; Wang, L.-T.; Chien, C.-T.; Hung, M.-C. *J. Nat. Prod.* **2002**, *65*, 1052–1055; (b) Kubo, M.; Chen, I.-S.; Minami, H.; Fukuyama, Y. *Chem. Pharm. Bull.* **1999**, *47*, 295–296; (c) Hashimoto, T.; Toyota, M.; Koyama, H.; Kikkawa, A.; Yoshida, M.; Tanaka, M.; Takaoka, S.; Asakawa, Y. *Tetrahedron Lett.* **1998**, *39*, 579–582.
- Fukuyama, Y.; Fujii, H.; Minami, H.; Takahashi, H.; Kubo, M. *J. Nat. Prod.* **2006**, *69*, 1098–1100.
- Kubo, M.; Kishimoto, Y.; Harada, K.; Hideaki, H.; Fukuyama, Y. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2566–2571.
- Chen, X.-Q.; Li, Y.; He, J.; Cheng, X.; Wang, K.; Li, M.-M.; Pan, Z.-H.; Peng, L.-Y.; Zhao, Q.-S. *Chem. Pharm. Bull.* **2011**, *59*, 496–498.
- Fukuyama, Y.; Kubo, M. *Curr. Top. Phytochem.* **2011**, *10*, 39–53.
- Kawazu, K. *Agric. Biol. Chem.* **1980**, *44*, 1367–1372.
- Fukuyama, Y.; Minami, H.; Takaoka, S.; Kodama, M.; Kawazu, K.; Nemoto, H. *Tetrahedron Lett.* **1997**, *38*, 1435–1438.
- Fukuyama, Y.; Esumi, T. *J. Syn. Org. Chem.* **2007**, *65*, 585–597.
- Fukuyama, Y.; Kubo, M.; Esumi, T.; Harada, K.; Hioki, H. *Heterocycles* **2010**, *81*, 1571–1602.
- (a) Tu, L.; Zhao, Y.; Yu, Z.-Y.; Cong, Y.-W.; Xu, G.; Peng, L.-Y.; Zhang, P.-T.; Cheng, X.; Zhao, Q.-S. *Helv. Chim. Acta* **2008**, *91*, 1578–1587; (b) Tu, L.; Xu, G.; Zhao, Y.; Peng, L.-Y.; He, J.; Guo, N.; Zhao, Q.-S. *Helv. Chim. Acta* **2009**, *92*, 1324–1332; (c) Gao, X.; Shao, L.-D.; Dong, L.-B.; Cheng, X.; Wu, X.-D.; Liu, F.; Jiang, W.-W.; Peng, L.-Y.; He, J.; Zhao, Q.-S. *Org. Lett.* **2014**, *16*, 980–983.
- (a) Glass, R. S.; Deardorff, D. R.; Henegar, K. *Tetrahedron Lett.* **1980**, *21*, 2467–2470; (b) Jung, M. E.; Deng, G. J. *Org. Chem.* **2012**, *77*, 11002–11005; (c) Singh, A. K.; Weaver, R. E.; Powers, G. L.; Rosso, V. W.; Wei, C.; Lust, D. A.; Kotnis, A. S.; Comezoglu, F. T.; Liu, M.; Bembenek, K. S.; Phan, B. D.; Vanyo, D. J.; Davies, M. L.; Mathew, R.; Palaniswamy, V. A.; Li, W.-S.; Gadamssetti, K.; Spagnuolo, C. J.; Winter, W. J. *Org. Process Res. Dev.* **2003**, *7*, 25–27.
- Fukuyama, Y.; Minami, H.; Kagawa, M.; Kodama, M.; Kawazu, K. *J. Nat. Prod.* **1999**, *62*, 337–339.