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Total Synthesis of (±)-Hyphodermins A and D

Wendy A. Loughlin,*[,†,‡] Ian D. Jenkins,[‡] Luke C. Henderson,[‡] Marc R. Campitelli,[‡] and Peter C. Healy[†,‡]

School of Biomolecular and Physical Sciences, Griffith University, Brisbane, QLD, 4111, Australia, and Eskitis Institute for Cell and Molecular Therapies, Griffith University, Brisbane, QLD, 4111, Australia.

w.loughlin@griffith.edu.au

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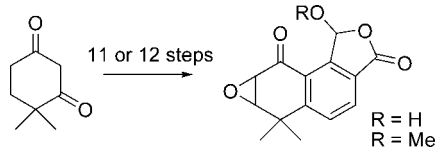
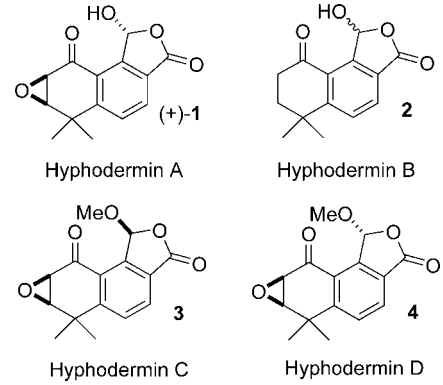


An efficient formal synthesis of (±)-hyphodermins A and D, metabolites of *Hyphoderma radula*, has been completed in 12 and 11 steps, respectively. The tricyclic carbon skeleton of enone **6** was rapidly assembled from diester **11** via an α brominationn−elimination sequence followed by anhydride formation. Regioselective reduction of the lactone group of enone **6** with LiAlH(*t*-BuO)$_3$ gave lactol **15**. Lactol **15** was converted in two steps to (±)-hyphodermin D, without the need for complex protection−deprotection strategies. Lactol **15** was converted in three steps to (±)-hyphodermin A, via the key step of epoxidation of an enone in the presence of a THP lactol. A combination of NMR and ab initio studies suggests that the structures of hyphodermin C and D should be interchanged.

Introduction

Hyphodermins A, B, C, and D (assigned as structures **1**, **2**, **3**, and **4**, respectively) are novel naphtho[1,2-*c*]furan-3,9-dione derivatives isolated in 1995 from a culture of the basidiomycete *Hyphoderma radula* (WP 2184), obtained from the trunk of a wild cherry tree in Wuppertal (Germany) as the major metabolites, in conjunction with other metabolites hyphodermins E−H.[1] Biological studies identified these metabolites as being potential drug leads for the treatment and prophylaxis of asthma, chronic bronchitis, as well as heart and CNS illnesses.[1] The hyphodermins are only available in milligram amounts from *Hyphoderma radula*, so there is considerable interest in developing syntheses for them.



We recently reported the first total synthesis of (±)-hyphodermin B (**2**)[2] but the synthesis of other major hyphodermins, such as A, C, and D (**1**, **3**, and **4**) has remained a challenge. Literature syntheses of related compounds containing an aromatic lactol structure (3-hydroxyphthalide) are limited. For example, the simple antibacterial corollosporine[3] has been made, whereas syntheses of more complex structures,[4,5] such as betolide,[6] remain unreported. Incorporation of the lactol unit, even in simple aromatic compounds, is often complicated by over-reduction,[7,8] generation of regioisomers,[8] and generation of unstable species,[9] or it occurs as a byproduct.[10] However,

* To whom correspondence should be addressed. Phone: + (07) 3735 7567. Fax: + (07) 3735 7656.
† School of Biomolecular and Physical Sciences, Griffith University.
‡ Eskitis Institute for Cell and Molecular Therapies, Griffith University.

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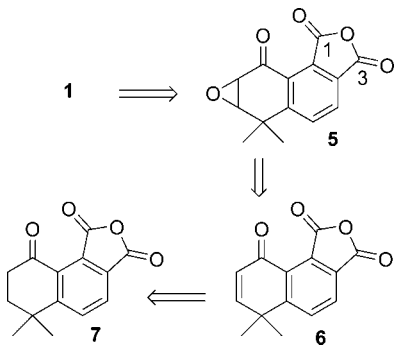
SCHEME 1. A Retrosynthetic Approach to Hyphodermin A (1)

