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Synthesis of the non-classical acetogenin mucocin: a modular approach based on olefinic coupling reactions†

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A three component modular synthesis of the potent antitumor agent mucocin, based on olefinic coupling reactions, is described. A cross-metathesis on tetrahydropyran and tetrahydrofuran alkene components was used to assemble a stereochemically complex, non-adjacently-linked bicyclic ether. The latter was elaborated to a sulfone and partnered with a butenolide aldehyde component in a Julia–Kocienski olefination to provide the mucocin framework, which was converted to the natural product after hydrogenation and alcohol deprotection.

Introduction

The tetrahydrofuran (THF) containing acetogenins are known for their potent antitumor properties.[1] The mechanism of action has been linked to inhibition of the NADH–ubiquinone oxidoreductase (complex I) of the mitochondrial electron transport system, as well as the ubiquinone-linked NADH oxidase in the plasma membrane of specific cancer cell lines.[2] Growth inhibition has also been observed for certain multi-drug resistant tumors.[3] Mucocin **1**[4] belongs to the acetogenin subgroup that contains two non-adjacent cyclic ether residues connected by a 1,4-dihydroxybutyl linker (Fig. 1). Mucocin is unique in that it comprises a THF and a tetrahydropyran (THP) residue, unlike other congeners which contain two THF rings. In spite of this structural variation, mucocin displays activity that is similar to other members of this subgroup. For example, **1** showed selective inhibitory effects against A-549 (lung cancer) and PACA-2 (pancreatic cancer), with potencies up to 10 000 times that of adriamycin.[4] That different non-adjacently-linked THF–THP and THF–THF analogues like **1** and bullatanocin **5**, and adjacently-linked bis-THF acetogenins, show comparable activity suggests that there is a relatively wide structure–activity tolerance with respect to the constitution of the bis-ether segment in these molecules.[5]

From a synthetic standpoint, non-adjacently-linked structures like **1** and **5** are attractive structure–activity probes because of the possibility of generating, in a convergent fashion, analogues with different combinations of THF and THP rings. Since activity also depends on the length and degree of hydroxylation of the linker that connects the cyclic ether segment to the butenolide, a triply convergent synthesis from individual cyclic ether and butenolide precursors is appealing. In this vein, we have previously reported a three component synthesis of bullatanocin **5**.[6] This synthesis entailed the Wittig coupling of a butenolide segment with a stereochemically complex bis-THF component, which was asembled *via* an olefin cross-metathesis of two relatively simple THF precursors. Herein, we describe the potential generality of this methodology in the synthesis of mucocin.[7]

Results and discussion

Our retrosynthetic analysis relates mucocin to three precursors: THP and THF alkenes **2** and **3**, and butenolide aldehyde **4** (Fig. 1). Components **3** and **4** are common to mucocin and bullatanocin, and their syntheses are described in our earlier report on the latter.[6] The pseudosymmetry in the C15–C20 segment of mucocin suggested that **2** and **3** could emmanate from a central precursor. Accordingly, aldehyde **6** (five steps from 3-hydroxy-1,4-pentadiene), which was previously used for **3**, was chosen as the starting material for **2** (Scheme 1). Addition of the anion derived from dithiane **7**, to **6**, gave an approximately

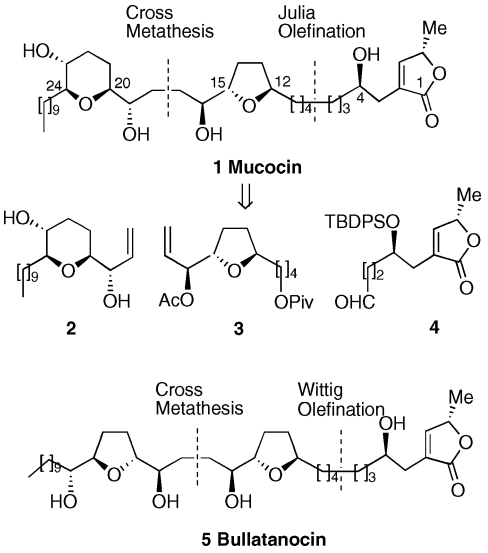
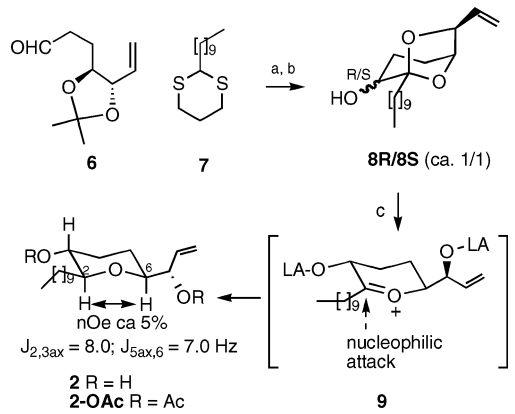


Fig. 1 Retrosynthesis for mucocin.



Scheme 1 *Reagents and conditions*: (a) **7**, BuLi, THF then **6**; (b) $Hg(ClO_4)_2$, THF, two steps, 63%; (c) **8*R***, Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −30 °C, 80%.

