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Efficient Formal Synthesis of (±)-Hyphodermin B

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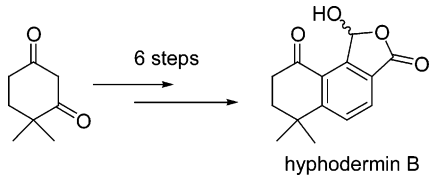

An efficient formal synthesis of hyphodermin B **1**, a metabolite of *Hyphoderma radula*, has been completed in 15% overall yield. The tricyclic carbon skeleton **3** was rapidly assembled from a novel vinyl enone via a Diels−Alder reaction, followed by dehydrogenation and anhydride formation. Selective reduction of anhydride **3** with LiAlH(*t*-BuO)$_3$ gave hyphodermin B **1** in 99% yield. The structure of hyphodermin B **1** was confirmed by X-ray crystallographic analysis. The anhydride **3**, bearing a γ-carbonyl group, displayed unexpected reactivity with the anhydride carbonyl closest to the γ-ketone being the most electrophilic site. This was confirmed by HF/6-31G* calculations. In the presence of base, **3** underwent a rearrangement to the novel lactone **16**.

Introduction

(±)-Hyphodermin B **1** is a novel naphtho[1,2-*c*]furan-3,9-dione isolated 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 metabolite in conjunction with other metabolites, hyphodermins A and C−H.[1] Biological studies identified these metabolites as being potential drug leads for the treatment and prophylaxis of asthma and chronic bronchitis as well as of heart and CNS illnesses.[1] Hyphodermin B **1** was first isolated in 1995 and reported as a racemic mixture at C1. The structure of **1** was determined by ^{1}H NMR spectroscopy,[1] but a synthesis of **1** has not been reported. Literature syntheses of related compounds containing an aromatic lactol structure (3-hydroxyphthalide) are limited. For example, the simple antibacterial corollosporine[2] (Figure 1) has been made, whereas syntheses of more complex structures such as betonicoside,[3] betonicolide,[3] betolide[4] (Figure 1), and jusmicranthin[5] remain unreported. The biological activity and novel skeleton incorporating the 3-hydroxyphthalide and adjacent ketone make hyphodermin B **1** a challenging and important synthetic target.

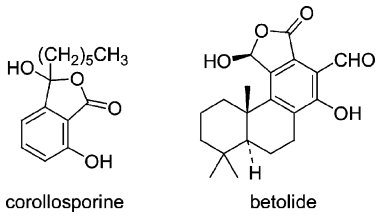

FIGURE 1. Some 3-hydroxyphthalide natural products.

Considering the synthesis of **1**, a literature survey revealed that incorporation of the lactol unit in simple aromatic compounds was not straightforward. Reduction of phthalic anhydrides was often complicated by overreduction[6,7] and generation of regioisomers.[7] Alternative routes required the lactol to be generated via unstable trimethylsiloxy isobenzofurans[8] or as the byproduct from oxidation of aromatic dialdehydes.[9] Retrosyn-

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SCHEME 1. Synthetic Approach to Hyphodermin B

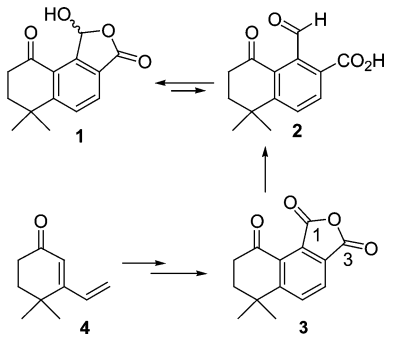


TABLE 1. Formation of Alkoxyenones 6−9 from Diketone 5

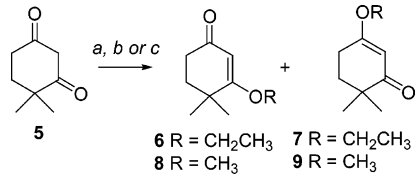
entry	reaction conditions	alcohol	products	product ratio **6/7** or **8/9**	yield %
1	10% HCl, reflux, 16 h	EtOH	**6** and **7**	1:2	47
2	10% HCl, reflux, 16 h	MeOH	**8** and **9**	1:2	39
3	*p*-toluenesulfonic acid, reflux, 90 min	MeOH	**8** and **9**	1:2.5	49
4	(a) $TiCl_4$, 15 min; (b) Et_3N, 45 min	MeOH	**8** and **9**	1:7	90
5	(a) $TiCl_4$, 15 min; (b) Et_3N, 45 min	EtOH	**6** and **7**	1:2	37

