ORGANIC LETTERS

2009
Vol. 11, No. 6
1253−1255

Total Synthesis of (±)-Neovibsanin B

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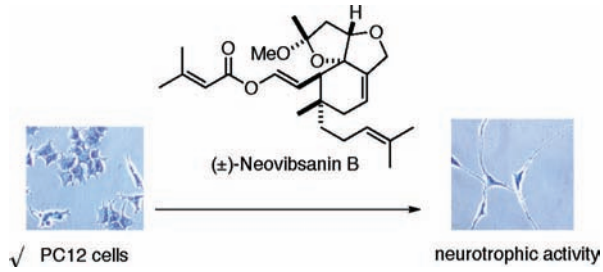
Received December 27, 2008

ABSTRACT



(±)-Neovibsanin B was synthesized based on a DMI-accelerated intramolecular Diels−Alder reaction followed by oxy-Michael addition−lactonization. The synthetic (±)-neovibsanin B induced similar morphological changes in NGF-mediated PC12 cells compared with natural (+)-neovibsanin B.

Neovibsanin A (**1**) and its isomer neovibsanin B (**2**) are rarely occurring natural products isolated from *Viburnum awabuki*.[1a] Both compounds display neurotrophic activity in PC12 cells as reported by Fukuyama's group in 1996.[1b] Thus, neovibsanin-type compounds, compact polyoxygenated natural products, are expected to act as lead compounds for the development of novel therapeutic agents to treat Alzheimer's disease.[2] However, to date, very few synthetic studies have been reported.[3] We describe herein the first total synthesis of (±)-**2** (Figure 1) based on an intramolecular Diels−Alder reaction accelerated with 1,3-dimethyl-2-imidazolidinone (**7**, hereafter DMI) and a subsequent oxy-Michael addition−lactonization reaction. We also describe the neurotrophic activity of (±)-**2** on PC12 cells.

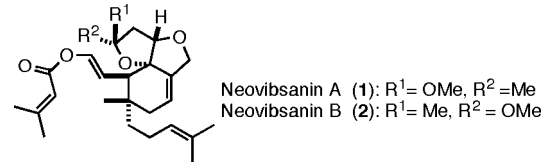


Figure 1. Structures of neovibsanins.

Starting material, homogeranic acid (**3**), was prepared in 76% yield in three steps from geranyl bromide by Tamao's protocol[4] and subsequent oxidations by Dess−Martin periodinane and $NaClO_2$. After chlorination of **3** with oxalyl chloride, the resulting chloride **4** was treated with lithium (*E*)-1,3-butadien-1-olate prepared from (*E*)-trimethylsilyl

(1) (a) Fukuyama, Y.; Minami, H.; Takeuchi, K.; Kodama, M.; Kawazu, K. *Tetrahedron Lett.* **1996**, *37*, 6767–6770. (b) Fukuyama, Y.; Esumi, T. *J. Org. Synth. Chem. Jpn.* **2007**, *65*, 585–597.

(2) (a) Fukuyama, Y.; Minami, H.; Yamamoto, I.; Kodama, M.; Kawazu, K. *Chem. Pharm. Bull.* **1998**, *46*, 545–547. (b) Kubo, M.; Minami, H.; Hayashi, E.; Kodama, M.; Kawazu, K.; Fukuyama, Y. *Tetrahedron Lett.* **1999**, *40*, 6261–6265. (c) Kubo, M.; Chen, I.-S.; Fukuyama, Y. *Chem. Pharm. Bull.* **2001**, *49*, 242–245. (d) Fukuyama, Y.; Kubo, M.; Minami, H.; Yuasa, H.; Matsuo, A.; Fujii, T.; Morisaki, M.; Harada, K. *Chem. Pharm. Bull.* **2005**, *53*, 72–80. (e) Fukuyama, Y.; Fujii, H.; Minami, H.; Takahashi, H.; Kubo, M. *J. Nat. Prod.* **2006**, *69*, 1098–1100.

(3) (a) Esumi, T.; Zhao, M.; Kawakami, T.; Fukumoto, M.; Toyota, M.; Fukuyama, Y. *Tetrahedron Lett.* **2008**, *49*, 2692–2696. (b) Gallen, M. J.; Williams, C. M. *Org. Lett.* **2008**, *10*, 713–715. Chen, A. P.-J.; Williams, C. M. *Org. Lett.* **2008**, *10*, 3441–3443.

