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

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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 Galed 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 Kawazu¹ in





1978, and the absolute stereochemistry was determined in 1980 by K. Y. Fukuyama.² Since then, Fukuyama,³ and to a

lesser extent Shen⁴ 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, Fukuyama⁴ has synthesized 6-*epi*-vibsanin F (**4**) proving the absolute configuration of vibsanin F (Figure 1).

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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smoothly, albeit in moderate yield (50%), using boron trifluoride etherate ($BF_3 \cdot Et_2O$). 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.



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–Hillman¹⁵ 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

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recovered starting material (27%)] after 10 h at 50 °C (Scheme 2). More recently reported procedures either failed



to react¹⁴ or gave a lower yield^{16,17} of product in our hands.

Utilizing the cyclization procedure reported by Fukuyama⁷ [38.4 mM (CH₂Cl₂), BF₃•Et₂O (10 equiv), -78 °C, 20 min] and variations thereof afforded only trace amounts of the desired cyclization product **11** (Scheme 3). It was soon



realized that $BF_3 \cdot Et_2O$ 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 -CCHN₂), known to insert regioselectively at the least subsituted carbon alpha to ketones, using $BF_3 \cdot Et_2O^{11}$ or Meerwein's salt¹⁸ 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 silvloxycyclopropane homologation.²¹ Considering ring expansion of 1.3-dicarbonyl functions are prevalent, for example, Beckwith-Dowd²² and variant²³ protocols, 11 was converted to 15 in 81% overall yield, via Mander's reagent²⁴ 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 formalin²⁵ 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 diiodide²⁶ afforded separable mixtures of cyclopropanol 16 (72%) and unidentified products, whereas recent developments with zinc metal²⁷ 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

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step the vibsanin E core 20^{29} in 50% yield (dr >95:5) (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 cyclohexenones³⁰ 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 ¹H and ¹³C NMR sprectra of compound 20. This material is available free of charge via the Internet at http://pubs.acs.org.

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