# Enantioselective Photocycloaddition of 3-Hydroxyflavones: Total Syntheses and Absolute Configuration Assignments of (+)-Ponapensin and (+)-Elliptifoline

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**S** *Supporting Information*

**ABSTRACT:** We have previously reported development of biomimetic, asymmetric [3 + 2] photocycloadditions between 3-hydroxyflavones and cinnamate dipolarophiles to access (−)-rocaglamide and related natural products. Herein, we describe enantioselective syntheses of aglain cycloadducts leading to the first total syntheses and absolute configuration assignments of the aglain natural products (+)-ponapensin and (+)-elliptifoline.
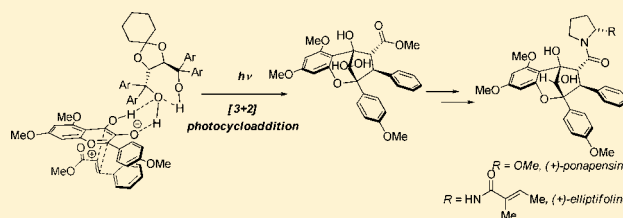
## INTRODUCTION

The plant genus *Aglaia* produces a series of secondary metabolites, including methyl rocaglate (**1**),[1] the densely functionalized cyclopenta[*b,c*]benzofuran (rocaglate) anticancer agent silvestrol (**2**),[2] and the cyclopenta[*b,c*]benzopyrans (aglains) (−)-ponapensin (**3**)[3] and (−)-elliptifoline (**4**)[4] (Figure 1). Relative stereochemical configurations of **3** and **4**
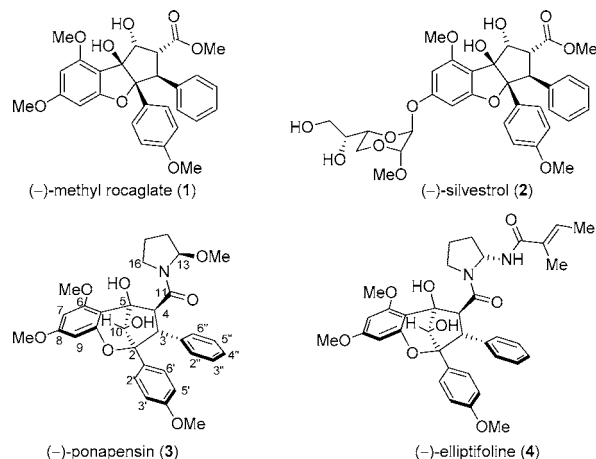


**Figure 1.** Representative natural products from the genus *Aglaia*.

were proposed in their respective isolation reports. Although aglains do not typically possess the strong biological activity of their rocaglate counterparts, (−)-ponapensin (**3**) was found to exhibit potent NF-κB inhibitory activity in an enzyme-based ELISA assay (IC$_{50}$ = 60 nM) while rocaglamide[5] and methyl rocaglate (**1**) exhibited IC$_{50}$ values of 2.0 and 2.3 $\mu$M, respectively.[3] Other aglain natural products including aglain B,[6] 4-*epi*-aglain A,[7] 10-*O*-acetylaglain B,[7] and aglain C[6] were not

active in the NF-κB assay (IC$_{50}$ > 5 $\mu$M).[3] Unlike silvestrol and related rocaglates,[8,9] thus far no total syntheses of aglain natural products including **3** and **4** have been reported to date.

We have developed a biomimetic approach to the rocaglates using [3 + 2] photocycloaddition between 3-hydroxyflavones (3-HF's) **5** and cinnamate derivatives **6** as dipolarophiles followed by a ketol rearrangement/reduction sequence.[8a,9b,10] Herein, we present the first enantioselective total syntheses and absolute configuration assignments of the aglain natural products (+)-ponapensin (**3**) and (+)-elliptifoline (**4**), the optical antipodes of metabolites found in nature.