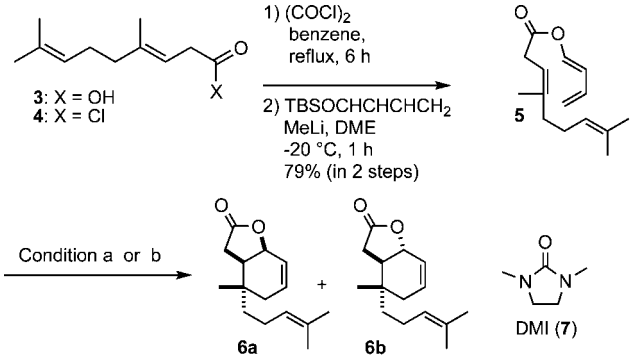
(4) Tamao, K.; Ishida, N.; Kumada, M. *J. Org. Chem.* **1983**, *48*, 2120–2122.

(5) (a) Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4464–4465. (b) Trost, B. M.; Chupak, L. S.; Lubbers, T. *J. Org. Chem.* **1997**, *62*, 736.

10.1021/ol802973f CCC: $40.75
Published on Web 02/12/2009

enolate according to Stork's protocol,[5] giving rise to tetraene **5** in 79% yield. Successful Diels−Alder reactions of trisubstituted nonconjugated olefins as dienophiles are not well-known.[6] Therefore, we explored conditions suitable for the intramolecular Diels−Alder reaction of **5**. Among the solvents and reaction temperatures examined, an 82:18 mixture of cycloadducts **6a** and **6b** was obtained in 18% yield by heating **5** in mesitylene at 200 °C for 10 h using a sealed tube. Furthermore, we found that the reaction in DMI (**7**) as solvent resulted in both an improved yield of up to 58% within a shorter reaction period and an improved *endo*-selectivity of up to 90:10 of **6a** and **6b** by heating at 200 °C for 3 h (Scheme 1). It is particularly noteworthy that a sealed tube is not required for this reaction, making it suitable for scale-up. The observed acceleration of the reaction rate may be due to a solvophobic packing effect of DMI based on its aprotic polar properties. General applicability of this solvent effect is currently under investigation.[7]

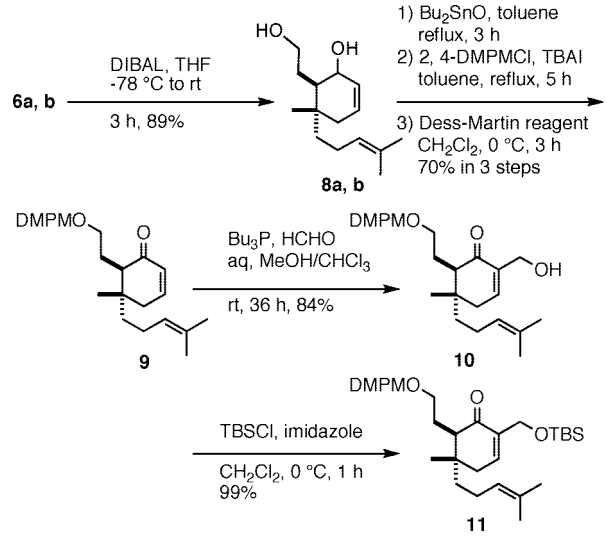
Scheme 1. Synthesis of Lactone **6**



Conditions: (a) 200 °C, 10 h, mesitylene in sealed tube, 18% (**6a**/**6b** 82 : 18) (b) 200 °C, 3 h, DMI, 58% (**6a**/**6b** 90 : 10).

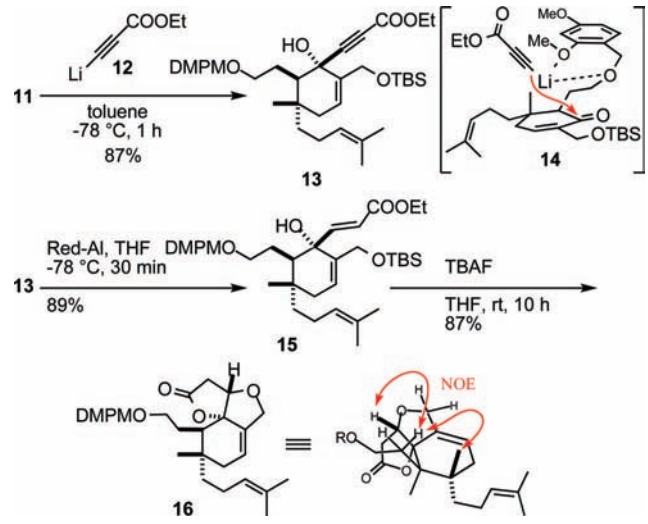
The reduction of **6a** and **6b** with DIBAL led to diols **8a** and **8b** in 89% yield. Selective protection of the primary alcohol of **8a** and **8b** by 2,4-DMPM (2,4-dimethoxybenzyl)[8] followed by oxidation of the secondary alcohol moiety resulted in the formation of a single cyclohexenone **9** in 70% yield (three steps). Introduction of a hydroxymethyl group into **9** was achieved by Baylis−Hillman reaction with formaldehyde using tributylphosphine.[9] The resulting hydroxy group of **10** was protected by TBS to give **11** (Scheme 2).

