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Synthesis of the Common Monomeric Unit of Uroleuconaphins and Viridaphins via Hauser–Kraus Annulation

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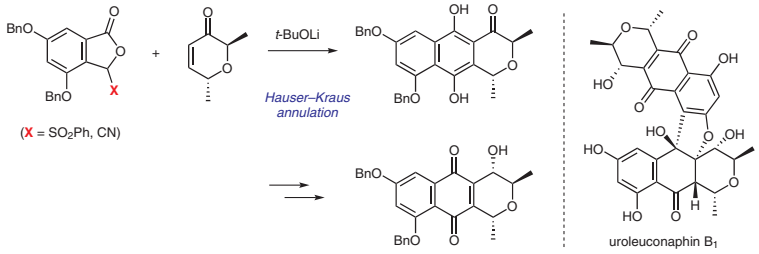

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Abstract A stereoselective synthesis of a pyranonaphthoquinone derivative found in aromatic polyketide-derived aphid pigments is reported herein. This approach features the anionic [4+2]-annulation of phthalides with a carbohydrate-derived optically active enone. Additional synthetic steps provide access to the monomer fragment of uroleuconaphins and viridaphins. The optimization for a facile preparation of phthalides bearing sulfonyl or cyano groups are also studied.

Key words aphid pigment, polyketide, dimeric pyranonaphthoquinone, total synthesis, natural product, anionic annulation, Hauser–Kraus annulation

Uroleuconaphins and viridaphins (Figure 1) are a family of aphid insect pigments,[1] which possess structurally complicated, polyketide-derived dimeric pyranonaphthoquinones.[2,3] They exhibit biological activities, such as antimicrobial activity and cytotoxicity.[4,5] In addition, these pigments can act as chemopreventive agents in the host defense system against infections caused by entomopathogenic fungi.[6] Regarding our long-standing interest in the synthesis of a series of aphid pigments,[7] the dimeric pyranonaphthoquinones, such as the uroleuconaphins, are a particularly difficult class of compounds for total synthesis. We report herein the concise synthesis of optically active pyranonaphthoquinone **1**, the monomer unit of the aphid pigments, by utilizing an anionic annulation of an activated phthalide with a carbohydrate-derived chiral enone as a key step.

We envisioned that the dibenzyl-protected pyranonaphthoquinone **2** would be a suitable synthetic precursor to **1**, which could be potentially derived from hydroquinone **3** by redox operations. The preparation of **3** could be achieved via Hauser–Kraus annulation of phthalide anion generated from **4** or **5**,[8] which could be combined with enone **6** (Scheme 1). The synthetic routes for the preparation of the substituted phthalides **4** and **5** are well-established.[9] However, their syntheses often involve long synthetic steps from commercially available compounds and we aim to optimize their synthesis to be more concise and practical.

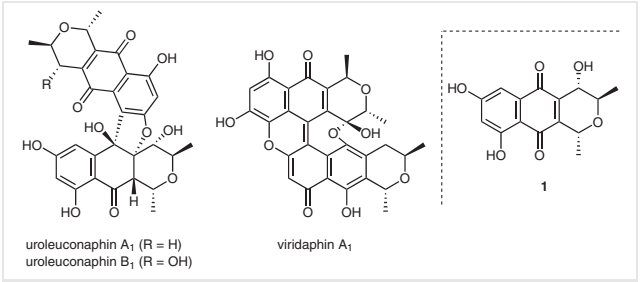
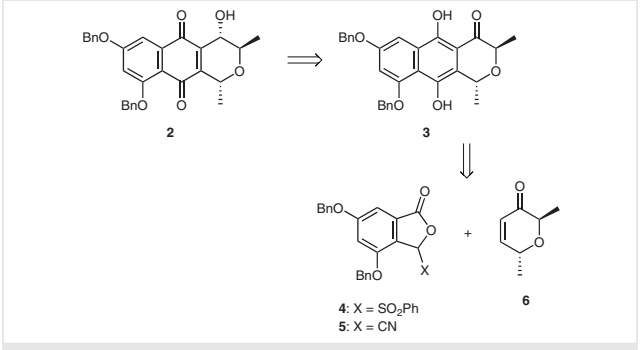


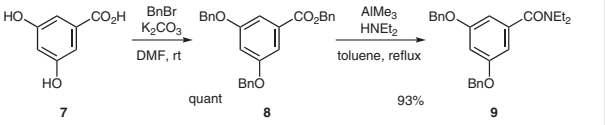
Figure 1 Structure of dimeric aphid pigments



