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A Concise Synthesis of the Naphthoic Acid Component of Neocarzinostatin Chromophore Featuring a New Photocyclization Reaction.

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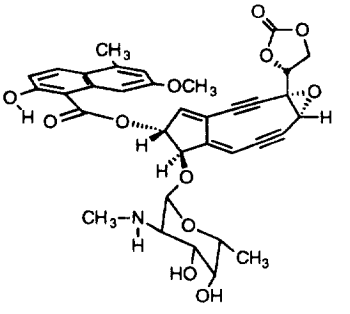
Abstract: A 6-step synthesis of the naphthoic acid component of the natural antitumor agent neocarzinostatin chromophore is described. The synthetic route employs 4-bromo-3-methylanisole as the starting material, proceeds in 31-37% yield for the 6 steps, and features as the key step a photocyclization reaction that is an interesting variant of known photocyclization reactions of stilbenes and phenylbutadienes.

The chromophore component (**1**) of the natural chromoprotein antitumor agent neocarzinostatin was the first of the enediyne antibiotics to be structurally characterized.[1] The chromophore is so designated on the basis of its ultraviolet absorption spectrum; long wavelength absorption by the naphthoic acid ester group distinguishes the chromophore from its binding protein.[2] Compelling evidence has established that the naphthoic acid ester plays a crucial role in the binding of **1** to DNA by functioning as an intercalating group.[3] It has also been shown to play a key role in the binding of **1** to the neocarzinostatin protein component, lying deep within a cleft in the chromoprotein complex.[4] As part of an effort to develop a laboratory synthetic route to neocarzinostatin chromphore, its aglycone, and nonnatural analogs, we required multi-gram quantities of the naphthoic acid **2**.[5] At the time we began our research, two syntheses of **2** had appeared,[6] to include the important initial work of Shibuya et al.,[6a] wherein the the structure of the naphthoate component was revised to **2** on the basis of an unequivocal synthesis of **2** methyl ester and the comparison of this synthetic material with an authentic sample obtained by degradation of **1** (the structure had originally been misassigned as the isomer in



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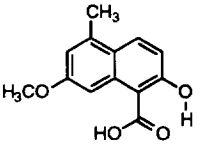
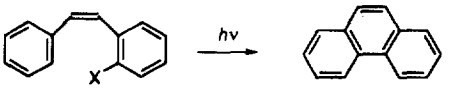


2

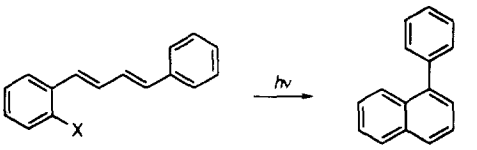
which the methyl and methoxyl groups were transposed).[7] Neither of the published synthetic routes was sufficiently concise for our purposes. Accordingly, we have developed, and report herein, a 6-step synthetic route that has reliably provided many tens of grams of **2** and which features a new photocyclization reaction as the key step. Recently, Hirama and co-workers have also described a 6-step synthesis of **2** (23% yield) proceeding by an alternative route.[8]

The strategy we chose for the construction of **1** was based upon the known ability of stilbene derivatives to undergo photoaromatization to form anthracenes (eq 1).[9] Unsubstituted stilbenes (X = H) have been shown to cycloaromatize upon irradiation in the presence of an oxidant such as iodine or dioxygen,[9c] whereas *ortho*-



(eq 1)