## RESULTS AND DISCUSSION

**Cyclopenta[*b,c*]benzopyran Core Synthesis.** Based on previous results,[10c] [3 + 2] photocycloaddition between oxidopyrylium **7** derived from Excited State Intramolecular Proton Transfer (ESIPT) of 3-HF **5** and methyl cinnamate **6a** afforded the hydrated aglain (±)-**8a** in 61% yield which was recrystallized from acetonitrile (Scheme 1).[11] Various conditions were evaluated on substrate **8a** in order to achieve stereoselective reduction of the bridgehead ketone including DIBAL-H, L-Selectride, and aluminum isopropoxide (Al-(O*i*Pr)$_3$), all of which did not lead to reduced products. When **8a** was treated with NaBH$_4$ in MeOH, no reaction was observed (Table 1, entry 1). NaBH$_4$ reduction proceeded when aglain **8a** was better solubilized in THF (entry 2) and afforded reduced products **9a** and **10a** in a 1:5 ratio. Improved diastereoselectivity was not observed using Bu$_4$NBH$_4$[12] which afforded reduced aglain **10a** as the major product (dr = 5:1) in 98% yield (Table 1, entry 3). Fortunately, treatment of **8a** with Me$_4$NBH(OAc)$_3$[13] in benzene (entry 4) afforded reduction

**Scheme 1. Cycloaddition of 3-HF 5 and Cinnamic Esters 6**



8a, R = Me, 61% yield, 3:1 dr
8b, R = Bn, 60% yield, 3:1 dr
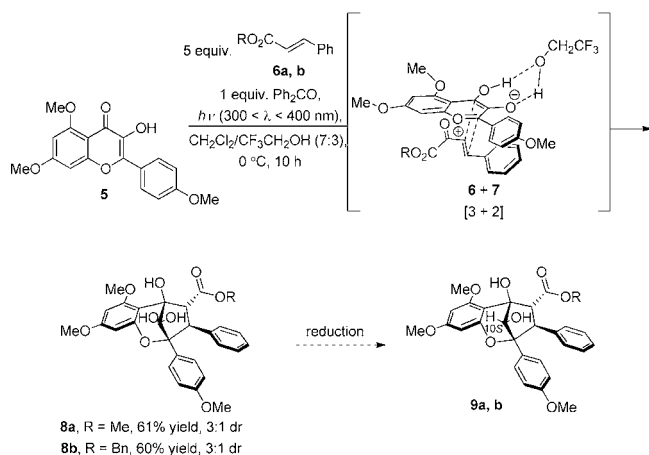
**Table 1. Diastereoselective Reduction of Aglain (±)-8a**



| entry | reagent[a] | solvent | additive | 9a:10a[b] | yield (%)[c] |
|-------|-----------|---------|----------|-----------|--------------|
| 1 | NaBH$_4$ | MeOH | — | — | 0 |
| 2 | NaBH$_4$ | THF | _ | 1:5 | 93 |
| 3 | Bu$_4$NBH$_4$ | THF | _ | 1:5 | 98 |
| 4 | Me$_4$NBH(OAc)$_3$ | benzene | AcOH | 3:1 | 95 |
| 5 | Me$_4$NBH(OAc)$_3$ | PhCF$_3$ | AcOH | 5:1 | 95 |
| 6 | NaBH(OAc)$_3$ | PhCF$_3$ | AcOH | 10:1 | 95 |

[a]See Supporting Information for detailed experimental procedures.
[b]Determined by $^1$H NMR analysis of the crude reaction mixture.
[c]Isolated after purification by silica gel chromatography.

product **9a** which has the 10S configuration required for synthesis of both ponapensin (**3**) and elliptifoline (**4**). The relative configuration assignment of C10 was determined via NOE correlation observed between H10/H4 of aglain **10a** and an absence of this correlation in its epimer **9a**.[11]

