ORGANIC LETTERS

2005
Vol. 7, No. 23
5155−5157

Construction of the Cyclovibsanin Core via a Biogenetically Modeled Approach

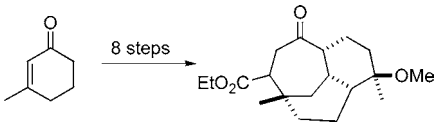
David P. Tilly, Craig M. Williams,* and Paul V. Bernhardt

School of Molecular and Microbial Sciences, University of Queensland, Brisbane, 4072 Queensland, Australia

c.williams3@uq.edu.au

Received August 7, 2005

ABSTRACT

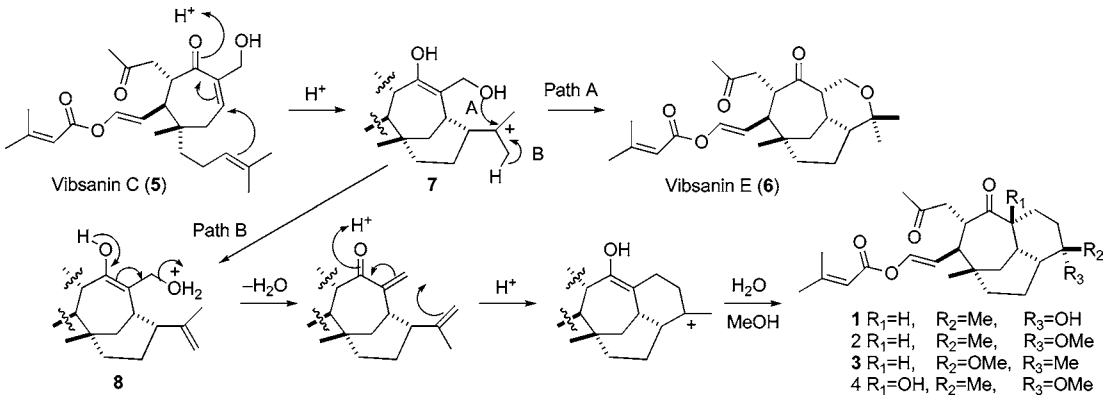


Construction of the 15-*O*-methylcyclovibsanin B core was achieved expediently in eight linear steps utilizing a biogenetically modeled approach.

The vibsanin family of diterpenes consists of a wide variety of structure types.[1,2] In terms of biosynthesis, all are related by plausible biosynthetic routes, many of which have either been postulated and/or confirmed by the elegant work of Fukuyama.[1,2] In the case of the cyclovibsanins[2] (**1**−**4**), however, Fukuyama proposed[2] that the same precusor [vibsanin C (**5**)] to vibsanin E (**6**) (path A) is involved in the formation of the cyclovibsanins (**1**−**4**), via intermediate **7** or **8** (path B) (Scheme 1). Considering our success with the construction of the vibsanin E core,[3] we endeavored to evaluate Fukuyama's hypothesis, the results of which are discussed herein.

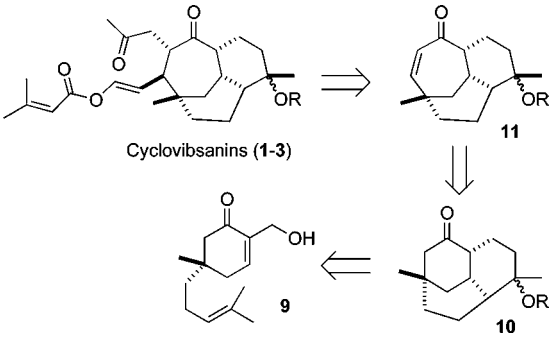
In view of Fukuyama's postulate, our synthetic strategy targeted cyclovibsanins **1**−**3** by utilizing the same starting cyclohexenone **9** used for constructing the core of vibsanin E[3]. The key step in our approach, however, would be the unprecendented carbocyclization to tricycle **10**. Ring expansion by the Zercher protocol[4] would then be expected to afford the core (i.e., **11**) (Scheme 2).

Scheme 1. Proposed Biosynthetic Pathway of Vibsanin E (**6**) and Cyclovibsanins (**1**−**4**) from Vibsanin C (**5**)



10.1021/ol051897d CCC: $30.25
Published on Web 10/14/2005

Scheme 2



Considering that the formation of the vibsanin E core had utilized hydrochloric acid to promote the cyclization of **9** to **12**, we initially envisaged that the alcohol functionality on **9** should be protected but with a protecting group that also possessed leaving group attributes, so as to facilitate formation of the exocyclic enone (i.e., **13**) (Figure 1).

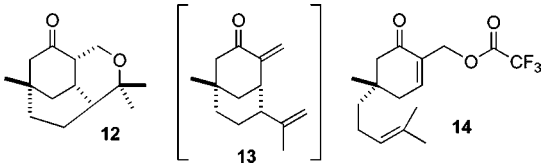
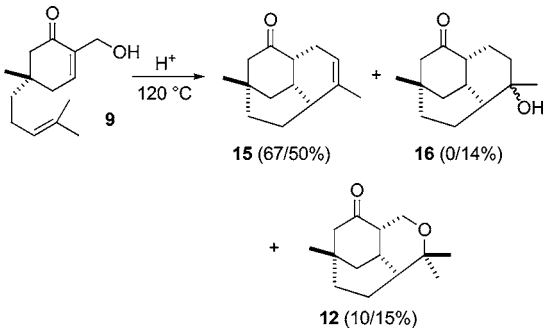


Figure 1. Structures of **12**−**14**.