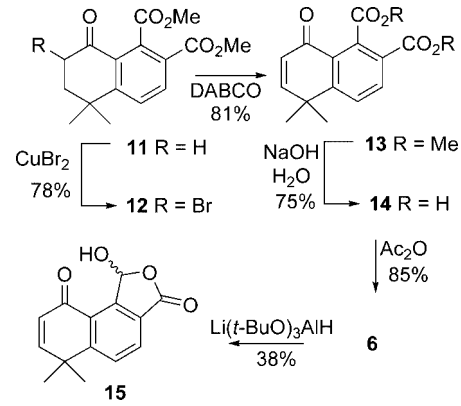


regioselective reduction of anhydride **7** was exploited in the synthesis of (±)-hyphodermin B (**2**).[2] Few literature syntheses exist of related compounds containing an aromatic conformationally rigid cyclic α,β-epoxy ketone. For example, epoxidation of conformationally rigid cyclic α,β-unsaturated ketones, with optically active hydroperoxides[11] or via a chlorohydrin,[12] give poor to moderate yields of the corresponding epoxy ketone. The biological activity and unique skeleton incorporating the 3-hydroxyphthalide and adjacent aromatic conformationally rigid cyclic α,β-epoxy ketone make hyphodermins A, C, and D (**1**, **3**, and **4**) challenging and important synthetic targets. There is only one other example in the literature of a compound that contains both an α-epoxycyclohexanone and a lactol, and it has not been synthesized.[13] Herein we report the first total synthesis of (±)-hyphodermins A and D (from commercially available 4,4-dimethylcyclohexan-1,3-dione), which represents the first successful synthesis of a molecule that contains this unique combination of reactive functional groups.

Results and Discussion

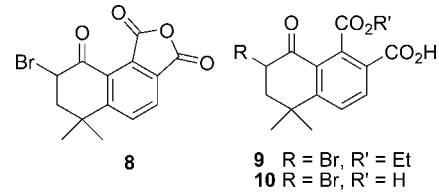
The previous synthesis of hyphodermin B (**2**)[2] had provided us access to the intermediate anhydride **7**. Initially we considered that conversion of anhydride **7** to enone **6**, followed by epoxidation to give **5** and subsequent reduction, would provide a facile route to hyphodermin A (**1**, Scheme 1). Whereas in the synthesis of the massileunicellins, an epoxy ketone intermediate was selectively reduced by LiAlH(*t*-BuO)$_3$ to the corresponding epoxy alcohol,[14] no precedent exists for the reduction of an epoxy ketone anhydride to an epoxy ketone lactol. To check the validity of the proposed reduction of epoxy ketone anhydride **5**, molecular modeling was carried out at the HF/6-31G* level

SCHEME 2. Synthetic Approach to Lactol 15



by using Spartan '04.[15] Analogous to our previous study with anhydride **7**,[2] the C1 carbon of **5** was the most electron deficient carbonyl and thus most likely to undergo reduction.

Treatment of anhydride **7** either with phenylselenium chloride then hydrogen peroxide[16] or with DDQ[17] gave complex mixtures. Installation of the α,β-double bond via a β-hydrohalo elimination was an alternative, and would require the α-bromo anhydride **8**. Treatment of anhydride **7** with NBS in THF/CCl_4 gave α-bromo anhydride **8** (19%). Addition of anhydride **7** (in $CHCl_3$) to a solution of copper(II) bromide in EtOAc at reflux gave the bromoethyl ester **9** (52%). The solid state structure of **9** was determined by X-ray crystallography (see the Supporting Information). Repeating the latter reaction in THF resulted in the formation of α-bromo anhydride **8** (20%) and bromo diacid **10** (35%). Treatment of anhydride **7** with elemental bromine[18] in THF at rt gave exclusively bromo anhydride **8** (64%).



Treatment of the anhydride **8** with potassium *tert*-butoxide gave a complex mixture along with recovered **8** (29%). Similar results were obtained with 2,6-lutidine, while DABCO or DBU gave diacid **14** (13–22%) as part of a complex mixture. It was clear that selective dehydrobromination was not possible in the presence of the anhydride moiety, so we turned our attention to the corresponding dimethyl ester **11**.[2] α bromination of diester **11** with either bromine or copper(II) bromide in MeOH gave bromo diester **12** in 50% or 78% yield, respectively. Treatment of bromo diester **12** with DABCO gave unsaturated diester **13** (81%), which was hydrolyzed with sodium hydroxide to diacid **14** (75%). The synthetic route from diester **11** to diacid **14** represented a robust and clean synthesis and was used in the generation of larger quantities of **14** (8–9 g) (Scheme 2).

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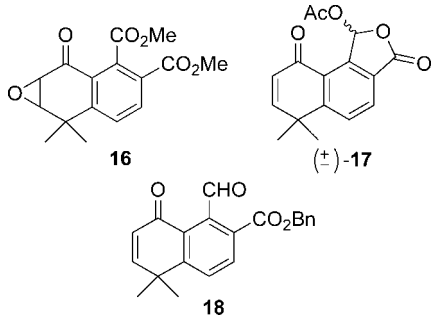
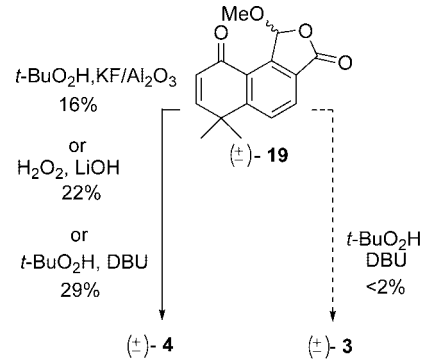
Treatment of diacid **14** with acetic anhydride in THF at 50 °C gave unsaturated anhydride **6** (85%), as a rather insoluble solid. Reduction of **6** with LiAlH(*t*-BuO)$_3$ under conditions of high dilution gave unsaturated lactol **15** with clean conversion and in an isolated yield of 38% (Scheme 2). Variation of the reaction temperature, solvent, and concentration did not increase the yield of lactol **15**. The solid-state structure of lactol **15** has been reported.[19] Treatment of **15** with dimethyldioxirane in acetone solution gave unsaturated anhydride **6** (45%) instead of hyphodermin A (**1**). This result highlighted the synthetic challenge of installation of the epoxide moiety in the presence of the lactol group.

