A Biomimetic Approach to the Rocaglamides Employing Photogeneration of Oxidopyryliums Derived from 3-Hydroxyflavones

The plant genus Aglaia (Meliaceae) from the tropical rain forests of Indonesia and Malaysia is the source of a unique group of natural products featuring unique and densely functionalized ring systems (Figure 1, Curr. Org. Chem. 2001, 5, 923-938). One class of compounds from this genus possess a cyclopenta[b]tetrahydrobenzofuran ring system and includes compounds such as rocaglamide (1), aglaroxin C (2), cyclorocaglamide (3), and the recently isolated dioxanyloxy-modified derivative silvestrol (4) (J. Org. Chem. 2004, 69, 3350-3358). The structurally related aglains containing a cyclopenta[bc]benzopyran ring system (e.g. thapsakon (5) and aglaforbesin (6)) have also been isolated from Aglaia. Finally, forbaglin derivatives (e.g. 7 and 8, Figure 1) are benzo[b]oxepines derived from formal oxidative cleavage of the aglайн core. Rocaglamides have been shown to display remarkable insecticidal activity (LC50 of 1 = 1-2 ppm against the larvae of S. littoralis). (Phytochemistry 1997, 44, 1455-1461). The original report on the isolation of rocaglamide revealed that 1 also exhibited potent anticancer activity (IC50 = 1.0 ng/mL) against KB and P388 human cancer cell lines. Subsequent studies have indicated that rocaglamides exhibit potent antiproliferative and antileukemic activities (Chemico-biological interactions 1998, 115, 215-228) and also inhibit TNF-α or PMA-induced NF-κB activity in the nanomolar range in human T cell lines. (J. Biol. Chem. 2002, 277, 44791-44800) The most recently isolated rocalate, silvestrol 4, displays cytotoxic activity against human cancer cell lines comparable to the anticancer drug paclitaxel (Taxol).

Figure 1: Rocaglamides and Related Compounds from Aglaia
Recently, we have reported a unified biomimetic approach to the aglain-forbaglin-rocaglamide classes of natural products ("A Biomimetic Approach to the Rocaglamides Employing Photogeneration of Oxidopyryliums Derived from 3-Hydroxyflavones." Gerard, B.; Jones, G., II.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2004**, *126*, 13620-13621). The overall approach (Figure 2) involves photogeneration of oxidopyryliums via Excited State Intramolecular Proton Transfer (ESIPT) of 3-hydroxyflavones followed by [3+2] dipolar cycloaddition to afford the aglain core. A α-ketol (acyloin) rearrangement was employed to transform the aglain core to the rocaglamide framework. This approach was successfully used for the synthesis of the natural product (±)-methyl rocaglate. Synthesis of additional rocaglamide family members is currently underway.

*Figure 2: Biomimetic Approach to the Rocaglamides and Related Compounds*