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Towards the Total Synthesis of 3-Hydroxyvibsanin E

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In 1999 Fukuyama reported the isolation of 3-hydroxyvibsanin E (**1**) (Figure 1) from *Viburnum awabuki*¹ with an additional finding in *Viburnum suspensum* three years later.² Across the entire spectrum of vibsanin natural products α -hydroxylation is very rare,^{3,4} occurring only at position 3 of the bridged 7-membered ring class [e.g. 3-hydroxy-15-O-methylcyclovibsanin A (**2**),⁵ furanovibsanin A (**3**),⁶ and 3-O-methylfuranovibsanin A (**4**)] (Figure 1). Although, the assumed later stage p450 enzymatic oxidation⁷ to introduce the single hydroxyl group at position 3 is biosynthetically elegant it poses a considerable increase in the degree of synthetic challenge over the non-hydroxylated family members. Recently, we disclosed a combined effort which resulted in the total syntheses of both (–)-*epi*-5-vibsanin E (**5**)⁸ and (±)-vibsanin E (**6**).⁹ On this basis we felt that the methodology devised to prepare **5** and **6**, and the experience gained from individual efforts^{10,11} on other vibsanin natural products, could be applied to the more challenging hydroxylated family members, specifically 3-hydroxyvibsanin E (**1**) (Figure 1).

Key to this endeavour would be the use of Davies' tricyclic advanced intermediate **7**,¹⁰ generated by means of two cycloadditions: 1) a rhodium-catalysed [4+3] cycloaddition to give **8** from **9**, and 2) a subsequent heteronuclear [4+2] cycloaddition (Scheme 1). The tricyclic intermediate **7** has been effectively used in the synthesis of both (–)-*epi*-5-vibsanin E (**5**)⁸ and (±)-vibsanin E (**6**)⁹ as summarized in scheme 1. In order to apply **7** to the synthesis of 3-hydroxyvibsanin E (**1**), a regioselective C–H hydroxylation of one of the intermediates in Scheme 1 would be required.¹² In this paper, we summarize the model studies to develop a selective C–H hydroxylation, followed by its application to studies toward the total synthesis of (±)-3-hydroxyvibsanin E (**1**).

Several reasonable approaches are available for the selective C–H hydroxylation of vibsanin-related intermediates. Williams reported^{11f} that Koser's reagent¹³ [PhI(OH)(OTs)] was superior to that of Davis' reagent (PhCHONSO₂Ph)¹⁴ in producing **16**, when investigating α -hydroxylation of tricycle **15**. In the case of **7**, however, Davies^{10b} found that the Davis' reagent was superior affording **17** in 53% yield.^{10b} Williams^{11g} found that a vastly improved protocol over both of the above procedures was the Rubottom oxidation¹⁵ of **18** giving **19** in 80% yield (Scheme 2).

With this knowledge in-hand the approach shown in scheme 3 toward 3-hydroxyvibsanin E (**1**) was taken. The stereospecific cuprate addition product **10**⁸ was doubly deprotected to unmask the ketone and primary alcohol. Treatment of **20** with *t*-butyldimethylsilyl

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trifluoromethanesulfonate (TBSOTf) reprotected the primary alcohol and trapped out regioselectively the thermodynamic silyl enol ether **21**. Subjecting **21** to dimethyl dioxirane (DMDO) provided the epoxide **22**, which could be isolated, but was directly treated with boron trifluoride etherate to facilitate epoxide ring opening. However, instead of the ring opening affording **24**, the hydroxyketone **23** was obtained. Subsequent exposure of **23** to sodium hydride was required to complete the transformation of **21** into **24** (as determined by X-ray crystal structure analysis, Figure 2), which occurred in high yield (71% over three steps) (Scheme 3).

O-Allylation of the lithium enolate derived from **24** proceeded smoothly in 81% yield. The Claisen rearrangement occurred in only moderate yield to give **26** and **27** (d.r. 3:1; respectively) [as determined by X-ray crystal structure analysis (Figure 2)], albeit stereoselectively in favour of the desired anti-isomer **26**, which is almost certainly due to the bulky OTBS group perturbing the upper face. Regioselective deprotection of the primary alcohol (i.e. **26**) was initially troublesome, but boron trifluoride etherate was found to be the reagent of choice providing the free alcohol **28** in 78% yield. Swern oxidation gave aldehyde **29** in modest yield (67%), which was directly converted to the tricarbonyl analogue **30** in 50% yield using the previously described Wacker protocol (Scheme 4).⁹

Application of the modified Anders-Gaßner reaction,¹⁶ via ylid **14**,¹⁷ to aldehyde **30** afforded 3-*O*-*t*-butyldimethylsilyloxyvibsanin E (**31**) in 40% yield as a single *E*-isomer. All attempts, however, to remove the TBS protecting group from this system proved impossible. Very aggressive protocols lead to hydrolysis of the enol acetate side chain, whereas all others returned starting material. Even the use of tetrafluorosilane, reported to remove problematical TBS groups from tertiary substituted OTBS groups,¹⁸ failed to deliver the target molecule **1** (Scheme 5).