Scheme 1 Synthetic plan of monomer **2**

We initiated our study by using 3,5-dihydroxybenzoic acid (**7**) as the starting material. Treatment of **7** with BnBr (3 equiv) and K_2CO_3 (6 equiv) resulted in tribenzylation to

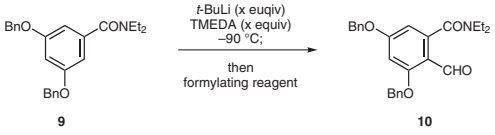
give ester **8** (Scheme 2). The conversion of the benzyl ester in **8** into the corresponding *N*,*N*-diethylamide was performed by treatment with diethylamine in the presence of $AlMe_3$ as Lewis acid in refluxing toluene.[10] After separation of the resulting benzyl alcohol by silica gel column chromatography, diethylamide **9** was obtained in 93% yield.



Scheme 2 Synthesis of *N*,*N*-diethylamide **9**

The optimization for *ortho*-formylation of amide **9** to aldehyde **10** is shown in Table 1. Although a two-step procedure for the introduction of the formyl group via bromination for **9** was reported,[11] direct *C*-formylation with DMF was examined. First, treatment of **9** with *t*-BuLi (1.2 equiv) and TMEDA (1.2 equiv) in Et_2O gave no desired product due to poor solubility. Changing the solvent to THF gave the product in moderate yield (46%) and some of the starting material was also recovered (43%). Increasing the amount of *t*-BuLi (1.8 equiv) led to the formation of unidentified by-products. Changing the formylating agent from DMF to 4-formylmorpholine[12] gave a higher yield of the product. Finally, using 2-methyltetrahydrofuran (2-MeTHF) as the solvent gave aldehyde **10** in better yield (71%). This result is possibly attributed to the increased chemical stability of 2-MeTHF to organolithium compounds rather than THF.[13]

Table 1 Regioselective formylation of **9**

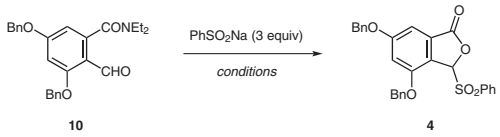


Entry	x equiv	Solvent[a]	Reagent[b]	Yield (%)
1	1.2	Et_2O	DMF	0
2	1.2	THF	DMF	46
3	1.8	THF	DMF	41
4	1.2	THF	4-formylmorpholine	59
5	1.2	2-MeTHF	4-formylmorpholine	71

[a] 0.1 M solution.
[b] 12 equiv of reagent.

Next, the direct conversion of aldehyde **10** into sulfonylphthalide **4** using sodium benzenesulfinate was examined (Table 2). By using the reaction conditions reported by Tatsuta,[14] treatment of **10** with AcOH at elevated temperatures led to no reaction with full recovery of the starting material. The use of a strong acid, such as CSA, led to decomposition of the starting material (DMF, 100 °C). Fortunately, the reaction performed with *p*-TsOH in toluene proceeded to give the desired formation of **4** in 35% yield (toluene, 60 °C). Homogeneous acidic conditions using 1 M HCl in THF did not give the desired product and the starting material was recovered.[15] Interestingly, the reaction proceeded smoothly under biphasic conditions in toluene to afford the desired sulfone **4** in 65% yield. Presumably, the generation of the sulfinic acid in the aqueous phase might be essential. Changing the acid to 1 M H_2SO_4 proceeded more efficiently, giving the product in 89% yield.

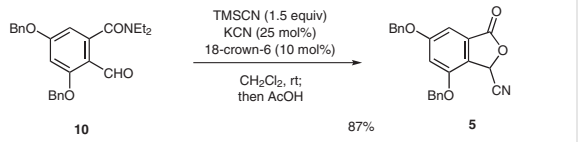
Table 2 Synthesis of sulfonylphthalide **4**



Entry	Reagent	Solvent	Temp (°C)	Yield (%)
1	AcOH	–	80	0
2	CSA[a]	DMF	100	0
3	*p*-TsOH[a]	toluene	60	35
4	1 M HCl	THF	80	0
5	1 M HCl	toluene	80	65
6	1 M H_2SO_4	toluene	80	89

[a] 3 equiv of acid.