After evaluation of solvents, we found that 2,2,2-trifluoromethylbenzene (PhCF$_3$) was an optimal solvent for hydroxyl-directed reduction of aglain **8a** to afford **9a** in 5:1 dr (entry 5). The counterion size of the reducing agent appears to be significant in enhancing the diastereoselectivity of the reduction, as NaBH(OAc)$_3$[14] provided the 10S diastereomer **9a** in 10:1 dr (Table 1, entry 6). Treatment of hydrated ketone **8a** with 4 Å MS in CH$_2$Cl$_2$ led to the formation of the derived bridgehead ketone **11** (Figure 2).[11] Reduction of **11** with NaBH(OAc)$_3$ led to full conversion to **9a** in a shorter time (2 h vs 16 h for **8a**) without loss of diastereoselectivity.
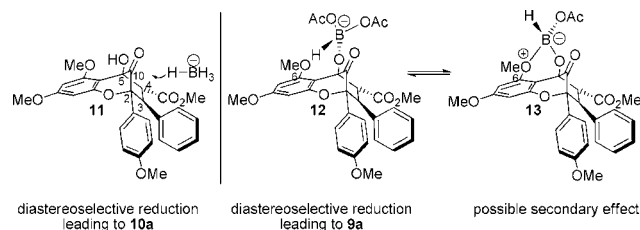


**Figure 2.** Proposed assemblies for diastereoselective reduction.

A rationale for reagent-controlled, diastereoselective reduction of bridgehead ketone **11** is shown in Figure 2. When using a borohydride reducing agent (e.g., NaBH$_4$, Bu$_4$NBH$_4$), the bridgehead ketone **11** may be preferentially attacked on the si face due to larger dihedral angles for O−C10−C5−C4 and O−C10−C2−C3 (134° and 138°, respectively) versus the smaller dihedral angles of O−C10−C5−C5a and O−C10−C2−O (113° and 102°, respectively), thereby allowing more optimal orbital alignment for hydride addition to the bridgehead carbonyl.[15] Furthermore, use of a borohydride with a large counterion (e.g., Bu$_4$N$^+$) does not affect the diastereoselectivity. When a hydroxyl-directed reducing reagent[13] was used (e.g., NaBH(OAc)$_3$), diastereoselectivity did not appear to be derived from the 5-hydroxyl group in the usual fashion as this moiety is coplanar with the C10-carbonyl. We propose that borate complexation with the 5-hydroxyl takes place (cf. Figure 2, assembly **12**) leading to selective hydride delivery to the re face of the activated carbonyl due to the preferred orientation of the borate near the less sterically encumbered phloroglucinol ring system. Furthermore, we considered that the oxygen lone pair of the 6-methoxy group may also exchange with the borate and further direct the reduction to the re face as a secondary effect (cf. Figure 2, assembly **13**). The latter issue was examined using the model aglain **14**[16] which lacks a methoxy at C6 (Scheme 2). Sodium triacetoxyborohydride reduction of **14**

**Scheme 2. Reductions of Demethoxy Aglain 14**
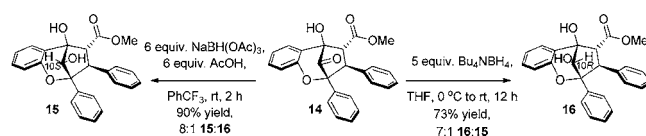


furnished reduced aglain **15** in an 8:1 dr which was not significantly different from the corresponding reduction of aglain **8a** (10:1 dr). Therefore, the secondary effect illustrated in assembly **13** (Figure 2) is not likely a significant factor to the diastereoselectivity for the reduction. Furthermore, reduction of ketone **14** with Bu$_4$NBH$_4$ yielded the reduced aglain **16** in 7:1 dr, which is comparable to the diastereoselectivity observed in the Bu$_4$NBH$_4$ reduction of aglain **8a** (5:1 dr). Relative configurations of **15** and **16** were determined by NOESY NMR spectroscopy.[11]