Other silyl protecting groups were then investigated, such as trimethylsilyl (TMS), but these protecting groups were found not to survive boron trifluoride treatment at either stage of the route present i.e. in scheme 4 and 5. Attempts to circumvent these issues, for example, deprotection of aldehyde **30** with a range of reagents either returned starting material or resulted in decomposition. Considering previous work has shown that the enol acetate sidechain does not survive Wacker conditions^{11g} we came to the disappointing conclusion that this approach would not yield 3-hydroxyvibsanin E (**1**).

In conclusion, application of a modified route to that used for the total synthesis of both (–)-*epi*-5-vibsanin E (**5**) and (±)-vibsanin E (**6**) afforded the TBS protected form of 3-hydroxyvibsanin E (**31**). Attempts at the deprotection of the TBS group to generate 3-hydroxyvibsanin E (**1**) were unsuccessful. We hope that this report inspires others to contemplate alternative approaches to this molecule, and related family members.

Experimental

¹H and ¹³C n.m.r spectra were recorded on Bruker AV400 (400.13MHz; 100.62 MHz), AV300 (300.13 MHz; 75.47 MHz) and DRX500 (500.13 MHz; 125.76 MHz) instruments in the solvents specified. Coupling constants are given in Hz and chemical shifts are expressed as δ values in ppm. High resolution electrospray ionisation (HRESIMS) accurate mass measurements were recorded in positive mode on a Bruker MicrOTOF-Q (quadrupole – Time of Flight) instrument with a Bruker ESI source. Accurate mass measurements were carried out with external calibration using sodium formate as reference calibrant. Low and high resolution electron impact ionisation mass measurements were recorded on a Finnigan MAT 900XL–TRAP (EI 70 eV) using perfluorokerosene–H as reference calibrant. Column chromatography was undertaken on silica gel (Flash Silica gel 230–400 mesh), with distilled solvents. Anhydrous solvents were prepared according to Perin and Armarego,

'Purification of laboratory solvents', 3rd Ed. Tetrahydrofuran was freshly distilled from a sodium/benzophenone still. Melting points were determined on a Fischer Johns Melting Point apparatus and are uncorrected. Fine chemicals were purchased from the Aldrich Chem. Co. Microwave irradiation was conducted with a CEM Discover microwave in 10 mL pressurized vials. Crystallographic data for structures **24**, **26**, and **27** have been deposited with the Cambridge Crystallographic Data Centre (CCDC 737635 - 737637) and may be obtained free of charge via <http://www.ccdc.cam.ac.uk/conts/retrieving.html>, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033, or e-mail: deposit@ccdc.cam.ac.uk.

Alcohol 20

A mixture of **10** (500 mg, 1.31 mmol) in MeOH (25 mL), water (3 mL) and aqueous hydrochloric acid (2 mL, 10M) was stirred at 55 °C for 2 hours. The mixture was quenched with saturated sodium bicarbonate solution (10 mL) and then the methanol was removed *in vacuo* and the mixture extracted with dichloromethane (3 × 15 mL). The combined organic layer was washed with brine (10 mL), dried (Na₂SO₄) and concentrated *in vacuo* which afforded an oil. The crude oil was purified by flash chromatography (1:1 ether:pet. spirit) to give **20** (0.29 g, 78%) as a white solid, m.p. 123–125 °C. ¹H NMR (300 MHz, CDCl₃) δ 1.02 (s, 3H), 1.08 (s, 3H), 1.10–1.17 (m, 3H), 1.23 (s, 3H), 1.40–1.48 (m, 2H), 1.52–1.63 (m, 2H), 2.08 (brs, OH), 2.18–2.27 (m, 2H), 2.55 (dd, *J* = 11.8, 2.9 Hz, 1H), 2.58–2.63 (m, 1H), 2.60–2.71 (t, *J* = 11.6 Hz, 1H), 3.49–3.57 (m, 2H), 3.73 (dd, *J* = 10.7, 4.9 Hz, 1H), 4.22 (dd, *J* = 12.0, 0.6 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 19.5, 23.4, 27.8, 28.6, 29.8, 32.9, 41.8, 42.5, 43.0, 44.3, 44.8, 49.9, 59.2, 64.8, 71.1, 213.4. HRMS Calculated for [C₁₆H₂₆NaO₃]⁺: 289.1774, Found: 289.1763

