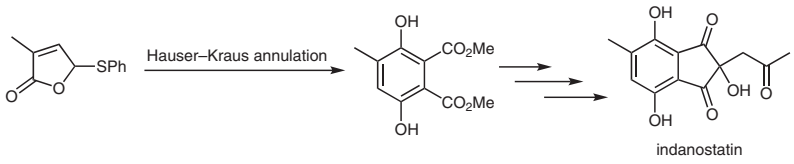
Synlett S. Wang, G. A. Kraus Letter

Annulations of 5-Phenylthiobutenolides and First Synthesis of (±)-Indanostatin

Shuai Wang
George A. Kraus*

Department of Chemistry, Iowa State University, Ames, IA 50010, USA
gakraus@iastate.edu



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Abstract The first synthesis of indanostatin was achieved in 6 steps. Key steps included a butenolide annulation, oxidation to an indanetrione, and reaction with acetone.

Key words 5-phenylthiobutenolides, indanostatin, Hauser–Kraus annulation, hydroquinones, indanedione

Acyl hydroquinones are common subunits in plant secondary metabolites. A few natural products are shown in Figure 1. Eurotiumide A (**1**) is isolated from a fungal strain and is an environmentally friendly antifouling agent.[1] Flavoglaucin (**2**) was isolated from extracts of marine fungus *Eurotium* sp. SF-5989 cultures and shows anti-inflammatory activity.[2] Aldehyde **2** inhibited lipopolysaccharide (LPS)-induced nitric oxide (NO) and prostaglandin E2 (PGE2) production.[3] Indanostatin (**3**) was isolated from *Streptomyces* sp. RAI20 and exhibits potent neuroprotective activity against glutamate toxicity.[4] No synthesis of indanostatin (**3**) has been reported.

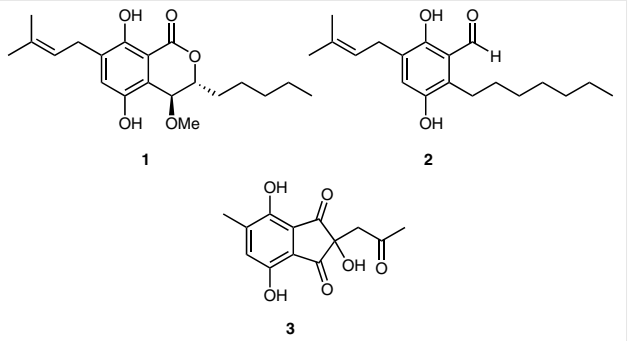
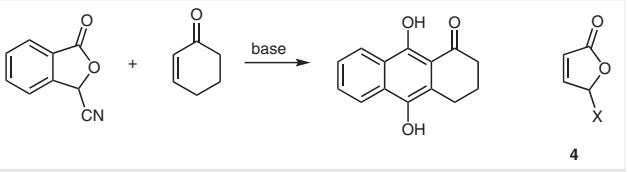


Figure 1 Structures of natural products **1–3**

The Hauser-Kraus annulation has been employed to produce many naphthoquinone and anthraquinone natural products.[5] The general reaction is depicted below in Scheme 1. In order to produce hydroquinones by this process, the substituted butenolide **4** would be required.

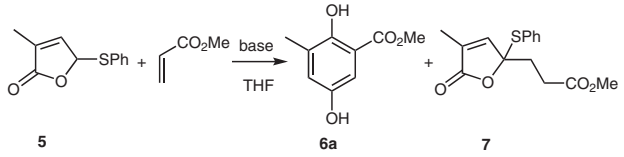


Scheme 1 Hauser–Kraus annulation

Although 5-hydroxy butenolides (**4**: X = OH) are readily available through furan oxidation protocols,[6] there is only one report of the synthesis of the butenolide with X = CN[7] and no reactions of it were reported. Fortunately, the preparation of the butenolide for which X = SPh had better precedent. Fariña reported that the alkylation of the anion of **4** (X = SPh) with alkyl halides afforded a regioisomeric mixture.[8]