Attempted epoxidation of the unsaturated anhydride **6** with excess dimethyldioxirane gave recovery of **6** (60%) and diacid **14** (40%). Treatment of **6** with an excess amount of *tert*-butyl hydroperoxide and DBU,[20] or with KF/Al_2O_3,[21] gave a complex mixture of compounds. The difficulty of working with **6**, compounded by its poor solubility and high susceptibility to hydrolysis, led to an examination of the more stable enone diester **13**. Treatment of **13** with *tert*-butyl hydroperoxide and DBU gave epoxy diester **16** (68%). However, attempted hydrolysis of the ester **16** with LiOH under very mild conditions (30 min at 0 °C) or with $Ba(OH)_2$ for 2 h at rt, followed by bubbling CO_2 through the solution,[22] gave a complex mixture of products. Epoxidation of enone diacid **14** was also attempted. Treatment of **14** with alkaline H_2O_2 or with *tert*-butyl hydroperoxide and NaOH gave a complex mixture of products, whereas treatment with *m*-CPBA in THF at reflux for 16 h returned unreacted starting material **14** (46%). An alternative synthetic route to hyphodermin A (**1**), involving protection of the lactol **15**, was considered.



Acetylation of lactol **15**, using acetic anhydride and DMAP, gave acetyl lactol **17** (83%). The solid state structure of acetyl lactol **17** was determined by X-ray crystallography (see the Supporting Information). Treatment of **17** with KF/Al_2O_3 and *tert*-butyl hydroperoxide gave a complex mixture of unidentified products. Attempted protection of lactol **15** by treatment with TBDMS-Cl in the presence of 2,6-lutidine[23] or with benzyl bromide followed by addition of Et_3N or with TIPS-OTf

SCHEME 3. Synthetic Approach to Hyphodermins C (3) and D (4)



followed by addition of Et_3N was unsuccessful. Under basic conditions a carboxylate intermediate is formed that is preferentially alkylated (as occurs with benzyl bromide in the formation of benzyl ester **18**).

As the C1 carbon of lactol **15** can be considered as having similar reactivity to the anomeric carbon of monosaccharides, it was proposed that acid-catalyzed glycosidation chemistry[24] might be applied to lactol **15**. Stirring lactol **15** in methanol containing dry HCl (generated in situ from the reaction between methanol and acetyl chloride) in the presence of 4 Å molecular sieves for 2 h gave the (±)-methyl "acetal" **19** (90%). Epoxidation of **19** was expected to give a mixture of hyphodermins C (**3**) and D (**4**) (Scheme 3), since based on the X-ray structure of the closely related **15**, both faces of **19** would be expected to be equally accessible (the *O*-methyl group is too remote to exert a steric effect). Treatment of **19** with *tert*-butyl hydroperoxide and DBU, gave (±)-hyphodermin D (**4**, 29%) containing a trace (~2%) of the diastereoisomeric hyphodermin C (**3**). Use of KF/Al_2O_3 and *tert*-butyl hydroperoxide in DCM or H_2O_2 and a catalytic amount of LiOH in THF/H_2O for 16 h gave a single product, (±)-hyphodermin D (**4**) (16 and 22%, respectively). Only (±)-hyphodermin D (**4**) was observed in the crude product mixture and subsequently isolated. If (±)-hyphodermin C (**3**) was formed it may have been unstable under the reaction and/or workup conditions, thus accounting for the low yields observed.

The ^{1}H and ^{13}C NMR data for isolated synthetic (±)-hyphodermin D (**4**) in $CDCl_3$ were consistent with the ^{1}H and ^{13}C NMR data reported for natural **4** isolated from *Hyphoderma radula*.[1] Although the trace of hyphodermin C (**3**) was not isolated, the ^{1}H NMR data of the crude product were consistent with the ^{1}H NMR data reported for natural **3** isolated from *Hyphoderma radula*.[1] In the original report,[1] there is no discussion as to how the relative stereochemical assignments were made of the natural products **3** and **4**. In an attempt to confirm the relative stereochemistry of synthetically derived **4**, a NOE NMR experiment was run on a pure sample of **4** in $CDCl_3$ at 400 MHz. No NOE correlation was observed between the H1 singlet of **4** at δ 6.74 ppm and the H8 epoxide doublet of **4** at δ 3.77 ppm. However, approximation of the interatomic distances [ab initio] between H1 and H8 for **4** indicated the distance between H8 and H1 was 5.033 Å, which is on the