† Electronic supplementary information (ESI) available: ^1H and ^{13}C NMR charts for selected compounds and comparison of spectra of the final product and mucocin. See http://dx.doi.org/10.1039/b504937g

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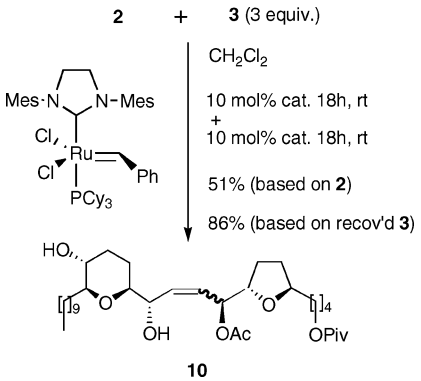
1 : 1 mixture of alcohol epimers, which was chromatographically inseparable. Treatment of this mixture with mercuric perchlorate resulted in hydrolysis of both the dithiane and acetal residues and concomitant formation of a mixture of bicyclic acetals **8*R*** and **8*S*** in 63% yield over two steps. Chromatography of this mixture provided the required acetal **8*R*** and the undesired isomer **8*S*** in similar amounts. Exposure of **8*R*** to triethylsilane and boron trifluoride etherate at low temperature afforded the THP alkene precursor **2** for the cross-metathesis step. The stereochemistry of **2** was assigned from J_{vic} values and NOE data for the diacetate derivative. The stereochemistry of reductive cleavage of acetal **8*R*** is consistent with axial attack on an oxocarbenium intermediate like **9**. This trajectory of attack is well-precedented in the reaction of related oxocarbenium systems.[7d,e,8] Compound **2** was obtained in an overall yield of 25% over three steps from **6**. In comparison, the THF alkene precursor **3** was obtained in 38% yield over four steps from **6**.[6] While this route to **2** is not stereoselective, it benefits from the use of a relay intermediate (*i.e.* **6**) and straightforward synthetic procedures. In principle, it should be possible to develop more stereoselective conditions for the dithiane coupling.[9]

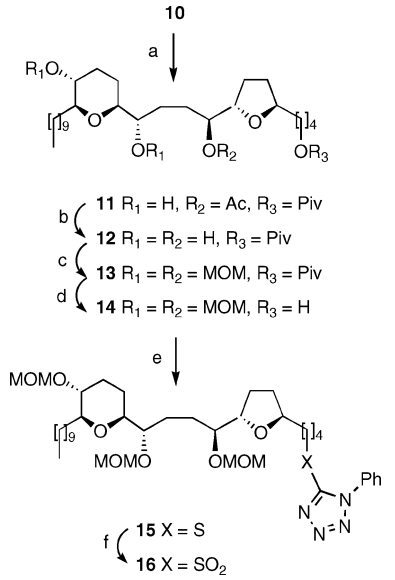
The cross-metathesis of **2** and **3** was next performed (Scheme 2). Following our earlier studies a more reactive precursor (*i.e.* allylic alcohol **2**) was paired with an excess of a less reactive partner (*i.e.* allylic acetate **3**).[10,11] Alcohol **2** was chosen as the limiting reactant because it is not as easily accessible as the reaction partner **3**. This plan was expected to favor the cross-metathesis product (together with unreacted **3**) over the homodimeric products, on the basis of statistical and reactivity considerations.[12] Indeed, reaction of **2** with three equivalents of **3** led to heterodimer **10** as the major metathesis product in 51% yield based on allylic alcohol **2** (86% based on consumed **3**), with less than 5% of homodimeric products. Alkene **10** was obtained as essentially a single compound, which was presumed to be the *E*-isomer. In view of the small amount of homodimer formation, the somewhat low conversion of **2** to **10** is likely a result of unproductive side reactions of **2**. This may be in part due to the diol nature of **2**, since higher conversions were obtained in our bullatanocin synthesis in which a mono-hydroxy, allylic alcohol substrate was used.



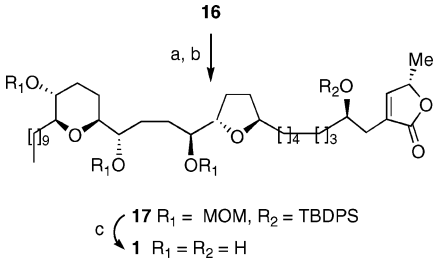
Scheme 2

For the connection of the bis-THF and butenolide segments, we explored a Julia–Kocienski strategy, in light of the success of this approach in a recent acetogenin synthesis (Scheme 3).[13] In our bullatanocin synthesis, we had adopted a Wittig methodology, which met with modest yield in the coupling step. Thus, **10** was hydrogenated to **11**, which was transformed to **14** *via* straightforward alcohol protecting group transformations. Primary alcohol **14** was converted to sulfone **16** in two additional steps through known procedures for thioether formation and oxidation.

Treatment of the anion generated from sulfone **16** with an excess of butenolide aldehyde **4** gave the desired alkene



Scheme 3 *Reagents and conditions*: (a) H_2, Pd/C, EtOAc, 99%; (b) K_2CO_3, MeOH, 79%; (c) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 90%; (d) NaOMe, MeOH, 93%; (e) Ph_3P, DIAD, 1-phenyl-1*H*-tetrazole-5-thiol, THF, 97%; (f) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 79%. DIAD = diisopropyl azodicarboxylate; *m*-CPBA = *m*-chloroperoxybenzoic acid.