**Enantioselective Photocycloaddition to the Aglain Core.** Having established a method to access aglain core structure **8a**, we synthesized enantioenriched aglain **9a** using the tetrakis-9-phenanthrenyl TADDOL **17** (Scheme 3).[10a] Host−guest complexation of **17** and 3-HF **5** promoted enantioselective [3 + 2] photocycloaddition leading to isolation of the hydrated-aglain cycloadduct (+)-**8a** in 69% yield and 85.5:14.5 er. We attempted recrystallization of (+)-**8a** to obtain enantiopure crystals. However, in this case we observed crystals of centrosymmetric racemate (±)-**8a**[10a,11] with enantiomeric enrichment of the mother liquor. Fortunately, enantiopure crystals of the reduction product (+)-**9a** were obtained after two recrystallizations (>96:04 er after recrystallization from isopropanol and >98.5:1.5 er after recrystallization from acetonitrile).[11] Relative and absolute stereochemistries of enantiopure aglain (+)-**9a** were confirmed by X-ray analysis using Cu K$\alpha$ radiation (Figure 3),[17] and the absolute configuration was further confirmed by conversion of (+)-**8a** to (−)-methyl rocaglate (**1**) (Scheme 4).[10a,11]

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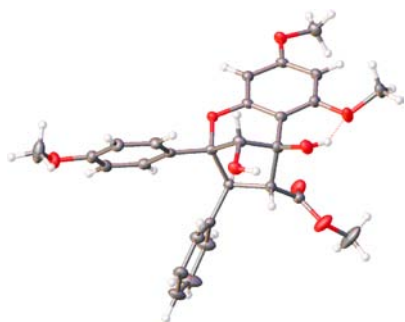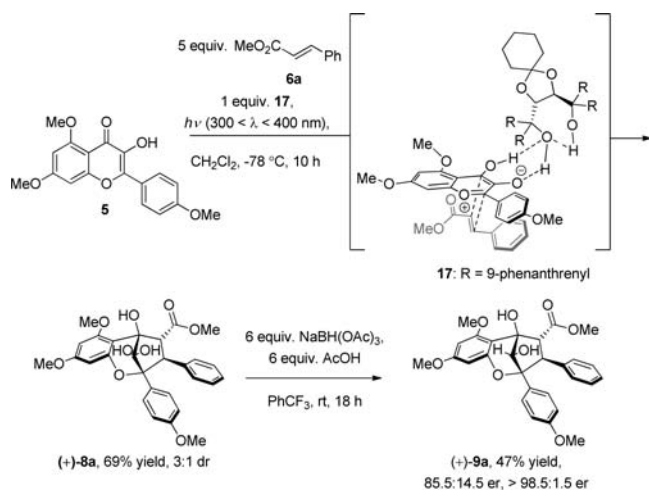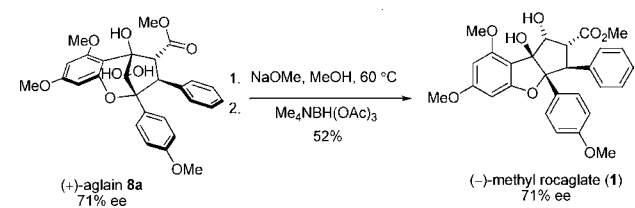**Scheme 3. Enantioselective Photocycloaddition and Subsequent Reduction**



**Figure 3.** Determination of the absolute stereochemistry of enantiopure aglain (+)-9a using Cu Kα radiation X-ray analysis.

**Scheme 4. Confirmation of the Absolute Stereochemistry of Aglain (+)-8a by Synthesis of (−)-Methyl Rocaglate (1)**
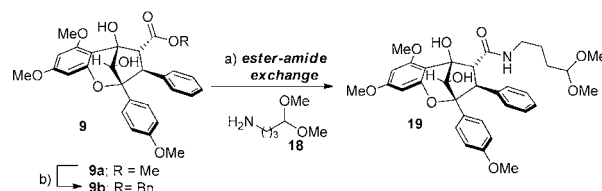