The trifluoroacetyl group (i.e., **14**) appeared to best fit this criteria, and it was hoped that under the conditions of protection (TFAA) cyclization might occur. Protection was observed, but no traces of carbocyclized material could be detected. Even after subjecting **14** to a wide variety of acid and temperature variations, no carbocyclized material was observed. More traditional leaving groups were then investigated, but *O*-mesylate and *O*-tosylate groups, for example, could not be encouraged to form.

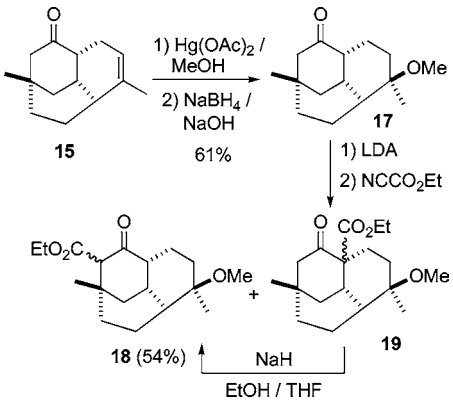
After reviewing the many failed attempts that used the protection approach, we decided to reinvestigate the use of hydrochloric acid. When **9** was heated in dioxane in the presence of 2 M hydrochloric acid only the oxygenated tricycle **12** was obtained (68%), which was a significant improvement over our previously reported[3] procedure. Increasing the temperature resulted in substantial decomposition, although when dioxane was removed and **9** (0.6 mmol) was heated in 3 M hydrochloric acid at 120 °C carbotricycle **15** was obtained in 67% along with **12** (10%). If the scale of the reaction was increased to 2.5 mmol **15** was obtained in 50% yield and **12** in 15% yield, but this time the hydroxylated carbotricycle **16** was also formed in 14% yield [mixture of diastereoisomers (∼1:1)] (Scheme 3).

Scheme 3



Even though **16** contained oxygen functionality at the required position it was not utilized further due to the low yield and lack of stereoselection. Methoxy functionality was introduced both regioselectively and stereoselectively by treating **15** with mercuric acetate in methanol, followed by sodium hydroxide (3 M) and sodium borohydride,[5] which afforded **17**[6] in 61% yield (Scheme 4). The methoxy derivative **17** was converted to **18** in 54% overall yield, via Mander's reagent[7] and subsequent treatment with ethoxide (retro Dieckmann/Dieckmann reaction). In this instance, ethoxide only converted the 1:1 (**18**:**19**) mixture, obtained from the reaction with Mander's reagent, into a mixture of 8:2 **18**/**19** (Scheme 4).

Scheme 4



Gratifyingly, treatment of **18** using the Zercher ring-expansion protocol afforded the core (i.e., **20**) in 15% yield; however, the choice of conditions was found to be critical

(1) Fukuyama, Y.; Kubo, M.; Minami, H.; Yuasa, H.; Matsuo, A.; Fujii, T.; Morisaki, M.; Harada, K. *Chem. Pharm. Bull.* **2005**, *53*, 72−80 and references therein.

(2) Fukuyama, Y.; Morisaki, M.; Minoshima, Y.; Minami, H.; Takahashi, H.; Asakawa, Y. *Lett. Org. Chem.* **2004**, *1*, 189−193

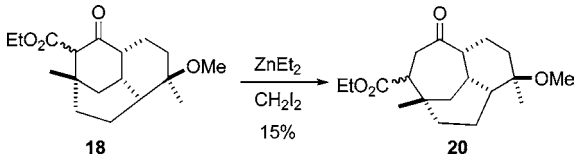
(3) Heim, R.; Wiedemann, S.; Williams, C. M.; Bernhardt, P. V. *Org. Lett.* **2005**, *7*, 1327−1329.

(4) Brogan, J. B.; Zercher, C. K. *J. Org. Chem.* **1997**, *62*, 6444−6446.

(5) Brown, H. C.; Kurek, J. T.; Rei, M.-H.; Thompson, K. L. *J. Org. Chem.* **1984**, *49*, 2551−2557.

(6) Compound **17** has been confirmed by X-ray crystal structure analysis.

Scheme 5



18 20

(Scheme 5). If the reaction was conducted in dichloromethane,[4] starting material was mostly recovered although a small amount of decomposition was observed. If tricycle **18** was reacted with diethylzinc (preforming the zinc enolate) before addition of diiodomethane[8] instead of the normal procedure[4] of adding diiodomethane to diethyl zinc followed by substrate no improvement was observed. Changing the solvent system to toluene[9] (5 equiv/$ZnEt_2$/CH_2I_2), however, gave **20** as a mixture of diastereoisomers (1:1) abeit with an unidentified product.[10] Surprisingly, this reaction through many attempts could not be repeated. However, if the number of equivalents was increased to 16 in toluene, without preforming the enolate, the reaction proceeded in 15% yield [dr (~1:1)] and was fully reproducible.

In conclusion, we have constructed the core (i.e., **20**) of 15-*O*-methylcyclovibsanin B **3** using a biomimetic-based approach. This work lends strong support to Fukuyama's proposed biosynthesis of the cyclovibsanins **1**−**4**.

Acknowledgment. We thank The University of Queensland for financial support.

Supporting Information Available: Characterization data of compounds **15**, **17**, **18**, and **20**, X-ray crystal structure analysis data of **17**, and copies of ^1H and ^{13}C NMR spectra of compound **15**, **17**, **18**, and **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL051897D

(7) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425−5428.
(8) Zercher, C. K. Personal communication.
(9) Ronsheim, M. D.; Zercher, C. K. *J. Org. Chem.* **2003**, *68*, 1878−1885
(10) According to mass spectral and ^1H NMR data the unidentified product is most likely a Zercher tandem chain extension derivative. See, for example: Hilgenkamp, R.; Zercher, C. K. *Org. Lett.* **2001**, *3*, 3037−3040.