Scheme 4 *Reagents and conditions*: (a) **16**, LiHMDS, THF, −78 °C then **4**; (b) H_2, $Rh(Ph_3P)_3Cl$, benzene–EtOH, 36%, two steps from **16**; (c) 5% AcCl, MeOH–CH_2Cl_2, 51%.

(Scheme 4). However the product was difficult to separate from unreacted **4** and by-products from the tetrazole residue, and purification was therefore deferred until after the subsequent step. Thus hydrogenation of the crude product in the presence of Wilkinson's catalyst gave a mixture from which the dihydro derivative **17** was easily obtained. Unfortunately the overall yield of **17** from sulfone **16** (36%) was similar to the yield for the analogous Wittig-reduction sequence that was used in the bullatanocin synthesis (40%).

Finally, removal of the alcohol protecting groups in **17**, provided a material that was essentially identical to samples of mucocin obtained from natural and synthetic sources ($[a]_D^{25}$, ^1H and ^{13}C NMR).

Conclusions

In summary, our earlier synthesis of bullatanocin and the route to mucocin described herein suggests a potentially general approach for non-adjacently-linked bis-THF/THP acetogenins. A tactical feature is the use of the operationally simple cross-metathesis protocol for the assembly of stereochemically complex bis-cyclic ether intermediates. The coupling of these core structures with butenolide or butenolide substitutes represents a second point of convergence, making the overall plan attractive for assembly of acetogenin libraries. The present execution of this methodology would benefit from improvements in the syntheses of the butenolide component and the coupling of the butenolide and bis-cyclic ether segments. Solutions to these

limitations are suggested in a number of other syntheses of the THF containing acetogenins and are currently being explored.

Experimental

Solvents were purified by standard procedures or used from commercial sources as appropriate. Petroleum ether refers to the fraction of petroleum ether boiling between 40 and 60 °C. Ether refers to diethyl ether. Unless otherwise stated thin layer chromatography (TLC) was done on 0.25 mm thick precoated silica gel 60 (HF-254, Whatman) aluminium sheets, and flash column chromatography (FCC) was performed using Kieselgel 60 (32–63 mesh, Scientific Adsorbents). Elution for FCC usually employed a stepwise solvent polarity gradient, correlated with TLC mobility. Chromatograms were observed under UV (short and long wavelength) light, and/or were visualized by heating plates that were dipped in a solution of ammonium(VI) molybdate tetrahydrate (12.5 g) and cerium(IV) sulfate tetrahydrate (5.0 g) in 10% aqueous sulfuric acid (500 mL). Optical rotations ($[\alpha]_D^{25}$ were recorded using a Rudolph Autopol III polarimeter which has a thermally jacketed 10 cm cell (path length of 1 dm) and are given in units of 10^{-1} deg cm^2 g^{-1} at 589 nm (sodium D-line). Infra-red spectra were obtained using a Perkin-Elmer 1600 FTIR spectrometer as thin film liquid samples between sodium chloride plates. Only selected absorbances (ν_{max}) are reported. NMR spectra were recorded using either Varian Unity Plus 500 or Bruker Ultra Shield instruments (^{1}H and ^{13}C; 500 and 125 MHz respectively). Spectra were recorded in $CDCl_3$ solutions with residual $CHCl_3$ as internal standard (δ_H 7.27 and δ_C 77.0 ppm). Chemical shifts are quoted in ppm relative to tetramethysilane (δs_H 0.00) and coupling constants (J) are given in Hertz. First order approximations are employed throughout. High resolution mass spectrometry was performed on an Ultima Micromass Q-Tof instrument at the Mass Spectrometry Laboratory of the University of Illinois, Urbana-Champaign.

(1*R*,2*R*,5*S*,7*S*)-Decyl-7-ethenyl-6,8-dioxabicyclo[3.2.1]octan-2-ol (8*R*) and (1*R*,2*S*,5*S*,7*S*)-decyl-7-ethenyl-6,8-dioxabicyclo[3.2.1]octan-2-ol (8*S*)

n-Butyllithium (2.5 M, 0.76 mL) was added to a solution of 2-decyl-1,3-dithiane **7** (0.62 g, 2.4 mmol) in anhydrous THF (4 mL) at 0 °C, under an atmosphere of argon. After 1 h at this temperature aldehyde **6** (0.29 g, 1.6 mmol) was added, and stirring continued at rt for 1.5 h. The reaction mixture was then diluted with ether, washed with saturated aqueous NH_4Cl and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. FCC of the residue afforded an inseparable mixture of alcohol epimers (533.0 mg, 76%): $R_f = 0.59$ (10% EtOAc in petroleum ether); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.9–5.7 (1 H, m), 5.6 (1H, d, *J* 17), 5.2 (1 H, d, *J* 9.5), 4.1–3.9 (2 H, m), 3.8–3.7 (1 H, m), 2.8–3.1 (4H, m), 2.7–2.5 (2 H, m), 2.2–1.5 (6H, m), 1.4 (3H, s), 1.4 (3H, s), 1.3 (16 H, br s), 0.90 (3 H, t, *J* 6.2).