Cyanophthalide **5**, another precursor for annulation, was prepared following a reported procedure (Scheme 3).[16] Aldehyde **10** was reacted with cyanotrimethylsilane in the presence of a catalytic amount of KCN and 18-crown-6 to produce the corresponding cyanohydrin, which was directly converted into cyanophthalide **5** in 87% yield by exposure to AcOH. Recrystallization from $CHCl_3$/hexane produced single crystals of **5** amenable for X-ray analysis (Figure 2).[17]



Scheme 3 Synthesis of cyanophthalide **5**

The optically active enone **6** was prepared starting from the commercially available D-fucose (**11**). A three-step procedure[18] involving peracetylation, bromination, and reduction was performed to give glycal **12** in 85% overall yield. Treatment of **12** with $TiCl_4$ and $AlMe_3$ resulted in stereospecific alkylation to introduce the methyl group[19] affording **13**. To convert acetate **13** into enone **6** via alcohol **14**, the hydrolysis of **13** was initially attempted in the presence of LiOH in THF/MeOH/H_2O. However, the extraction of **14** after an acidic workup proved to be troublesome due to the high

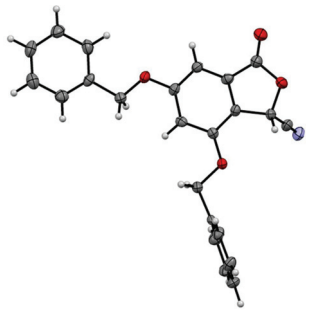
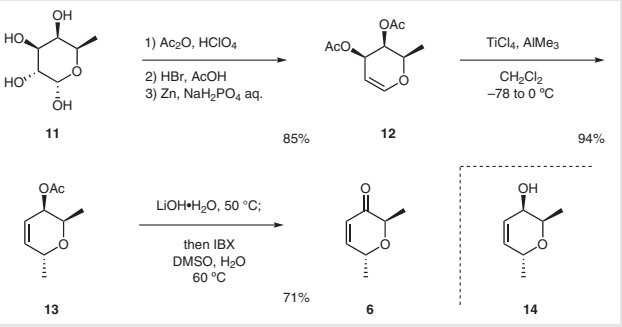


Figure 2 X-ray crystal structure of cyanophthalide **5**

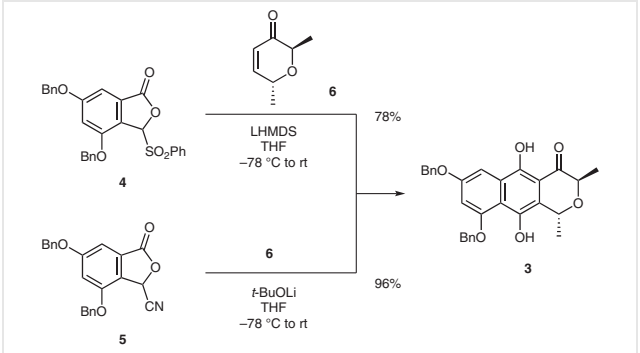
solubility of **14** in water. Accordingly, we developed a one-pot procedure to access **6** by a hydrolysis–oxidation sequence in order to circumvent the difficult extraction process. Treatment of **13** with LiOH in aqueous DMSO at 50 °C followed by subsequent addition of IBX[20] at 60 °C afforded enone **6** in 71% yield (Scheme 4).



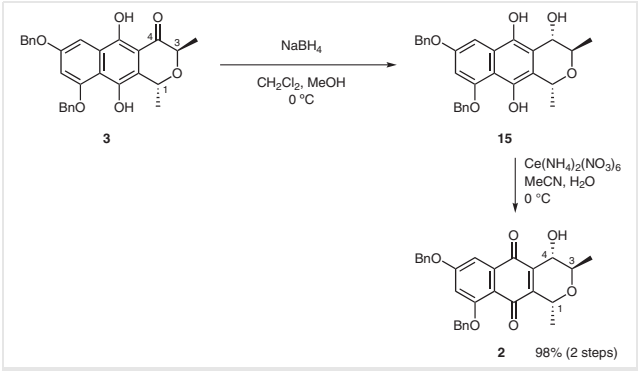
Scheme 4 Preparation of the optically active enone **6**

With both the synthetic fragments in hand, we examined the anionic [4+2] cycloaddition using phthalides **4** and **5** with enone **6** (Scheme 5). First, sulfonylphthalide **4** was treated with LHMDS (3.0 equiv) at –78 °C, which was then reacted with **6** (1.0 equiv) by gradual warming to room temperature to give hydroquinone **3** in 78% yield.[21] Although various strong bases were screened for this reaction, the yield of the product could not be improved. Comparatively, the use of cyanophthalide **5** resulted in a higher yield of **3**. By treatment with *t*-BuOLi (THF, –78 °C → rt), product **3** was obtained in 96% yield.[22] In both cases the epimerization at the C3 position in hydroquinone **3** was not observed.