TBS-protection of alcohol 20

To a solution of alcohol **20** (600 mg, 2.24 mmol) in anhydrous DCM (20 mL) at –78 °C was added anhydrous triethylamine (1.25 mL, 8.96 mmol) followed by *tert*-butyldimethylsilyltrifluoromethane sulfonate (1.29 mL, 5.60 mmol) dropwise. The reaction was stirred at –78 °C for 30 mins then stirred for a further 30 mins at 0 °C. The reaction was then poured onto ice-cold saturated sodium bicarbonate solution (10 mL) and then extracted with diethyl ether (3 × 15 mL). The combined organic layer was washed with brine (10 mL), dried (Na₂SO₄) and concentrated *in vacuo* which gave an oil that was purified by flash chromatography (1:20 ether:pet. spirit) to give **21** (1.12 g, 88%) as a white solid, m.p. 58–61 °C. ¹H NMR (400 MHz, C₆D₆) δ 0.07 (s, 3H), 0.08 (s, 3H), 0.09 (s, 3H), 0.16 (s, 3H), 0.81 (s, 3H), 0.82–0.91 (m, 2H), 0.98 (s, 9H), 1.00 (s, 9H), 1.07–1.08 (m, 1H), 1.14 (s, 3H), 1.24 (s, 3H), 1.38 (ddd, *J* = 14.8, 7.4, 3.8 Hz, 1H), 1.61 (app. dq, *J* = 13.2, 3.3 Hz, 1H), 1.89 (qd, *J* = 13.4, 3.7 Hz, 1H), 2.15–2.23 (m, 2H), 2.26–2.32 (m, 1H), 2.47–2.56 (m, 1H), 2.67–2.72 (m, 1H), 3.35 (dd, *J* = 9.8, 8.2 Hz, 1H), 3.57 (dd, *J* = 9.8, 5.4 Hz, 1H), 3.86 (d, *J* = 11.9 Hz, 1H), 4.77 (d, *J* = 11.9 Hz, 1H). ¹³C NMR (100 MHz, C₆D₆) δ –5.3, –5.2, –4.2, –3.8, 18.3, 18.5, 19.9, 24.1, 25.8, 26.0 (3C), 26.2 (3C), 27.8, 32.5, 33.3, 34.8, 39.7, 42.0, 46.4, 47.7, 61.4, 64.9, 73.5, 115.9, 147.1. HRMS Calculated for C₂₈H₅₄O₃Si₂: 494.3611, Found: 494.3611.

Hydroxylation of 21

To a solution of **21** (1.12 g, 2.19 mmol) in distilled acetone (10 mL) at –78 °C was added a solution of dimethyl dioxirane (27 mL, 2.19 mmol, 0.06 M solution in acetone) over 5 mins. After stirring for a further 5 mins the cold-bath was removed and the solvent removed *in vacuo* [the acetone was removed into an in-line trap cooled with liquid nitrogen and excess dimethyl dioxirane in the trap was quenched with cyclohexene (5 mL)] which afforded **22** as a white solid (1.13 g), m.p. 54–56 °C which was used immediately in the next step without further purification. ¹H NMR (400 MHz, C₆D₆) δ 0.10 (s, 3H), 0.11 (s, 3H), 0.23 (s, 3H),

0.34 (s, 3H), 0.60 (dd, $J = 14.4, 4.6$ Hz, 1H), 0.73 (s, 3H), 0.87 (td, $J = 13.5, 13.4, 4.1$ Hz, 1H), 0.98 (s, 9H), 0.99 (s, 9H), 1.04–1.09 (m, 1H), 1.10 (s, 3H), 1.16 (s, 3H), 1.36–1.44 (m, 1H), 1.69 (ddd, $J = 13.4, 6.4, 3.3$ Hz, 1H), 1.78–1.89 (m, 2H), 2.13 (dd, $J = 13.8, 10.7$ Hz, 1H), 2.22–2.28 (m, 1H), 2.29 (d, $J = 14.0$ Hz, 1H), 2.44 (dd, $J = 7.6, 3.8$ Hz, 1H), 3.43 (dd, $J = 9.8, 7.3$ Hz, 1H), 3.59 (dd, $J = 9.8, 5.6$ Hz, 1H), 3.70 (d, $J = 12.1$ Hz, 1H), 4.12 (d, $J = 12.1$ Hz, 1H). ^{13}C NMR (100 MHz, C_6D_6) δ –5.2 (2C), –3.3, –2.8, 18.0, 18.6, 20.6, 23.3, 26.0 (3C), 26.0, 26.3 (3C), 27.3, 33.2, 34.4, 35.5, 37.9, 38.1, 42.0, 44.3, 41.1, 63.0, 65.0, 73.2, 91.5

The crude epoxide was dissolved in anhydrous dichloromethane (25 mL), under an atmosphere of argon, cooled to -78°C and then freshly distilled boron trifluoride diethyl etherate (27 μL , 0.22 mmol) was added dropwise. The reaction was stirred for 10 mins then poured onto ice–cold saturated sodium bicarbonate solution (10 mL) and then extracted with dichloromethane (3×15 mL). The combined organic layer was washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo* which afforded an oil. Purification by flash chromatography (1:1 ethyl acetate:pet. spirit) gave **23** (0.69 g, 80%, 2 steps) as a white solid, m.p. 108–109 $^\circ\text{C}$. ^1H NMR (400 MHz, CDCl_3) δ 0.01 (s, 3H), 0.03 (s, 3H), 0.87 (s, 9H), 0.87–0.89 (m, 1H), 0.96 (s, 3H), 1.14 (s, 3H), 1.33 (s, 3H), 1.17–1.26 (m, 1H), 1.38–1.46 (m, 1H), 1.48–1.58 (m, 2H), 1.62–1.72 (m, 2H), 2.11 (dt, $J = 15.0, 2.3$ Hz, 1H), 2.34 (td, $J = 6.0, 1.9$ Hz, 1H), 2.81 (dd, $J = 12.0, 4.0$ Hz, 1H), 3.04 (dd, $J = 12.0, 8.2$ Hz, 1H), 3.17 (s, OH), 3.45 (d, $J = 12.2$ Hz, 1H), 3.48 (dd, $J = 10.0, 7.3$ Hz, 1H), 3.63 (dd, $J = 10.0, 4.7$ Hz, 1H), 3.84 (d, $J = 12.1$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ –5.5 (2C), 18.2, 21.9, 24.3, 25.9 (3C), 26.8, 29.8, 32.8, 36.3, 36.6, 40.4, 41.7, 42.4, 45.7, 63.9, 66.6, 73.8, 75.7, 211.8. HRMS Calculated for $[\text{C}_{22}\text{H}_{40}\text{NaO}_4\text{Si}]^+$: 419.2588, Found: 419.2586.