$Hg(ClO_4)_2$ (1.00 g, 2.5 mmol) was added at 0 °C to a solution of the product mixture from the previous step (0.58 g, 1.3 mmol) in anhydrous THF (25 mL). The mixture was maintained at this temperature for 1 h, then warmed and stirred for an additional 1 h at rt. The solution was diluted with saturated aqueous $NaHCO_3$ and extracted with ether. The organic phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. FCC of the residue gave **8*R*** (158.3 mg, 41%) and **8*S*** (161.8 mg, 42%). For **8*R***: $R_f = 0.32$ (15% EtOAc in petroleum ether, neutral Al_2O_3); ν_{max}(thin film) 3462 (m), 1644 (vw); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.90–5.70 (1 H, m, C*H*=CH$_2$), 5.33 (1H, d, *J* 17.1, CH=CH*H*), 5.12 (1H, d, *J* 10.2, CH=CH*H*), 4.39 (1 H, d, *J* 7.5, *H*-7), 4.21 (1 H, br s, *H*-5), 3.54 (1H, d, $J_{2,OH}$ 10.3, *H*-2), 2.00–2.18 (3 H, m, 3 × C*H*H), 1.88–1.76 (2 H, m, 2 × C*H*H), 1.70 (1 H, m), 1.55–1.40 (3 H, m, O*H*, 2 × C*H*H), 1.40–1.25 (14 H, m, 7 × CH$_2$), 0.90 (3 H, t, *J* 6.7, C*H*$_3$); ^{13}C ($CDCl_3$, 125 MHz) δ 137.8, 116.5, 110.0, 80.0, 79.5, 68.4, 33.5, 31.9, 29.8, 29.6, 29.6, 29.6, 29.3, 25.0, 24.2, 22.7, 22.5, 14.1; *m*/*z* (ESI) 319.2242 (M + Na, $C_{18}H_{32}O_3Na$ requires 319.2249). For **8*S***: $R_f = 0.21$ (15% EtOAc in petroleum ether); ν_{max}(thin film) 3461 (m), 1644 (vw); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.90–5.70 (1 H, m, C*H*=CH$_2$), 5.32 (1H, d, *J* 17.1, CH=CH*H*), 5.11 (1H, d, *J* 10.2, CH=CH*H*), 4.39 (1 H, d, *J* 7.5, *H*-7), 4.21 (1 H, br s, *H*-5), 3.55 (1 H, ddd, *J* 6.0, 10.0 and 10.1, *H*-2), 2.14 (1 H, m, C*H*H), 1.90–1.80 (3 H, m, 3 × C*H*H), 1.71 (1 H, m, C*H*H), 1.58 (1 H, m, C*H*H), 1.48 (3 H, m, O*H*, 2 × C*H*H), 1.45–1.25 (14 H, m, 7 × CH$_2$), 0.90 (3 H, t, *J* 6.8, C*H*$_3$); ^{13}C ($CDCl_3$, 125 MHz) δ 138.0, 116.4, 110.9, 81.0, 78.8, 70.4, 33.1, 31.9, 29.9, 29.6, 29.3, 28.4, 27.6, 22.9, 22.7, 14.1.

(2*S*,3*R*,6*S*)-2-Decyl-6-[(1*S*)-1-(1-hydroxy)prop-2-en-1-yl]tetrahydro-2*H*-pyran-3-ol (2)

A mixture of $BF_3{\cdot}Et_2O$ (76 μL) and Et_3SiH (405 μL) was added dropwise to a solution of **8*R*** (0.15 g 0.50 mmol) in CH_2Cl_2 (7 mL) at −40 °C, and the reaction maintained at this temperature for 3.5 h. Saturated aqueous $NaHCO_3$ was then added and the mixture extracted with CH_2Cl_2. The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. FCC of the residue afforded **2** (118 mg, 80%): $R_f = 0.34$ (30% EtOAc in petroleum ether); ν_{max}(thin film) 3400 (s), 1646 (vw); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.90–5.70 (1 H, m, C*H* = CH$_2$), 5.31 (1H, d, *J* 17.5, CH = CH*H*), 5.10 (1H, d, *J* 10.0, CH = CH*H*), 3.87 [1 H, t, *J* 7.0, C*H*(OH)CH=CH$_2$], 3.26 (1 H, m, *H*-3), 3.13 (1 H, t, *J* 7.0, *H*-6), 3.04 (1 H, dt, t, *J* 2.0 and 8.0 *H*-2), 2.76 (1 H, br s, O*H*), 2.15 (1 H, s, O*H*), 2.05 (1 H, m, C*H*H), 1.80 (1 H, m, C*H*H), 1.62 (1 H, m, C*H*H), 1.60–1.20 (19 H, m, 19 × C*H*H), 0.85 (3 H, t, *J* 6.5, C*H*$_3$); ^{13}C ($CDCl_3$, 125 MHz) δ 136.4, 117.6, 82.1, 79.9, 75.9, 70.5, 32.6, 32.0, 31.9, 29.7, 29.6, 29.3, 26.9, 25.4, 22.7, 14.1; *m*/*z* (ESI) 321.2399 (M + Na, $C_{18}H_{34}O_3Na$ requires 321.2406).