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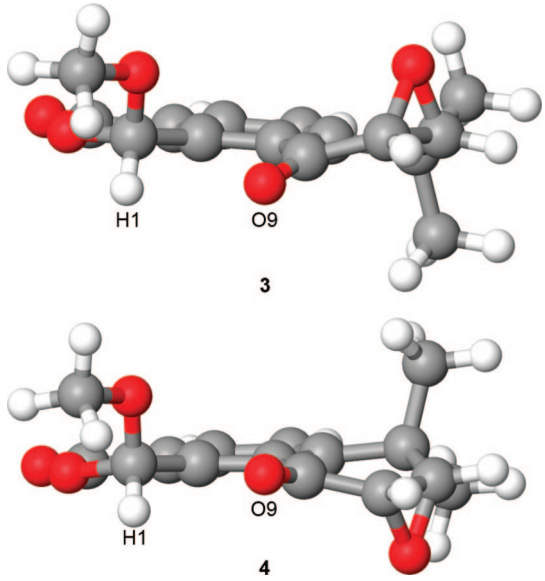


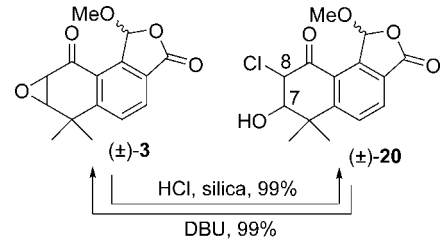
FIGURE 1. Representations of energy-minimized structures of (top) **3** and (bottom) **4** (Jaguar 7.0, B3LYP/6-31G**). O9···H1 distance: **3**, 2.625 Å; **4**, 2.611 Å.

threshold of a NOE correlation distance (5.0 Å). The model also revealed that the direct line between H1 and H8 is blocked by the ketone moiety, which makes observing a NOE correlation in **4** highly unlikely. A chemical approach was also considered. Reduction of the ketone group in **4** would introduce a stereocenter at C9, thereby providing an additional hydrogen at C9, the proximity of which to H1 would be well within NOE distances. Treatment of **4** with ethanolic $NaBH_4$ under very mild conditions (0 °C, 10 min) gave a complex mixture of products.

In the absence of X-ray structures for **3** and **4**, NMR shift analysis and ab initio calculations were carried out. In the ^{1}H NMR of synthetic **3** and **4**, H1 of **4** (δ 6.74 ppm) is downfield of H1 of **3** (δ 6.43 ppm), whereas the *O*-methyl group of **4** (δ 3.7 ppm) is upfield of the *O*-methyl of **3** (δ 3.82 ppm).[25] This is explained if the deshielding zone of the ketone carbonyl group[26] is orientated such that H1 is in a more deshielded zone (therefore further downfield) and the *O*-methyl group is in a less deshielded zone, (therefore further upfield) than in **3**. In support of these predictions, the ab initio calculations on structures **3** and **4** confirm that in **4**, the ketone carbonyl group moves out of the plane of the aromatic ring toward the *O*-methyl group, giving a dihedral angle of −49.8° between the carbonyl group and the H1−C1 bond, whereas in **3**, the ketone carbonyl group moves out of the plane of the aromatic ring toward H1, giving a dihedral angle of −29.7° between the carbonyl and the H1−C1 bond (Figure 1). Moreover, these calculations predict that H1 in structure **4** has a higher NMR shielding constant (25.45) than H1 in structure **3** (shielding constant 25.06), i.e., H1 in **4** is further upfield than H1 in **3**.

On the basis of these considerations (Figure 1), it is more likely that hyphodermin C, with the more upfield chemical shift for H1 (δ 6.43 ppm), has the *anti* structure **4**, and hyphodermin D (δ 6.74 ppm) the *syn* structure **3**. These assignments are

SCHEME 4. Attempted Cleavage of Methyl "Acetal"



opposite to those given in the literature.[1] Definitive proof of the structure of synthetic hyphodermin C and D could be obtained from X-ray crystallography; however, given synthetic hyphodermin D was isolated as an oil this is unlikely. For the remainder of this paper, synthetic hyphodermin D will be referred to by the more likely structure (±)-**3**, and synthetic hyphodermin C will be referred to by the more likely structure (±)-**4**.

Treatment of synthetic hyphodermin D ((±)-**3**) with HCl/silica in $CHCl_3$ gave the chlorohydrin (±)-**20** (99%) (Scheme 4). Presumably, attack of the chloride ion at C7 is hindered by the geminal dimethyl group, thus preventing the nucleophile from achieving the required trajectory to open the epoxide ring at the β-position. The formation of an α-halo species is unusual with only a few examples in the literature.[27] Analysis of the ^{1}H NMR ^3J couplings between H7 and H8 in **20** (∼12 Hz) suggested that H7 and H8 were pseudo-trans-diaxially orientated in **20**, thus implying that the chlorine and hydroxyl groups were in a pseudo-trans-diequatorial orientation. Hyphodermin D ((±)-**3**) could be quantitatively regenerated from **20** by treatment with DBU. This would occur via a (less stable) conformation in which the chlorine and hydroxyl groups adopt a pseudo-trans-diaxial arrangement. Given the apparent stability of the methyl acetal protecting group, a tetrahydropyranyl ether was examined next.

