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Total Synthesis of (±)-Vibsanin E

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Vibsanine E (**1**), [now known as vibsanin E (**1**)] isolated by Kawazu[1] from the Japanese fish poison plant *Viburnum odoratissimum* (Sangoju) in 1978 (Figure 1), was amongst the first vibsane natural products to be isolated. Since this time an entire vibsane family has been isolated from the *Viburnum* species[2] as elucidated by Fukuyama,[3] Shen[4] and Duh.[5] Biological activity in this natural product family is prevalent,[3] for example, vibsanin A displayed piscicidal activity, vibsanin B inhibited rice seedling root growth, vibsanins B and C exhibited cytotoxic activities on KB cells, aldolvibsanin B showed lethal brine shrimp activity, vibsanin O demonstrated cytotoxicity against P- 388 cells as did vibsanins P and W, vibsanin K exhibited cytotoxicity against human gastric (NUGC) and oral epidermoid (HONE-1) tumor cells, and vibsanins P and W were cytotoxic against A549 and HT-29 cells. Considering the amount of anti-cancer and cytotoxic activity displayed by the vibsane family of natural products, and our interest in the cancer field,[6] we were attracted to vibsanin E (**1**) as to-date its biological activity had not been reported. We embarked on firstly attempting to confirm the structure of vibsanin E (**1**) and secondly devise a route that would provide sufficient material for extensive biological evaluation.

Only very recently have vibsane natural product family members succumbed to total synthesis. So far, the synthesis of (±)-2-*O*-methylneovibsain H (**2**),[7] (±)-neovibsanin B (**3**)[8] and (−)-5-*epi*-vibsanin E (**4**)[9] (Figure 2) have been achieved. The stereocontrol in these systems has been challenging, and on many occasions the synthetic efforts have resulted in formation of diastereomers of the natural products [i.e. (+)-6-*epi*-vibsanin F (**5**),[10] (±)-5,10-bis-*epi*-vibsanin E (**6**),[11] and (±)-5,14-bis-*epi*-spirovibsanin A[12]] or deadend synthetic explorations (Figure 2).[13-16] As vibsanin E (**1**) has a highly functionalized fused seven-membered ring and is one of the original vibsanes, we consider it the pinnacle target in this family of natural products.

Both Williams and Davies have worked independently towards a total synthesis of vibsanin E (**1**). The Queensland group pursued a biogenetically modeled approach giving access to bicycle **8**,[17,18] which, although led to many advanced intermediates (i.e. **9**), did not yield the target.[19,20] The Davies group utilised three key cycloadditions to achieve a total synthesis of 5-*epi*-10-*epi*-vibsanin E **6**; a rhodium-catalysed [4+3] and a subsequent heteronuclear [4+2] afforded bicycle **10**, followed by a photochemically induced [4+2] (Scheme 1).[11]

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Accessory Publication

General methods, experimental, scanned copies of ^{1}H and ^{13}C NMR spectra, comparison ^{1}H NMR spectra for vibsanin E and comparison table of ^{1}H and ^{13}C NMR shifts for vibsanin E.

In the view that the Davies strategy readily provided multi-gram quantities of bicycle **10**[11] and the Queensland group had significant end game experience with molecules of this type,[19] including the development of a novel method utilising ylid **11** for introducing the enol ester side chain,[20] it made sense to join forces in this common quest. In fact the initial fruits of this collaboration led to the first total synthesis of the natural product (−)-5-*epi*-vibsanin E (**4**)[9] in which many of the previous difficulties encountered with both introduction and stereocontrol of the side chains were overcome. Highlights of this successful pathway included, conjugate addition of an α-oxa methylene anion (i.e. $MOMOCH_2Li$ derived from $MOMOCH_2SnBu_3$)[21] to bicycle **10**, using $TMSCl$[22] activation, affording **12**. Metallation then subsequent *O*-allylation of **12** afforded **13**, which gave a mixture of epimers **14** and **15**. Ketone **14** was then carried through a series of deprotection oxidation steps to provide aldehyde **16**, which afforded (−)-5-*epi*-vibsanin E (**4**) on treatment with ylid **11** (Scheme 2).