Compound **2** was characterized as the diacetate derivative. To a solution of **2** (8 mg, 27 μmol) in ethyl acetate (1.0 mL) was added DMAP (1 mg, 10.8 μmol) and acetic anhydride (15 μL, 0.16 mmol) at rt. The reaction mixture was stirred for 1 h, quenched with MeOH, and the solvent was removed *in vacuo*. The crude product was purified by FCC to afford **2-di-*O*-acetate** (10.2 mg, 99%): $R_f = 0.30$ (10% EtOAc in petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.75 (1 H, m, C*H* = CH$_2$), 5.27 [3 H, m, C*H*(OH), CH = C*H*$_2$], 4.43 (1 H, ddd, J 4.0, 9.5 and 10, *H*-3), 3.37 (1 H, br dd, J 7.0 and 8.5, *H*-6), 3.17 (1 H, dt, J 2.0 and 9.5, *H*-2), 2.16 (1 H, m, C*H*H), 2.05, 2.00 (3 H ea, both s, 2 × C*H*$_3$CO), 1.63 (1 H, m, C*H*H), 1.56–1.20 (20 H, m, 20 × C*H*H), 0.85 (3 H, t, *J* 6.0, C*H*$_3$).

Cross-metathesis of 2 and 3: (5*R*,8*S*,9*S*,12*S*,13*S*,16*R*,17*S*)-5,8:13,17-dioxido-9-acetoxy-1-pivaloxy-10-heptacosan-12,16-diol (10)

Grubb's catalyst second generation (17 mg, 20 μmol) in CH_2Cl_2 (2 mL) was injected at rt into a degassed solution of diol **2** (60 mg, 0.2 mmol) and acetate **3** (197 mg, 0.6 mmol) in CH_2Cl_2 (12 mL). After 18 h at this temperature, additional catalyst (17 mg, 20 μmol) in CH_2Cl_2 (1 mL) was introduced. The mixture was stirred for an additional 18 h at rt, then quenched by addition of DMSO (150 μL), stirred for an additional 18 h and concentrated *in vacuo*. The residue was purified by FCC to afford **10** (61 mg, 86% based on recovered **3**, 51% relative to **2**) and recovered **3** (159 mg). For **10**: $R_f = 0.26$ (30% EtOAc in petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.76 (2 H, m, C*H*=C*H*), 5.26 (1 H, m, *H*-9), 4.06, 3.93 (3 H, 2 H respectively, both m, C*H*$_2$-1, *H*-5, 8, 12), 3.29 (1 H, m, *H*-16), 3.17 (1 H, m, *H*-13), 3.08 (1 H, dt, *J* 2.3 and 8.8, *H*-17), 2.80 (1 H, br s, O*H*), 2.05 (3 H, s, C*H*$_3$CO), 2.00 (2 H, m, 2 × C*H*H), 1.85 (1 H, m, C*H*H), 1.75–1.30 (30 H, m, O*H*, 29 × C*H*H), 1.20 [9 H, s, (C*H*$_3$)$_3$C], 0.90 (3 H, t, *J* 6.8, C*H*$_3$-24); ^{13}C ($CDCl_3$, 125 MHz) δ 178.6, 170.2, 132.5, 127.9, 82.2, 79.9, 79.3, 79.1, 75.5, 74.7, 70.4, 64.2,

38.7, 35.1, 32.5, 32.0, 31.9, 31.8, 29.8, 29.7, 29.6, 29.3, 28.6, 28.1, 27.2, 26.9, 25.4, 22.7, 22.6, 14.1; *m/z* (ESI) 619.4167 (M + Na, $C_{34}H_{60}O_8Na$ requires 619.4186).

(5*R*,8*S*,9*S*,12*S*,13*S*,16*R*,17*S*)-5,8:13,17-Dioxido-9-acetoxy-1-pivaloxy-heptacosan-12,16-diol (11)

A mixture of alkene **10** (86 mg, 0.14 mmol) and 10% Pd/C (86 mg) in ethyl acetate (10 mL) was stirred under an atmosphere of hydrogen (balloon) at rt, for 18 h. The suspension was then filtered through Celite and the filtrate concentrated under reduced pressure. FCC of the residue provided **11** (86.7 mg, 99%): $R_f = 0.26$ (30% EtOAc in petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.90 (1 H, m, *H*-9), 4.07 (t, 2H, *J* 6.6, C*H*$_2$-1), 4.0 (1 H, apparent q, *J* 6.8, *H*-8), 3.9 (1 H, m, *H*-5), 3.5 (1 H, m, *H*-12), 3.3 (1 H, m, *H*-16), 3.1 (1 H, m, *H*-13), 3.06 (1 H, dt, *J* 2.1 and 8.8, *H*-17), 2.59 (1 H, d, *J* 3.3, O*H*), 2.12 (1 H, m, C*H*H), 2.10 (3 H, s, C*H*$_3$CO), 1.99 (2 H, m, 2 × C*H*H), 1.86 (1 H, m, C*H*H), 1.81–1.23 (33 H, m, O*H*, 32 × C*H*H), 1.20 [9 H, s, (C*H*$_3$)$_3$C], 0.90 (3 H, t, *J* 6.8, C*H*$_3$-24); ^{13}C ($CDCl_3$, 125 MHz) δ 178.6, 171.0, 82.0, 80.0, 79.3, 79.0, 75.0, 73.1, 70.5, 64.3, 38.7, 35.1, 32.6, 32.1, 32.0, 31.9, 29.7, 29.6, 29.3, 28.6, 28.5, 28.3, 27.2, 27.0, 26.6, 25.5, 22.7, 22.6, 21.1, 14.1; *m/z* (ESI) 621.4355 (M + Na, $C_{34}H_{62}O_8Na$ requires 621.4342).