thetic analysis of hyphodermin B **1** (Scheme 1) suggested that elaboration of anhydride **3** to acid aldehyde **2**, followed by ring closure of **2** at equilibrium, could give the lactol group of hyphodermin B **1**. The ring system of anhydride **3** could be formed through a Diels−Alder reaction on enone **4** and anhydride formation from a diacid precursor. Herein, we report the first total synthesis of hyphodermin B **1** from diketone **5** via anhydride **3**.

Results and Discussion

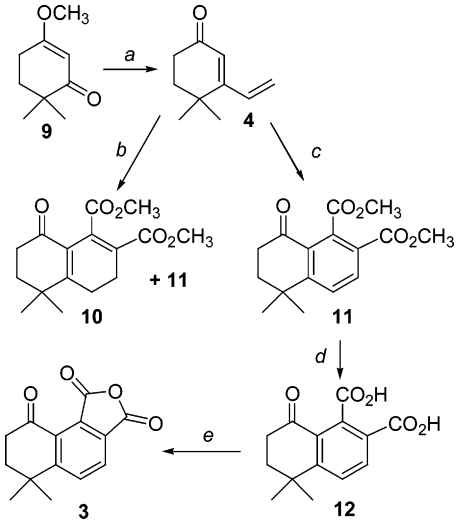
Initially, we planned to form vinylcyclohexenone **4**[10] via a 1,4-addition of vinylmagnesium bromide to ethoxyenone **6**. Ethoxyenones **6** and **7**[11] and methoxyenones **8** and **9** were obtained by treatment of diketone **5** with ethanolic HCl or methanolic HCl or methanol and *p*-toluenesulfonic acid, respectively (entries 1−3, Table 1; Scheme 2). A trial reaction of purified methoxyenone **8** with vinylmagnesium bromide led to the recovery of unreacted **8**. It was considered that 1,2-addition of the Grignard to the isomeric methoxyenone **9**, catalyzed by cerium(III) chloride,[12] might provide an alternative route to **4**. A marked improvement in the yield of methoxyenone **9** from diketone **5** was observed when the diketone **5** was treated with titanium(IV) tetrachloride in methanol[13] (entry 4, Table 1; Scheme 2). Thus, the synthesis of anhydride **3** was continued

SCHEME 2. Synthesis of Alkoxyenones 6−9[a]



[a] Reagents and conditions: (a) 10% HCl, MeOH or EtOH; (b) *p*-toluenesulfonic acid, MeOH; (c) $TiCl_4$, MeOH or EtOH, Et_3N, room temperature.

SCHEME 3. Synthesis of Anhydride 3[a]



[a] Reagents and conditions: (a) $CeCl_3$, $BrMgCH{=}CH_2$, THF, room temperature, 16 h, 93%; (b) dimethylacetylene dicarboxylate, 1% hydroquinone, toluene, reflux, 60 h; **10** 6%, **11** 17%; (c) dimethylacetylene dicarboxylate, 1% hydroquinone, toluene, reflux, 60 h then Pd/C, acetic acid, reflux, 24 h, **11** from **4** in 57%; (d) 10% NaOH, reflux, 3.5 h; 2 M HCl, 91%; (e) acetic anhydride, 50 °C, 16 h, 88%.

using methoxyenone **9**, with application of aspects of the methodology used for the synthesis of angucyclinones.[14]