The carbonyl group in hydroquinone **3** was stereoselectively reduced by $NaBH_4$ at 0 °C to afford alcohol **15** as a single diastereomer. Although alcohol **15** was slowly oxidized upon exposure to air, the cerium(IV)-mediated oxidation proceeded quickly and cleanly to afford naphthoquinone **2** in 98% yield over two steps (Scheme 6).



Scheme 5 Anionic [4+2] cycloaddition of phthalides **4** and **5**



Scheme 6 Synthesis of naphthoquinone **2**

The stereochemistry of alcohol **2** was assigned by ^1H NMR study ($J_{3,4}$ = 8.0 Hz).[23] The 1,3-*trans* relationship of the C1 methyl and C3 methyl groups in **2** was also confirmed by NOESY spectroscopy (Figure 3A). The stereochemical model showing the reduction of **3** is depicted in Figure 3B, where the C1 and C3 methyl groups are positioned at the pseudo-axial and equatorial positions, respectively. Thus, the hydride agent approached from the β-face for the axial attack.

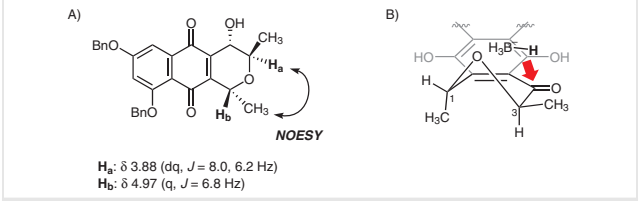


Figure 3 Stereochemical analysis of **2** and stereochemical reduction model

In summary, we developed a facile and practical synthetic route to optically active pyranonaphthoquinone, which is commonly found in aphid insect pigments. Further efforts towards the total syntheses of uroleuconaphins and viridaphins are currently underway in our laboratory.

All experiments dealing with air- and moisture-sensitive compounds were conducted under an atmosphere of dry argon. THF, toluene, DMF, and CH_2Cl_2 (dehydrated; Kanto Chemical Co., Inc.) were used as received. For thin-layer chromatography (TLC) analysis, Merck precoated plates (silica gel 60 F_{254}, Art 5715, 0.25 mm) were used. For column chromatography, Fuji Silysia BW-127ZH silica (100–270 mesh) was used. Optical rotations were measured with a JASCO P-2300 polarimeter. Melting points were determined on a Büchi B-545 apparatus and were uncorrected. Infrared (IR) spectra were recorded using a JASCO Model FTIR-410 spectrophotometer. ^{1}H and ^{13}C NMR were measured on a Bruker AVANCE III HD-500 (500 MHz/125 MHz). High resolution mass spectra (HRMS) were recorded with a JEOL JMS-700 (EI/CI), Waters SYNAPT G2-Si HDMS (ESI), or a JEOL SpiralTOF JMS-S3000 mass spectrometers (MALDI).

Benzyl Ester 8

To a solution of 3,5-dihydroxybenzoic acid (**7**; 2.01 g, 13.0 mmol) in DMF (26 mL) were successively added K_2CO_3 (10.8 g, 77.9 mmol) and BnBr (4.8 mL, 40 mmol) at rt. After stirring for 24 h at this temperature, the reaction was quenched with 2 M aq HCl at 0 °C. The products were extracted with Et_2O (×3) and the combined extracts were washed with sat. aq $NaHCO_3$ and brine, and dried (Na_2SO_4). Concentration and purification by column chromatography (silica gel, hexane/EtOAc 95:5 to 9:1) gave benzyl ester **8** (5.53 g, quant) as a white solid; mp 65–66 °C.