In view of these complications and the recognition that compounds **1–3** would likely arise from a 3,5-disubstituted butenolide, we prepared butenolide **5** from the known hydroxy butenolide.[9] The results with methyl acrylate are shown in Table 1. The most commonly used bases for the Hauser–Kraus annulation are lithium diisopropylamide (LDA) and potassium- and lithium tert-butoxide. As seen in Table 1, lithium tert-butoxide is the most effective base for the production of hydroquinone **6a**, as the LDA-promoted reaction afforded mostly butenolide **7**. Regioisomers were not detected.

Table 1 Hauser–Kraus Annulation of 5-Phenylthiobutenolide

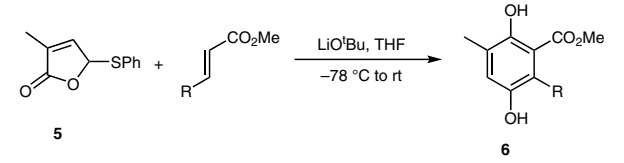


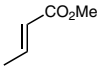
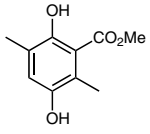
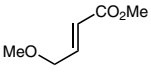
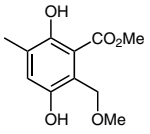
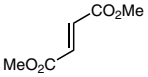
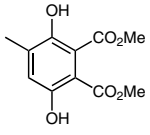
Entry	Base (3.0 equiv)	Temp	Yield (%)[a]
1	LDA	–78 °C to rt	**6a** 33, **7** 60
2	KO^{t}Bu	rt	many products
3	LiO^{t}Bu	–78 °C to rt	**6a** 82

[a] Isolated yield.

With the optimal conditions defined, other esters were reacted with butenolide **5**. As shown in Table 2, isolated yields were moderate to good. Adduct **6c** might be converted into an analogue of **1** by phenol protection and lateral metalation followed by an aldol reaction.

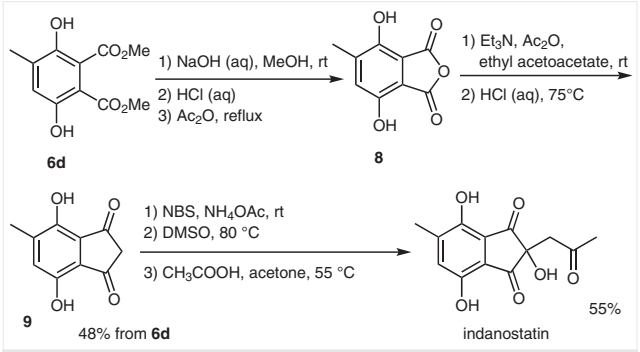
Table 2 Substrates Scope



Reactant	Product (%)[a]
	 **6b** 77
	 **6c** 59
	 **6d** 57

[a] Isolated yield.

As shown in Scheme 2, adduct **6d** was hydrolyzed to the diacid and cyclized to the anhydride **8**. The anhydride **8** was converted into the indanedione **9** using the method of Smith.[10] Indanedione **9** was produced in 48% overall yield from **6d**. Attempts to oxidize **9** to the indanetrione led to complex mixtures, presumably due to the hydroquinone subunit. The trione was ultimately synthesized via the 2,2-dibromide of **9**. The resulting trione was treated with excess acetone in acetic acid to produce indanostatin in 55% yield from **9**.[11] The ^{1}H NMR and ^{13}C NMR spectra of our synthetic compound matched the literature spectra.



Scheme 2 Synthesis of indanostatin

The first synthesis of indanostatin was accomplished in 6 steps. It utilizes a butenolide annulation to construct the skeleton.[12]

Acknowledgment

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611462.