Addition of cerium(III) chloride to methoxyenone **9** for 1 h followed by addition of vinylmagnesium bromide and stirring at room temperature for 12 h gave vinylcyclohexenone **4** in high yield (93%) and purity (>95%). The crude product was used immediately in the next step as it decomposes on storage or attempted chromatographic purification. Diels−Alder reaction of vinylcyclohexenone **4** with dimethylactetylene dicarboxylate in refluxing toluene for 60 h, under an atmosphere of nitrogen or air, gave a mixture of hexahydronaphthalene dimethylester **10** and tetrahydronaphthalene dimethylester **11** in a ratio of 40:60 (nitrogen; 54%) or 20:80 (air; 42%) for **10**/**11**, respectively (Scheme 3). The difference in the ratio of **10**/**11** obtained is suggestive of autoxidation of **10** occurring in situ. Various oxidation reagents have been used to dehydrogenate polycyclic hydroaromatic compounds.[15] Isolated hexahydronaphthalene dimethylester **10** was unstable upon isolation and storage but could be directly converted to tetrahydronaphthalene dimethyl-

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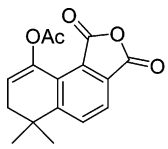
ester **11** (70%) by heating at reflux overnight with Pd on charcoal in toluene (DDQ gave no reaction). However, we found a more efficient process. A crude mixture of **10** and **11** was heated at reflux in acetic acid with Pd/C which resulted in conversion of **10** to **11**. Using the Diels−Alder reaction and then Pd/C oxidation as a two-step process, we easily converted diene **4** to tetrahydronaphthalene dimethylester **11** in 57% overall yield (Scheme 3).

Treatment of isolated hexahydronaphthalene dimethyl ester **10** with sodium hydroxide at reflux gave diacid **12** (89%). However, the problems with isolation of **10** prevented scale-up. Instead, treatment of tetrahydronaphthalene dimethylester **11** with sodium hydroxide at reflux for 3 h, followed by acidification, gave **12** (91%) (Scheme 3). This was converted to the anhydride **3** (88%) by treatment with acetic anhydride[16] at 50 °C overnight. Use of refluxing acetic anhydride with or without an acid catalyst (H_2SO_4) led to concurrent formation of the enol acetate **13** (typically 10%). In summary, anhydride **3** was made in five steps from diketone **5** and in 15% unoptimized overall yield. Elaboration of anhydride **3** to hyphodermin B **1** was examined next.



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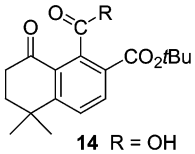
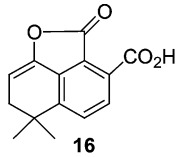


14 R = OH
15 R = H

It was envisaged that the anhydride **3** could be ring opened regioselectively with *tert*-butyl alcohol to give the acid **14** (it was assumed that C1 of anhydride **3** would be sterically hindered to attack). Subsequent reduction of the carboxylic acid of **14** to a primary alcohol followed by PCC oxidation to aldehyde **15** and TFA cleavage of *tert*-butyl ester **15** should give acid aldehyde **2**. In the event, anhydride **3** was treated with *tert*-butyl alcohol, DMAP, triethylamine, and *N*-hydroxysuccinimide and heated at reflux in toluene according to a literature procedure.[17] Surprisingly, lactone **16** was obtained along with recovery of anhydride **3** (45:55, anhydride/lactone, 48%). However, purification and full characterization of lactone **16** was complicated by partial hydrolysis of lactone **16** to diacid **12**, which occurred rapidly upon standing. The structure of **16** was further confirmed by reduction of **16** with sodium borohydride in THF and methanol to give the stable ether derivative **17**. The connectivity of ether **17** was unequivocally assigned using gCOSY, gHSQC, and gHMBC spectroscopy. In addition, methyl ester **18** was isolated and assumed to have arisen from nucleophilic attack of methanol on lactone **16**.