(5*R*,8*S*,9*S*,12*S*,13*S*,16*R*,17*S*)-5,8:13,17-Dioxido-1-pivaloxy-heptacosan-9,12,16-triol (12)

A solution of acetate **11** (125 mg, 0.2 mmol) in dry methanol (13 mL) was treated with K_2CO_3 (57.7 mg, 0.4 mmol). The reaction mixture was stirred for 18 h at rt, then neutralized with 5% HCl, and concentrated under reduced pressure. The residue was extracted with EtOAc, and the organic phase was dried (Na_2SO_4), filtered, and evaporated *in vacuo*. FCC of the residue gave **12** (83.5 mg, 79%) and recovered **11** (11.4 mg). For **12**: $R_f = 0.24$ (60% EtOAc in petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.02 (2 H, t, *J* 6.5), 3.84 (1 H, m), 3.75 (1 H, apparent q, *J* 6.5), 3.42 (1 H, m), 3.38 (1 H, m), 3.21 (1 H, m), 3.10 (1 H, m), 3.00 (1 H, t, *J* 8.0), 2.79 (1 H, br s, O*H*), 1.75–2.10 (5 H, m), 1.70–1.17 (32 H, m), 1.15 (9 H, s), 0.83 (3 H, t, *J* 6.5); ^{13}C ($CDCl_3$, 75 MHz) δ 178.6, 82.3, 82.2, 80.4, 79.3, 74.0, 73.7, 70.7, 64.4, 39.0, 35.5, 33.0, 32.7, 32.3, 32.2, 30.0, 29.9, 29.6, 29.1, 29.0, 28.6, 27.5, 27.2, 25.8, 22.9, 14.4; *m/z* (ESI) 557.4404 (M + Na, $C_{32}H_{61}O_7$ requires 557.4417).

(5*R*,8*S*,9*S*,12*S*,13*S*,16*R*,17*S*)-5,8:13,17-Dioxido-9,12,16-tris(methoxymethoxy)-1-pivaloxy-heptacosane 13

MOMCl (91 μL, 1.2 mmol) was added to a solution of triol **12** (83 mg, 0.2 mmol) and *i*-Pr$_2$NEt (392 mL, 2.3 mmol) in anhydrous CH_2Cl_2 (10 mL) at 0 °C. The mixture was stirred for 24 h at rt, then diluted with saturated aqueous NH_4Cl and extracted with ether. The organic layer was washed with water and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. FCC of the residue afforded **13** (92 mg, 90%): $R_f = 0.90$ (40% EtOAc in petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.85, 4.78, 4.41, 4.70, 4.68 and 4.62 (1 H ea, all apparent d, *J* 6.8), 4.07 (2 H, t, *J* 6.6), 4.00 (1 H, m), 3.92 (1 H, m), 3.5 (2 H, m), 3.41 (3 H, s), 3.40 (3 H, s), 3.39 (3 H, s), 3.35 (1 H, m), 3.22 (1 H, m), 3.12 (1 H, dt, *J* 2.3 and 8.9), 2.2 (1 H, m), 2.00–1.90 (2 H, m), 1.81 (1 H, m), 1.80–1.30 (32 H, m), 1.22 (9 H, s), 0.90 (3 H, t, *J* 6.8); ^{13}C ($CDCl_3$, 125 MHz) δ 178.6, 97.0, 96.8, 95.4, 81.1, 81.0, 79.9, 79.5, 79.3, 79.0, 75.9, 64.3, 55.7, 55.5, 38.7, 35.4, 32.2, 32.1, 31.9, 30.1, 29.8, 29.7, 29.6, 29.3, 28.9, 28.6, 27.2, 27.0, 26.7, 26.4, 25.5, 22.8, 22.7, 14.1; *m/z* (ESI) 711.5035 (M + Na, $C_{38}H_{72}O_{10}Na$ requires 711.5023).

(5*R*,8*S*,9*S*,12*S*,13*S*,16*R*,17*S*)-5,8:13,17-Dioxido-9,12,16-tris(methoxymethoxy)-heptacosan-1-ol (14)

Sodium methoxide (37 mg, 0.7 mmol) was added to a solution of pivalate **13** (92 mg, 0.14 mmol) in anhydrous MeOH (8 mL) at rt. The mixture was heated at reflux for 12 h, then cooled to rt and neutralized with 5% HCl. Most of the methanol was evaporated under reduced pressure and the residue extracted with EtOAc. The organic layer was washed with water and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. FCC of the residue provided **14** (75 mg, 93%): $R_f = 0.28$ (40% EtOAc in petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.90–4.50 (6 H, m), 4.01 (1 H, m), 3.92 (1 H, m), 3.66 (2 H, t, *J* 6.5), 3.50 (2 H, m), 3.41 (3 H, s), 3.40 (3 H, s), 3.39 (3 H, s), 3.35 (1 H, m), 3.22 (1 H, m), 3.12 (1 H, dt, *J* 2.3 and 8.9), 2.22 (1 H, m), 2.00–1,90 (2 H, m), 1.8 (1 H, m), 1.80–1.30 (17 H, m), 1.32 (16 H, br s), 0.90 (3 H, t, *J* 6.8); ^{13}C ($CDCl_3$, 125 MHz) δ 97.0, 96.8, 95.4, 81.0, 79.9, 79.5, 79.2, 79.2, 75.9, 62.8, 55.7, 55.7, 55.5, 35.4, 32.7, 32.2, 32.1, 31.9, 30.1, 29.8, 29.7, 29.7, 29.6, 29.3, 28.5, 26.9, 26.7, 26.4, 25.5, 22.7, 22.5, 14.1; *m/z* (ESI) 627.4429 (M + Na, $C_{33}H_{64}O_9Na$ requires 627.4448).