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(12) **3-Methyl-5-(phenylthio)furan-2(5*H*)-one (5)**

To a stirred solution of 5-hydroxy-3-methylfuran-2(5*H*)-one (1.14 g, 10 mmol) in toluene (100 mL) was added *p*-toluenesulfonic acid (PTSA, 50 mg) followed by thiophenol (1.10 g, 10 mmol), and the mixture was heated at 80 °C for 15 h. Toluene was removed under reduced pressure. The crude residue was then diluted with EtOAc (50 mL) and washed by water and brine, dried over Na_2SO_4, and concentrated. Purification by column chromatography gives the product as solid **5** (1.80 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64–7.46 (m, 2 H), 7.40–7.28 (m, 3 H), 6.96 (p, J = 1.6, 1 H), 6.11 (p, J = 1.9, 1 H), 1.83 (t, J = 1.8, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.84, 144.96, 134.12, 132.15, 130.20, 129.27, 129.15, 85.86, 10.59. HRMS (ESI-QTOF): *m/z* calcd for $[M + H]^+$: 207.0474; found: 207.0470.

General Procedure for Hauser–Kraus Annulation of 5

To a stirred solution of **5** (206 mg, 1.0 mmol, 1.0 equiv) in THF (3.0 mL) was added LiO^tBu (1.0 M in THF, 3.0 mL, 3.0 equiv) at –78 °C. And the mixture was stirred for 30 min at the same temperature. Then the unsaturated ester (1.5 equiv, 1.5 mmol) in THF (1.0 mL) was added dropwise to the mixture, and the mixture was stirred at –78 °C for 30 min. Then the mixture was warmed to room temperature and stirred overnight. HCl (aq, 2 N, 10 mL) was added to quench the reaction, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. Purification by column chromatography gives the product.

Methyl 2,5-Dihydroxy-3-methylbenzoate (6a)

White solid, 150 mg, yield 82%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.61 (s, 1 H), 7.10 (d, J = 3.2, 1 H), 6.89 (d, J = 3.2, 1 H), 5.54 (br, 1 H), 3.89 (s, 3 H), 2.21 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.80, 154.32, 147.08, 128.15, 125.17, 112.10, 111.42, 52.48, 15.91. HRMS (ESI-QTOF): *m/z* calcd for $[M – H]^-$: 181.0506; found: 181.0502.

Methyl 2,5-Dihydroxy-3,6-dimethylbenzoate (6b)

White solid, 151 mg, yield 77%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.78 (s, 1 H), 6.83 (s, 1 H), 3.96 (s, 1 H), 2.39 (s, 3 H), 2.19 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.41, 154.90, 145.75, 124.76, 123.91, 122.33, 112.68, 52.31, 15.98, 14.38. HRMS (ESI-QTOF): *m/z* calcd for $[M – H]^-$: 195.0663; found: 195.0662.

Methyl 2,5-Dihydroxy-6-(methoxymethyl)-3-methylbenzoate (6c)

White solid, 133 mg, yield 59%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.40 (s, 1 H), 8.10 (br, 1 H), 6.90 (s, 1 H), 4.98 (s, 2 H), 3.95 (s, 3 H), 3.44 (s, 3 H), 2.21 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.21, 153.90, 149.28, 127.88, 125.66, 118.16, 110.60, 72.36, 58.51, 52.51, 16.16. HRMS (ESI-QTOF): *m/z* calcd for $[M – H]^-$: 225.0768; found: 225.0771.

Dimethyl 3,6-Dihydroxy-4-methylphthalate (6d)

White solid, 136 mg, yield 57%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.95 (s, 1 H), 8.89 (s, 1 H), 6.89 (s, 1 H), 3.85 (s, 3 H), 3.84 (s, 3 H), 2.21 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.87, 169.45, 152.14, 150.87, 134.80, 124.02, 111.80, 109.74, 52.62, 52.53, 16.44. HRMS (ESI-QTOF): *m/z* calcd for $[M – H]^-$: 239.0561; found: 239.0559.