TBS–protection of **23**

To a solution of hydroxyketone **23** (0.69 g, 1.75 mmol) in anhydrous THF (25 mL) under an atmosphere of argon at 0°C was added NaH (175 mg, 4.4 mmol, 60% dispersion in mineral oil) in one portion. After 5 mins *tert*–butyldimethylsilyl chloride (0.34 g, 2.28 mmol) was added and the reaction was then stirred at 55°C for 2 hours. The mixture was poured onto ice–cold saturated sodium bicarbonate solution (10 mL) and then extracted with ether (3×15 mL). The combined organic layer was washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo* which gave an oil that was purified by flash chromatography (1:10 ether: pet. spirit) affording **24** (0.80 g, 89%) as a white solid, m.p. 115.5–116.5 $^\circ\text{C}$. ^1H NMR (400 MHz, CDCl_3) δ –0.04 (s, 3H), –0.01 (s, 6H), 0.06 (s, 3H), 0.86 (s, 9H), 0.86 (s, 9H), 0.98–1.09 (m, 1H), 0.99–1.10 (m, 2H), 1.05 (s, 3H), 1.10 (s, 3H), 1.21–1.27 (m, 1H), 1.29 (s, 3H), 1.37–1.43 (m, 1H), 1.44–1.51 (m, 2H), 2.11 (dd, $J = 11.0, 2.2$ Hz, 1H), 2.26 (app. t, $J = 5.3$ Hz, 1H), 2.46 (dt, $J = 14.9, 2.1, 2.1$ Hz, 1H), 3.20 (dd, $J = 13.0, 11.0$ Hz, 1H), 3.37 (d, $J = 11.1$ Hz, 1H), 3.61 (m, 2H), 4.07 (d, $J = 11.1$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ –5.6, –5.6, –3.2, –1.8, 18.1, 18.3, 19.4, 23.6, 25.8 (3C), 25.9 (3C), 27.4, 28.3, 33.1, 37.4, 39.1, 41.4, 42.8, 43.9, 44.2, 64.5, 65.8, 73.1, 75.9, 211.5. HRMS Calculated for $[\text{C}_{28}\text{H}_{54}\text{NaO}_4\text{Si}_2]^+$: 533.3453, Found: 533.3433.

Allylation of **24**

To a solution of ketone **24** in (0.35 g, 0.69 mmol), in THF (6 mL) at -78°C under an atmosphere of argon was added a freshly prepared solution of lithium diisopropylamide dropwise [generated from *n*–butyllithium (0.52 mL, 0.76 mmol, 1.48 M in hexanes) and diisopropylamine (116 μL , 0.83 mmol) at 0°C in THF (2 mL)]. After 5 mins the reaction was warmed to 0°C and stirred for 30 mins, after which time anhydrous HMPA (1.5 mL) and allyl iodide (140 mg, 0.83 mmol) were added consecutively, dropwise. After 5 mins TLC analysis showed complete consumption of starting material and the mixture was poured onto ice–cold saturated sodium bicarbonate solution (10 mL) and then extracted with

diethyl ether (3 × 15 mL). The combined organic layer was washed with aqueous lithium chloride (2 × 15 mL, 10%), brine (10 mL), dried (Na₂SO₄) and concentrated *in vacuo* which gave a residue that was purified by flash chromatography (1:20 ether: pet. spirit) affording **25** (0.31 g, 81%) as a colourless oil. ¹H NMR (300 MHz, CDCl₃) δ -0.08 (s, 3H), 0.00 (s, 3H), 0.01 (s, 3H), 0.04 (s, 3H), 0.81–0.85 (m, 1H), 0.83 (s, 9H), 0.86 (s, 9H), 1.03–1.10 (m, 1H), 1.07 (s, 3H), 1.31 (s, 3H), 1.19–1.37 (m, 3H), 1.63–1.72 (m, 1H), 1.98–2.14 (m, 2H), 2.16–2.22 (m, 1H), 2.47 (dt, *J* = 14.3, 2.3 Hz, 1H), 3.11 (d, *J* = 10.8 Hz, 1H), 3.40 (dd, *J* = 9.6, 7.3 Hz, 1H), 3.77 (dd, *J* = 9.6, 5.8 Hz, 1H), 4.25–4.07 (m, 2H), 4.08–4.25 (m, 2H), 4.40 (d, *J* = 10.8 Hz, 1H), 4.89 (d, *J* = 8.2 Hz, 1H), 5.15 (app. dq, *J* = 10.5, 1.5 Hz, 1H), 5.30 (app. dq, *J* = 17.3, 1.7 Hz, 1H), 5.99 (dddd, *J* = 17.3, 10.4, 5.4, 4.9 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃) δ -5.4, -5.3, -3.8, -1.9, 18.1, 18.3, 22.3, 24.2, 25.9 (6C), 27.2, 32.1, 32.5, 33.7, 40.7, 43.5, 44.7, 50.3, 66.2, 67.8, 68.1, 73.5, 75.7, 105.8, 116.4, 134.0, 154.6. HRMS Calculated for [C₃₁H₅₈NaO₄Si₂]⁺: 573.3766, Found: 573.3765.