**Further Elaboration of the Aglain Core.** Before using enantiopure material, we first optimized our synthetic route to ponapensin (3) and elliptifoline (4) using chiral, racemic materials. In initial experiments, several attempts to hydrolyze methyl ester (±)-9a were made. However, in general decomposition resulted under basic or nucleophilic (e.g., LiBr) deprotection conditions (Scheme 5). We next turned our attention to hydrolysis and further advancement of the

**Scheme 5. Attempted Hydrolysis of 9a**
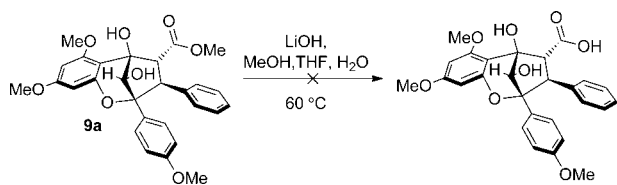


reduced aglain core structure 9b. Photocycloaddition of 3-HF 5 and benzyl cinnamate 6b led to the production of benzyl ester aglain (±)-8b in 60% yield (Scheme 1). The corresponding endo cycloadduct was then recrystallized from acetonitrile[11] and was subsequently reduced to afford the 10S-aglain (±) 9b (10:1 dr). Benzyl ester 9b was hydrogenolyzed and the derived carboxylic acid was subsequently coupled with 4,4-dimethoxy-1-butanamine[18] 18 to provide amidoacetal (±)-19 in 95% yield (two steps, Scheme 6). In an alternative pathway, trans-

**Scheme 6. Transesterification/Ester Amide Exchange toward Ponapensin and Elliptifoline[a]**



[a](a) From 9a: Me$_3$Al (20 equiv), amine 18 (20 equiv) toluene (0.3 M) 70 °C for 12 h (64%); from 9b: (i) H$_2$−Pd/C then (ii) EDCI (1.5 equiv), HOBt (1.2 equiv), amine 18 (2.5 equiv) (95%, 2 steps); (b) Otera's catalyst (20 mol %), BnOH, 110 °C, house vacuum, 24 h (64%, 28% recovery of 9b).

esterification of methyl ester (±)-9a was achieved using Otera's catalyst[19] in benzyl alcohol as solvent to afford benzyl ester (±)-9b in 63% yield along with recovered starting material (28%). Several reagents were evaluated in order to achieve direct ester−amide exchange of 9a including Otera's catalyst, Sc(OTf)$_3$, Zn$_4$(OCOCF$_3$)$_6$O, Mg(OTf)$_2$, and Zr(O$^t$Bu)$_4$ as either catalysts or stoichiometric additives.[20] Modest conversions of aglain (±)-9a to (±)-19 were observed using Otera's catalyst and Mg(OTf)$_2$ in 25% and 38% yields, respectively. Interestingly, when using trimethylaluminum-(III)[21] for ester amide exchange, we observed the clean formation of amido acetal (+)-19 in 64% yield without epimerization of (+)-19 (Scheme 6).

**Final Cyclizations to Ponapensin and Elliptifoline.** With enantiopure aglain amide (+)-19 in hand, we next examined cyclization to the hemiaminal of ponapensin (Scheme 7).[22] Treatment of amido acetal (+)-19 with CSA (50 mol %) in EtOAc led to a mixture of products that were isolated after two purifications. The major product observed was (+)-ponapensin in 30% yield as a single hemiaminal diastereomer ($[\alpha]_D^{25}$ = +170° synthetic (c 0.2, CHCl$_3$), $[\alpha]_D^{22}$

