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Total Syntheses of the Isomeric Aglain Natural Products Foveoglin A and Perviridisin B *via* Selective ESIPT Photocycloaddition

Wenyu Wang, Dr[a], **Prof. Anthony Clay, Dr**[b,d], **Retheesh Krishnan, Dr**[c], **Neil J. Lajkiewicz, Dr**[a], **Prof. Lauren E. Brown, Dr**[a], **Jayaraman Sivaguru**[b,d], and **John A. Porco Jr**[a]

[a]Department of Chemistry, Center for Molecular Discovery (BU-CMD), Boston University, 590 Commonwealth Avenue, Boston, Massachusetts 02215, United States

[c]Department of Chemistry, Government College for Women, Thiruvananthapuram 695014, India

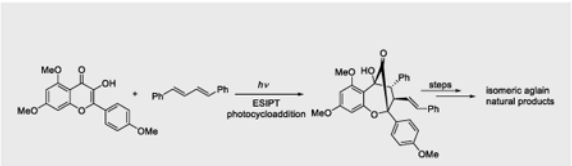
[d]The work was performed at North Dakota State Universit

Abstract

Selective ESIPT photocycloaddition of 3-hydroxyflavones with *trans, trans*-1,4-diphenyl-1,3-butadiene is described. Using this methodology, total syntheses of the natural products (±)-foveoglin A and (±)-perviridisin B have been accomplished. Enantioselective ESIPT photocycloaddition using TADDOLs as chiral hydrogen-bonding additives provided access to (+)-foveoglin A. Mechanistic studies have revealed the possibility for a photoinduced electron transfer (PET) pathway.

Graphical abstract

Selective ESIPT photocycloaddition of 3-hydroxyflavones with *trans,trans*-1,4-diphenyl-1,3-butadiene has been achieved which enabled the total syntheses of isomeric aglain natural products foveoglin A and perviridisin B. Mechanistic studies have revealed the possibility of a photoinduced electron transfer (PET) pathway.



Keywords

ESIPT photocycloaddition; Total synthesis; Photoinduced electron transfer; Asymmetric photoreaction

Correspondence to: Jayaraman Sivaguru; John A. Porco, Jr.

[b]Present address: Department of Chemistry and Center for Photochemical Sciences Bowling Geen State University, Bowling Green, OH 43403. USA sivagj@bgsu.edu

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Flavagline (rocaglate) natural products are compounds[1] which are biosynthetically derived from a flavonoid and a cinnamic amide derivative and include the cyclopenta[*b*]benzofuran rocaglamide (**1**)[2] and the cyclopenta[*b,c*]benzopyran (aglain) ponapensin (**2**)[3] (Figure 1). Both natural and synthetic rocaglates have been shown to exhibit anticancer and antiviral activities.[4] Due to their structural complexity and intriguing biological activities, a number of groups have reported chemical syntheses of rocaglates and analogues.[5] Previously, we reported a biomimetic approach towards these compounds in which 3-hydroxyflavone (3-HF) **5** undergoes ESIPT (excited state intramolecular proton transfer)-mediated (3+2) photocycloaddition[6] with dipolarophiles including methyl cinnamate **6a**.[7] Although this approach rapidly provides access to rocaglates, recent isolation reports of the aglain derivatives foveoglin A (**3**)[8] and perviridisin B (**4**),[9] as well as the related aglapervirisins, [10] suggested new challenges to employ ESIPT photocycloaddition to access their isomeric core structures in comparison to ponapensin (**2**).

We have previously reported that *trans*-stilbene **6**may be used as a dipolarophile in ESIPT photocycloadditions of 3-hydroxyflavones **5** (Scheme 1).[11] In the current study, we have evaluated *trans,trans*-1,4-diphenyl-1,3-butadiene (DPBD, **8**) as dipolarophile. By extending the conjugation of the reaction partner, we expected that four possible isomers could be formed (Scheme 1b). In particular, preferential formation of **11/12** *vs*. **9/10** would provide access to aglain scaffolds required for syntheses of **3** and **4** wherein the styrene moiety serves as an amide precursor.