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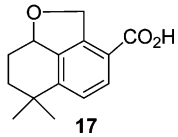

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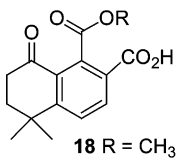

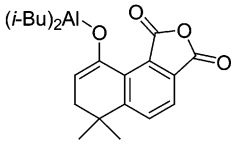

18 R = CH_3
19 R = CH_2Ph

20

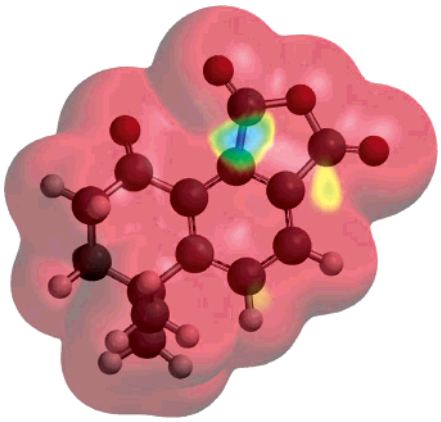

FIGURE 2. Representation of energy-minimized structure of **3** (Spartan 04, V1.0.1, HF/6-31G*). For clarity, the LUMO map has been adjusted to make only the most electron-deficient region of **3** visible (shown in blue then green).

Formation of lactone **16** also occurred in 46% yield when anhydride **3** was treated with DMAP and triethylamine in refluxing toluene in the absence of *tert*-butyl alcohol. This suggested that nucleophilic attack on anhydride **3** by DMAP followed by attack of the enol on the resultant acylpyridinium intermediate gives ring closure to lactone **16**. As the *tert*-butyl ester **14** was unable to be obtained, we turned our attention to formation of a benzyl ester, which could be selectively cleaved by catalytic hydrogenation. Treatment of anhydride **3** with sodium benzyloxide in THF gave benzyl ester **19** (24%). The regiochemistry of addition at C1 was confirmed through gCOSY, gHSQC, and gHMBC spectroscopy. The carbonyl peaks of the carboxylic acid/benzyl ester groups at C1 and C2 were coincident at 400 MHz but resolvable at 600 MHz (δ 169.0, 169.3 ppm) allowing the regiochemical assignment to be made. Because of the formation of lactone **16** and the unexpected regioselectivity of the ring opening of anhydride **3** by benzyl alcohol, modeling studies on anhydride **3** were carried out at the HF/6-31G* level using Spartan 04.[18]

The energy-minimized structure of anhydride **3** is shown in Figure 2. The LUMO was mapped onto the electron density surface and then adjusted to make only the most electron-deficient region visible. This resulted in identification of regions of **3** most susceptible to nucleophilic attack. Notably, electron deficiency is heavily centralized on C1 of the anhydride ring of **3**. The modeling results support the experimental observations seen with the reaction of anhydride **3** with methanol and benzyl alcohol. This suggested that the direct and regioselective reduction of anhydride **3** to the lactol represented by hyphodermin B **1** (Scheme 1) was feasible.

Initial attempts at reduction of the C1 carbonyl group of anhydride **3** with DIBALH at 0 °C gave 50% conversion to lactone **16** or a complex mixture. Formation of lactone **16** may be facilitated by a diisobutylaluminum enolate[19] intermediate, such as **20**, acting as a nucleophile to open and activate the anhydride for internal displacement. By changing the reducing

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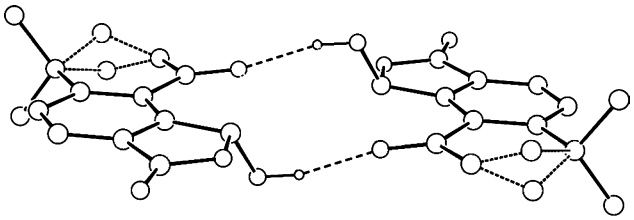

FIGURE 3. Representation of the dimeric H-bonding structure of **1** (H2···O4^{i} = 1.84, O2···O4^{i} = 2.728(6) Å, and O2−H2···O4^{i} = 165° [symmetry code (i) − x, 1 − y, 2 − z]).

agent to LiAlH(t-BuO)$_3$, we anticipated that acid/base effects should be diminished and reduction at the most electron-deficient carbonyl (C1) of anhydride **3** promoted. Anhydride **3** was reacted with LiAlH(t-BuO)$_3$ at 0 °C for 4 h, and hyphodermin B **1** was isolated as a racemic mixture in 99% yield. This result, together with the formation of **18** and **19** and the molecular modeling studies above, suggests that electronic factors are responsible for the regioselective reactions of the anhydride **3**. The ^{1}H NMR spectrum of synthetic (±)-hyphodermin B **1** in d_4-methanol was consistent with the reported ^{1}H NMR data for (±)-hyphodermin B[1] **1** isolated from *Hyphoderma radula*.

