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Expedient Construction of the Vibsanin E Core without the Use of Protecting Groups

Ralf Heim, Stefan Wiedemann, Craig M. Williams,* and Paul V. Bernhardt

School of Molecular and Microbial Sciences, University of Queensland, St. Lucia, 4072 Queensland, Australia

c.williams3@uq.edu.au

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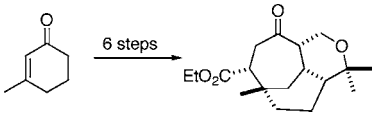
ABSTRACT



The tricyclic core of vibsanin E was constructed without the use of a protecting group in six steps. The El Gaïed Baylis–Hillman variant was key to allowing the Brønsted acid induced tandem cyclization forming rings B and C in one operation.

Vibsanine E (**1**) (Figure 1), later truncated to vibsanin E, was first isolated from *Viburnum awabuki* by Kawazu[1] in 1978, and the absolute stereochemistry was determined in 1980 by K. Y. Fukuyama.[2] Since then, Fukuyama,[3] and to a lesser extent Shen[4] and Duh,[5] have studied the *Viburnum* species elucidating an entire vibsane family [e.g., vibsanin C (**2**) and vibsanin B (**3**)] (Figure 1). In addition, Fukuyama[4] has synthesized 6-*epi*-vibsanin F (**4**) proving the absolute configuration of vibsanin F (Figure 1).

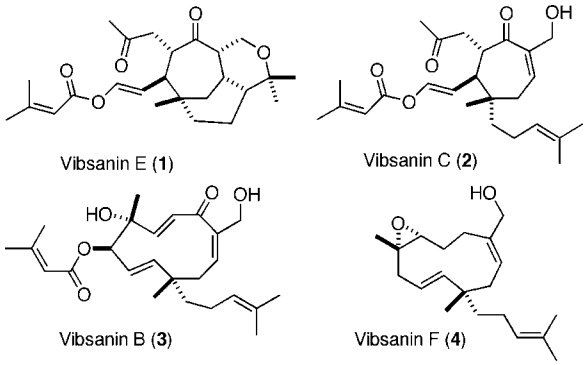


Figure 1. Strutures of vibsanin B, C, E, and F.

Vibsanin E (**1**), however, has a slightly more complex and unique tricyclic structure than the other family members, which attracted the interest of our group. Considering no synthetic endeavors to this system have been reported,[6] we undertook a brief investigation into the construction of the central core, details of which are disclosed herein.

In the process of elucidating vibsane biochemical pathways, Fukuyama investigated the conversion of vibsanin C (**2**) to vibsanin E (**1**)[7] and found that conversion proceeded

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(4) (a) Shen, Y.-C.; Prakash, C. V. S.; Wang, L.-T.; Chien, C. Y.; Hung, M.-C. *J. Nat. Prod.* **2002**, *65*, 1052−1055. (b) Shen, Y.-C.; Lin, C.-L.; Chien, S.-C.; Khalil, A. T.; Ko, C.-L.; Wang, C.-H. *J. Nat. Prod.* **2004**, *67*, 74−77.

(5) (a) Duh, C.-Y.; El-Gamal, A. A. H.; Wang, S.-K. *Tetrahedron Lett.* **2003**, *44*, 9321−9322. (b) El-Gamal, A. A. H.; Wang, S. K.; Duh, C.-Y. *J. Nat. Prod.* **2004**, *67*, 333−336.

(6) Studies toward the total synthesis of vibsanin E were recently presented: Davies, H. M. L.; Loe, Ø. *Abstract of Papers.* 228th ACS Meeting, Aug 22−27, Philadelphia, PA; American Chemical Society: Washington, DC, 2004; Abstract No. 563.

