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Studies toward the Synthesis of the Epoxykinamycin FL-120B′: Discovery of a Decarbonylative Photocyclization

Stephen S. Scully and John A. Porco Jr.*

Department of Chemistry and Center for Chemical Methodology and Library Development (CMLD), Boston University, Boston, Massachusetts 02215, United States

porco@bu.edu

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ABSTRACT

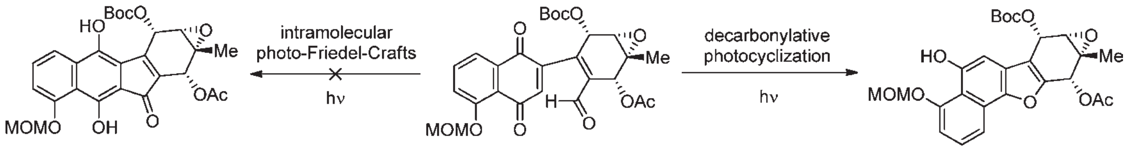

Photo-Friedel–Crafts acylation of a naphthoquinone was attempted in an effort to access a diazobenzofluorenone en route to the epoxykinamycin natural product FL-120B′. Photoirradiation of the naphthoquinone substrate which resulted in the unexpected formation of a tetracyclic naphthofuran *via* a decarbonylative photocyclization process is described.

Kinamycin C (**1**)[1] and the epoxykinamycin FL-120B′ (**2**)[2] belong to the family of diazobenzofluorene natural products which possess broad antibacterial and antitumor activities (Figure 1). The unique diazo functionality and its involvement in the diazobenzofluorenes' ability to damage DNA have made this class of molecules attractive targets for synthetic organic chemists.[3] In 2006 and 2011, our laboratory reported the total syntheses of kinamycin C and FL-120B′, respectively.[4] Our approach to **1** and **2** involved elaboration of a benzofluorenone intermediate **3** which was accessed from a trifluoroacetic anhydride (TFAA)-mediated intramolecular Friedel–Crafts cyclization of carboxylic acid precursor **4**. During our studies toward the synthesis of FL-120B′, an alternative cyclization involving intramolecular photoacylation of an aldehyde substrate containing a naphthoquinone chromophore was also explored. In the present study, we describe our efforts to implement the intramolecular photo-Friedel–Crafts acylation which resulted in the serendipitous discovery[5] of a novel decarbonylative photocyclization to form naphthofurans.[6]

Historically, intermolecular photo-Friedel–Crafts acylations of quinones and aldehydes have been demonstrated to yield acylated hydroquinones.[7] For example, photoirradiation of 1,4-napthoquinone **5** in the presence of propionaldehyde **6** provided the acylated hydroquinone **7** (Scheme 1).[7i] This reaction serves as an environmentally

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(1) (a) Ito, S.; Matsuya, T.; Omura, S.; Otani, M.; Nakagawa, A. *J. Antibiot.* **1970**, *23*, 315–317. (b) Hata, T.; Omura, S.; Iwai, Y.; Nakagawa, A.; Otani, M. *J. Antibiot.* **1971**, *24*, 353–359. (c) Omura, S.; Nakagawa, A.; Yamada, H.; Hata, T.; Furusaki, A. *Chem. Pharm. Bull.* **1973**, *21*, 931–940.

(2) (a) Lin, H. C.; Chang, S. C.; Wang, N. L.; Chang, L. R. *J. Antibiot.* **1994**, *47*, 675–680. (b) Young, J.-J.; Ho, S. N.; Ju, W. M.; Chang, L. R. *J. Antibiot.* **1994**, *47*, 681–687.

(3) For a recent review including synthetic and mechanism-of-action studies of diazobenzofluorene natural products, see: Herzon, S. B.; Woo, C. M. *Nat. Prod. Rep.* **2012**, *29*, 87–118.

(4) (a) Lei, X.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2006**, *128*, 14790–14791. (b) Scully, S. S.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2011**, *50*, 9722–9726.