Claisen rearrangement of **25**

A solution of *O*-allylated material **25** (260 mg, 0.47 mmol) in solution of anhydrous toluene (4 mL) and DMSO (0.5 mL) under an atmosphere of argon was heated under microwave irradiation for 95 min. (maximum temperature 180 °C, 300 W). The solvent was removed *in vacuo* which afforded crystals that were purified by flash chromatography (1:10 ether:pet. spirit) giving *C*-allylated isomers *anti* (**26**) (150 mg, 58%), m.p. 116–119°C and *syn* (**27**) (45 mg, 17%) m.p. 122–123°C as colourless crystals. *Anti-isomer 26* ¹H NMR (400 MHz, CDCl₃) δ 0.02 (s, 3H), 0.03 (s, 3H), 0.05 (s, 3H), 0.17 (s, 3H), 0.81–0.86 (m, 2H), 0.86 (s, 9H), 0.88 (s, 9H), 1.03 (ddd, *J* = 17.1, 14.7, 3.1 Hz, 1H) 1.11 (s, 3H), 1.15 (s, 3H), 1.25–1.33 (m, 1H), 1.13–1.24 (m, 2H), 1.30 (s, 3H), 1.45 (dq, *J* = 12.7, 2.9 Hz, 1H), 2.20 (app. t, *J* = 4.9, Hz, 1H), 2.25–2.32 (m, 1H), 2.41–2.50 (m, 1H), 2.55 (dt, *J* = 14.9, 2.2 Hz, 1H), 3.43–3.52 (m, 1H), 3.49 (d, *J* = 11.4 Hz, 1H), 3.68 (dd, *J* = 10.8, 4.1 Hz, 1H), 3.74 (dd, *J* = 10.8, 1.7 Hz, 1H), 3.97 (d, *J* = 11.2 Hz, 1H), 4.88–4.81 (m, 1H), 4.96 (ddd, *J* = 17.0, 3.5, 1.3 Hz, 1H), 5.66 (ddt, *J* = 17.0, 10.1, 7.0 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃) δ -5.8, -5.7, -1.7 (2C), 17.9, 18.5, 18.9, 23.8, 25.8 (3C), 26.1 (3C), 27.4, 30.4, 34.0, 34.3, 37.2, 37.8, 43.0, 44.2, 45.2, 47.0, 61.0, 64.5, 73.1, 76.6, 116.1, 137.5, 213.1. HRMS Calculated for [C₃₁H₅₈NaO₄Si₂]⁺: 573.3766, Found: 573.3756. *Syn-isomer 27* ¹H NMR (300 MHz, CDCl₃) δ 0.00 (s, 3H), 0.02 (s, 3H), 0.07 (s, 3H), 0.08 (s, 3H), 0.83 (s, 9H), 0.85 (s, 9H), 0.85–0.86 (m, 1H), 0.94 (s, 3H), 1.14–1.21 (m, 1H), 1.16 (s, 3H), 1.36 (s, 3H), 1.43 (dd, *J* = 14.3, 6.8 Hz, 1H), 1.56–1.65 (m, 2H), 1.65–1.75 (m, 1H), 1.77–1.89 (m, 1H), 1.91–2.07 (m, 1H), 2.08–2.19 (m, 1H), 2.40 (td, *J* = 6.8, 1.8 Hz, 1H), 2.58–2.69 (m, 1H), 3.21 (dd, *J* = 11.3, 6.7 Hz, 1H), 3.50 (d, *J* = 12.5 Hz, 1H), 3.55 (dd, *J* = 11.4, 1.9 Hz, 1H), 3.58–3.61 (m, 1H), 3.65 (d, *J* = 12.5 Hz, 1H), 4.97–5.01 (m, 1H), 5.00–5.08 (m, 1H), 5.70 (ddt, *J* = 17.1, 10.1, 7.0 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃) δ -5.5, -5.4, -2.8, -2.4, 18.0, 18.7, 24.3, 24.5, 25.9 (3C), 26.1 (3C), 26.4, 32.5, 32.9, 34.6, 34.7, 37.9, 39.9, 40.3, 49.1, 53.3, 60.5, 69.3, 74.2, 80.8, 116.9, 136.2, 211.8. HRMS Calculated for [C₃₁H₅₈NaO₄Si₂]⁺: 573.3766, Found: 573.3774.

