

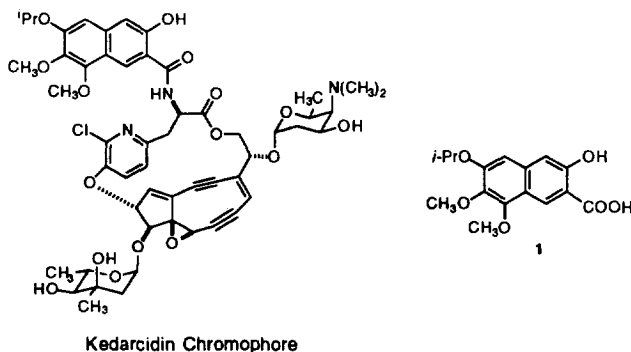
## Synthesis of the Naphthoic Acid Component of Kedarcidin Chromophore by Routes Employing Photochemical and Thermal Electrocyclic Ring Closure Reactions.

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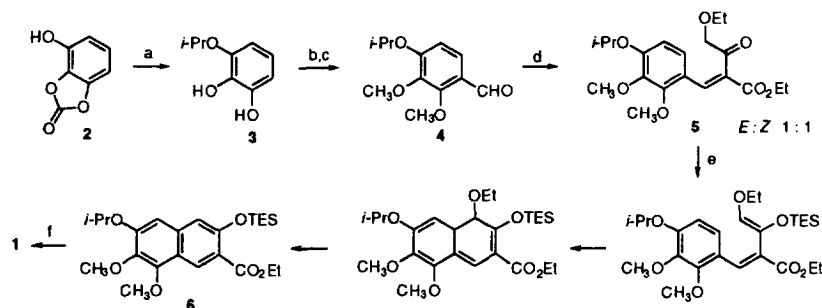
**Abstract:** Two different synthetic routes to the naphthoic acid component of kedarcidin chromophore were developed featuring photochemical and thermal electrocyclic ring closure reactions, respectively, as the key step. X-ray crystallographic analysis of the synthetic naphthoic acid confirmed its structure and comparison of  $^1\text{H}$  and  $^{13}\text{C}$  NMR data from its methylamide derivative with those reported for kedarcidin chromophore correspond closely, suggesting that this component of the natural product is correctly assigned. © 1997 Elsevier Science Ltd.

Kedarcidin is one of the most complex and reactive of the enediyne antitumor agents reported to date.<sup>1,2</sup> The development of a synthetic route to the highly reactive chromophore component of kedarcidin surely represents one of the most challenging of current problems in synthetic chemistry. The most significant development in this area to date is a report by Iida and Hiramasa describing the remarkable synthesis of a model structure bearing the epoxy enediyne functionality of the chromophore core.<sup>3</sup> As part of a program directed toward the preparation of the natural product itself, we describe herein two synthetic routes to the naphthoic acid component of kedarcidin chromophore featuring new electrocyclic annelation reactions. Comparison of spectroscopic data from synthetic materials with those from the natural product supports the assigned structure of this component of kedarcidin chromophore.



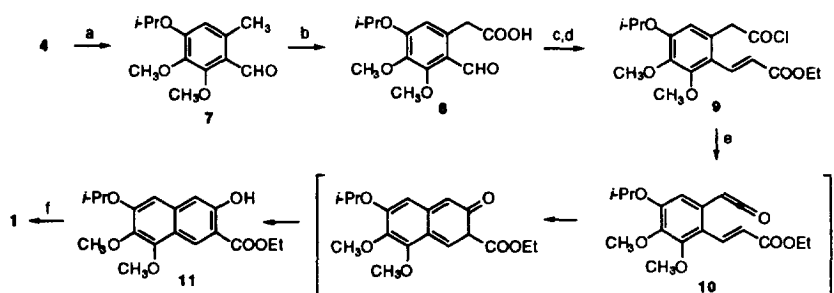
Our initial approach to the synthesis of **1** involved a photochemical electrocyclic reaction (see **5** → **6** below) and was patterned after a related strategy used for the synthesis of the naphthoic acid component of neocarzinostatin chromophore.<sup>4</sup> Mitsunobu coupling of pyrogallol cyclic carbonate **2**<sup>5</sup> with isopropanol followed