Treatment of lactol **15** with 3,4-dihydropyran in the presence of ethereal HCl gave crude tetrahydropyranyl (THP) ether **21** (91%), as a mixture of diastereomers (by NMR). Purification of **21** was complicated by rapid decomposition, so the crude THP ether **21**was reacted directly with *tert*-butyl hydroperoxide and DBU to give the THP epoxide **22**. Crude THP epoxide **22** was treated immediately with a solution of THF/aqueous HCl (5% w/w) (7:3) at rt for 5 h to give synthetic (±)-hyphodermin A (**1**, 24%; 2 steps from THP ether **21**, Scheme 5). Unfortunately, **1** was also unstable and repeated chromatography resulted in a product of ∼70% purity. Nonetheless, use of the THP protecting group has resulted in the successful conversion of lactol **15** to (±)-hyphodermin A (**1**/**23**) in three steps.

The ^{1}H and ^{13}C NMR spectra and HRMS data of synthetic hyphodermin A (**1**) in methanol-d_4 were consistent with the data reported for (+)-**1** isolated as a single diasteromer from *Hyphoderma radula*.[1] However, there was no justification given in the original report[1] for the assignment of an *anti* relative configuration of the epoxy and hydroxyl groups (structure **1**). If **22** is the *syn* product (by analogy with **3**), then cleavage of the THP group from **22** should give the *syn* lactol **23** as the initial product (Scheme 5). This could then undergo ring-opening

(25) For comparison, H1 in 3-methoxy-1(3*H*)-isobenzofuranone is at δ 6.25 ppm while the *O*-methyl group is at δ 3.61 ppm: Sloan, K. B.; Koch, S. A. M. *J. Org. Chem.* **1983**, *48*, 3777–3783.

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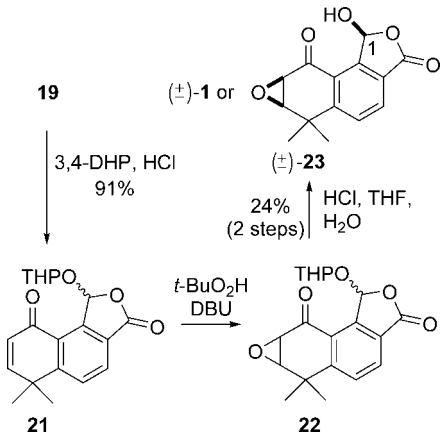
SCHEME 5. Synthetic Approach to Hyphodermin A (1)



to give an aldehyde acid followed by ring-closure on the opposite face (analogous to mutarotation) to give the *anti* compound **1**.

As in the case of hyphodermins C and D, the chemical shift of H1 would be expected to be more deshielded by the ketone carbonyl in the *syn* structure **23** than in the *anti* structure **1**. For comparison, the chemical shift of H1 in 3-hydroxy-1(3*H*)-isobenzofuranone is δ 6.65 ppm[28] whereas in hyphodermin A it is δ 6.97 ppm, a downfield shift of 0.32 ppm. The analogous H1 downfield shift observed for hyphodermin D (*syn*, (±)-**3**) versus 3-methoxy-1(3*H*)-isobenzofuranone was 0.49 ppm, whereas for hyphodermin C (*anti*, (±)-**4**) it was 0.18 ppm. A downfield shift of 0.32 ppm for hyphodermin A is between these two values, so in the absence of the second "anomer", an unequivocal assignment based on ^{1}H NMR is not possible. Ab initio calculations on structures **1** and **23** indicate that the energy difference between them is only 5 kJ/mol, with the *anti* structure **1** being the more stable of the two. This provides some evidence for the original assignment of hyphodermin A as structure **1**.

In summary, NMR studies suggest that synthetic hyphodermin C has an *anti* arrangement and synthetic hyphodermin D a *syn* arrangement of the epoxide and *O*-Me groups, respectively, which is the opposite of that reported previously. The stereochemistry of synthetic hyphodermin A also remains in doubt. X-ray structures would be required to unequivocally prove the relative stereochemistry of synthetic **1/23**, **3**, and **4**. The total synthesis of synthetic hyphodermins D (±-**3**) and A (**1/23**) was achieved from 4,4-dimethylcyclohexan-1,3-dione in 11 steps and 12 steps, respectively. With larger quantities of synthetic hyphodermins A and D (**1/23** and (±)-**3**) now in hand, further investigations into the biological activity of these compounds and their simple derivatives will be carried out.

Experimental Section

Density Functional Theory Calculations. All hybrid DFT calculations were performed with Jaguar 7.0[29] on a dual-core SGI Tezro running IRIX 6.5. Equilibrium geometries of compounds **3**, **4**, **1**, and **23** and NMR shielding constants of compounds **3** and **4** were calculated at the B3LYP/6-31G** (6d) level following preoptimization of the global minimum energy structure located by using a Macromodel 9.5[30] MMFFs conformational search. Default Jaguar optimization parameters were employed with the following additional options: symmetry = off; Grid density = fine; Diffuse = none; Accuracy level = accurate. The final geometries were characterized as an energy minimum on the potential energy surface by the absence of any negative (imaginary) vibrational frequencies at the stationary point.