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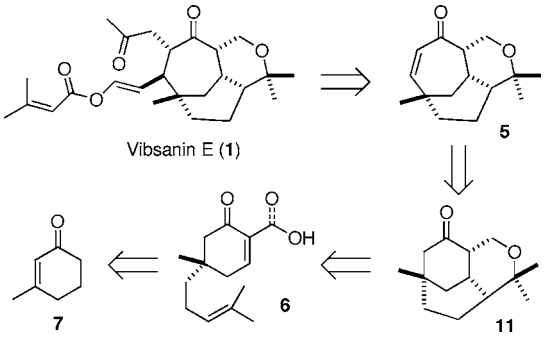
smoothly, albeit in moderate yield (50%), using boron trifluoride etherate (BF_3·Et_2O). This precedent formed the basis of our retrosynthetic frame (Scheme 1) and is in effect the key step for the formation of rings B and C.

Scheme 1

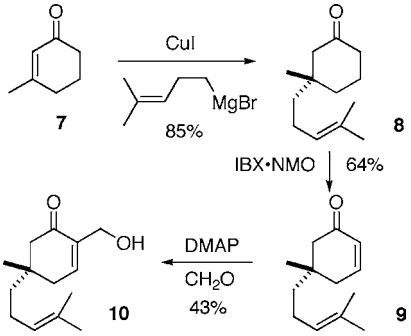


It was envisaged that 3-methylcyclohex-2-enone **7** could be converted to a cyclohexenone of type **6** which would set the stage for boron trifluoride etherate mediated ring formation (i.e., **11**).

In the event that this failed, "fall back" measures, such as Danishefsky's reductive cyclization of mercurial enones,[8] Semmelhack's tandem oxy-palladation vinylation,[9] and Bartlett's thallium(III)-induced tetrahydropyran synthesis,[10] were expected to suffice. Following tandem cyclization, regioselective 6- to 7-membered ring expansion (e.g., **5**) would be induced with stablized carbenes.[11]

Cyclohexenone **7** was reacted with the homoprenylcuprate giving the 1,4-addition product **8** in 85% yield. Dehydrogenation with IBX·NMO, as reported by Nicolaou,[12] proceeded smoothly, affording the α,β-unsaturated ketone **9** (64%). At this point we utilized the increasingly important work of El Gaïed[13,14] who reported modified Baylis–Hillman[15] conditions suitable for cyclic enones. Of the two procedures available, that is, using *N*,*N*-(dimethylamino)-pyridine [DMAP/60 °C/5 days][13] or imidazole [imid/rt/17 days][14] as the catalyst, the lower yielding DMAP procedure was chosen based on time conservation. In our case, considerable optimization and modification was required. However, it wasfound that reaction of **9** using DMAP afforded the allylic alcohol **10** in 32% yield [43% based on recovered starting material (27%)] after 10 h at 50 °C (Scheme 2). More recently reported procedures either failed

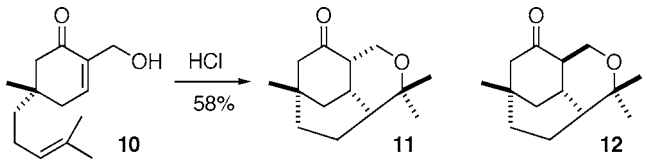
Scheme 2



to react[14] or gave a lower yield[16,17] of product in our hands.

Utilizing the cyclization procedure reported by Fukuyama[7] [38.4 mM (CH_2Cl_2), BF_3·Et_2O (10 equiv), −78 °C, 20 min] and variations thereof afforded only trace amounts of the desired cyclization product **11** (Scheme 3). It was soon

Scheme 3



realized that BF_3·Et_2O was most likely not the active agent, but rather hydrofluoric acid. Treating **10** with anhydrous ethereal hydrochloric acid conversely gave cyclized product **11** in 58% yield with no accompanying diastereoisomers (e.g., **12**) (Scheme 3).

Conformational analysis of the stereochemical models (i.e., **13** and **14**) suggests **14** is significantly more strained than **13**; however, these two compounds are epimeric alpha to a carbonyl. Therefore, irrespective of the kinetic ratio of **11** and **12**, the reaction should be under thermodynamic control because **11** and **12** would easily equilibrate under the reaction conditions (Figure 2).