Deprotection of **26**

To a solution of **26** (260 mg, 0.47 mmol) in anhydrous acetonitrile (20 mL) under an atmosphere of argon at 0 °C was added dropwise, freshly distilled, boron trifluoride diethyl etherate (70 μL, 0.57 mmol). After 5 minutes the ice bath was removed and the reaction stirred for 40 minutes at room temperature after which time TLC analysis revealed complete consumption of starting material. A saturated solution of sodium bicarbonate (10 mL) was then added and the acetonitrile was removed *in vacuo*. The mixture was then extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were washed with brine (10 mL), dried (Na₂SO₄) and concentrated *in vacuo* which afforded a residue that was purified by flash chromatography (1:20, ether:dichloromethane) affording alcohol **28** as a colourless

solid (160 mg, 78%), mp. 182–184 °C. ^1H NMR (300 MHz, CDCl_3) δ 0.05 (s, 3H), 0.16 (s, 3H), 0.87 (s, 9H), 0.97–1.08 (m, 1H), 1.11 (s, 3H), 1.13–1.26 (m, 4H), 1.27–1.38 (m, 2H), 1.18 (s, 3H), 1.30 (s, 3H), 1.47–1.54 (m, 1H), 2.22 (app. t, $J = 5.3$ Hz, 1H), 2.29–2.39 (m, 1H), 2.46–2.59 (m, 2H), 3.39 (ddd, $J = 11.5, 8.7, 5.0$ Hz, 1H), 3.48 (d, $J = 11.3$ Hz, 1H), 3.74–3.88 (m, 2H), 3.99 (d, $J = 11.2$ Hz, 1H), 4.90 (ddt, $J = 10.3, 2.2, 1.1$ Hz, 1H), 5.04 (ddd, $J = 17.1, 3.4, 1.6$ Hz, 1H), 5.69 (dddd, $J = 16.5, 10.1, 7.7, 6.3$ Hz, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ -1.9, -1.7, 18.5, 19.1, 23.8, 26.0 (3C), 27.2, 29.9, 34.1, 34.3, 37.2, 38.1, 42.3, 44.0, 45.1, 47.1, 61.4, 64.4, 73.1, 76.6, 116.2, 137.6, 212.5. HRMS Calculated for $[\text{C}_{25}\text{H}_{44}\text{NaO}_4\text{Si}]^+$: 459.2901, Found: 459.2923.

Aldehyde 29

To a stirred solution of oxalyl chloride (64 μL , 0.73 mmol) in anhydrous dichloromethane (10 mL) under an argon atmosphere at -78°C was added dimethylsulfoxide (65 μL , 0.92 mmol) dropwise. After 10 mins a solution of alcohol **28** (160 mg, 0.37 mmol) in dichloromethane (2 mL) was added dropwise. After 1 hour at -78°C excess anhydrous triethylamine (308 μL , 2.2 mmol) was added and stirring continued at that temperature for a further 15 mins. The solution was warmed to 0°C and stirred for 20 mins, then diluted with dichloromethane (30 mL), washed with brine (10 mL) and dried (MgSO_4). Evaporation *in vacuo* gave a residue which was subjected to column chromatography (1:20, ether:dichloromethane) affording ketoaldehyde **29** (108 mg, 67 %) as a colourless solid, mp. 87–89 °C. ^1H NMR (300 MHz, CDCl_3) δ 0.06 (s, 3H), 0.17 (s, 3H), 0.86–0.91 (m, 1H), 0.89 (s, 9H), 1.00 (s, 3H), 1.07–1.15 (m, 1H), 1.12 (s, 3H), 1.17–1.28 (m, 2H), 1.31 (s, 3H), 1.35–1.45 (m, 1H), 1.59–1.67 (m, 1H), 1.86–1.96 (m, 2H), 2.29 (app. t, $J = 5.2$ Hz, 1H), 2.46 (dddd, $J = 14.0, 9.4, 6.8, 1.3$ Hz, 1H), 2.64 (dt, $J = 15.0, 2.2$ Hz, 1H), 3.52 (d, $J = 11.2$ Hz, 1H), 3.67 (ddd, $J = 12.1, 9.6, 3.5$ Hz, 1H), 4.00 (d, $J = 11.2$ Hz, 1H), 4.87–5.00 (m, 2H), 5.59 (ddt, $J = 17.2, 10.1, 7.0, 7.0$ Hz, 1H), 9.51 (d, $J = 5.7$ Hz, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ -1.9, -1.68, 18.5, 18.8, 23.6, 26.0 (3C), 27.3, 30.2, 33.6, 34.5, 36.5, 38.2, 43.7, 44.0, 59.3, 64.7, 73.1, 77.2, 117.6, 129.0, 135.5, 201.8, 209.0. HRMS Calculated for $[\text{C}_{25}\text{H}_{42}\text{NaO}_4\text{Si}]^+$: 457.2745, Found: 457.2759.

