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

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The plant genus *Aglaia*, native to the tropical rain forests of Indonesia and Malaysia, is the source of a unique group of densely functionalized natural products (Figure 1).[1] The rocaglamides, including the parent (**1**)[2] and the recently isolated dioxanyloxy-modified derivative silvestrol (**2**),[3] possess the cyclopenta[*b*]-tetrahydrobenzofuran ring system. The structurally related cyclopenta-[*bc*]benzopyran-containing aglains (e.g., **3** and **4**) have also been isolated from *Aglaia*.[4] The forbaglins (e.g., **5**, Figure 1) are benzo-[*b*]oxepines derived from formal oxidative cleavage of the aglain core. The rocaglamides exhibit potent anticancer[2] and antileukemic activity,[5] as well as NF-κB inhibitory activity at nanomolar concentrations in human T cells.[6] The rocaglate silvestrol **2** displays cytotoxic activity against human cancer cells comparable to the anticancer drug Taxol.[3]

As proposed by Proksch and co-workers[1] and Bacher and co-workers,[7] the rocaglamides may be biosynthetically derived from reaction of 3-hydroxyflavone (3-HF) with cinnamide derivatives to afford the aglain core followed by skeletal rearrangement. Although the rocaglamides have been the subject of a number of synthetic investigations,[8] syntheses of the related aglains,[4] aglaforbesins,[4] and forbaglins have not been reported. Moreover, a unified synthetic approach to these molecules based on biosynthetic considerations still remains to be developed.[8c] Herein, we report a biomimetic approach to the rocaglamides and the related aglains and forbaglins involving excited-state intramolecular proton transfer (ESIPT) of 3-HF derivatives[9] and dipolar cycloaddition of the resulting oxidopyrylium[10] species.

Our approach is outlined in Scheme 1. Generation of oxidopyryllium **8** from 3-HF derivative **6** or **7** and subsequent dipolar cycloaddition to cinnamate derivatives should directly afford the aglain core **9**. Literature reports have documented excited-state intramolecular proton transfer[9] of 3-HF derivatives leading to the formation of the requisite oxidopyrylliums **8**. Oxidative cleavage of **9** to forbaglin **10** core may be conducted using $Pb(OAc)_4$.[11] Core structure **9** may alternatively be converted to dehydrorocaglate **11** by α-ketol (acyloin) rearrangement.[12] Such rearrangements have been conducted using acidic or basic conditions or employing metal catalysis and have been used with success in a number of natural product syntheses.[13] Hydroxyl-directed reduction of **11**[8b] should afford rocaglates **12**.

In initial studies, we evaluated photoirradiation of commercially available 3-hydroxyflavone **6** and dipolarophile **13** using a 450 W medium-pressure mercury lamp (uranium filter, $\lambda > 350$ nm, Scheme 2). After irradiation in MeCN (rt, 2 h), the 3-HF was consumed and a mixture of products was observed resulting from presumed [3+2] cycloaddition (Scheme 1). According to spectroscopic data and X-ray analysis of a crystalline derivative,[14] the major compound (56%) was confirmed to be endo cycloadduct **15** in which the phenyl ring of the dipolarophile is anti to the oxido bridge.[10b] Interestingly, an equilibrium between **15** and the benzo-

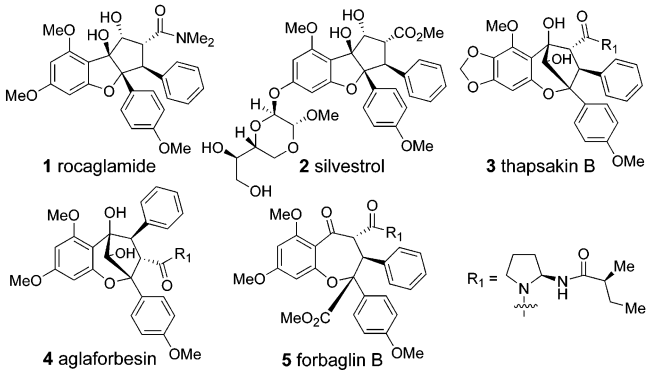
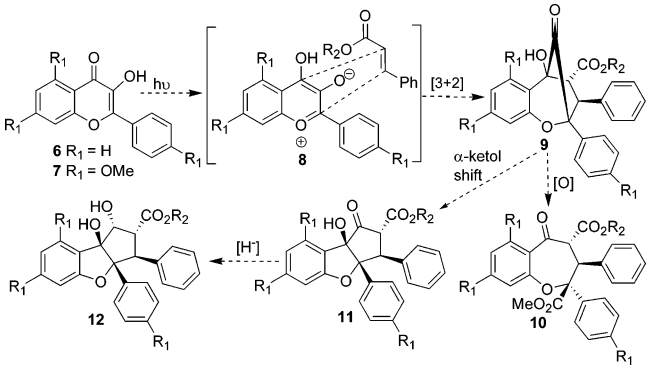
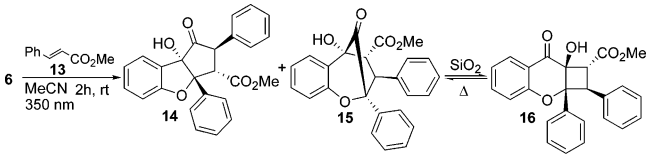


Figure 1. Rocaglamides and related compounds from *Aglaia*.