At the time, however, considerable difficulties were being encountered with the Claisen rearrangement in that the *anti*-isomer **15** was only obtained in low yield preventing a synthesis of vibsanin E (**1**), but also a considerable amount of by-product **17** was being observed (Scheme 3). If this could be overcome a total synthesis of vibsanin E (**1**) would be possible.

After considerable experimentation it was discovered that *C*-allylated material **17** could be significantly reduced if the microwave induced Claisen rearrangement was performed in a dilute solution [i.e. toluene (0.02M)]. In addition it was also found that the *syn*-isomer **14** could be epimerised to the *anti*-isomer **15** in 51% (K_2CO_3/MeOH), with further material obtained on recycling. With these developments the *anti*-isomer **15** could be obtained in 44% yield (56% with recovery) and reasonable quanitity. Subjecting **15** to the same deprotection oxidation sequence used for (−)-5-*epi*-vibsanin E (**4**) (see scheme 2) afforded aldehyde **18**. Treatment of **18** with ylid **11** produced vibsanin E (**1**),[23] which was an identical ^1H and ^{13}C NMR spectroscopic match to the natural material,[24] albeit accompanied by trace amounts of the tentatively assigned by-product **19** (Scheme 4).

In conclusion, vibsanin E (**1**), a structurally rare complex diterpene, has been efficiently synthesised in 14 steps confirming the proposed relative stereochemistry. The synthesis combines the rhodium catalyzed [4+3] cycloaddition strategy to rapidly generate the tricyclic core with an effective end game strategy to introduce the remaining side-chains. This represents the first total synthesis of Vibsanin E (**1**), 31 years since it was isolated, and paves the way for derivative synthesis should structure activity studies be deployed. Vibsanin E (**1**) is currently undergoing biological evaluation, results of which will be reported in due course.

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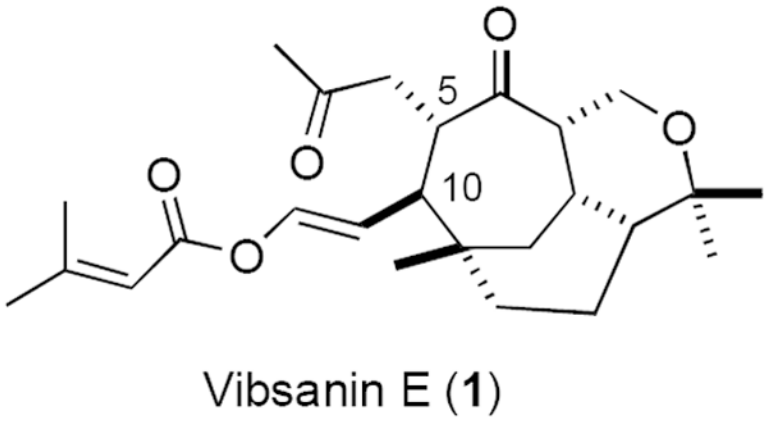
23. Note: non-stabilized ylids as a general rule give rise to *cis* (or *Z*) double bond products, but it has been found[20] that steric hindrance dramatically influences the selectivity in the case of **18**, hence the observation of an ~10:1 *E/Z* ratio observed for synthetic vibsanin E (**1**).
24. See supporting information for comparative ^{1}H and ^{13}C NMR spectra of synthetic and natural vibsanin E (**1**).



Vibsanin E (**1**)

Figure 1.
Relative stereochemical representation of vibsanin E (**1**)