Scheme 2. Preparation of Cyclopentenone **11**



The reaction of the ketone **11** with 15 equiv of lithio ethyl propiolate (**12**) in toluene took place successfully to give the alkylated product **13** in 87% yield as a single diastereomer.[10] We concluded that the newly generated stereochemistry of **13** was completely controlled to give the desired β-configuration based upon the coordination effect of the 2,4-DMPM group with nucleophile **12** as shown in **14** (Scheme 3).[11] Red-Al reduction of **13** afforded **15** in 89% yield.[12] The α,β-unsaturated ester **15** was then treated with TBAF to cleave the TBS group; however, subsequent oxy-

Scheme 3. Synthesis of Tricyclic Lactone **16**



(6) The examples for Diels−Alder reactions of sterically hindered diene or dienophile: (a) Sugiyama, S.; Tsuda, T.; Mori, A.; Takeshita, H.; Kodama, M. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3633–3638. (b) Boger, D. L.; Robarge, K. D. *J. Org. Chem.* **1988**, *53*, 3377–3379. (c) Nicolaou, K. C.; Hwang, C.-K.; Sorensen, E. J.; Claiborne, C. F. *J. Chem. Soc., Chem. Commun.* **1992**, 1117–1118. (d) Engler, T. A.; Sampath, U.; Vander, D. V.; Takusagawa, F. *Tetrahedron* **1992**, *48*, 9399–16. (e) Gacem, B.; Jenner, G. *J. Phys. Org. Chem.* **2004**, *17*, 221–225. (f) Jung, M. E.; Ho, D.; Chu, H. V. *Org. Lett.* **2005**, *7*, 1649–1651. The examples for Diels−Alder reactions of isolated-trisubstituted olefin: (g) Begue, J.-P.; Bonnet-Delpon, D.; Lequeux, T.; Angelo, J.; Guingant, A. *Synlett* **1992**, 146–149. (h) Heiner, T.; Michalski, S.; Gerke, K.; Kuchta, G.; Buback, M.; Meijere, A. *Synlett* **1995**, 355–357. (i) Shrestha, K. S.; Honda, K.; Asami, M.; Inoue, S. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 73–83. (j) Wada, E.; Kumaran, G.; Kanemasa, S. *Tetrahedron Lett.* **2000**, *41*, 73–76.

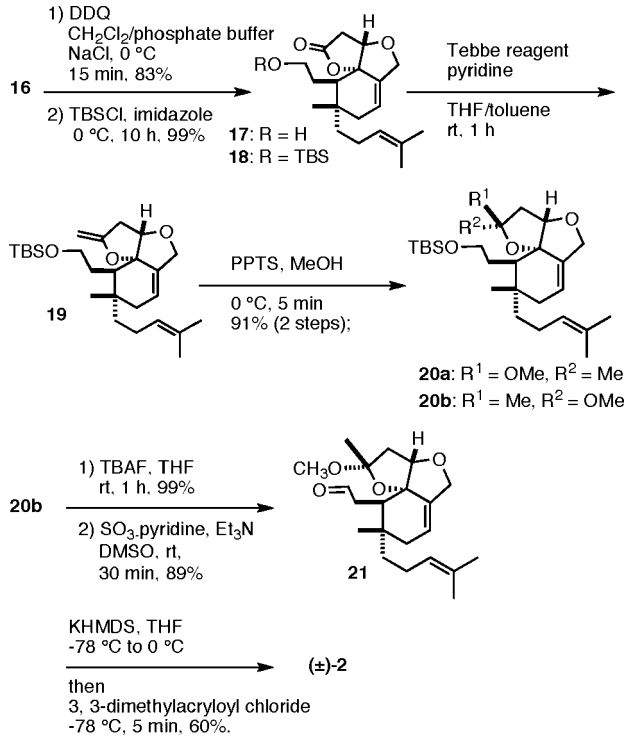
(7) The pioneering work for Diels−Alder reaction in water. Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816–7817. *Organic Reactions in Water*; Grico, P. A., Ed.; Blackle Academic Professional: London, 1998.

(8) Guibe, F. *Tetrahedron* **1997**, *53*, 13509–13556.

Michael addition and lactonization took place giving rise to a tricyclic lactone **16** in 87% yield (Scheme 3). The stereochemistry of **16** was confirmed by NOE experiments.