IR (ATR): 1715, 1596, 1455, 1347, 1297, 1220, 1164, 1030, 771, 696 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.30–7.44 (m, 17 H), 6.80 (t, *J* = 2.2 Hz, 1 H), 5.34 (s, 2 H), 5.06 (s, 4 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 166.1, 159.7, 136.4, 135.9, 132.0, 128.61, 128.57, 128.2, 128.13, 128.11, 127.6, 108.5, 107.2, 70.3, 66.8.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{28}H_{24}NaO_4$: 447.1572; found: 447.1565.

Diethylamide 9

To a solution of $HNEt_2$ (5.2 mL, 50 mmol) in toluene (15 mL) was added $AlMe_3$ (2.0 M in hexane, 13.7 mL, 27.4 mmol) at 0 °C. To this mixture was added a solution of benzyl ester **8** (5.53 g, 13.0 mmol) in toluene (20 mL) at rt. After stirring for 10 h under reflux, the mixture was cooled to 0 °C and then carefully poured into ice-cold 2 M aq HCl. The products were extracted with EtOAc (×3) and the combined extracts were washed with H_2O and brine, and dried (Na_2SO_4). Concentration and purification by column chromatography (silica gel, hexane/Et_2O 7:3 to 5:5) gave diethylamide **9** (4.70 g, 93%) as a white solid; mp 90.6–91.1 °C.

IR (ATR): 1643, 1594, 1509, 1429, 1295, 1220, 1160, 1037, 773 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.30–7.42 (m, 10 H), 6.63 (t, *J* = 2.3 Hz, 1 H), 6.58 (d, *J* = 2.3 Hz, 2 H), 5.04 (s, 4 H), 3.51 (br, 2 H), 3.21 (br, 2 H), 1.22 (br, 3 H), 1.02 (br, 3 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 170.7, 159.9, 139.1, 136.6, 128.6, 128.0, 127.5, 105.4, 103.0, 70.2, 43.2, 39.1, 14.2, 12.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{28}NO_3$: 390.2069; found: 390.2072.

Aldehyde 10

To a mixture of amide **9** (772 mg, 1.98 mmol) and TMEDA (360 μL, 2.40 mmol) in 2-MeTHF (20 mL) was added *t*-BuLi (1.60 M in pentane, 1.5 mL, 2.4 mmol) at –90 °C. After stirring for 5 min, 4-formylmorpholine (2.4 mL, 24 mmol) was added and the mixture was stirred for 10 min at this temperature. After further stirring for 2 h at rt, the reaction was quenched with H_2O. The products were extracted with EtOAc (×3) and the combined extracts were washed with brine, and dried (Na_2SO_4). Concentration and purification by column chromatography (silica gel, hexane/EtOAc = 75:25 to 6:4) gave aldehyde **10** (585 mg, 71%) as a white solid; mp 112–113 °C.

IR (ATR): 1678, 1592, 1427, 1323, 1219, 1163, 1054, 773, 696 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 10.39 (s, 1 H), 7.31–7.42 (m, 10 H), 6.59 (d, *J* = 1.8 Hz, 1 H), 6.42 (d, *J* = 1.8 Hz, 1 H), 5.13 (s, 2 H), 5.09 (s, 2 H), 3.56 (br, 2 H), 3.04 (q, *J* = 7.1 Hz, 2 H), 1.31 (t, *J* = 7.1 Hz, 3 H), 0.93 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 187.4, 169.5, 164.4, 163.1, 141.2, 135.5, 128.7, 128.4, 128.3, 127.4, 127.2, 115.5, 105.6, 100.1, 70.7, 70.4, 42.2, 38.5, 13.4, 12.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{27}NNaO_4$: 440.1838; found: 440.1836.

Sulfonylphthalide 4

To a mixture of aldehyde **10** (216 mg, 0.517 mmol) in 1 M aq H_2SO_4 (5.2 mL) and toluene (5.2 mL) was added $PhSO_2Na$ (255 mg, 1.55 mmol). The mixture was stirred at 80 °C for 9 h and then diluted with EtOAc and sat. aq $NaHCO_3$. The products were extracted with EtOAc (×3) and the combined extracts were washed with brine, and dried (Na_2SO_4). Concentration and purification by column chromatography (silica gel, hexane/EtOAc 8:2) gave sulfonylphthalide **4** (225 mg, 89%) as a white solid; mp 155–156 °C.