We first examined photocycloadditions of 3-hydroxyflavone **5** and DPBD **8** (Scheme 2). Upon photoirradiation of **5** and **8** using TFE/CHCl3 (3:7) in a continuous photoflow reactor, [5c] only diastereomers **11** and **12** were produced (d.r. = 5:1). The inseparable mixture was treated with $NaBH_4$ to afford the corresponding secondary alcohols (d.r.= 5:1) and isolation of the major product **13** in 44% yield (2 steps). Compound **13** was subsequently acylated to provide the (±)-*p*-bromobenzoate (±)-**14** whose structure was established by single crystal X-ray diffraction.[12]

The total synthesis of (±)-foveoglin A (**3**) was next accomplished as illustrated in Scheme 3. *Bis*-trimethylsilyl protection of **13** to block cleavage of the C5-C10 bond followed by OsO_4-catalyzed dihydroxylation and subsequent oxidative cleavage of the derived diol using $Pb(OAc)_4$ provided aldehyde **15** (70% yield, 2 steps). Compound **15** was further treated with amine **16** to generate the corresponding imine which was transformed to an amide using oxidative amidation conditions.[13] Subsequent silyl deprotection using tetrabutylammonium fluoride furnished (±)-foveoglin A (**3**).

In order to achieve the synthesis of the congener perviridisin B (**4**), practical access to the *exo*-diastereomer **12** was required. After thorough evaluation of conditions, flow photocycloaddition of **5** and **8** using 2:1 CH_2Cl_2:isopropanol as solvent afforded a 52% yield of photocycloadducts **11** and **12** (d.r. = 1:1). The corresponding 10*S*-alcohol epimers were produced in 96% yield and in 10:1 diastereoselectivity by reduction with $NaBH(OAc)_3$ in trifluorotoluene. Subsequent trimethylsilyl protection furnished the mono-silylated product **18** which was subjected to oxidative double bond cleavage to afford aldehyde 19 in 68%

yield. Oxidative amidation[13] of **19** with amine **20**, followed by TMS deprotection and *in situ* acetate hydrolysis, afforded (±)-perviridisin B (**4**) (Scheme 4).

We next studied the corresponding enantioselective ESIPT photocycloaddition using chiral hydrogen-bonding additives.[14] Although we have reported use of TADDOL derivatives to mediate enantioselective ESIPT photocycloaddition of 3-hydroxyflavones, thus far dipolarophiles have been limited to cinnamates. Use of DPBD **8** which lacks the ester moiety as a potential hydrogen-bonding acceptor in comparison to dipolarophile **6a** provides further support for our proposal that host-guest complexation of 3-HF **5** by hydrogen-bonding additives controls enantioselectivity.[14a] In the presence of a stoichiometric amount of a hydrogen-bonding additive, 3-HF **5** and DPBD **8** were irradiated for 10 h at -78 °C. Limited solubility of DPBD **8** at low temperatures was observed which prompted us to dilute the reaction (0.005 M) to achieve homogeneity. Using TADDOL **21** as a stoichiometric additive, we obtained two inseparable diastereomers which were reduced with $NaBH_4$ to obtain major diastereomer **13** for enantiomeric excess (e.e.) determination. As maintaining low temperature is helpful for enantioselectivity,[14] and to overcome significant heat release from use of traditional UV lamp, a UV-LED (λ = 365 nm) was chosen as a light source[15] After condition optimization,[16] TADDOL **21** was found to be an optimal additive to provide compound (+)-**13** in 67% yield and 83% e.e., whereas TADDOL **22** was able to facilitate the photocycloaddition in a similar yield and in 49% e.e. (Scheme 5). Interestingly, use of the chiral trifluoroethanol, Pirkle's alcohol **23**, led to **13** in 71% e.e. Although Pirkle's alcohol **23** was previously reported as an NMR chiral shift reagent,[17] this study represents the first application of Pirkle's alcohol as a chiral hydrogen bonding additive.

Due to difficulties in achieving absolute stereochemistry assignment of (+)-13 or (+)-**14** by X-ray crystal structure analysis, the absolute configuration of (+)-**13** was determined by VCD analysis[18] of *p*-bromobenzoate (+)-**14**.[16] Further conversion of (+)-**13** (Scheme 5) afforded (+)-foveoglin A in 96% ee ($[\alpha]_D$[20] -30.0 natural (c 0.16, $CHCl_3$), $[\alpha]_D$[23] +25.3 synthetic (c 0.16, $CHCl_3$)). The absolute configuration of natural (-)-foveoglin A (**3**) is in agreement with the aglain natural product, (-)-ponapensin (**2**).[3]