**Scheme 7. Acid-Catalyzed Cyclization without Additional Methanol**
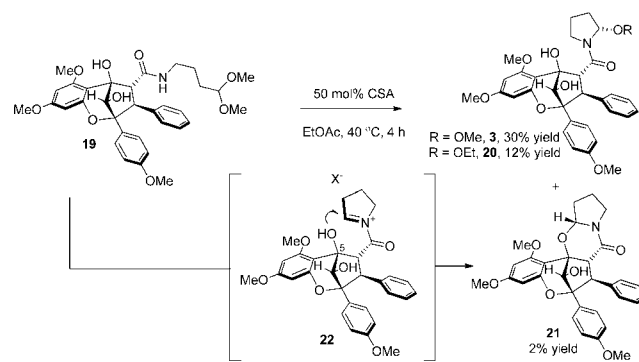
= −167° natural (*c* 0.4, CHCl₃)). The other major product isolated was the ethyl hemiaminal derivative of ponapensin, aglain **20**, isolated in 12% yield. The production of this compound was due to trace ethanol present in the ethyl acetate. Cyclic intermediate **21** was also isolated in 2% yield, and its relative configuration was assigned *via* NOE correlation observed between H13 and H4 (Figure 4). Cyclic intermediate
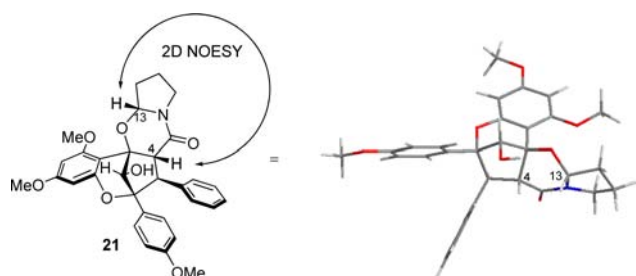


**Figure 4.** B3LYP/6-31G* ground state conformer of cyclic aminal **21** and assigned relative configuration based on the observed 2D NOESY.

**21** provides important evidence for the intermediacy of acyliminium[23] **22** and accounts for formation of a single diastereomer of **3**. However, the tertiary hydroxyl may not be the only contributing factor to the diastereoselectivity. Figure 5
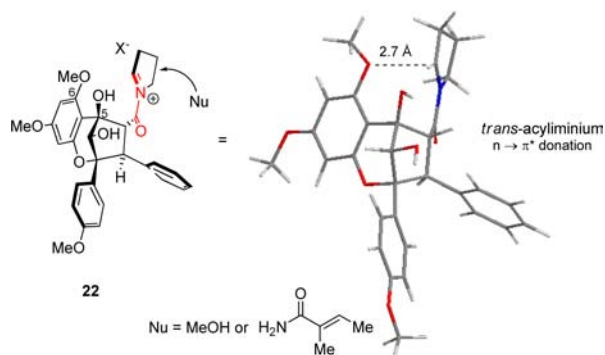


**Figure 5.** B3LYP/6-31G** ground state conformer of acyliminium **22** and stereoselective approach of the nucleophile.

shows a *Spartan '10* model of the ground state conformation (B3LYP/6-31G**) of putative acyliminium intermediate **22**. *trans*-Acyliminium[24] **22** may be formed to avoid unfavorable A¹,³ strain interactions[25] leading to the conformer depicted in Figure 5. In this conformer, the oxygen of the 6-methoxy group is approximately 2.7 Å from C13 which bears a π* orbital.[26] An n → π* interaction appears to stabilize this conformation and allows nucleophilic attack specifically from the opposite face of iminium **22**. Furthermore, we also isolated trace amounts of the dihydropyrrole derived from **22** and possible dimeric products from the reaction mixture. Cyclizations were attempted in other solvents such as THF and 1,4-dioxane to avoid formation of 13-OEt derivative **20**, in which case ponapensin was still not produced cleanly. After considerable optimization, we found that treatment of (+)-**19** with CSA in EtOAc containing methanol (15 equiv) led to the production of ponapensin (**3**) in 68% yield (Scheme 8) as a single diastereomer. When methanol was used as solvent, the reaction stopped at approximately 50% conversion to **3** suggesting that an equilibrium had been reached. In a similar manner, treatment of aglain (+)-**9a** with 5 equiv of tigloyl amide and 50 mol %