The 2,4-DMPM was cleaved by using DDQ under a two-phase system of CH_2Cl_2 and NaCl saturated-phosphate buffer to give a desired alcohol **17** in 83% yield.[13] After protection of the alcohol as the TBS ether, the resulting **18** was treated with Tebbe reagent affording **19**.[14] Treatment of the crude enol ether **19** with PPTS in methanol provided acetals **20a** and **20b** in 91% yield (two steps) in a 1:4.5 ratio (Scheme 4). After separation of **20a** and **20b** by HPLC, the TBS group of the major isomer **20b** was removed with TBAF quantitatively, and the resulting alcohol was oxidized with SO_3-pyridine-DMSO to give the aldehyde **21** in 89% yield.[15] Finally, a potassium enolate derived from **21** with KHMDS was trapped with 3,3-dimethylacryloyl chloride completing the first total synthesis of (±)-**2** in 60% yield (Scheme 4).

Scheme 4. Syntheses of Neovibsanins



The neurotrophic activity of (±)-**2** was confirmed by an assay using PC12 cells (JCRB0733).[16] (±)-Neovibsanin B (**2**) significantly promoted neurite outgrowth in NGF (10 ng/mL)-mediated PC12 cells at concentrations ranging from 10 to 40 μM (Figure 2C, D). This is similar to the degree of activity observed for natural (+)-**2** (Figure 2B).

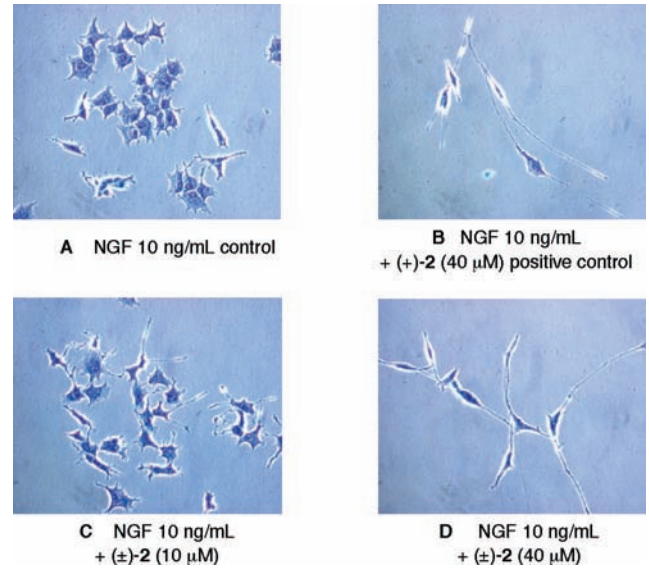


Figure 2. Morphological changes of PC12 cells after treatment of NGF with natural or synthetic neovibsanin B. A: No clear neurite outgrowth was observed. B: The clear neurite outgrowth was observed. (positive control). C: Some neurite outgrowth was observed. D: The similar degree of activity compared with natural (+)-**2** was observed.

Acknowledgment. This study was financially supported by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology of the Japanese Government (20590028), and the Open Research Center program of MEXT.

Supporting Information Available: Experimental procedures and spectral data for all new compounds and detail of assay for neurotrophic activity. This material is available free of charge via the Internet at http://pubs.acs.org.

OL802973F

(9) (a) McDougal, N. T.; Schaus, S. E. *J. Am. Chem. Soc.* **2003**, *125*, 12094–12095. (b) Ito, H.; Takenaka, Y.; Fukunishi, S.; Iguchi, K. *Synthesis* **2005**, 3035–3038.

(10) Boche, G.; Bigalke, J. *Tetrahedron Lett.* **1984**, *25*, 955–958.

(11) Reaction of nonchelating 4-MPM protected ketoalcohol resulted in low yield.

(12) (a) Meta, C. T.; Koide, K. *Org. Lett.* **2004**, *11*, 1785–1787. (b) Rao, K. S.; Mukkanti, K.; Reddy, D. S.; Pala, M.; Iqba, J. *Tetrahedron Lett.* **2005**, *46*, 2287–2290.

(13) Reaction in CH_2Cl_2 resulted in giving a complex mixture due to the acidity of in situ formed DDQH.

(14) Pine, H. S.; Pettit, R. J.; Geib, G. D.; Cruz, S. G.; Gallego, C. H.; Tijerina, T.; Pine, R. D. *J. Org. Chem.* **1985**, *50*, 1212–1216.

(15) Parikh, J. R.; Doering, W. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505–5507.

(16) Lloyd, A. G.; Arthur, S. T. *Proc. Natl. Acad. Sci. U.S.A.* **1976**, *73*, 2424–2428.