Mechanistic studies were next conducted to provide a rationale for the selectivity of the photocycloaddition. In polar protic solvents (*e.g.* trifluoroethanol), dual fluorescence emission (fluorescence of the normal state N and tautomer state T) was observed both at room temperature and 77 K[16] Based on the fast ESIPT process and the singlet state energy for **5**, singlet energy transfer from excited **5** to **8** was ruled out.[20] As determined by the phosphorescence spectrum, the lowest triplet excited state of 3-HF **5** was found to be ~54 kcal/mol[16] In addition, using the Rehm-Weller equation,[21] the feasibility for photoinduced electron transfer (PET)[22] initiating the photocycloaddition from the triplet excited state was ascertained. The free energy for electron transfer from the triplet excited state was exergonic (ΔG_{ET} = -5.3 kcal/mol) suggesting a facile PET pathway initiating the photocycloaddition. To ascertain that photoexcitation of 3-HF **5** rather than DPBD **8** is crucial for photoreactivity, a control experiment using a purple LED (λ_{max} = 395 nm) as light source for selective excitation of **5** was found to cleanly produce the photocycloadduct. [16] As shown in Figure 2, the triplet excited state of **5** may initiate the photocycloaddition

via radical and/or electron transfer pathways. Formation of the triplet diradical **25** either by direct addition of **8** to ^{3}**5*** or through radical ion pair **24** followed by subsequent intersystem crossing (ISC) leads to singlet diradical 26. Ring closure of **26** affords **11** and **12**. The selectivity in the system is dictated by the electronics (due to charge transfer interactions) as well as the approach of **8** towards [3]$\mathbf{5}_{T}$* Based on our photophysical measurements,[16] we did not observe an electron donor-acceptor (EDA) complex[23] between **5** and **8** in the ground state. The lack of a ground state EDA complex is expected as triplet state **5** initiates the electron transfer pathway.

To further evaluate dipolarophile scope, we synthesized a number of unsymmetrical DPBDs and tested their feasibility in ESIPT photocycloaddition.[16] Use of the electron deficient pentafluorophenyl DPBD **27**[24] cleanly afforded photocycloadducts which were subjected to the previously described reduction, silylation, and alkene cleavage sequence to afford two aldehyde products **30** and **15** in a 4:1 ratio (Scheme 6). This outcome indicates that the pentafluorophenyl moiety of **27** may stabilize negative charge after formation of a radical ion pair (*cf.* **24**, Figure 2) which appears to dominate the selectivity for the photocycloaddition. Additionally, a **π-π** stacking (donor-acceptor) interaction *(cf.* **28**, Scheme 6) between **5** and **27** also appears to orient photocycloaddition site-selectivity. This selectivity was also observed with other fluorinated dipolarophiles including *bis*-trifluoromethylphenyl DPBD and pentafluorostilbene.[16]

In summary, total syntheses of the aglain natural products foveoglin A (**3**) and perviridisin B (**4**) have been accomplished employing selective ESIPT photocycloaddition of 3-HF **5** with DPBD **8**. Enantioselective ESIPT photocycloaddition was also demonstrated using chiral hydrogen-bonding additives to access (+)-foveoglin A. Mechanistic studies were conducted leading to the identification of a photoinduced electron transfer (PET) pathway. ESIPT photocycloadditions of 3-HF **5** with substituted, unsymmetrical DPBDs have also been conducted leading to site-selective photocycloadditions. Further applications of ESIPT photocycloaddition towards the syntheses of complex natural products and derivatives are currently in progress and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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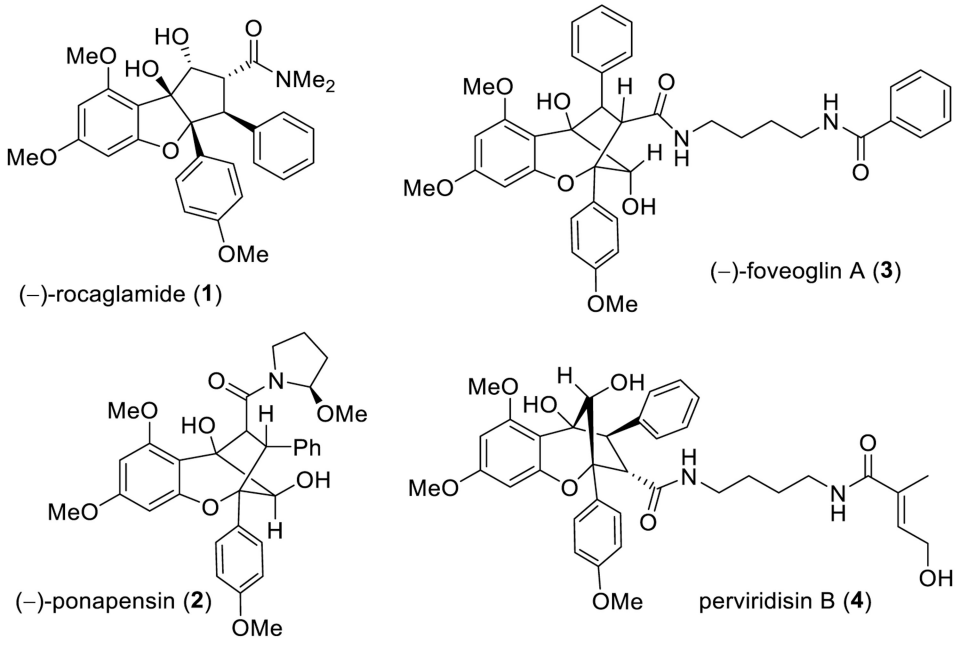