**Scheme 8. Optimized Syntheses of Ponapensin (3) and Elliptifoline (4)**
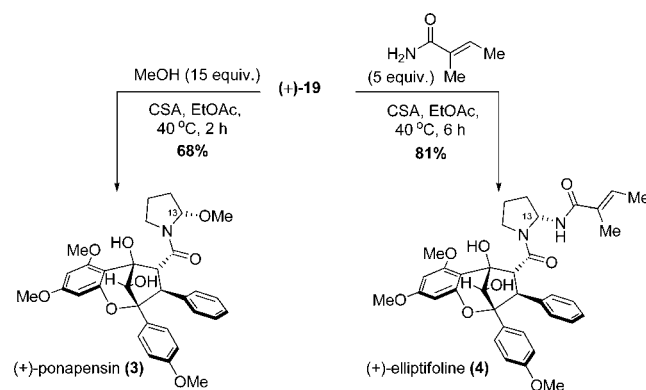


CSA in EtOAc led to the production of (+)-elliptifoline (**4**) as a single diastereomer. Elliptifoline was isolated in 81% yield ([α]ᴅ²⁵ = +172° synthetic (*c* 0.2, CHCl₃), [α]ᴅ²² = −88.9° natural (*c* 0.6, CHCl₃)).

The relative configurations at C13 of both **3** and **4** were confirmed *via* X-ray crystallography using chiral, racemic natural products to be the same for ponapensin (**3**) and elliptifoline (**4**) (Figure 6). The X-ray structures show that the
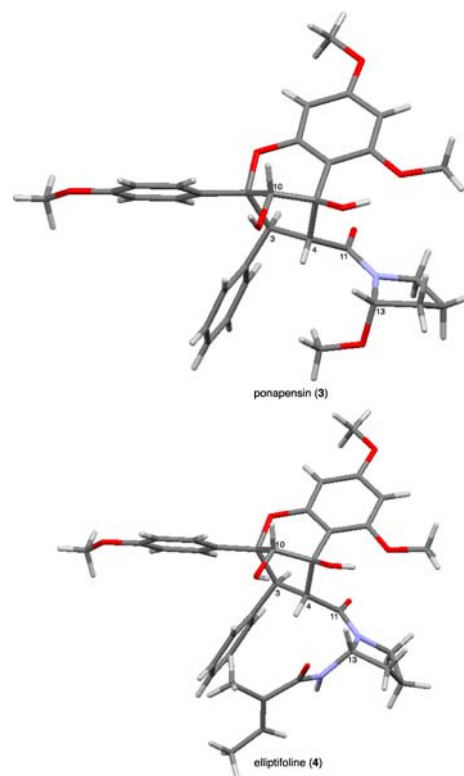


**Figure 6.** X-ray crystal structures of the racemic natural products. The structures shown have the absolute configuration of (+)-ponapensin (**3**) and (+)-elliptifoline (**4**), enantiomers of the natural products.

proline amide moiety is folded as a *trans*-rotamer over the neighboring aromatic ring. A C−H−π interaction may also stabilize this conformation where the phenyl ring donates electron density to the electron-deficient C−H bonds of the 13-OMe in ponapensin (**3**).[24a] Kinghorn and co-workers correctly predicted this conformation for ponapensin (**3**) using

molecular modeling and observed the ^{1}H NMR shielding of the C13 methoxy protons.[3] It should be noted that synthetic elliptifoline (**4**) was determined to have the opposite configuration at C13 than reported by Duh and co-workers (cf. Scheme 8).[4] The crucial NOE between H4 and H13 was observed in our hands as reported by Duh and co-workers.[4] The major rotamer in solution is likely the *trans* conformation displayed in the crystal structure (Figure 6). Although there is a large discrepancy in magnitude between the synthetic and natural samples' specific rotations (172° vs 88.9°), the ^{1}H and ^{13}C NMR data support that we have made elliptifoline (**4**)[11] and the configuration at C13 is therefore opposite of what Duh and co-workers reported.[4]