Scheme 1. Unified Biomimetic Approach to the Aglains−Forbaglins−Rocaglamides



Scheme 2. Photochemical [3+2] Cycloaddition



[*b*]cyclobutapyran-8-one **16** is observed during silica gel purification resulting from an acid-mediated ketol shift.[15] This equilibrium between the two core structures was found to be controlled by heating the mixture (EtOAc, 65 °C) to afford **15**. Monitoring of the photocycloaddition by ^{1}H NMR (CD_3CN) also confirmed formation of **15** as the major product.[14] Compound **14** (14%) was identified as a cyclopenta[*b*]tetrahydrobenzofuran by further conversion into a crystalline derivative.[14] In contrast to **15**, compound **14** is derived from exo [3+2] cycloaddition to an aglaforbesin-type derivative (cf. **4**, Figure 1) followed by acyloin rearrangement during the photoirradiation process.[16]

We next proceeded to evaluate conditions for conversion of aglain core structure **15** to both the rocaglamide and forbaglin ring

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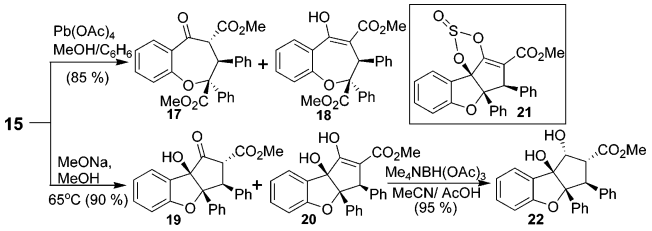
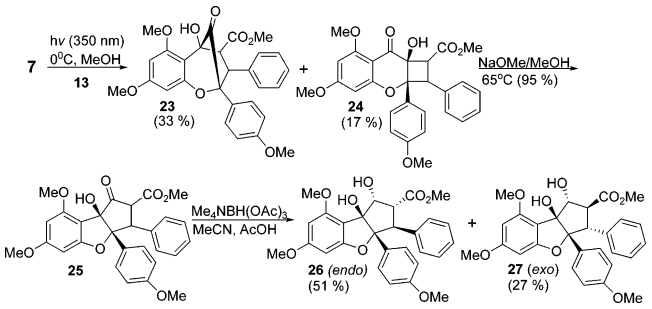
Scheme 3. Conversion of the Aglain to the Forbaglin and Rocaglamide Ring Systems



Scheme 4. Synthesis of (±)-Methyl Rocaglate



systems (Scheme 3). Treatment of aglain **15** with $Pb(OAc)_4$ in benzene/MeOH[11] at room temperature afforded benzo[*b*]oxepines **17** and **18** as a 2:1 mixture of keto−enol tautomers (85%). Attempted thermal acyloin rearrangement[17] of **15** did not afford any observable ketol shift product. Alternate treatment of **15** with protic or Lewis acidic conditions ($BF_3{\cdot}Et_2O$, $ZnCl_2$) resulted in decomposition of starting material. However, treatment of **15** under basic conditions (2.5 equiv of NaOMe,[15] MeOH), afforded a 1:1 mixture of keto−enol tautomers **19** and **20**. The success of such basic conditions for α-ketol rearrangement may be explained by formation of the enolate of **20** under basic conditions, which may drive the ketol shift equilibrium[18] toward the rocaglamide core. Further proof for this assumption was provided by treatment of **15** with NaH (2.1 equiv, THF, rt) and quenching the reaction mixture with thionyl chloride to afford the stable 1,3,2-dioxathiolane **21** (48%).[19] Hydroxyl-directed reduction[8b] of **19**/**20** afforded rocaglate **22** (95%).

We next proceeded to evaluate 3-HF derivatives with trimethoxy substitution suitable for the synthesis of the rocaglamides and related compounds (Scheme 4). Photoirradiation (uranium filter) of kaempferol[20] derivative **7** and methyl cinnamate **13** (MeOH, 0 °C) afforded the aglain **23**, as well as benzo[*b*]cyclobutapyran-8-one **24** (33% and 17%, respectively) after purification on SiO_2. Basic conditions (NaOMe, MeOH) were used to effect α-ketol rearrangement of both **23** and **24** to afford a mixture of endo and exo cycloadducts **25** in which the endo isomer was obtained as a mixture of keto−enol tautomers.[14] Reduction of **25** afforded (±)-methyl rocaglate **26** (51%) and the corresponding exo stereoisomer **27** (27%).[8a,14] Spectral data for synthetic **26** were in full agreement with those reported for natural methyl rocaglate.[21]

In conclusion, we have developed a biomimetic approach to the aglain/rocaglamide/forbaglin classes of natural products. The key strategy involves dipolar cycloaddition of oxidopyrylium ylides derived from excited-state intramolecular proton transfer of 3-hydroxyflavones. Methodology has been developed to transform the initially formed aglain structures to rocaglamide derivatives using a base-mediated α-ketol rearrangement. Further studies, including asymmetric synthesis of the rocaglamides and further applications of the photocycloaddition process, are in progress and will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds (PDF), including X-ray crystal structure coordinates and files in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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