by basic workup afforded pyrogallol monoisopropyl ether **3** in 93% yield.<sup>6-8</sup> Regioselective formylation of **3** was achieved by its treatment with triethyl orthoformate and stannic chloride in dichloromethane at  $-78\text{ }^{\circ}\text{C}$  and warming to  $-40\text{ }^{\circ}\text{C}$ . Methylation of the resultant aldehyde diphenol with excess methyl iodide and potassium carbonate in dimethylformamide at  $23\text{ }^{\circ}\text{C}$  then afforded the aldehyde dimethyl ether **4** in 79% yield for the two steps. Condensation of **4** with ethyl 4-ethoxyacetoacetate (1.05 equiv)<sup>9</sup> in benzene in the presence of acetic acid (4.0 equiv), piperidine (2.0 equiv), and 3A molecular sieves provided the cinnamate ester derivative **5** as a 1:1 mixture of geometrical isomers in 91% yield. Enolization of **5** with potassium hexamethyldisilazide in a mixed solvent of tetrahydrofuran and toluene (1:1) and trapping of the resultant enolate with triethylsilyl chloride formed the corresponding enol silyl ether (stereochemistry not determined), which was not isolated. Addition of benzene to the crude silylation reaction mixture and irradiation of the dilute substrate solution ( $\sim 0.005\text{ M}$ ) with a 450-watt Hanovia medium pressure mercury arc lamp (Pyrex reactor, without external cooling) led to the formation of the naphthoic acid derivative **6**, presumably via a photo-induced  $6\pi$  electrocyclic reaction followed by elimination of ethanol.<sup>4</sup> Exposure of the crude photocyclization product to aqueous ethanolic sodium hydroxide effected both the desilylation and saponification of the product to afford the target structure **1** in  $\sim 67\%$  yield for the 4-step operation (from **5**). The yield of this sequence was found to vary as a function of scale; the yield was 67% in a 0.84-mmol scale reaction and only 40% in an 8.4-mmol reaction. The high dilution conditions also proved to be inconvenient for scale-up. For these reasons, an alternative route was developed that has proven to be more amenable for the large-scale synthesis of **1**.



**Reagents and conditions:** a) i.  $\text{Ph}_3\text{P}$ , DEAD, *i*-PrOH, THF,  $0\text{ }^{\circ}\text{C}$ ; ii. NaOH,  $\text{H}_2\text{O}$  (93%); b)  $\text{CH}(\text{OEt})_3$ ,  $\text{SnCl}_4$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78 \rightarrow -40\text{ }^{\circ}\text{C}$ ; c)  $\text{CH}_3\text{I}$ ,  $\text{K}_2\text{CO}_3$ , DMF,  $23\text{ }^{\circ}\text{C}$  (79%, 2 steps); d)  $\text{EtOCH}_2\text{COCH}_2\text{COOEt}$ , AcOH, piperidine, 3A MS,  $\text{C}_6\text{H}_6$ ,  $23\text{ }^{\circ}\text{C}$  (91%); e) i.  $(\text{TMS})_2\text{NK}$ , TESCl, 1:1 THF/toluene,  $-78 \rightarrow 23\text{ }^{\circ}\text{C}$ ; ii. dilution with  $\text{C}_6\text{H}_6$  (to  $\sim 0.005\text{ M}$ ); iii. *h\nu*; f) NaOH, 10:1 EtOH: $\text{H}_2\text{O}$ ,  $50 \rightarrow 80\text{ }^{\circ}\text{C}$  (40-67%, 2 steps).

The second route to the naphthoic acid **1** featured an electrocyclic ring closure reaction of the aryl ketene intermediate **10**. Electrocyclizations of this sort are well preceded for ketene intermediates generated by the cycloreversion of aryl cyclobutenone intermediates, by the Wolff rearrangement of  $\alpha$ -diazoketones, and from Fischer carbene complexes.<sup>10,11</sup> In the present case, the ketene intermediate was imagined to arise from the readily available acid chloride **9** by a  $\beta$ -elimination process. The synthesis began with the aldehyde **4**, described above, whose ortho-lithiation was accomplished by the method of Comins and Brown<sup>12</sup> using lithium



**Reagents and conditions:** a) i.  $(\text{CH}_3)_2\text{NCH}_2\text{CH}_2\text{N}(\text{CH}_3)\text{Li}$  (1.2 equiv), THF,  $-20\text{ }^\circ\text{C}$ , 15 min; ii.  $n\text{-BuLi}$  (3.0 equiv),  $-20\text{ }^\circ\text{C}$ , 11 h; iii.  $\text{CH}_3\text{I}$  (6.0 equiv),  $-78 \rightarrow 23\text{ }^\circ\text{C}$  (92%); b) i.  $(\text{CH}_3)_2\text{NCH}_2\text{CH}_2\text{N}(\text{CH}_3)\text{Li}$  (1.2 equiv), THF,  $-20\text{ }^\circ\text{C}$ , 15 min; ii.  $n\text{-BuLi}$  (3.0 equiv),  $-20\text{ }^\circ\text{C}$ , 1.5 h; iii.  $\text{CO}_2$  (Dry Ice),  $-78 \rightarrow 23\text{ }^\circ\text{C}$  (88%); c)  $\text{EtOOCCH}(\text{Li})\text{PO}(\text{OEt})_2$  (2.5 equiv), THF,  $-78 \rightarrow 0\text{ }^\circ\text{C}$  (96%); d)  $(\text{COCl})_2$ ,  $\text{C}_6\text{H}_6$ ,  $50\text{ }^\circ\text{C}$ ; e)  $(i\text{-Pr})_2\text{NEt}$ ,  $\text{C}_6\text{H}_6$ ,  $23\text{ }^\circ\text{C}$  (89%, 2 steps); f)  $\text{NaOH}$ , 10:1  $\text{EtOH}:\text{H}_2\text{O}$ ,  $60\text{ }^\circ\text{C}$  (99%).