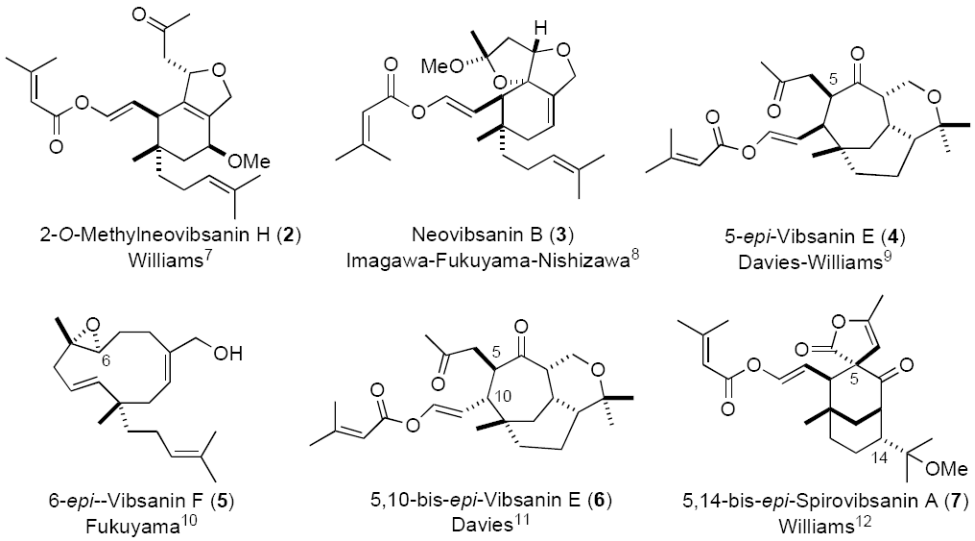
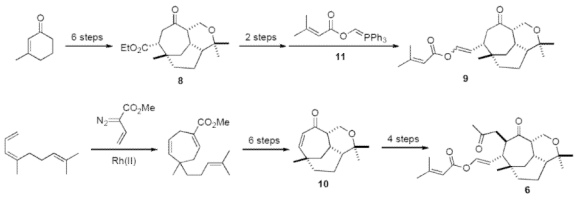
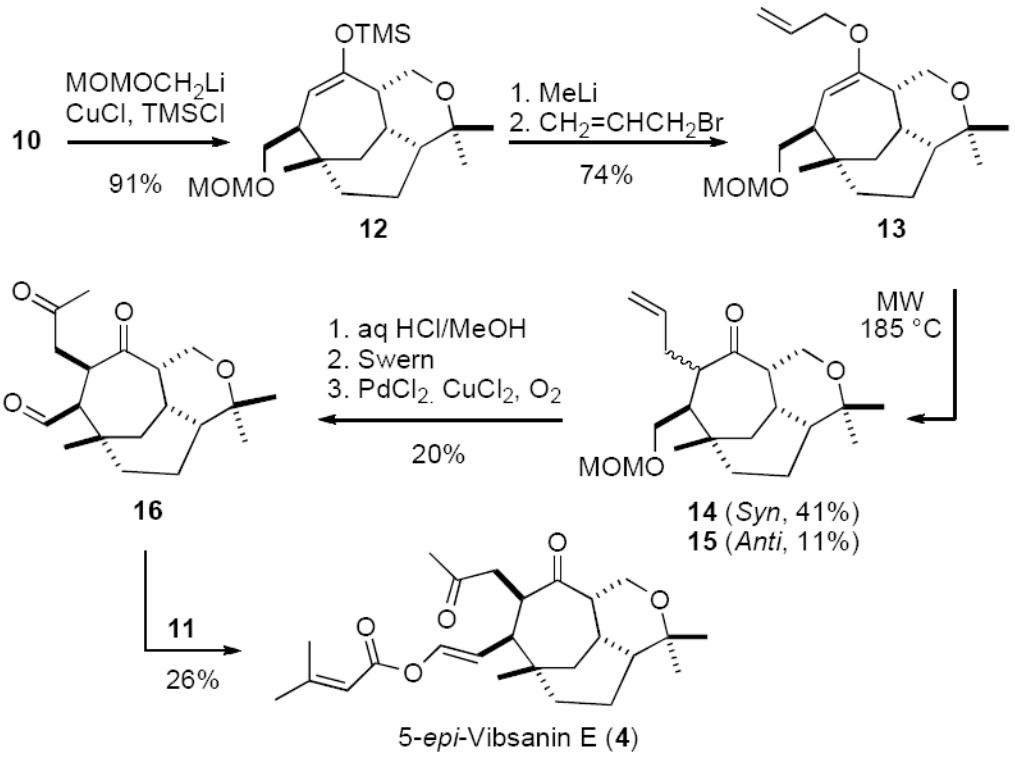


