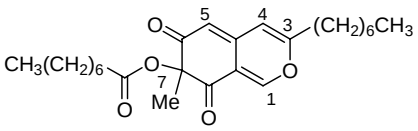
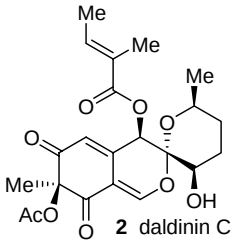
Studies Towards the Synthesis of Azaphilone Natural Products

The azaphilones represent a structurally diverse family of natural products containing a highly oxygenated bicyclic core and quaternary center (*cf.* **1-7**, **Figure 1**) This class of molecules is characterized by a wide range of biosynthetic modifications of the bicyclic ring system, including oxidation of the *4H*-pyran ring (*cf.* **2** and **3**), annulation, (*cf.* **4**), and halogenation.. These molecules exhibit a wide range of biological activities, including sphingosine kinase, fatty acid synthase, gp120-CD4, Grb2-SH2, telomerase, p53-MDM2 interaction, and HIV REV/RRE binding inhibition. The potent and varied biological activities of azaphilones may be related to reaction of the *4H*-pyran nucleus with amines to produce the corresponding vinylogous 4-pyridones (*cf. Figure 1*, **6** and **7**). Identification of molecules such as the Grb2-SH2 antagonist **7** also indicates that modifications of the pyran moiety (*e.g.* vinylogous pyridinone or isoquinolinone formation) can afford substances with important biological activities including inhibition of cancer cell proliferation.

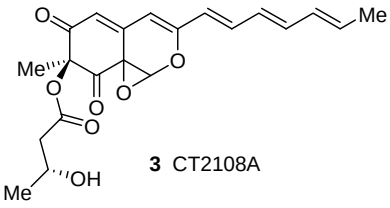
Figure 1. *Representative Azaphilone Natural Products*



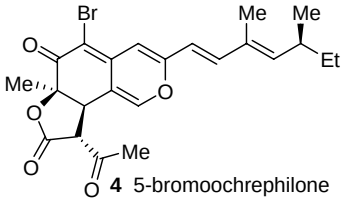
1 S-15183a



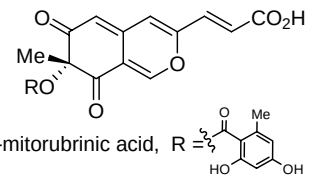
2 daldinin C



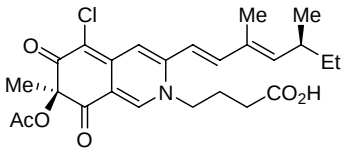
3 CT2108A



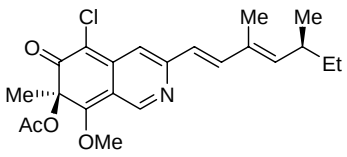
4 5-bromoochrephilone



5 (-)-mitorubrinic acid, R =



6 isochromophilone IX



7 8-*o*-methylsclerotiorinamine

Our initial studies have shown that *o*-alkynylbenzaldehyes such as **8** may be quantitatively transformed into 2-benzopyrylium salts **9** using gold (III)-catalyzed cycloisomerization in the presence of a protic acid (**Scheme 1**, *Angew. Chem. Int. Ed. Engl.*, **2004**, *43*, 1239 -1241). Subsequent *in situ* oxidation of the 2-benzopyrylium salt to the corresponding azaphilone was successfully accomplished employing IBX (*o*-iodoxybenzoic acid) and catalytic amounts of tetrabutylammonium iodide as a phase transfer catalyst and apparent IBX activator. The azaphilone core **10** was further acylated to the natural product S-15183a, chlorinated to azaphilone **11**, and finally converted to vinylogous pyridone **12**. Studies towards the asymmetric synthesis of the azaphilone core and select natural product targets are currently in progress in the Porco laboratory.

Scheme 1. *Cycloisomerization of Alkynylbenzaldehydes Enroute to the Azaphilones*