Tetrazole thioether (15)

To a stirred solution of alcohol **14** (52 mg, 87 μmol) in THF (1.2 mL) was added PPh_3 (35 mg, 0.13 mmol) and 1-phenyl-1*H*-tetrazole-5-thiol (24 mg, 0.13 mmol). The mixture was cooled to 0 °C and DIAD (26 mL, 0.13 mmol) was then slowly introduced. The resulting yellow solution was maintained at this temperature for 5 min, then warmed to rt and stirred for an additional 0.5 h. The reaction mixture was concentrated *in vacuo*. FCC of the residue afforded **15** (64.2 mg, 97%): $R_f = 0.60$ (40% EtOAc in petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.53 (5 H, m), 4.90–4.50 (6 H, m), 3.98 (1 H, apparent q, *J* 6.5), 3.92 (1 H, m), 3.49 (2 H, m), 3.42 (2 H, t, *J* 7.4), 3.41 (3 H, s), 3.40 (3 H, s), 3.39 (3 H, s), 3.35 (1 H, m), 3.22 (1 H, m), 3.12 (1 H, dt, *J* 2.2 and 8.9), 2.22 (1 H, m), 2.05–1.90 (2 H, m), 1.90–1.30 (17 H, m), 1.31 (16 H, br s), 0.9 (3 H, t, *J* 6.7); ^{13}C ($CDCl_3$, 125 MHz) δ 154.4, 130.0, 129.8, 123.9, 97.0, 96.8, 95.4, 81.1, 81.0, 79.9, 79.5, 79.3, 78.9, 75.9, 55.7, 55.5, 35.1, 33.3, 32.2, 32.1, 31.9, 30.1, 29.8, 29.7, 29.6, 29.3, 29.2, 28.6, 27.0, 26.6, 26.4, 25.5, 25.4, 22.7, 14.1; *m/z* (ESI) 787.4652 (M + Na, $C_{40}H_{68}N_4O_8NaS$ requires 787.4656).

Sulfone (16)

To a stirred solution of thioether **15** (64 mg, 84 μmol) in CH_2Cl_2 (4 mL) was added *m*-CPBA (58 mg, 0.34 mmol) and $NaHCO_3$ (56 mg, 0.67 mmol) in one portion. The suspension was stirred for 12 h at rt, then diluted with 10% aqueous $Na_2S_2O_3$ (4 mL). The mixture was extracted with CH_2Cl_2, the organic phase washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. FCC of the residue provided **16** (39.9 mg, 79% based on recovered **14**): $R_f = 0.76$ (5% acetone in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.80 (2 H, m), 7.60 (3 H, m), 4.83, 4.78 and 4.75 (1 H ea, all apparent d, *J* 6.8), 4.70 (2 H, apparent br d, *J* 6.8), 4.62 (1 H, apparent d, *J* 6.8), 4.00 (1 H, apparent q, *J* 6.5), 3.92 (1 H, m), 3.76 (2 H, m), 3.50 (2 H, m), 3.41 (3 H, s), 3.40 (3 H, s), 3.39 (3 H, s), 3.35 (1 H, m), 3.22 (1 H, m), 3.12 (1 H, dt, *J* 2.0 and 8.8), 2.21 (1 H, m), 2.04–1.92 (4 H, m), 1.80 (1 H, m), 1.80–1.30 (14 H, m), 1.30 (16 H, br s), 0.90 (3 H, t, *J* 6.6); ^{13}C ($CDCl_3$, 125 MHz) δ 153.5, 131.4, 129.7, 125.1, 97.0, 96.8, 95.4, 81.2, 81.0, 79.8, 79.6, 79.3, 78.6, 75.9, 56.0, 55.8, 55.7, 55.5, 35.0, 32.3, 32.1, 31.9, 30.1, 29.8, 29.7, 29.6, 29.3, 28.5, 27.0, 26.6, 26.4, 25.5, 25.1, 22.7, 22.1, 14.1; *m/z* (ESI) 819.4536 (M + Na, $C_{40}H_{68}N_4O_{10}NaS$ requires 819.4554).

Julia–Kocienski coupling: protected mucocin (17)

To a solution of sulfone **16** (30 mg, 37.7 μmol) in toluene (1.5 mL) was added LiHMDS (1.0 M in THF, 98 μL) at −78 °C. After stirring the yellow mixture for 1 h, aldehyde **4** (27 mg, 62.0 μmol) in toluene (1.0 mL) was slowly added. The mixture was stirred for another 1 h at −78 °C, warmed to rt, and maintained at this temperature for an additional 1 h. The reaction was then quenched with saturated aqueous NH_4Cl and extracted

with ether. The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. FCC (25% EtOAc in petroleum ether) of the residue provided an unseparated mixture (24 mg, $R_f = 0.47$) which contained the desired alkene together with **4** and another unidentified reaction product. For alkene: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.9 (1H, d, *J* 1.2), 5.12 (1 H, m), 5.27 (1 H, m), 4.87 (1 H, m), 4.85–4.60 (6 H, m), 4.04 (1 H, m), 4.0 (1 H, m), 3.92 (1 H, m), 3.48 (2 H, m), 3.41 (3 H, s), 3.40 (3 H, s), 3.39 (3 H, s), 3.35 (1 H, m), 3.23 (1 H, m), 3.12 (1 H, dt, *J* 2.2 and 8.8), 2.45 (2 H, m), 2.22 (1 H, m), 1.30 (3 H, d, *J* 6.8), 0.90 (3 H, t, *J* 6.8).