IR (ATR): 2987, 1792, 1621, 1502, 1449, 1382, 1321, 1143, 1010, 837, 737, 688, 583 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.85–7.89 (m, 2 H), 7.62–7.66 (m, 1 H), 7.56–7.59 (m, 2 H), 7.47–7.52 (m, 2 H), 7.34–7.45 (m, 8 H), 6.93 (d, *J* = 2.0 Hz, 1 H), 6.88 (d, *J* = 2.0 Hz, 1 H), 6.25 (s, 1 H), 5.25 (d, *J* = 12.1 Hz, 1 H), 5.18 (d, *J* = 12.1 Hz, 1 H), 5.06 (s, 2 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 167.6, 163.2, 155.8, 135.49, 135.45, 135.4, 134.6, 129.8, 129.4, 129.1, 128.8, 128.7, 128.5, 128.3, 127.6, 127.3, 120.6, 107.7, 101.2, 90.2, 71.0, 70.8.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{28}H_{22}NaO_6S$: 509.1035; found: 509.1039.

Cyanophthalide 5

To a solution of aldehyde **10** (2.01 g, 4.81 mmol) in CH_2Cl_2 (20 mL) were successively added TMSCN (900 μL, 7.21 mmol), KCN (80.1 mg, 1.23 mmol), and 18-crown-6 (122 mg, 0.46 mmol) at 0 °C. After stirring for 15 h at rt, AcOH (18 mL) was added and the mixture was further stirred for 8 h. The reaction was quenched with 2 M aq NaOH and the products were extracted with EtOAc (×3) and the combined extracts were washed with brine, and dried ($MgSO_4$). Concentration and purification by column chromatography (silica gel, hexane/EtOAc 7:3) gave cyanophthalide **5** (1.55 g, 87%) as a white solid; mp 139.8–140.4 °C.

IR (ATR): 2359, 1780, 1610, 1506, 1328, 1220, 1166, 1093, 1009, 843, 772, 696 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.34–7.46 (m, 10 H), 7.03 (d, *J* = 1.9 Hz, 1 H), 6.90 (d, *J* = 1.9 Hz, 1 H), 5.93 (s, 1 H), 5.21 (d, *J* = 11.8 Hz, 1 H), 5.16 (d, *J* = 11.8 Hz, 1 H), 5.09 (s, 2 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 167.6, 163.2, 154.2, 135.4, 134.9, 128.9, 128.8, 128.6, 128.5, 127.6, 127.4, 127.0, 122.8, 113.3, 107.6, 101.0, 71.0, 70.9, 64.1.

HRMS (ESI): *m*/*z* [M – H]⁻ calcd for $C_{23}H_{16}NO_4$: 370.1079; found: 370.1083.

Diacetate 12

To a suspension of D-fucose (**11**; 5.31 g, 32.4 mmol) in Ac_2O (25 mL) was added one drop of $HClO_4$ (60%) at 0 °C. After stirring at rt for 2 h, the mixture was concentrated in vacuo to give the corresponding peracetate as a colorless syrup. The peracetate was dissolved in CH_2Cl_2 (15 mL), which was treated with HBr (30% in AcOH, 10 mL). After stirring at rt for 12 h, the mixture was diluted with CH_2Cl_2 and H_2O and then neutralized with sat. aq $NaHCO_3$. The organic phase was separated and concentrated in vacuo to give the bromide as a brown oil. To the mixture of the bromide in EtOAc (99 mL) and sat. aq NaH_2PO_4 (49 mL) was added Zn (21 g) and it was vigorously stirred at rt for 19 h. The mixture was passed through a Celite® pad and the products were extracted with EtOAc (×3) and the combined extracts were successively washed with sat. aq $NaHCO_3$ and brine, and dried (Na_2SO_4). Concentration and purification by column chromatography (silica gel, hexane/EtOAc 8:2) gave diacetate **12** (5.88 g, 85% over 3 steps) as a colorless oil; $[\alpha]_D^{22}$ –14.0 (*c* 1.03, $CHCl_3$).

IR (ATR): 1740, 1650, 1369, 1281, 1029, 926, 803, 731, 625 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 6.47 (dd, *J* = 6.3, 1.5 Hz, 1 H), 5.58 (dd, *J* = 4.7, 1.5 Hz, 1 H), 5.29 (d, *J* = 4.7 Hz, 1 H), 4.64 (brd, *J* = 6.3 Hz, 1 H), 4.22 (brq, *J* = 6.7 Hz, 1 H), 2.16 (s, 3 H), 2.02 (s, 3 H), 1.28 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 170.7, 170.4, 146.1, 98.2, 71.5, 66.2, 65.0, 20.8, 20.7, 16.5.