Tricarbonyl 30

Ketoaldehyde **29** (134 mg, 0.31 mmol) was dissolved in a mixture of *N,N*-dimethylformamide and water (7:1, 4 mL), and to this was added palladium dichloride (5 mg, 28 μmol) and copper (II) chloride dihydrate (53 mg, 0.31 mmol). The reaction mixture was then stirred under a balloon of oxygen for 1 hour. Filtration through celite followed by evaporation under high vacuum gave a residue which was subjected to column chromatography (1:20, ether : dichloromethane) affording tricarbonyl **30** (70 mg, 50%) as a colorless low melting wax. ^1H NMR (400 MHz, C_6D_6) δ 0.10 (s, 3H), 0.12 (s, 3H), 0.69 (td, $J = 13.3, 4.9$ Hz, 1H), 0.81 (s, 3H), 0.82–0.99 (m, 4H), 1.04 (s, 9H), 1.06 (s, 3H), 1.07–1.14 (m, 1H), 1.16 (s, 3H), 1.30–1.37 (m, 1H), 1.62 (s, 3H), 2.15 (app. t, $J = 4.9$ Hz, 1H), 2.21 (dd, $J = 18.2, 5.6$ Hz, 1H), 2.66–2.71 (m, 1H), 2.74 (dd, $J = 18.2, 6.8$ Hz, 1H), 3.54 (d, $J = 11.0$ Hz, 1H), 4.18 (ddd, $J = 12.1, 6.7, 5.6$ Hz, 1H), 4.36 (d, $J = 11.0$ Hz, 1H), 9.34 (d, $J = 5.5$ Hz, 1H). ^{13}C NMR (100 MHz, C_6D_6) δ -2.3, -1.6, 18.8, 19.2, 23.6, 26.3 (3C), 27.5, 29.8, 30.2, 34.2, 36.3, 39.1, 39.8, 43.6, 43.9, 44.0, 60.4, 65.3, 72.8, 77.5, 201.0, 204.8, 209.0. HRMS Calculated for $[\text{C}_{25}\text{H}_{42}\text{NaO}_5\text{Si}]^+$: 473.2694, Found: 473.2684.

3-OTBS-Vibsanin E 31

A suspension of [(3-methylbut-2-enyloxy)methyl]triphenylphosphonium chloride^{11h} (127 mg, 0.31 mmol) in anhydrous tetrahydrofuran (5 mL) under an argon atmosphere was sonicated for 10 minutes until a uniform milky dispersion had formed. The mixture was then cooled to -78°C and a solution of sodium bis(trimethylsilyl)amide solution (340 μL , 0.34 mmol, 1M solution in THF) was added strictly dropwise. The brightly orange coloured

reaction mixture was stirred for 10 minutes then a solution of tricarbonyl **30** (70 mg, 0.16 mmol) in anhydrous tetrahydrofuran (5 mL) was added dropwise and after complete addition the solution turned colourless. The reaction was stirred for 2 minutes then the mixture was poured onto saturated ice-cold sodium bicarbonate (5 mL) and extracted with diethyl ether (3 × 15 mL). The combined organic layer was washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by flash chromatography (1:10, ethyl acetate : pet. spirit) affording **31** (34 mg, 40%) as a colourless paste. ¹H NMR (400 MHz, C₆D₆) δ 0.03 (s, 3H), 0.09 (s, 3H), 0.74 (ddd, *J* = 13.5, 13.3, 4.8 Hz, 1H), 0.81–0.87 (m, 1H), 0.85 (s, 3H), 0.90–0.99 (m, 2H), 1.01 (s, 9H), 1.12–1.29 (m, 2H), 1.13 (s, 3H), 1.20 (s, 3H), 1.36 (d, *J* = 1.3 Hz, 3H), 1.67 (app. t, *J* = 11.7 Hz, 1H), 1.75 (s, 3H), 2.04 (d, *J* = 1.2 Hz, 3H), 2.22 (app. t, *J* = 4.0 Hz, 1H), 2.52 (dd, *J* = 18.4, 3.7 Hz, 1H), 2.69 (dd, *J* = 18.3, 8.6 Hz, 1H), 2.77 (dt, *J* = 14.9, 2.1 Hz, 1H), 3.55 (d, *J* = 11.0 Hz, 1H), 4.13 (ddd, *J* = 12.1, 8.6, 3.8 Hz, 1H), 4.43 (d, *J* = 11.0 Hz, 1H), 5.34 (dd, *J* = 12.0, 11.7 Hz, 1H), 5.60–5.58 (m, 1H), 7.19 (d, *J* = 12.3 Hz, 1H). ¹³C NMR (100 MHz, C₆D₆) δ –2.5, –1.6, 18.7, 19.5, 20.3, 23.7, 26.2 (3C), 27.0, 27.6, 30.0, 31.5, 34.9, 36.3, 39.4, 41.6, 43.3, 44.1, 45.3, 48.3, 65.2, 72.9, 77.2, 115.2, 116.7, 135.4, 159.6, 163.3, 205.5, 210.6. HRMS Calculated for [C₃₁H₅₀NaO₆Si]⁺: 569.3269, Found: 569.3251.