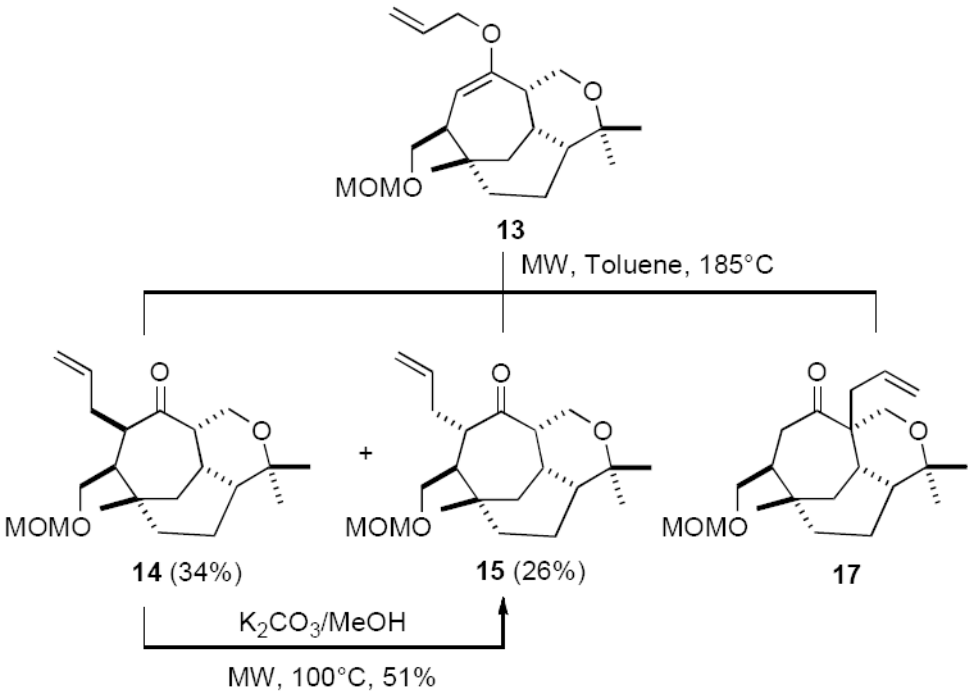
Figure 2.
Vibsanin, and *epi*-vibsanin, family members that have previously been synthesised.



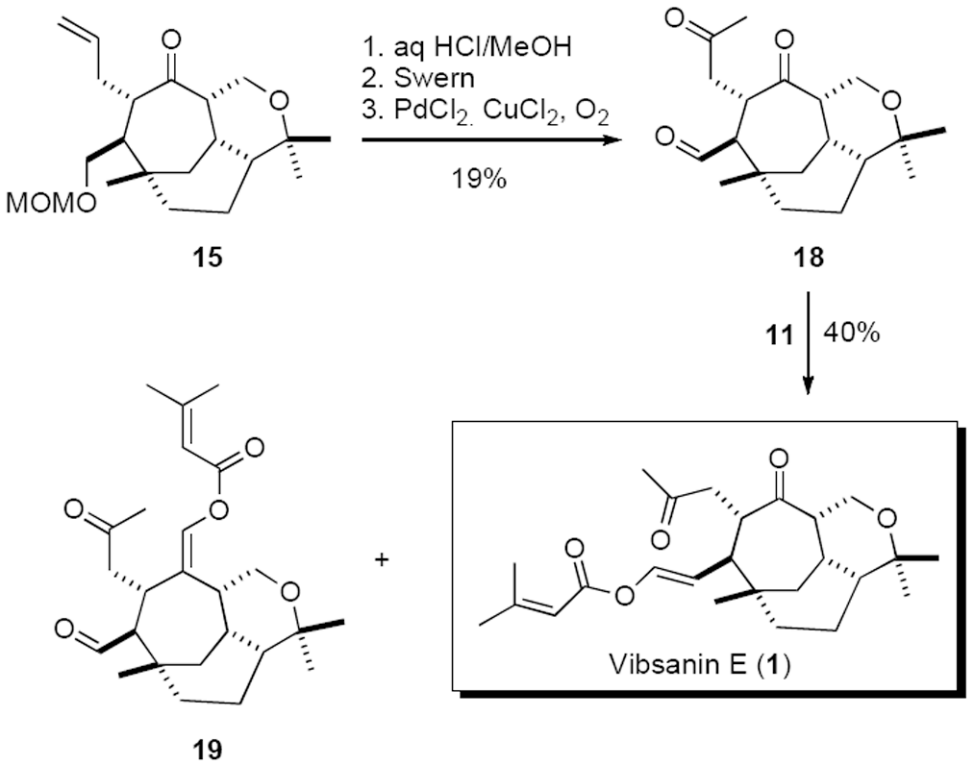
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.