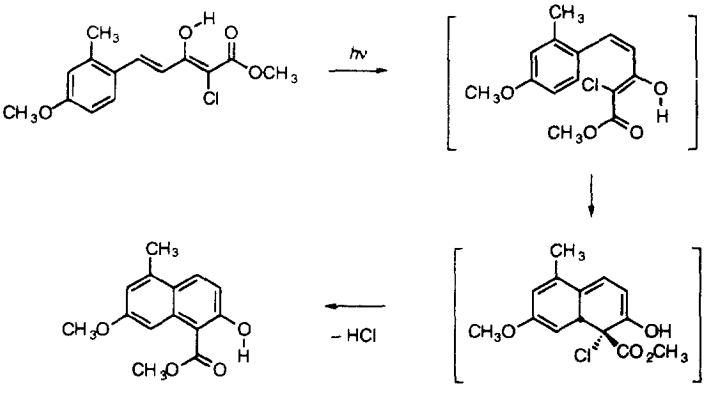
X = H, halogen



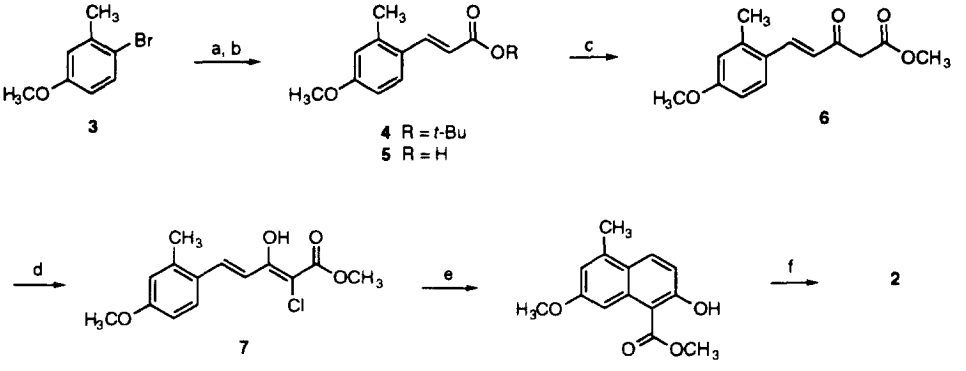
(eq 2)

X = H, halogen

halostilbenes are observed to photoaromatize without an added oxidant.[9a,b] Both the oxidative and nonoxidative protocols were subsequently extended to include phenylbutadienes (eq 2).[10] On the basis of these precedents, the pathway shown in the scheme below was proposed as a possible route to **2** methyl ester. In this proposal, the halogen has been placed on the diene system, rather than the *ortho*-position of the benzene ring, and one double bond of the diene is part of the enol form of a β-keto ester. The synthesis of the proposed photocyclization substrate and its successful conversion into **2** are described below.



The synthesis began with a Heck coupling reaction of 4-bromo-3-methylanisole **3**[11] with *tert*-butyl acrylate to afford the α,β-unsaturated ester **4**,[12] which was subsequently treated with trifluoroacetic acid to provide the corresponding carboxylic acid (**5**) in 89% yield for the two steps. Following a known acylation protocol, the latter product was treated with carbonyldiimidazole in tetrahydrofuran (THF) and the resulting acyl imidazolide was trapped in situ with magnesium methyl malonate to provide the β-keto ester **6** in 78% yield.[13] Exposure of **6** to sulfuryl choride in benzene at 66 °C produced the photocyclization precursor **7** in 92% yield.[14] Irradiation of a deoxygenated methanolic solution of **7** and triethylamine (25 equiv) with a 450-watt Conrad-Hanovia medium pressure arc lamp (quartz immersion well) for 1 h at 23 °C produced **2** methyl ester (mp 103-104 °C, lit mp 104-105 °C) in 53-63% yield after column chromatography. Saponification of **2** methyl ester with sodium hydroxide in aqueous methanol afforded synthetic **2** (153-154 °C, lit[8] mp 136-138 °C) in 91% yield. Synthetic **2** provided ^{1}H NMR, ^{13}C NMR, IR, and mass spectroscopic data that was identical to reported values.[8] The combined yield of **2** from 4-bromo-3-methylanisole is 31-37%.



Reagents and conditions: a) *tert*-butyl acrylate, Et_3N, P(*o*-tol)$_3$, $Pd(OAc)_2$, 108 °C (89%); b) TFA, CH_2Cl_2, 23 °C (quantitative); c) i. CDI, THF, 23 °C; ii. magnesium methyl malonate, THF, 23 °C (78%); d) SO_2Cl_2, C_6H_6, 66 °C (92%); e) *hv*, Et_3N, CH_3OH (53-63%); f) NaOH, 3:1 CH_3OH/H_2O, 80 °C (91%).

Scheme 1

Although the proposed photochemical electrocyclization pathway shown in the scheme above was used to derive a successful route to **2**, we have no evidence that this mechanism is, in fact, operative. Mechanistic studies of the photochemical cyclization of *o*-halogenated stilbenes have supported such a pathway, although, in a few instances, radical-mediated cycloaromatizations have also been invoked.[9a,b,15] During the course of our investigations, we also examined the photocyclization of intermediate **6** in the presence of various oxidants. Although we did observe the formation of **2** methyl ester in many instances, the yields were uniformly low. We believe that this may reflect the fact that oxidative aromatization of the electrocyclic intermediate, presumably formed reversibly, is slow. The corresponding intermediate formed from **7** likely undergoes rapid elimination of hydrogen chloride, thus precluding cycloreversion.

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