As previously described, the specific optical rotations of synthetic **3** and **4** were determined to be dextrorotatory. Accordingly, the enantiomers of both natural products **3** and **4** were synthesized. Figure 7 shows the assigned absolute
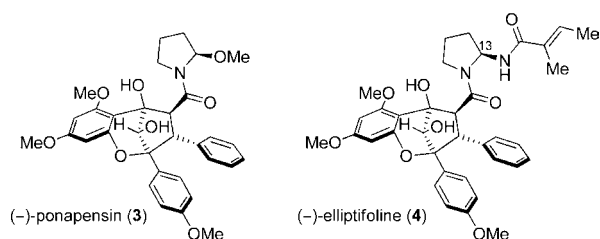


**Figure 7.** Relative and absolute stereochemical assignments of (−)-ponapensin (**3**) and (−)-elliptifoline (**4**). (−)-Elliptifoline (**4**) is drawn with its reassigned configuration at C13.

configurations of the natural products which were further confirmed by the synthesis of enantioenriched (−)-methyl rocaglate (**1**) from enantioenriched (71% ee) (+)-**9a** (cf. Scheme 4).[11] We propose that a kinetic resolution may occur in nature wherein (−)-aglain ketone core structures undergo reduction and (+)-aglains do not (Figure 8).[8a,27] Racemic
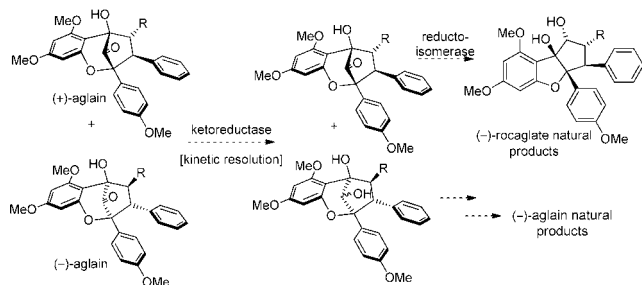


**Figure 8.** Proposed kinetic resolution of racemic aglains.

bridgehead ketones have been utilized as substrates for kinetic resolution using microbes such as *C. lunata* and *R. rubra* and also in the presence of ketoreductase/NADP.[28] (+)-Aglains may then be converted to their (−)-rocaglate counterparts via a reductoisomerase/NADPH pathway (e.g., DXR, ketol-acid reductoisomerase). Keto-acid reductoisomerase is known to catalyze the conversion of 2-acetolactate to 2,3-dihydroxyiso-valerate, and DXR is involved in terpenoid biosynthesis in *E. coli*.[29] Furthermore, it is also possible that a parallel kinetic resolution (PKR)[30] may occur where (+)-aglains selectively undergo ketol rearrangement/reduction, and (−)-aglains are reduced via reductoisomerase/NADPH leading to enantiopure (−)-rocaglates and (−)-aglain structures, respectively.

## CONCLUSION

In summary, we have employed enantioselective [3 + 2] photocycloaddition methodology to synthesize the aglain natural products (+)-ponapensin and (+)-elliptifoline. Diastereoselective, reagent-controlled reduction of the hydrated bridgehead ketone led to an intermediate with the correct *S* configuration at C10. Subsequent ester–amide exchange and acid-catalyzed cyclization provided the natural products. These expedient syntheses demonstrated that late stage installation of the C13 hemiaminal and aminal stereocenters may be substrate controlled by stereoelectronic stabilization of an acyliminium species. This may explain why the relative stereochemical outcome at C13 is similar for both (−)-ponapensin and (−)-elliptifoline. The unexpected finding that (−)-ponapensin and (−)-elliptifoline are enantiomeric to (−)-methyl rocaglate has led to the hypothesis for biosynthesis involving kinetic resolution of aglain ketone core structures. Further work toward development of enantioselective photocycloadditions as well as syntheses and biological evaluations of additional aglain natural products is currently in progress and will be reported in due course.

## ASSOCIATED CONTENT

**⑤ Supporting Information**

Experimental procedures, and characterization data for all new compounds described herein, including CIF files for compounds **3**, **4**, and **9a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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**Notes**

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

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