7-Bromo-5,5-dimethyl-8-oxo-5,6,7,8-tetrahydronaphthalene-1,2-dicarboxylic Acid Dimethyl Ester (12). Diester **11**[2] (2.0 g, 6.9 mmol), copper(II) bromide (3.02 g, 13.8 mmol), and MeOH (25 mL) were heated at reflux for 16 h. A white precipitate formed. The suspension was filtered (celite), and the solvent removed in vacuo. Analysis of the brown foam (2.28 g) by ^{1}H NMR spectroscopy showed bromodimethyl ester **12** (1.98 g, 78%) in >95% purity. Purification by silica gel chromatography (EtOAc:hexane; 1:1) gave bromodiester **12** (1.91 g, 75%) as a yellow powder. Mp 137–140 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.44 (s, 3H), 1.51 (s, 3H), 2.45–2.65 (m, 2H), 3.91 (s, 3H), 4.03 (s, 3H), 5.08 (dd, 1H, J = 7.6, 11.3 Hz), 7.56 (d, 1H, J = 8.4 Hz), 8.21 (d, 1H, J = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.9, 30.5, 37.4, 47.8, 49.6, 52.8, 53.0, 127.3, 127.4, 127.6, 135.4, 136.8, 156.3, 164.7, 169.0, 189.5. HRMS ESI (+ve) $C_{16}H_{17}O_5{}^{79}Br$ calcd for $[M]^+$ 368.0259, found 368.0257.

5,5-Dimethyl-8-oxo-5,8-dihydronaphthalene-1,2-dicarboxylic Acid Dimethyl Ester (13). Bromo dimethyl ester **12** (1.93 g, 5.2 mmol), DABCO (3.5 g, 31.2 mmol), and MeOH (25 mL) were heated at reflux for 16 h. The methanol was removed under reduced pressure. The brown resin was dissolved in CH_2Cl_2 (25 mL) and the organic phase was washed with HCl (2 M) (2 × 30 mL), water (1 × 40 mL), and brine (3 × 25 mL) then dried ($MgSO_4$, anhydrous) and the solvent was removed in vacuo. The crude product was obtained as a brown resin (1.48 g). Analysis by ^{1}H NMR spectroscopy showed enone diester **13** (1.98 g, 78%) (1.20 g, 81%) in >90% purity. Purification by silica gel chromatography (EtOAc:hexane; 1:1) gave pure **13** as a resin. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.51 (s, 6H), 3.92 (s, 3H), 4.06 (s, 3H), 6.36 (d, 1H, J = 10 Hz), 6.90 (d, 1H, J = 10 Hz), 7.68 (d, 1H, J = 8.4 Hz), 8.24 (d, 1H, J = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.7, 38.4, 52.9, 53.0, 126.6, 126.9, 127.9, 128.4, 133.8, 136.0, 155.0, 156.5, 165.1, 169.9, 183.3. HRMS ESI (+ve) $C_{16}H_{16}O_5$ calcd for $[M]^+$ 288.0998, found 288.0997.

5,5-Dimethyl-8-oxo-5,8-dihydronaphthalene-1,2-dicarboxylic Acid (14). Dimethyl ester **13** (733 mg, 2.55 mmol) in NaOH (aq, 2 M, 15 mL) was reacted and worked up as above. Recrystallization (CH_2Cl_2/hexane) of the crude yellow foam (496 mg) gave enone diacid **14** as a white powder (385 mg, 58%). Mp 141 °C dec. ^{1}H NMR (200 MHz, acetone-d_6) δ 1.55 (s, 6H), 6.28 (d, 1H, J = 10.4 Hz), 7.09 (d, 1H, J = 9.8 Hz), 7.93 (d, 1H, J = 8.4 Hz), 8.23 (d, 1H, J = 8.6 Hz), 2 × COOH not observed. ^{13}C NMR (100 MHz, acetone-d_6) δ 29.7, 39.1, 126.8, 128.3, 128.6, 134.4, 134.5, 137.5, 155.7, 157.6, 166.5, 169.8, 183.5. Anal. Calcd for $C_{14}H_{12}O_5.2H_2O$: C 56.76; H 5.44. Found: C 56.86, H 5.27. HRMS ESI (+ve) $C_{14}H_{12}O_5Na$ calcd for $[M + Na]^+$ 283.0582, found 283.0577.