2-(dimethylamino)ethylmethylamide and *n*-butyllithium at  $-20\text{ }^\circ\text{C}$ . Trapping of the resultant aryllithium intermediate with methyl iodide then afforded the tetrasubstituted benzaldehyde **7** in 92% yield. Repetition of the Comins-Brown metalation protocol<sup>12</sup> on the latter product and trapping with dry ice produced the carboxylic acid **8** in 88% yield. Horner-Wadsworth-Emmons olefination<sup>13</sup> of **8** with lithio triethyl phosphonoacetate (2.5 equiv) in tetrahydrofuran ( $-78 \rightarrow 0\text{ }^\circ\text{C}$ ) produced the ethyl cinnamate derivative as a 95:5 mixture of *E*:*Z* stereoisomers, respectively, at the newly formed carbon-carbon double bond, in 96% yield. Conversion of the resultant carboxylic acid into the corresponding acid chloride (**9**) occurred cleanly using oxalyl chloride in benzene at  $50\text{ }^\circ\text{C}$ . Rapid addition of Hünig's base (3 equiv) to a solution of the crude acid chloride in benzene at  $23\text{ }^\circ\text{C}$  rapidly formed the desired naphthoylester **11**, which was isolated in 86-89% yield for the two steps. Saponification of the ester **11**, as above, then provided the naphthoic acid **1** as a crystalline solid (99% yield, 50% overall yield for the 9 steps from **2**). The structure of the synthetic naphthoic acid was secured unambiguously by X-ray crystallographic analysis.<sup>14</sup> The procedure described for the synthesis of **1** has proven to be amenable to scale-up, at least to the level of gram quantities. The exceedingly mild conditions of the key cyclization reaction contrast favorably with earlier reported photochemical and thermal processes for ketene generation<sup>10</sup> and should serve to extend the utility of such cyclization reactions in synthesis.

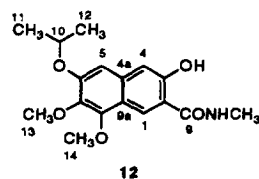
Because the structure of kedarcidin chromophore rests upon an involved series of NMR spectroscopic studies,<sup>2</sup> we hoped to gain further evidence that the naphthoic acid component of the chromophore structure was correctly assigned (it should be noted that the naphthoic acid **1** has never been isolated from natural sources). Toward this end, stirring the synthetic ethyl ester **11** with methanolic methylamine at  $23\text{ }^\circ\text{C}$  provided the corresponding methylamide derivative **12**. Comparison of  $^1\text{H}$  and  $^{13}\text{C}$  NMR data from synthetic **12** in  $d_6$ -dimethyl sulfoxide with corresponding data from kedarcidin chromophore in the same solvent provided excellent corroborating evidence for the proposed structure (see listing below, NMR assignments for **12** were made in correspondence with those of kedarcidin chromophore and were not independently determined).

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, ppm)

proton	1	4	5	10	11	12	13	14
kedarcidin	8.48	7.11	6.97	4.75	1.35	1.35	3.78	3.95
12	8.48	7.10	6.97	4.74	1.35	1.35	3.80	3.97

<sup>13</sup>C NMR (DMSO-d<sub>6</sub>, ppm)

carbon	1	2	3	4	4a	5	6	7	8	8a	9	10	11	12	13	14
kedarcidin	124.0	115.9	155.4	110.0	134.3	102.1	153.3	139.0	148.4	117.1	167.3	70.1	21.9	21.9	60.7	61.6
12	122.8	115.1	156.1	109.9	134.2	102.1	153.1	139.0	148.3	116.9	169.3	70.0	21.7	21.7	60.6	61.5



**Acknowledgment** This research was generously supported by the National Institutes of Health. YH acknowledges the Ministry of Education, Science, and Culture of Japan for a postdoctoral fellowship.

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- Coordinates for the X-ray data have been deposited in the Cambridge Crystallographic data base. Physical data for **1** follow: mp (toluene) 166.5–168.5 °C (dec); IR (thin film) 3238, 2975, 2831, 2542, 1667, 1625, 1454, 1232, 1193, 1112, 1020, 855 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>)  $\delta$  11.07 (br s, 1H), 8.48 (s, 1H), 7.15 (s, 1H), 7.01 (s, 1H), 4.75 (sep, 1H,  $J = 5.4$  Hz), 3.98 (s, 3H), 3.79 (s, 3H), 1.35 (d, 6H,  $J = 5.4$  Hz); <sup>13</sup>C NMR (75 MHz, DMSO-d<sub>6</sub>)  $\delta$  171.9, 156.5, 154.0, 148.2, 138.9, 135.6, 126.0, 117.0, 112.1, 109.8, 102.1, 70.2, 61.4, 60.7, 21.7; HRFABMS calcd for C<sub>16</sub>H<sub>18</sub>O<sub>6</sub> 306.1103, found 306.1097. Anal calcd for C<sub>16</sub>H<sub>18</sub>O<sub>6</sub>: C, 62.74; H, 5.92. found: C, 62.72; H, 5.65.

(Received in USA 20 March 1997; accepted 25 April 1997)