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References

1. Fukuyama Y, Minami H, Kagawa M, Kodama M, Kawazu K. *J. Nat. Prod* 1999;62:337. [PubMed: 10075780]
2. Fukuyama Y, Minami H, Fujii H, Tajima M. *Phytochemistry* 2002;60:765.
3. Fukuyama Y, Esumi T. *J. Org. Syn. Chem. (Japan)* 2007;65:585.
4. Wang L-Q, Chen Y-G, Xu J-J, Liu Y, Li X-M, Zhao Y. *Chem. Biodiversity* 2008;5:1879.
5. Fukuyama Y, Morisaki M, Minoshima Y, Minami H, Takahashi H, Asakawa Y. *Lett. Org. Chem* 2004;1:189.
6. Fukuyama Y, Kubo M, Fujii T, Matsuo A, Minoshima Y, Minami H, Morisaki M. *Tetrahedron* 2002;58:10033.
7. Cryle MJ, Stok JE, De Voss JJ. *Aust. J. Chem* 2003;56:749.
8. Schwartz BD, Denton JR, Lian Y, Davies HML, Williams CM. *J. Am. Chem. Soc* 2009;131:8329–8332. [PubMed: 19445507]
9. Schwartz BD, Denton JR, Davies HML, Williams CM. *Aust. J. Chem.* accepted.
10. a) Davies HML, Loe Ø, Stafford DG. *Org. Lett* 2005;7:5561. [PubMed: 16320991] b) Nikolai J, Loe Ø, Dominiak PM, Gerlitz OO, Autschbach J, Davies HML. *J. Am. Chem. Soc* 2007;129:10763. [PubMed: 17691775]
11. a) Gallen MJ, Williams CM. *Org. Lett* 2008;10:713. [PubMed: 18247495] b) Gallen MJ, Goumont R, Clark T, Terrier F, Williams CM. *Angew. Chem. Int. Ed* 2006;45:2929. c) Gallen MJ, Williams CM. *Eur. J. Org. Chem* 2008;4697. d) Tilly DP, Williams CM, Bernhardt PV. *Org. Lett* 2005;7:5155. [PubMed: 16268526] e) Heim R, Wiedemann S, Williams CM, Bernhardt PV. *Org. Lett* 2005;7:1327. [PubMed: 15787498] f) Schwartz BD, Tilly DP, Heim R, Wiedemann S, Williams CM, Bernhardt PV. *Eur. J. Org. Chem* 2006;3181. g) Schwartz BD, Williams CM, Bernhardt PV. *Beilstein J. Org. Chem* 2008;4(No. 34) h) Schwartz BD, Williams CM, Anders E, Bernhardt PV. *Tetrahedron* 2008;64:6482. i) Chen AP-J, Williams CM. *Org. Lett* 2008;10:3441. [PubMed: 18620414]
12. For recent examples of selective C—H hydroxylation applied to natural product synthesis, see: (a) Chen K, Baran PS. *Nature* 2009;459. in press. (b) Kim J, Ashenhurst JA, Movassaghi M. *Science*

- 2009;324:238. [PubMed: 19359584] (c) Chen MS, White MC. Science 2007;318:783. [PubMed: 17975062] (d) Wender PA, Hilinski MK, Mayweg AVW. Org. Lett 2005;7:79. [PubMed: 15624982]
13. Koser GF, Relenyi AG, Kalos AN, Rebrovic L, Wettach RH. J. Org. Chem 1982;47:2487–2489.
14. Davis FA, Chattopadhyay S, Towson JC, Lal S, Reddy T. J. Org. Chem 1988;53:2087–2089.
15. Rubottom GM, et al. Tetrahedron Lett 1974:4319.
16. a) Anders E, Gassner T. Angew. Chem. Int. Ed 1982;21:289. b) Anders E, Gaßner T. Angew. Chem. Suppl 1982:675. c) Anders E, Gassner T. Angew. Chem. Int. Ed 1983;22:619. d) Anders E, Gaßner T. Chem. Ber 1984;117:1034. e) Anders E, Gaßner T, Stankowiak A. Chem. Ber 1985;118:124. f) Anders E, Clark T, Gaßner T. Chem. Ber 1986;119:1350.
17. a) Linderman RJ, Godfrey A, Horne K. Tetrahedron 1989;45:495. b) Mander LN, Thomson RJ. J. Org. Chem 2005;70:1654. [PubMed: 15730285]
18. a) Kadota I, Yamamoto Y. J. Org. Chem 1998;63:6597. b) Nicolaou KC, Reddy KR, Skokotas G, Sato F, Xiao X-Y. J. Am. Chem. Soc 1992;114:7935.

Figure 1.
 α -Hydroxylated and related vibsane family members

24 **26**

27

Figure 2.

X-Ray crystal structure analysis of compounds **24**, **26** and **27** at the 30% ellipsoid probability level

Scheme 1.

Scheme 2.

Scheme 3.

Scheme 4.

Scheme 5.