(5) For a recent example of serendipitous reaction discovery in studies toward diazobenzofluorene natural products, see: Baranczak, A.; Sulikowski, G. A. *Org. Lett.* **2012**, *14*, 1027–1029.

(6) For an alternative synthesis of naphthofurans *via* [2 + 2] photocycloaddition/rearrangement, see: Liu, H.-J.; Chan, W. H. *Can. J. Chem.* **1980**, *58*, 2196–2198.

(7) For select examples, see: (a) Klinger, H.; Kolvenbach, W. *Chem. Ber.* **1898**, *31*, 1214. (b) Bruce, J. M.; Cutts, E. *J. Chem. Soc. C* **1966**, 449–458. (c) Maruyama, K.; Miyagi, Y. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1303–1304. (d) Kraus, G. A.; Kirihara, M. *J. Org. Chem.* **1992**, *57*, 3256–3257. (e) Kraus, G. A.; Liu, P. *Tetrahedron Lett.* **1994**, *35*, 7723–7726. (f) Schiel, C.; Oelgemöller, M.; Mattay, J. *Synthesis* **2001**, 1275–1279. (g) Schiel, C.; Oelgemöller, M.; Ortner, J.; Mattay, J. *Green Chem.* **2001**, *3*, 224–228. (h) Waske, P. A.; Mattay, J.; Oelgemöller, M. *Tetrahedron Lett.* **2006**, *47*, 1329–1332. (i) Friedrichs, F.; Murphy, B.; Nayrat, D.; Ahner, T.; Funke, M.; Ryan, M.; Lex, J.; Mattay, J.; Oelgemöller, M. *Synlett* **2008**, 3137–3140. (j) Benites, J.; Rios, D.; Díaz, P.; Valderrama, J. A. *Tetrahedron Lett.* **2011**, *52*, 609–611.

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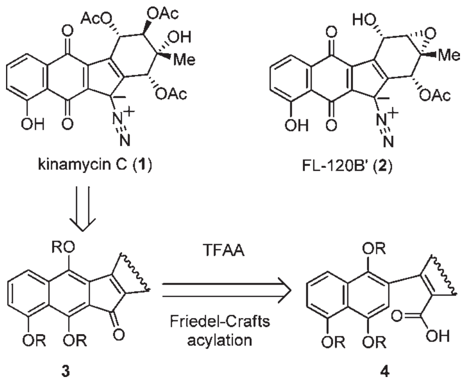
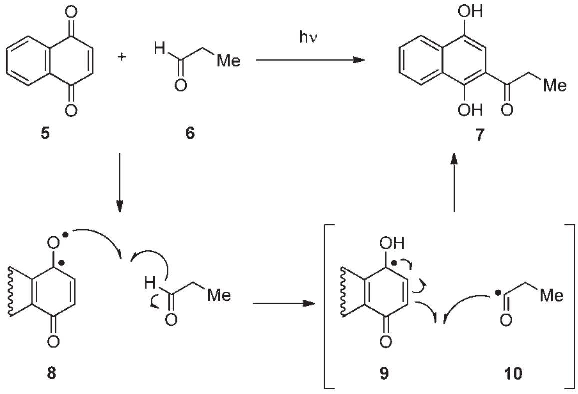


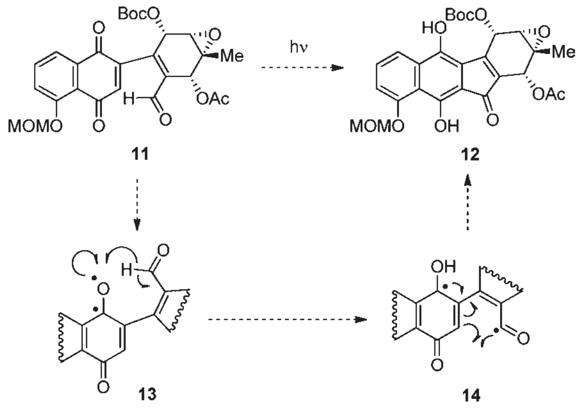
Figure 1. Synthetic approaches to kinamycin C and FL-120B′.