Ring expansion of the cyclohexanone moiety of **11** to the vibsanin E core with stabilized carbenoids (e.g., EtO_2-$CCHN_2$), known to insert regioselectively at the least subsituted carbon alpha to ketones, using BF_3·Et_2O[11] or Meerwein's salt[18] failed.

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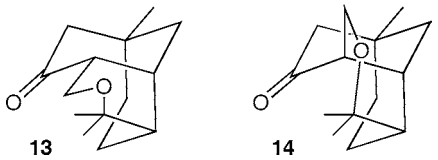
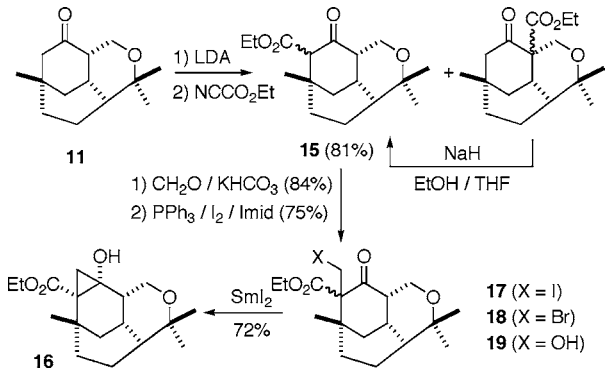


Figure 2. Stereochemical models **13** and **14**,

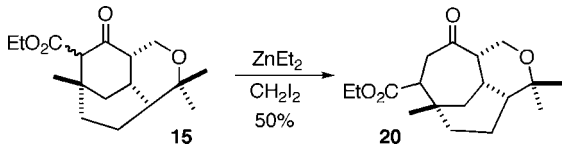
In addition, failed attempts at ring expansion were also experienced with nonstabilized carbenoids,[19] ethyl diazolithioacetate,[20] and silyloxycyclopropane homologation.[21] Considering ring expansion of 1,3-dicarbonyl functions are prevalent, for example, Beckwith-Dowd[22] and variant[23] protocols, **11** was converted to **15** in 81% overall yield, via Mander's reagent[24] and subsequent treatment with ethoxide (retro Claisen/Claisen reaction). A requirement of the Beckwith−Dowd protocol is the installation of a methylene halide function, however, all attempts to convert **15** to the methylene iodide **17** or bromide **18** failed when **15** was reacted directly with diiodo- or dibromomethane. Reaction of **15** with formalin[25] gave the methylene hydroxy derivative **19** in 84% yield, which underwent smooth conversion to the methylene iodide **17** in 75% yield, using triphenylphosphine, iodine and imidazole. Unfortunately, treating iodide **17** with samarium diiodide[26] afforded separable mixtures of cyclopropanol **16** (72%) and unidentified products, whereas recent developments with zinc metal[27] promoted ring expansion returned only starting material (Scheme 4). Surprisingly, brief attempts (e.g., DBU, NaOEt) to ring open **16** have been disappointing.

Thanks to the ingenious Zercher reaction,[28] however, treating **15** with diethyl zinc and diiodomethane gave in one step the vibsanin E core **20**[29] in 50% yield (dr >95:5) (Scheme 5).

Scheme 4



Scheme 5



In conclusion, we have demonstrated that the core of vibsanin E (**1**) can be constructed expediently and astonishingly without the use of a single protecting group. We believe that new developments in asymmetric 1,4-additions to cyclohexenones[30] in conjunction with the El Gaïed Baylis−Hillman variant and the remarkable Zercher reaction will pave the way for a successful total synthesis and structural confirmation of vibsanin E (**1**).

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Supporting Information Available: Characterization data of compounds **8**−**11**, **15**, and **20**, X-ray crystal structure analysis data of **11**, and copies of ^{1}H and ^{13}C NMR sprectra of compound **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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