The synthetic sample of hyphodermin B **1** crystallizes from chloroform as pale yellow square plates suitable for the single-crystal X-ray structure determination. A representative view of the molecular structure of **1** is shown in Figure 3. In this structure, the benzofuranone ring system is essentially planar. The carbonyl oxygen atom O4 lies 0.24 Å out of the plane with the pseudo torsion angle Oa−C9···C9b−C1 = −12.3(5)°. Difference Fourier maps showed elongated residual electron density about the C7 atom above and below the plane of the cyclohexanone ring. This was modeled as two disordered C atoms with 50% occupancy. Residual electron density in the vicinity of the C1 proton suggested the presence of minor enantiomeric disorder in the crystal lattice. This was modelled with occupancy factors of 0.9 for the major component and 0.1 for the minor component. In the crystal lattice, pairs of molecules associate across a center of symmetry through classical $R_2^2(14)^i$ O−H···O intermolecular hydrogen-bonding interactions[20] between the hydroxy proton and the carbonyl oxygen, with H2a···O4^{i} = 1.75, O2a···O4^{i} = 2.724(5) Å, and O2a−H2a−O4^{i} = 165° (symmetry code (i) − x, 1 − y , 2 − z]).

Conclusions

Total synthesis of (±)-hyphodermin B **1** was achieved from diketone **5** in six steps and 15% overall yield. Notably, the synthesis was developed without the need for complex protection−deprotection strategies and exploited the unexpected regioselective reduction of anhydride **3**. The solid-state structure of **1** is reported for the first time. Computer modeling studies of **3** and X-ray crystallographic data for **1** provide supporting evidence for the unexpected reactivity of C1 of anhydride **3** to oxygen nucleophiles. With synthetic quantities of hyphodermin B **1** now in hand, further investigations into the biological activity of hyphodermin B **1** and its simple derivatives will be carried out.

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Experimental Section

4,4-Dimethyl-3-vinylcyclohex-2-en-1-one 4. A solution of **9** (6.28 g, 41 mmol) in anhydrous THF (20 mL) was added to cerium(III) chloride (1.1 g, 4.5 mmol). The suspension was stirred at room temperature for 1 h. Vinylmagnesium bromide was added (52 mL). The resulting solution was stirred at room temperature overnight. Ammonium chloride (saturated, 15 mL) then hydrochloric acid (2 M, 30 mL) were added, and the combined aqueous phase was extracted with ether (3 × 40 mL). The combined organic phases were washed with hydrochloric acid (1 × 40 mL), sodium bicarbonate (3 × 25 mL), and brine (3 × 30 mL) and dried ($MgSO_4$, anhydrous), and the solvent was removed in vacuo. Crude **4**[10] (5.74 mg, 93%) was obtained as an unstable dark yellow oil. Analysis by ^{1}H NMR spectroscopy showed **4** in >95% purity. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.16 (s, 6 H, 2 × CH_3), 1.84 (t, 2 H, J = 6.8 Hz, 2 × H5), 2.46 (t, 2 H, J = 6.4 Hz, 2 × H6), 5.34 (dd, 1 H, J = 1.2, 11 Hz, CH=CH_2), 5.67 (dd, 1 H, J = 1.2, 17.2 Hz, CH=CH_2), 6.04 (s, 1 H, H2), 6.46 (ddd, 1 H, J = 0.8, 11.2, 17.7 Hz, CH=CH$_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.8 (2 × CH_3), 34.5 (C5), 34.6 (C4), 37.6 (C6), 120.2 (CH=CH_2), 122.6 (C2), 134.2 (CH=CH$_2$), 166.7 (C3), 199.9 (C=O). HREIMS calcd for $C_{10}H_{14}O$ m/z 150.1045, found m/z 150.1048.