4,7-Dihydroxy-5-methyl-1*H*-indene-1,3(2*H*)-dione (9)

To a solution of **6d** (240 mg, 1.0 mmol, 1.0 equiv) in methanol (5.0 mL) and water (5.0 mL) was added NaOH (400 mg, 10.0 equiv) in an ice bath. The mixture was stirred at room temperature for 1 h. After the completion of the reaction, methanol was removed in vacuo, and the residue was acidified by concd HCl in an ice bath. The mixture was extracted with EtOAc (2 × 10 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated. The residue was dissolved in acetic anhydride (10 mL), the mixture was heated overnight at reflux, and then was cooled down. Acetic anhydride was removed by distillation under reduced pressure. The residue was dissolved in acetic anhydride (2.0 mL) containing Et_3N (1.0 mL), and the solution was treated with ethyl acetoacetate (156 mg, 1.2 mmol). After stirring overnight, HCl (aq, 6 N, 10 mL) was added to the dark solution at room temperature. The solution was heated to 75 °C for 1.0 h. Aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over $Na_2SO_4$and concentrated. Hexane was added to the residue and solid was precipitated out. Product was collected by filtration. Brown solid, 92 mg, yield 48%. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.03 (s, 1 H), 9.17 (s, 1 H), 7.05 (s, 1 H), 3.23 (s, 2 H), 2.19 (s, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 200.43, 195.76, 148.25, 146.48, 136.80, 127.19, 126.39, 124.63, 46.41, 16.15. HRMS (ESI-QTOF): *m/z* calcd for $[M – H]^-$: 191.0350; found: 191.0353.

2,4,7-Trihydroxy-5-methyl-2-(2-oxopropyl)-1*H*-indene-1,3(2*H*)-dione (or Indanostatin)

To a solution of **9** (92 mg, 0.48 mmol, 1.0 equiv) and ammonium acetate (3.7 mg, 0.048 mmol, 0.1 equiv) in diethyl ether (5.0 mL) was added *N*-bromosuccinimide (NBS, 170 mg, 0.96 mmol, 2.0 equiv). The mixture was stirred at room temperature for overnight. After the completion of the reaction, the solution was diluted with diethyl ether (10 mL) and was washed with HCl (1 N, 5 mL) followed by brine. The organic layer was dried over Na_2SO_4 and concentrated. The residue was dissolved in DMSO (1.0 mL) and heated at 80 °C for 2.0 h. After cooling down, 1.0 mL water was added to the solution, and the mixture was stirred at room temperature for 1.0 h. Water and DMSO were removed by distillation under reduced pressure. And the residue was diluted with EtOAc (20 mL) and washed with HCl (1 N, 10 mL) followed by brine. The organic layer was dried over Na_2SO_4 and concentrated. The residue was dissolved in acetic acid (1.0 mL), and a few drops of acetone were added to the mixture. The reaction was heated at 55 °C for 6 h. After cooling down, acetic acid was evaporated in vacuo, the residue was diluted with EtOAc (10 mL) and was washed with HCl (1 N, 5 mL) followed by brine. The organic layer was dried over Na_2SO_4 and concentrated. Purification by column chromatography gives the product. Yellow solid, 69.1 mg, yield 55% ^{1}H NMR (400 MHz, acetone-d_6): δ = 8.64 (s, 2 H), 7.19 (d, J = 0.9, 1 H), 3.39 (d, J = 1.4, 2 H), 2.32 (d, J = 0.8, 3 H), 2.11 (s, 3 H). ^{13}C NMR (100 MHz, acetone-d_6): δ = 205.63, 201.18, 198.51, 149.11, 148.07, 137.65, 127.10, 122.73, 121.50, 73.62, 47.61, 28.49, 14.92. HRMS (ESI-QTOF): *m/z* calcd for $[M – H]^-$: 263.0561; found: 263.0561.