friendly alternative to the classical Friedel–Crafts acylation. In this regard, Mattay and co-workers performed this photoacylation on a 500 g scale using a solar-chemical reactor.[7f,g] One mechanism accounting for formation of **7** involves abstraction of the acyl hydrogen by photoexcited naphthoquinone **8** to give semiquinone **9** and acyl radical **10**. Subsequent carbon–carbon bond formation *via* an in-cage coupling[8] of **9** and **10** provides the observed acyl hydroquinone **7**.[9] On this mechanistic basis, we hypothesized that photoirradiation of naphthoquinone **11** may provide benzofluorenone **12** as a useful intermediate for our synthesis of FL-120B′ (Scheme 2). This photo-Friedel–Crafts cyclization would require diradical **13** to undergo intramolecular hydrogen abstraction through a seven-membered[10] cyclic transition state, in which the resulting biradical species **14** would further cyclize to **12**.

Scheme 1. Intermolecular Photo-Friedel–Crafts Acylation[7i]



Scheme 2. Proposed Intramolecular Photo-Friedel–Crafts Acylation



Naphthoquinone substrate **11** was obtained in six steps from epoxyketone **15**,[4a] an intermediate in our synthesis of kinamycin C (Scheme 3). Acetylation of **15** followed by reduction ($LiEt_3BH$) provided *syn*-epoxyalcohol **16** (5:1 dr)[11] which was protected as Boc-carbonate **17**. Desilylation and oxidation with Dess-Martin periodinane (DMP)[12] afforded aldehyde **18**. Oxidative dealkylation with ceric ammonium nitrate (CAN) provided **11** as our desired substrate for intramolecular photo-Friedel–Crafts acylation studies.

Photoirradiation of **11** in a Rayonet reactor (315–400 nm) gave full conversion to a product that could not be identified as the expected benzofluorenone **12** (Scheme 4). In addition, lactone **19** was not observed. Photochemical studies on a substrate closely resembling **11** by Echavarren and co-workers led to observation of a lactone byproduct in their synthetic efforts toward prekinamycin.[13] Analysis of ^{13}C NMR and mass spectra suggested formation of a decarbonylated product which was tentatively assigned as naphthofuran **20**. However, a supporting correlation between the C(4)-proton and C(16)-carbon was not revealed in the HMBC spectrum given that they are four bonds removed and connected through a heteroatom.

To support the structural assignment for **20**, the decarbonylative photocyclization was performed on the simplified naphthoquinone **21** which provided naphthofuran **22** (Scheme 5). In addition to **22**, a nondecarbonylated byproduct arising from putative allylic hydrogen abstraction was formed.[11] Fortunately, an X-ray crystal structure of **22** was obtained, confirming the predicted carbon and oxygen connectivities which can be directly correlated to the more complex naphthofuran **20**. The yield for formation of **22** was calculated to be 61% using nitromethane (CH_3NO_2) as internal standard. However, purification by silica gel chromatography resulted in a lower isolated yield

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(8) (a) Maruyama, K.; Miyagi, Y. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1303–1304. (b) Maruyama, K.; Sakurai, H.; Otsuki, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2777–2779. (c) Maruyama, K.; Takuwa, A.; Matsukiyo, S.; Sogo, O. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1414–1419.