Figure 1.
Rocaglamide (**1**), ponapensin (**2**), and the isomeric aglain natural products (**3**) and (**4**).

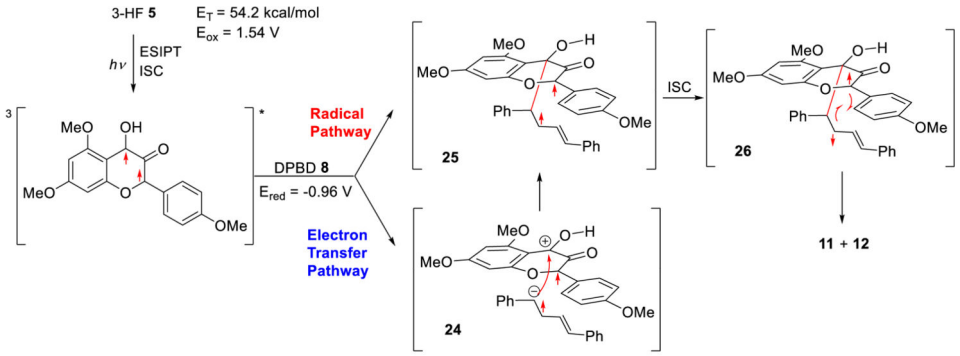
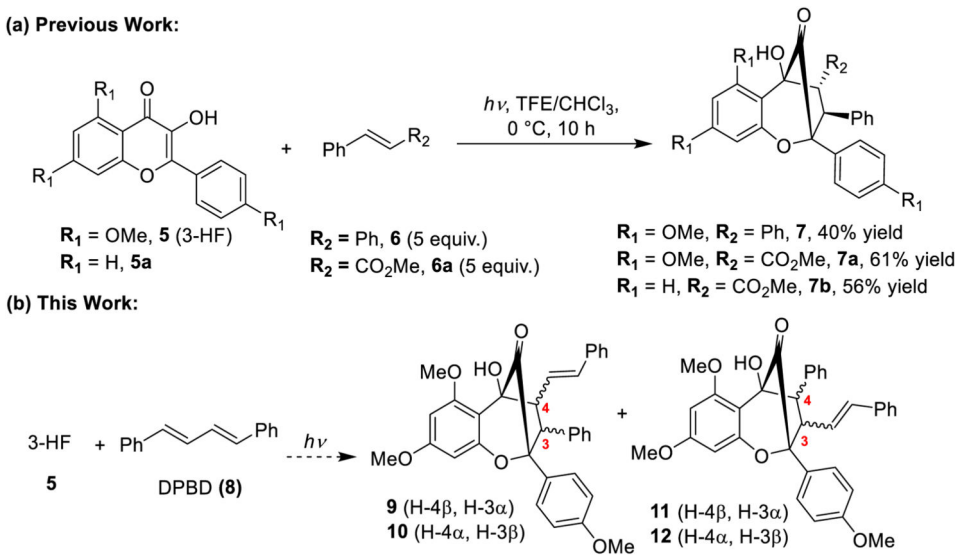
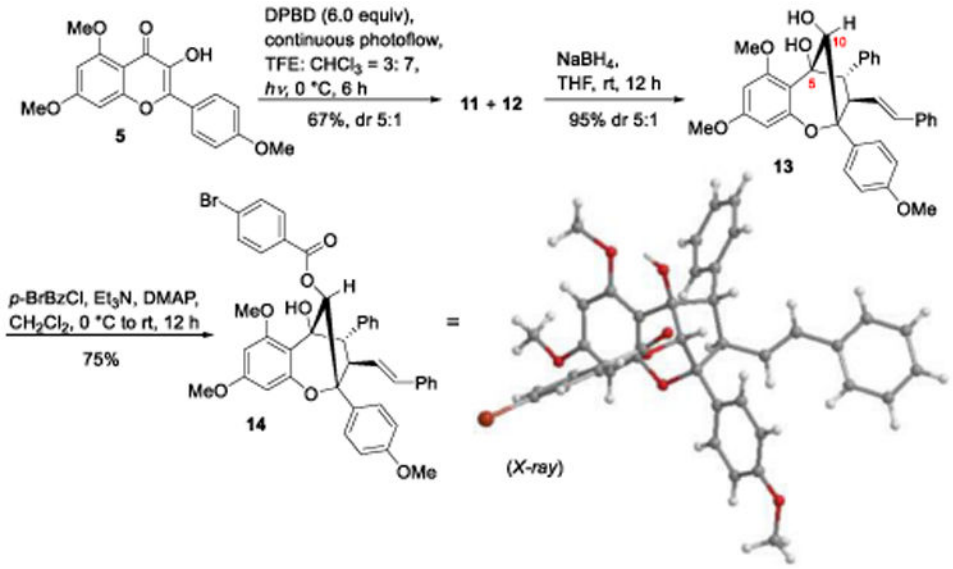