Dimethyl 5,5-Dimethyl-8-oxo-3,4,5,6,7,8-hexahydronaphthalene-1,2-dicarboxylate 10 from 4 with Reflux in Air. Dimethylacetylene dicarboxylate (116 mg, 0.813 mmol, 0.14 mL) and **4** (111 mg, 0.739 mmol) in toluene (5 mL) were heated at reflux for 60 h under an air atmosphere. The solvent was removed in vacuo. The crude mixture was obtained as an oil (254 mg) and was purified by silica gel chromatography (ethyl acetate/hexane 1:1). Fraction 1 gave **11** (37 mg, 17%) as identified by ^{1}H NMR spectroscopy. Fraction 2 gave **10** (9 mg, 6%) as an unstable yellow powder after drying. Mp 120−122 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (s, 6 H), 1.90 (t, J = 3.2 Hz, 2 H), 2.4−2.5 (m, 4 H), 2.52 (t, J = 3.4 Hz, 2 H), 3.76 (s, 3 H), 3.86 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.8, 24.8, 26.3, 34.1, 36.2, 36.3, 52.2, 52.4, 126.6, 128.1, 135.2, 166.6, 169.2, 170.7, 194.2. HREIMS calcd for $C_{16}H_{20}O_5$ m/z 292.1310, found m/z 292.1314.

Dimethyl 5,5-Dimethyl-8-oxo-5,6,7,8-tetrahydronaphthalene-1,2-dicarboxylate 11 from 4. Dimethylacetylene dicarboxylate (3.1 g, 21.8 mmol, 2.7 mL) and hydroquinone (1%) were added to a stirred solution of crude **4** (2.86 g, 19.1 mmol) in anhydrous toluene (30 mL). The resulting solution was heated at reflux in air for 60 h. The solvent was removed in vacuo to give a yellow resin. The crude product was dissolved in acetic acid (30 mL) and heated at reflux in the presence of Pd/C (10%, 600 mg) for 24 h in air. The suspension was filtered through Celite, and the filtrate was evaporated to dryness under reduced pressure. Analysis by ^{1}H NMR spectroscopy of the crude mixture obtained indicated the presence of **11**, acetic acid, and water (6.51 g). The crude mixture was purified by silica gel chromatography (ethyl acetate/hexane 50:50). Fraction 1 gave **11** as an orange viscous oil (3.14 g, 57%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.41 (s, 6 H), 2.03 (t, J = 6.6 Hz, 2 H), 2.76 (t, J = 7.4 Hz, 2 H), 3.90 (s, 3 H), 4.02 (s, 3 H), 7.57 (d, J = 8.4 Hz, 1 H), 8.17 (d, J = 8.4 Hz, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 29.9, 35.0, 35.4, 36.2, 52.8, 52.9, 126.6, 127.4, 129.2, 134.9, 136.1, 157.5, 165.1, 168.8, 196.6. Anal. Calcd for $C_{16}H_{18}O_5 \cdot H_2O$: C, 62.33%; H, 6.54%. Found: C, 62.55%; H, 6.52%.

5,5-Dimethyl-8-oxo-5,6,7,8-tetrahydronaphthalene-1,2-dicarboxylic Acid 12. Compound **11** (527 mg, 1.82 mmol) was dissolved in sodium hydroxide (10%, 10 mL), heated at reflux in air for 3.5 h, and worked up as above. Compound **12** was obtained as an orange foam (435 mg, 91%) in >95% purity after drying, as determined by analysis by ^{1}H NMR spectroscopy. Mp 266−267 °C. ^{1}H NMR (200 MHz, d_6-DMSO): δ = 1.36 (s, 6 H), 1.97 (t, J = 6.8 Hz, 2 H), 2.70 (d, J = 7.2 Hz, 2 H), 3.34 (s, 2 H), 7.69 (d, J = 8.8 Hz, 1 H), 8.03 (d, J = 8 Hz, 1 H). ^{13}C NMR (100 MHz, d_6-DMSO): δ = 29.2, 34.5, 35.0, 35.5, 126.9, 127.6, 128.4, 134.1,

136.2, 156.3, 166.4, 169.2, 196.4. HREIMS calcd for $C_{14}H_{14}O_5$ *m*/*z* 262.0841, found *m*/*z* 262.0843.