HRMS (MALDI): *m*/*z* [M + Na]⁺ calcd for $C_{10}H_{14}NaO_5$: 237.0733; found: 237.0733.

Allyl Acetate 13

To a solution of diacetate **12** (2.01 g, 9.36 mmol) in CH_2Cl_2 (46 mL) was added $TiCl_4$ (1.2 mL, 11 mmol) at –78 °C. After stirring for 15 min, $AlMe_3$ (2.0 M in hexane, 7.0 mL, 14 mmol) was added to this mixture. After gradual warming to 0 °C, the mixture was stirred for 5 h. The reaction was carefully quenched by sat. aq $NaHCO_3$ and the mixture was filtered through a Celite® pad. The products were extracted with CH_2Cl_2 (×3) and the combined extracts were washed with brine, and dried (Na_2SO_4). Concentration and purification by column chromatography (silica gel, pentane/Et_2O 4:1) gave allyl acetate **13** (1.49 g, 94%) as a pale yellow oil; $[\alpha]_D^{22}$ –377 (*c* 1.02, $CHCl_3$).

IR (ATR): 1729, 1367, 1232, 1054, 917, 823, 739 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 5.99 (ddd, *J* = 0.65, 3.1, 10.2 Hz, 1 H), 5.87 (ddd, *J* = 2.1, 5.1, 10.2 Hz, 1 H), 4.99 (ddd, *J* = 2.1, 2.8, 3.1 Hz, 1 H), 4.43 (ddq, *J* = 0.65, 5.1, 6.9 Hz, 1 H), 4.05 (dq, *J* = 2.8, 6.5 Hz, 1 H), 2.11 (s, 3 H), 1.26 (d, *J* = 6.9 Hz, 3 H), 1.20 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 170.9, 136.2, 121.7, 68.5, 66.2, 65.4, 21.0, 18.2, 16.1.

HRMS (CI): *m*/*z* [M + H]⁺ calcd for $C_9H_{15}O_3$: 171.1016; found: 171.1016.

Enone 6

To a mixture of acetate **13** (376 mg, 2.21 mmol) in DMSO (10 mL) and H_2O (1 mL) was added $LiOH{\cdot}H_2O$ (278 mg, 6.63 mmol). After stirring at 50 °C for 5 h, the mixture was cooled to rt and then IBX (1.87 g, 6.69 mmol) was added. The mixture was stirred at 60 °C for 24 h and the reaction was quenched with 2 M aq $Na_2S_2O_3$ at 0 °C. The products were extracted with CH_2Cl_2 (×3) and the combined extracts were successively washed with H_2O and brine, and dried (Na_2SO_4). Concentration and purification by column chromatography (silica gel, hexane/Et_2O 4:1) gave enone **6** (199 mg, 71%) as a colorless oil; $[\alpha]_D^{21}$ –112 (*c* 1.07, $CHCl_3$).

IR (ATR): 2980, 1689, 1449, 1373, 1232, 1096, 1023, 818, 736 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 6.92 (dd, *J* = 2.3, 10.4 Hz, 1 H), 6.22 (dd, *J* = 1.3, 10.4 Hz, 1 H), 4.61 (ddq, *J* = 1.3, 2.3, 7.0 Hz, 1 H), 4.34 (q, *J* = 7.0 Hz, 1 H), 1.41 (d, *J* = 7.0 Hz, 3 H), 1.38 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 197.1, 151.8, 124.5, 73.2, 65.8, 18.7, 15.1.

HRMS (EI): *m*/*z* [M]⁺ calcd for $C_7H_{10}O_2$: 126.0675; found: 126.0689.

Hydroquinone 3

*From sulfone **4***: To a solution of sulfone **4** (513 mg, 1.06 mmol) in THF (18 mL) was added LHMDS (1.0 M in THF, 3.0 mL, 3.0 mmol) at –78 °C. After stirring for 30 min, a solution of enone **6** (126 mg, 1.00 mmol) was added dropwise at this temperature. The mixture was gradually warmed to rt and stirring was continued for 6 h. The reaction was quenched with sat. aq NH_4Cl at 0 °C. The products were extracted with EtOAc (×4) and the combined extracts were washed with brine, and dried ($MgSO_4$). Concentration and purification by column chromatography (silica gel, hexane/acetone 9:1) gave hydroquinone **3** (369 mg, 78%) as a yellow solid; mp 171–172 °C; $[\alpha]_D^{22}$ –20.1 (*c* 0.45, $CHCl_3$).