Figure 2.
Proposed mechanism for ESIPT photocycloaddition of 3-HF **5** and DPBD **8**.

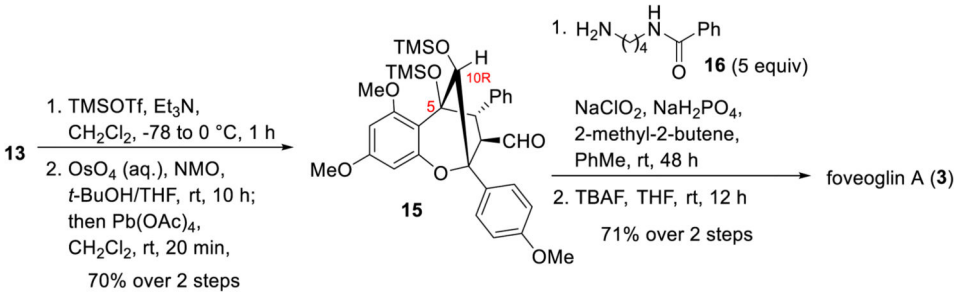


Scheme 1.

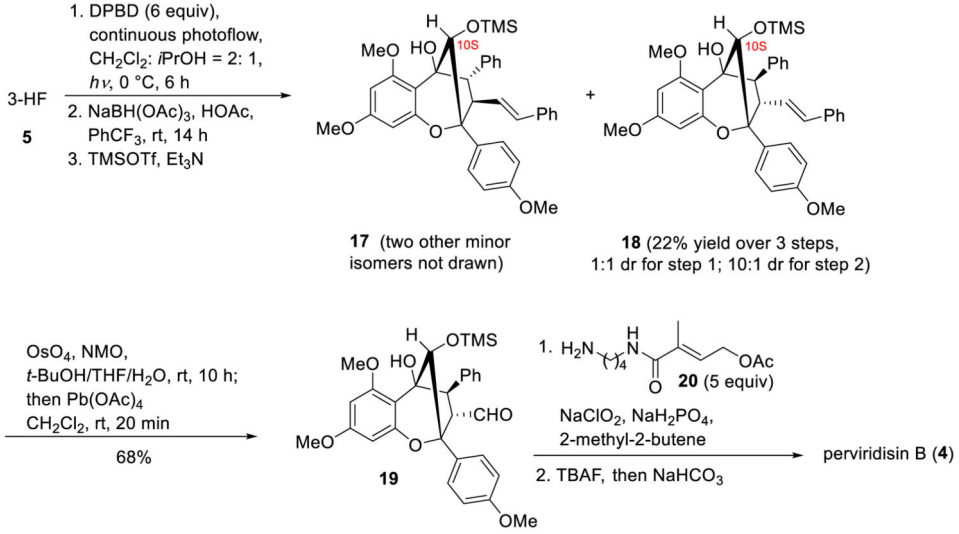
(3+2)-Photocycloaddition of 3-hydroxyflavones with dipolarophiles **6**, **6a**, and **8**.