6,6-Dimethyl-7,8-dihydronaphtho[1,2-*c*]furan-1,3,9(6*H*)-trione 3. Compound **12** (1.68 g, 6.41 mmol) was dissolved in acetic anhydride (12 mL), and the solution was heated to 50 °C overnight under a nitrogen atmosphere. The acetic anhydride was removed in vacuo to give a black resin. The crude resin was azeotroped with toluene (20 mL) to give **3** (1.37 g, 88%) as a gray powder. Mp 229−231 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.46 (s, 6 H), 2.12 (t, J = 7.0 Hz, 2 H), 2.90 (t, J = 7.2 Hz, 2 H), 7.96 (d, J = 8.0 Hz, 1 H), 8.10 (d, J = 8.2 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.7, 35.7, 35.8, 36.5, 128.4, 131.8, 132.6, 134.1, 136.9, 159.3, 161.3, 162.4, 194.8. HREIMS calcd for $C_{14}H_{12}O_4$ *m*/*z* 244.0736, found *m*/*z* 244.0735.

Hydroxy-6,6-dimethyl-7,8-dihydronaphtho[1,2-*c*]furan-3,9-(1*H*,6*H*)-dione (Hyphodermin B) 1. Compound **3** (50 mg, 0.21 mmol) was added to a solution of lithium tri-*tert*-butoxyaluminohydride (53 mg, 0.21 mmol) in THF (15 mL) at 0 °C. The solution was stirred at 0 °C for 4 h under a nitrogen atmosphere. Ammonium chloride (saturated, 5 mL) and hydrochloric acid (2 M, 10 mL) were added, and the aqueous phase was extracted with DCM (3 × 30 mL). The combined organic layers were washed with brine (2 × 40 mL) and dried ($MgSO_4$), and solvent was removed in vacuo to give a brown foam. The crude foam was purified by silica gel flash chromatography (ethyl acetate/heptane; 1: 1). Compound **1** was obtained as a white powder (51 mg, 99%). Mp dec 200 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.46 (s, 3 H), 1.47 (s, 3 H), 2.11 (t, J = 7 Hz, 2 H), 2.84 (t, J = 7.2 Hz, 2 H), 6.95 (s, 1 H), 7.74 (d, J = 8.2 Hz, 1 H), 8.03 (d, J = 7.8 Hz, 1 H). ^{1}H NMR (200 MHz, CD_3OD): δ = 1.47 (s, 3 H), 1.49 (s, 3 H), 2.11 (t, J = 5.4 Hz, 2 H), 2.78 (t, J = 6.2 Hz, 2 H), 7.06 (s, 1 H), 7.87 (d, J = 8.2 Hz, 1 H), 7.99 (d, J = 8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.2, 30.2, 35.2, 35.6, 36.7, 97.4, 127.2, 129.7, 130.4, 132.4, 148.3, 160.0, 167.0, 199.7. Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28%; H, 5.73%. Found: C, 68.36%; H, 6.10%.

Computer Calculations. All calculations were performed using Spartan 04 (Windows Edition) V1.0.1[18] on a dual-core Pentium III Xeon (2 × 1 GHz) running Windows XP Professional SP2. Equilibrium geometries of **3** were calculated at the HF/6-31G* level following a preoptimization using the AM1 semiempirical method. Default optimization parameters were employed. The final geometry was characterized as an energy minimum on the potential energy surface by the absence of any negative (imaginary) vibrational frequencies at the stationary point. The electron density surface is drawn at an IsoVal of 0.002 electrons/au^3 with the LUMO property map set to a range of 0.020−0.033 eV.

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Supporting Information Available: (1) Additional experimental procedures, (2) MS and FTIR data for **1**, **3**, **4**, **10**−**12**, (3) ^{1}H NMR spectra for **1**, **3**, **4**, **6**, **10**, **12**, **13**, **17**−**19**, (4) Cartesian coordinates and computed total energy for **3**, (5) crystal data, data collection, structure solution, and refinement for **1** and ORTEP plot of conformer 2 for **1**, (6) picture of the dimeric H-bonding structure of **1**, and (7) CIF for **1**. This material is available free of charge via the Internet at http:/pubs.acs.org.

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