1-Hydroxy-6,6-dimethylnaphtho[1,2-*c*]furan-3,9-(1*H*,6*H*)-dione (15). (i) Enone Anhydride 6. (i) Enone Anhydride 6. Acetic anhydride (1 M in dichloromethane, 2 mL, 3.0 mmol) was added to a solution of dicarboxylic acid **14** (702 mg, 2.7 mmol) in THF (20 mL) and the solution was stirred under nitrogen atmosphere at 50 °C for 16 h. The solvent was removed in vacuo to give a yellow/brown powder. Recrystallization of the powder from THF/hexane gave 6,6-dimethyl-6*H*-naphtho[1,2-*c*]furan-1,3,9-trione **6** (555 mg, 85%) as an insoluble yellow powder that could not be purified further, and was used directly in the next step. The ^{1}H NMR spectrum was consistent with structure **6**. ^{1}H NMR (200 MHz, acetone-d_6 + methanol-d_4) δ 1.62 (s, 6H), 6.38 (d, 1H, J = 9.8 Hz), 7.16 (d, 1H, J = 10 Hz), 7.99 (d, 1H, J = 8.6 Hz), 8.05 (d, 1H, J = 8.2 Hz). **(ii) Lactol 15.** Compound **6** (307 mg, 1.21 mmol) was added to a solution of LiAlH(*t*-BuO)$_3$ (295 mg, 1.21 mmol) in THF (10 mL) at 0 °C. The solution was stirred at 0 °C for 4 h under nitrogen atmosphere. Ammonium chloride (saturated, 5 mL) and HCl (2 M, 10 mL) were added and the aqueous phase extracted

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(29) *Jaguar*, version 7.0; Schrödinger, LLC: New York, NY, 2007.
(30) *Macromodel*, version 9.5; Schrödinger, LLC: New York, NY, 2007.

with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine (2 × 40 mL) then dried ($MgSO_4$, anhyd.) and solvent was removed in vacuo. The crude product was obtained as a brown solid (222 mg). Purification by silica gel chromatography (EtOAc:hexane; 1:1) gave lactol **15** (112 mg, 38%) as colorless crystals. Mp 179–181 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.57 (s, 6H), 6.48 (d, 1H, J = 10.2 Hz), 7.04 (s, 1H), 7.08 (d, 1H, J = 10.2 Hz), 7.84 (d, 1H, J = 8 Hz), 8.08 (d, 1H, J = 8.4 Hz), OH not observed. ^{13}C NMR (50 MHz, $CDCl_3$) δ 29.0, 39.0, 97.5, 126.5, 126.7, 129.1, 130.0, 132.0, 148.3, 157.0, 159.2, 167.9, 185.7. HRMS ESI (-ve) $C_{14}H_{12}O_4$ calcd for $[M - H]^-$ 243.0657, found 243.0656.

1-Methoxy-6,6-dimethylnaphtho[1,2-*c*]furan-3,9(1*H*,6*H*)-dione (19). Acetyl chloride (0.2 mL, 221 mg, 2.8 mmol) was added to MeOH (6 mL) in the presence of a 4 Å molecular sieve. The solution was stirred for 20 min at rt under a nitrogen atmosphere. A solution of unsaturated lactol **15** (98 mg, 0.4 mmol) in MeOH (3 mL) was added and the solution stirred at rt for 2 h. The molecular sieve was removed and the solvent was removed in vacuo. Analysis of the crude yellow powder by ^{1}H NMR spectroscopy showed methyl "acetal" **19** (93 mg, 90%) in >97% purity. Mp 156 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54 (s, 6H), 3.82 (s, 3H), 6.42 (d, 1H, J = 10.4 Hz), 6.79 (s, 1H), 6.97 (d, 1H, J = 10 Hz), 7.82 (d, 1H, J = 8.4 Hz), 8.03 (d, 1H, J = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.5, 30.0, 38.7, 59.1, 105.1, 126.7, 126.9, 127.2, 128.5, 130.2, 145.2, 156.6, 157.4, 168.3, 183.8. HRMS ESI (+ve) $C_{15}H_{14}O_4Na$ calcd for $[M + Na]^+$ 281.0790, found 281.0781.

Hyphodermin D ((±)-3). *tert*-Butyl hydroperoxide (69 mg, 1.5 equiv) and DBU (0.18 mL, 183 mg, 1.5 equiv) were added to methyl acetal **19** (75 mg, 0.3 mmol) in CH_2Cl_2 (5 mL), and the solution was stirred at rt for 16 h under nitrogen. The organic phase was washed with ice-cold HCl (2 M, 20 mL) and worked up as above. The crude product was obtained as a yellow oil (67 mg). Analysis of the crude oil by ^{1}H NMR spectroscopy showed incomplete conversion of **19**. The crude oil was treated with *tert*-butyl hydroperoxide (69 mg, 1.5 equiv) and DBU (0.18 mL, 183 mg, 1.5 equiv) as above and worked up as above. The crude product was obtained as a yellow oil (70 mg). Trace peaks for hyphodermin C ((±)-**4**) in the ^{1}H NMR spectrum of the crude product were in agreement with the reported values.[1]Hyphodermin C ((±)-**4**): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.39 (s, 3H), 1.76 (s, 3H), 3.61 (d, 1H, J = 4 Hz), 3.74 (d, 1H, J = 4.4 Hz), 3.82 (s, 3H), 6.43 (s, 1H), 7.71 (d, 1H, J = 8.4 Hz), 8.06 (d, 1H, J = 8.4 Hz). Purification to 95% purity by repeated silica gel chromatography (CH_2Cl_2:Et_3N, 99:1) gave hyphodermin D ((±)-**3**) as a colorless oil (25 mg, 29%). The ^{1}H and ^{13}C NMR spectra of (±)-**3** were in agreement with the reported values.[1] (±)-**3**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.35 (s, 3H), 1.74 (s, 3H), 3.62 (d, 1H, J = 4 Hz), 3.70 (s, 3H), 3.77 (d, 1H, J = 4.4 Hz), 6.74 (s, 1H), 7.66 (d, 1H, J = 8 Hz), 8.02 (d, 1H, J = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.7, 30.1, 37.5, 55.9, 58.9, 63.0, 104.0, 125.6, 127.1, 129.79, 129.81, 145.5, 154.0, 167.9, 193.6. HRMS ESI (+ve) $C_{15}H_{15}O_5$ calcd for $[M + H]^+$ 275.0920, found 275.0916.