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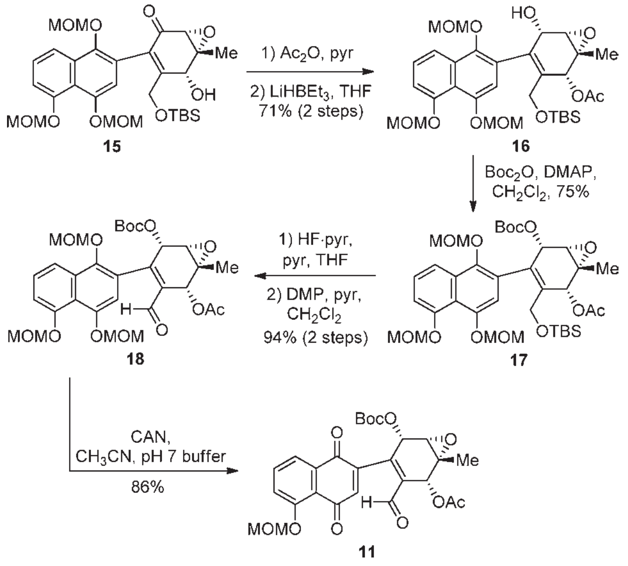
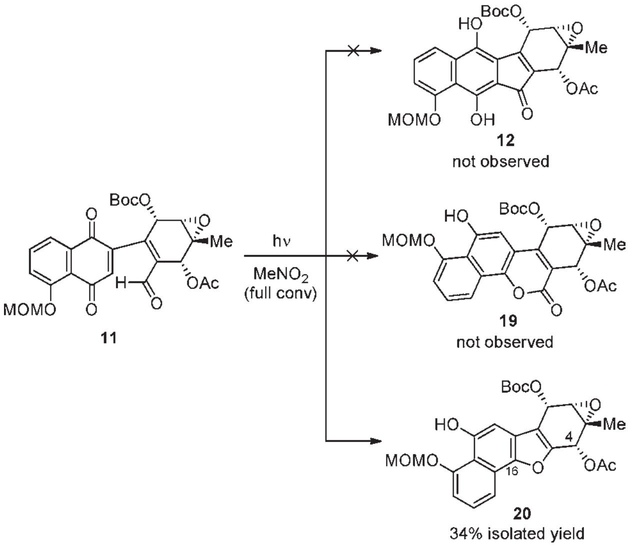
Scheme 3. Synthesis of Naphthoquinone **11**



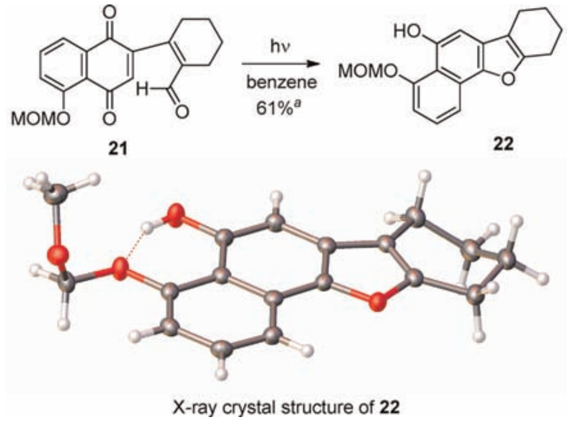
Scheme 4. Unexpected Decarbonylative Photocyclization to **20**



(37%) of **22** which was consistent with the isolated yield (34%) for **20**.

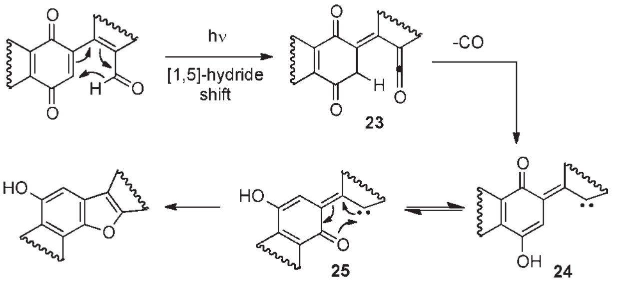
A mechanism for the decarbonylative photocyclization may involve a photochemical, concerted [1,5]-hydride shift of the acyl hydrogen to the vinylic carbon to afford ketene intermediate **23** (Scheme 6). A photoinduced hydride shift for *o*-vinylbenzaldehydes has been demonstrated in several studies[14,15] and in some instances decarbonylation products have been reported.[15] In this regard, decarbonylation of the derived vinyl ketene **23** may provide *β*-acyl alkenyl carbene intermediate **24**. Isomerization of **24** to carbene **25** would provide a suitable orientation for naphthofuran formation upon 6*π*-electrocyclization.[16]

Scheme 5. Synthesis and X-ray Crystal Structure of **22**[a]



[a] Yield determined by ^1H NMR analysis using CH_3NO_2 as an internal standard.