Chlorotris(triphenylphosphine)rhodium(I) (3.9 mg) was added to a degassed solution of the material obtained from the previous step in a mixture of benzene (1.1 mL) and EtOH (0.6 mL). The reaction mixture was stirred under an atmosphere (balloon) of hydrogen for 24 h. The solvent was removed under reduced pressure, and the residue purified by FCC to give **17** (13.6 mg, 36% from **16**): $R_f = 0.47$ (25% EtOAc in petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.70–7.60 (4 H, m), 7.50–7.30 (6 H, m), 6.93 (1 H, d, *J* 1.2 Hz), 4.91 (1 H, br q, *J* 6.8), 4.86, 4.78, 4.75, 4.71, 4.70, 4.65 (1 H ea, all apparent d, *J* 6.7), 4.04 (1 H, m), 4.00 (1 H, apparent q, *J* 6.7), 3.89 (1 H, m), 3.5 (2 H m), 3.42 (3 H, s), 3.40 (3 H, s), 3.39 (3 H, s), 3.35 (1 H, m), 3.22 (1 H, m), 3.12 (1 H, dt, *J* 2.2 and 8.8), 2.46 (2 H, m), 2.23 (1 H, m), 1.95 (2 H, m), 1.80 (1 H, m), 1.75–1.20 (42 H, m), 1.34 (3 H, d, *J* 6.8), 1.06 (9 H, br s), 0.9 (3 H, t, *J* 6.8); ^{13}C ($CDCl_3$, 125 MHz) δ 173.9, 151.1, 135.8, 135.8, 135.7, 134.2, 134.1, 130.7, 129.7, 129.6, 127.6, 127.6, 97.0, 96.9, 95.4, 81.0, 79.9, 79.6, 79.3 (2C), 77.4, 77.3, 75.9, 71.8, 55.7, 55.5, 36.4, 35.9, 32.2, 32.1, 31.9, 31.8, 30.2, 29.8, 29.7, 29.6, 29.4, 29.3, 28.6, 27.0, 26.9, 26.7, 26.4, 26.2, 25.5, 24.9, 22.7, 18.9, 14.1; *m/z* (ESI) 1031.6605 (M + Na, $C_{59}H_{96}O_{11}NaSi$ requires 1031.6620).

Mucocin (1)

5% Acetyl chloride in MeOH (0.59 mL) was added at rt to a solution of **17** (13.6 mg, 13.5 μmol) in CH_2Cl_2 (1.0 mL). The mixture was stirred at this temperature for 4 h, then diluted with CH_2Cl_2, and washed with saturated aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure. FCC of the residue (EtOAc) afforded **1** (4.2 mg, 51%) and a mixture of less polar products (7.1 mg) that appeared to be partially deprotected products. For **1**: wax; $R_f =$ 0.63 (EtOAc); $[\alpha]_D^{25}$ −12.4 (*c* 0.42, CH_2Cl_2); lit[14]: −13.9 (*c* 0.11, CH_2Cl_2); ν_{max}(thin film) 3426 (s), 2834 (s), 2852 (s), 1745 (s); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.16 (1H, br s), 5.07 (1 H, dq, *J* 1.2 and 6.8), 3.94–3.82 (2 H, m), 3.83 (1 H, q, *J* 7.1), 3.50 (1 H, m), 3.45 (1 H, br t, *J* 7.3), 3.30 (1 H, m), 3.18 (1 H, m), 3.09 (1 H, dt, *J* 2.2 and 8.9), 2.85 (1 H, d, *J* 2.4, O*H*), 2.73 (1 H, br s, O*H*), 2.55 (1 H, dt, A of ABX_2, J_{AX} 1.6 and J_{AB} 15.2), 2.42 (1 H, dd, B of ABX_2, J_{BX} 8.2 and J_{AB} 15.2), 2.27 (1 H, br s, O*H*), 2.16–2.10 (1 H, m), 2.08–1.97 (2 H, m), 1.90–1.82 (1 H, m), 1.75–1.20 (41 H, m), 1.46 (3 H, d *J* 6.8), 0.9 (3 H, t *J* 6.9); ^{13}C ($CDCl_3$, 125 MHz) δ 174.55, 151.74, 131.23, 82.06, 81.92, 80.18, 79.34, 77.94, 73.79, 73.52, 70.60, 69.99, 37.40, 35.60, 33.38, 32.68, 32.40, 32.00, 31.91, 29.73, 29.69, 29.63, 29.54, 29.45, 29.41, 29.32, 28.85, 28.74, 28.35, 26.94, 26.16, 25.52, 25.48, 22.67, 19.11, 14.09; *m/z* (ESI) 639.4811 (M + Na, $C_{37}H_{67}O_8$ requires 639.4836).

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