Hyphodermin A ((±)-1). (i) 6,6-Dimethyl-1-(tetrahydro-2H-pyran-2-yloxy)naphtho[2,1-*c*]furan-3,9(1*H*,6*H*)-dione (21). 3,4-Dihydropyran (26 mg, 28 μmol) was added to a solution of unsaturated lactol **15** (39 mg, 0.16 mmol) followed by HCl (diethyl ether solution, 1 M, 5 drops). The solution was stirred at rt under nitrogen for 16 h. The solvent, excess 3,4-dihydropyran, and HCl were removed in vacuo to give a tacky resin (62 mg). Purification via silica gel chromatography (ethyl acetate:hexane 1:1) gave THP ether **21** as a resin (48 mg, 91%), which was unstable and was used directly in the next step. The ^{1}H NMR spectrum was consistent with that of **21**. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.55 (s, 3H), 1.57 (s, 3H), 1.59–1.91 (m, 6H), 3.6 −3.70 (m, 2H), 5.35 (m, 1H), 6.40 (d, 1H, J = 10.2 Hz), 6.98 (d, 1H, J = 9.2 Hz), 7.03 (s, 1H), 7.82 (d, 1H, J = 8 Hz), 8.06 (d, 1H, J = 7.8 Hz). **(ii) (±)-Hyphodermin A ((±)-1) via THP Epoxide 22.** DBU (22 mg, 22 μL, 1 equiv), *tert*-butyl hydroperoxide (0.22 mmol, 1.5 equiv), and THP lactol **21** (48 mg, 0.146 mmol) in CH_2Cl_2 (4 mL) were reacted and worked up as above. Crude THP ether **22** was obtained as a pale yellow oil (44 mg), which rapidly decomposed upon standing or attempted purification by column chromatography, and was used directly. The yellow oil (44 mg) was dissolved in THF/HCl (5% w/w) (7:3) (10 mL) and the solution was stirred at rt for 5 h. The solution was worked up as above. The crude product was obtained as a pale yellow oil (44 mg). Purification by repeated silica gel chromatography (EtOAc:hexane; 1:1) gave impure (±)-hyphodermin A ((±)-**1**), 9 mg, 24%, 2 steps from THP ether **21** in ~70% purity). The ^{1}H and ^{13}C NMR spectra of (±)-**1** matched the reported values.[1] ^{1}H NMR (400 MHz, 95:5 d_4-methanol:$CDCl_3$) δ 1.36 (s, 3H), 1.76 (s, 3H), 3.63 (d, 1H, J = 4.4 Hz), 3.75 (d, 1H, J = 4 Hz), 6.97 (s, 1H), 7.67 (d, 1H, J = 8 Hz), 8.04 (d, 1H, J = 8.4 Hz). ^{1}H NMR (600 MHz, methanol-d_4) δ 1.35 (s, 3H), 1.73 (s, 3H), 3.74 (d, 1H, J = 4.2 Hz), 3.75 (d, 1H, J = 4.2 Hz), 6.97 (s, 1H), 7.86 (d, 1H, J = 7.8 Hz), 8.04 (d, 1H, J = 7.8 Hz). ^{13}C NMR (150 MHz, methanol-d_4) δ 24.9, 28.7, 37.7, 55.7, 63.1, 103.0, 126.1, 126.7, 129.3, 130.3, 147.4, 155.5, 170.5, 194.9. HRMS ESI (+ve) $C_{14}H_{13}O_5$ calcd for $[M + H]^+$ 261.0763, found 261.0759.

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Supporting Information Available: Additional experimental procedures; MS and FTIR data for (±)-**1**, (±)-**3**, **6**, **8**–**10**, and **12**–**21**; ^{1}H NMR spectra for **8**–**10**, **12**–**21**, (±)-**1**, and (±)-**3**; table comparing ^{1}H NMR and ^{13}C NMR data (where available)[1] of natural and synthetic hyphodermins A, C, and D (**1**, **4**, and **3**); representation of energy minimized structure, Cartesian coordinates, and computed total energy for **5**; Cartesian coordinates, computed total energy, and selected dihedral angles, and NMR shielding constants for **3** and **4**; representation of energy minimized structure, Cartesian coordinates, and computed total energy for **1** and **23**; data collection, structure solution, refinement, and crystal data for **9** and **17**; and an ORTEP plot of **9** and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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