Scheme 6. Proposed Mechanism for Decarbonylative Photocyclization



To explore the reaction mechanism, deuterium-labeled aldehyde **26**[11] was prepared to study the photocyclization to naphthoquinone **27** and the possibility for deuterium incorporation at the C(8)-position (Scheme 7).[17] However, photoirradiation of **26** in benzene-d_6 provided **22** in which **27** or deuterium incorporation of the phenol was not observed. The half-life of **27** may be relatively short in

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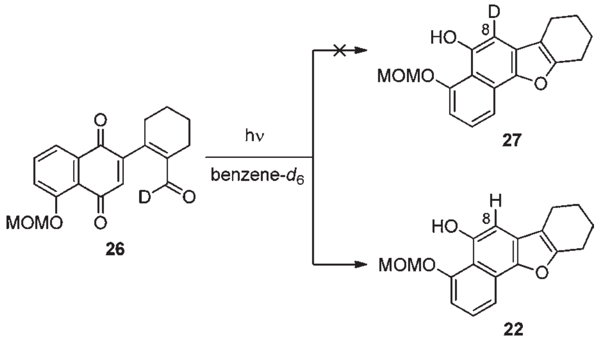
(17) For analogous deuterium-labelling studies for [1,5]-hydride shifts of *o*-vinylbenzaldehydes, see ref 15b.

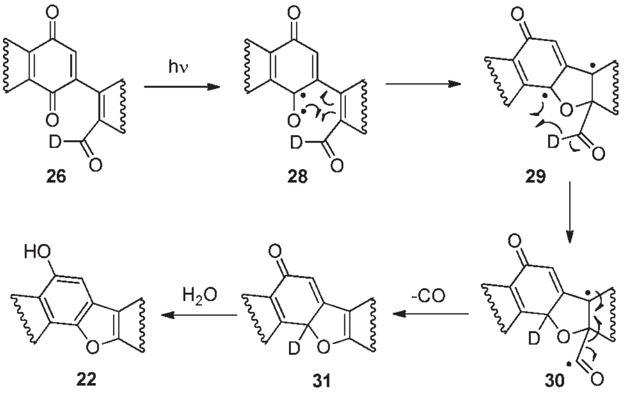
the presence of small amounts of water through keto−enol tautomerization. The latter hypothesis was disproved upon failure to observe the reverse process, deuterium incorporation at the C(8)-position after exchange of **22** with D_2O. Furthermore, deuterium exchange was not observed when **22** was photoirradiated in a 10% solution of D_2O in anhydrous benzene.[18]

Scheme 7. Deuterium-Labeling Studies



An alternative mechanism accounting for the deuterium-labeling studies may not involve direct transfer of deuterium to the C(8)-carbon. For example, photoexcited quinone **28** may cyclize to form biradical **29** (Scheme 8). Benzoquinones bearing an alkenyl moiety with a vinyl hydrogen have been demonstrated to undergo photocyclization to diradical intermediates, in which a subsequent hydrogen shift yields benzofurans.[19] Likewise, intramolecular abstraction of the deuterium in **29** would provide acyl radical **30** which upon decarbonylation[20] may afford furan intermediate **31**. Rearomatization with water would give naphthofuran **22** without deuterium incorporation.

Scheme 8. Alternative Mechanism for Decarbonylative Photocyclization



The serendipitous discovery of the decarbonylative photocyclization represents a novel synthesis of a benzofuran containing a highly substituted, fused cyclohexene moiety.[21] This motif is found in natural products (e.g. propolis-benzofuran B)[22] in which application of this photochemical methodology may prove beneficial for total synthesis. Moreover, the methodology provides neutral conditions to synthesize the benzofuran unit without using harsh acidic or basic conditions that may compromise the integrity of functionalized cyclohexenes. Further mechanistic studies and applications of the decarbonylative photocyclization are currently in progress and will be reported in due course.

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Supporting Information Available. Experimental procedures, compound characterization data, and X-ray crystallographic information files. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.