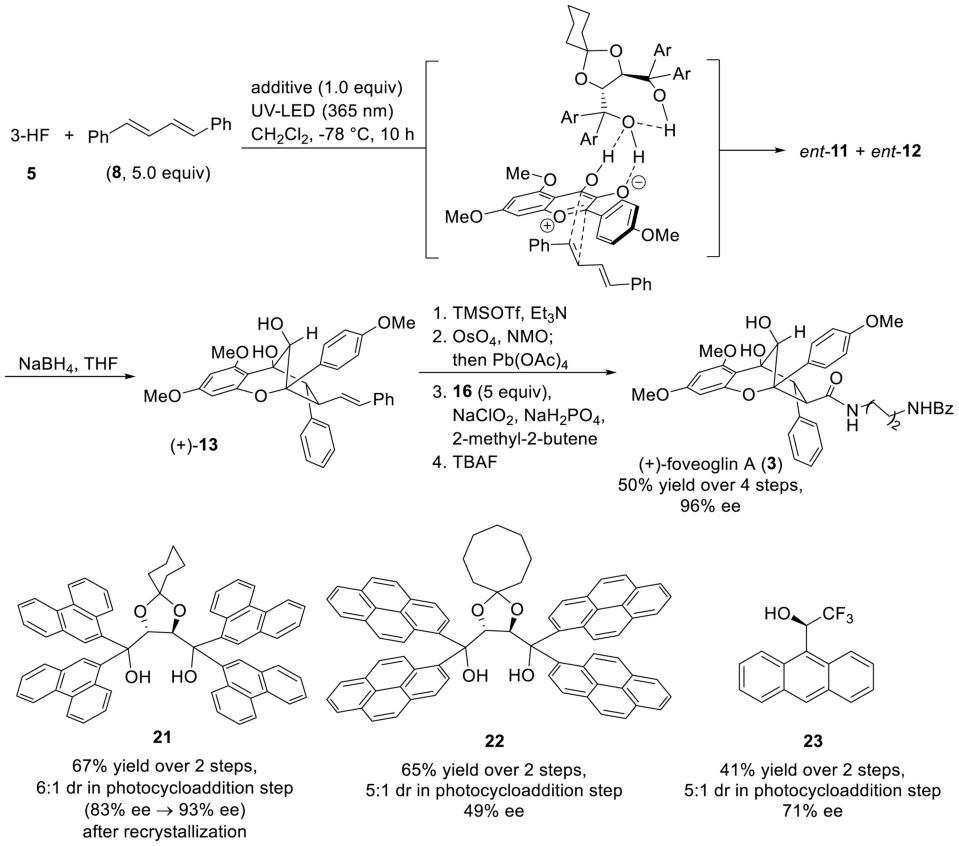
Scheme 2.
ESIPT photocycloaddition of 3-HF **5** with DPBD **8**.



Scheme 3.
Total synthesis of (±)-foveoglin A.

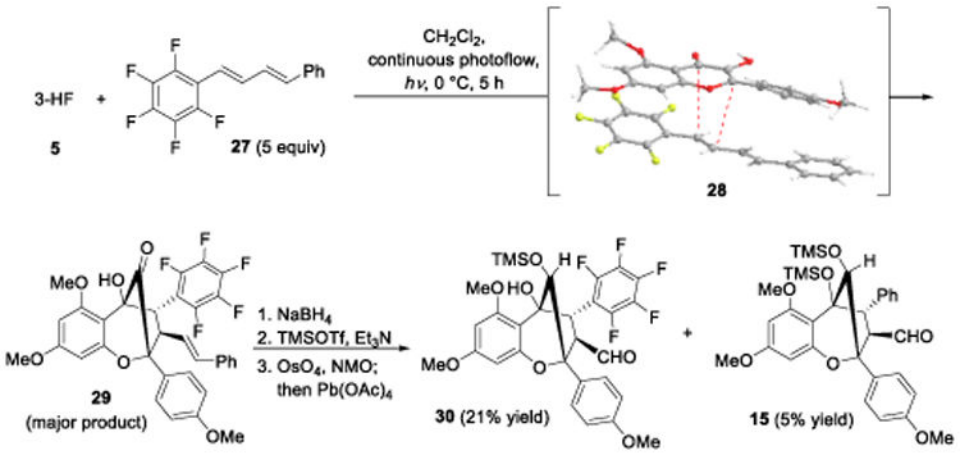


Scheme 4.
Total synthesis of (±)-perviridisin B.



Scheme 5.

Enantioselective ESIPT photocycloaddition and asymmetric synthesis of (+)-foveoglin A.



Scheme 6.

Use of pentafluorophenyl dipolarophile **27** in ESIPT photocycloaddition.