*From cyanide **5***: To a solution of *t*-BuOH (320 µL, 3.35 mmol) in THF (4 mL) was added *n*-BuLi (1.59 M in hexane, 1.9 mL, 3.0 mmol) at 0 °C. After stirring for 10 min, cyanophthalide **5** (411 mg, 1.11 mmol) was added at –78 °C in one portion and the mixture was stirred for 15 min. A solution of enone **6** (140 mg, 1.11 mmol) in THF (1 mL) was then added dropwise and the mixture was gradually warmed to rt. After further stirring for 2 h, the reaction was quenched with sat. aq NH_4Cl at 0 °C. The products were extracted with EtOAc (×4) and the combined extracts were washed with brine, and dried ($MgSO_4$). Concentration and purification by column chromatography (silica gel, hexane/EtOAc 9:1) gave hydroquinone **3** (501 mg, 96%) as a yellow solid.

IR (ATR): 3378, 3016, 1617, 1582, 1365, 1219, 1145, 966, 773, 696 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 12.75 (s, 1 H), 8.79 (s, 1 H), 7.33–7.51 (m, 11 H), 6.85 (s, 1 H), 5.41 (q, *J* = 6.7 Hz, 1 H), 5.21 (s, 2 H), 5.18 (s, 2 H), 4.67 (q, *J* = 6.6 Hz, 1 H), 1.60 (d, *J* = 6.7 Hz, 3 H), 1.52 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 203.1, 156.6, 156.0, 153.2, 139.6, 136.3, 134.6, 129.14, 129.11, 128.7, 128.3, 128.1, 127.9, 126.5, 119.0, 115.5, 108.1, 103.7, 97.3, 72.0, 70.4, 69.4, 67.3, 17.5, 16.3.

HRMS (MALDI): *m*/*z* [M + Na]⁺ calcd for $C_{29}H_{26}NaO_6$: 493.1622; found: 493.1607.

Naphthoquinone 2

To a suspension of hydroquinone **3** (482 mg, 1.03 mmol) in CH_2Cl_2 (12 mL) and MeOH (12 mL) was added $NaBH_4$ (89.0 mg, 2.35 mmol) at 0 °C. After stirring for 20 min at this temperature, the reaction was quenched with 1 M aq HCl. The products were extracted with CH_2Cl_2 (×3) and the combined extracts were washed with brine, and dried ($MgSO_4$). After concentration, the crude alcohol **15** was diluted with MeCN (18 mL) and H_2O (2 mL) and then $Ce(NH_4)_2(NO_3)_6$ (1.27 g, 2.31 mmol) was added at 0 °C. After stirring for 30 min at this temperature, the mixture was diluted with H_2O. The products were extracted with CH_2Cl_2 (×3) and the combined extracts were washed with brine, and dried ($MgSO_4$). Concentration and purification by column

chromatography (silica gel, hexane/acetone 80:20) gave naphthoquinone **2** (471 mg, 98% over 2 steps) as a yellow solid; mp 186–187 °C; $[\alpha]_D^{22}$ –24.7 (*c* 0.72, $CHCl_3$).

IR (ATR): 3539, 2891, 1647, 1592, 1437, 1314, 1270, 1167, 1060, 822, 733, 694, 630, 503 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 7.50–7.54 (m, 2 H), 7.30–7.43 (m, 9 H), 6.83 (d, *J* = 2.2 Hz, 1 H), 5.21 (s, 2 H), 5.15 (s, 2 H), 4.97 (q, *J* = 6.8 Hz, 1 H), 4.44 (brd, *J* = 8.0 Hz, 1 H), 3.88 (dq, *J* = 8.0, 6.2 Hz, 1 H), 3.79 (brs, 1 H), 1.60 (d, *J* = 6.8 Hz, 3 H), 1.40 (d, *J* = 6.2 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 186.2, 181.1, 163.6, 160.8, 149.5, 138.1, 135.8, 135.5, 135.4, 128.8, 128.7, 128.6, 128.0, 127.6, 126.6, 114.8, 106.7, 104.6, 70.9, 70.7, 67.61, 67.57, 67.2, 19.2, 18.6.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{29}H_{26}NaO_6$: 493.1627; found: 493.1632.

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Supporting Information

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