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

Neil J. Lajkiewicz, **Stéphane P. Roche**[†], **Baudouin Gerard**[‡], and **John A. Porco Jr.**
Department of Chemistry, Center for Chemical Methodology and Library Development (CMLD-BU), Boston University, 590 Commonwealth Avenue, Boston, MA 02215, United States

John A. Porco: porco@bu.edu

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** 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 μM, respectively.[3] Other aglain natural products including 4-*epi*-aglain A,[3] aglain B,[6] 10-*O*-acetylaglain B,[7] and aglain C[6] were not active in the NF-κB assay (IC_{50} > 5 μM).[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.

Correspondence to: John A. Porco, Jr., porco@bu.edu.
[†]Present address: Department of Chemistry and Biochemistry, Florida Atlantic University, 777 Glades Road, Boca Raton, FL 33431, United States.
[‡]Present address: H3 Biomedicine Inc., 300 Technology Square, Fifth Floor, Cambridge, MA 02139, United States.

Supporting Information Available: 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.

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 ($Al(OiPr)_3$), 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_4NBH_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 $Me_4NBH(OAc)_3$[13] in benzene (entry 4) afforded reduction product **9a** which has the 10*S* configuration required for synthesis of both ponapensin (**3**) and elliptifoline (**4**). 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 10:1 dr (Entry 5). The counterion size of the reducing agent appears to be significant in enhancing diastereoselectivity of the reduction as $NaBH(OAc)_3$[14] provided the 10*S* diastereomer **9a** in 10:1 dr (Table 1, Entry 6). Treatment of hydrated ketone **8a** with 4Å MS in CH_2Cl_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.

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_4NBH_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_4N^+) 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 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** furnished reduced aglain **15** in 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_4NBH_4 yielded the reduced aglain **16** in 7:1 dr, which is comparable to the diastereoselectivity observed in the Bu_4NBH_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_α radiation (Figure 3)[17] and the absolute configuration further confirmed by conversion of (+)-**8a** to (−)-methyl rocaglate (**1**) (Scheme 4).[10a, 11]

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 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 10*S*-aglain (±) **9b** (10:1 dr). Benzyl ester **9b** was hydrogenolyzed and the derived carboxylic acid 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, transesterification 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, $Sc(OTf)_3$, $Zn_4(OCOCF_3)_6O$, $Mg(OTf)_2$, and $Zr(O^tBu)_4$ either as 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 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, $CHCl_3$), $[\alpha]_D^{22}$ = −167° natural (*c* 0.4, $CHCl_3$)). 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 **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 shows a *Spartan '10* model of the ground state conformation (B3LYP/6-31G**) of putative acyliminium intermediate **22**. *Trans*[24] acyliminium **22** may be formed to avoid unfavorable

$A^{1,3}$ 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] A 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 equivalents of tigloyl amide and 50 mol% CSA in EtOAc led to the production of (+)-elliptifoline (**4**) as a single diastereomer. Elliptifoline was isolated in 81% yield ($[\alpha]_D^{25}$ = +172° synthetic (*c* 0.2, $CHCl_3$), $[\alpha]_D^{22}$ = −88.9° natural (*c* 0.6, $CHCl_3$)).

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 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 coworkers 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 coworkers (*cf.* Scheme 8).[4] The crucial NOE between H4 and H13 was observed in our hands as reported by Duh and coworkers.[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 coworkers 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 configurations of the natural products which were further confirmed by the synthesis of enantioenriched (−)-methyl rocaglate (**1**) from enantioenriched (71% ee) (+)-**9a** (*c.f.* 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 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-dihydroxyisovalerate 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 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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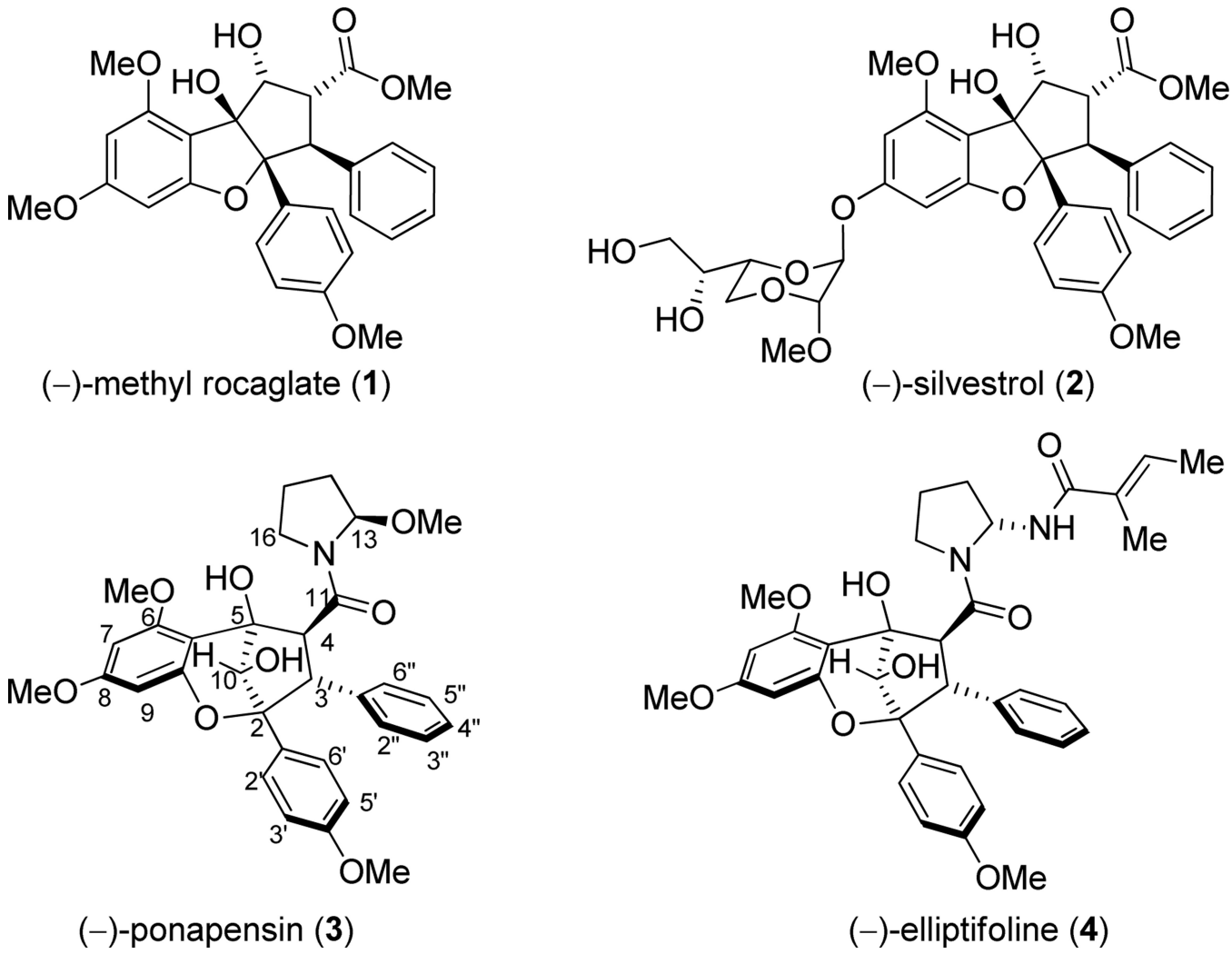


Figure 1.
Representative natural products from the genus *Aglaia*.

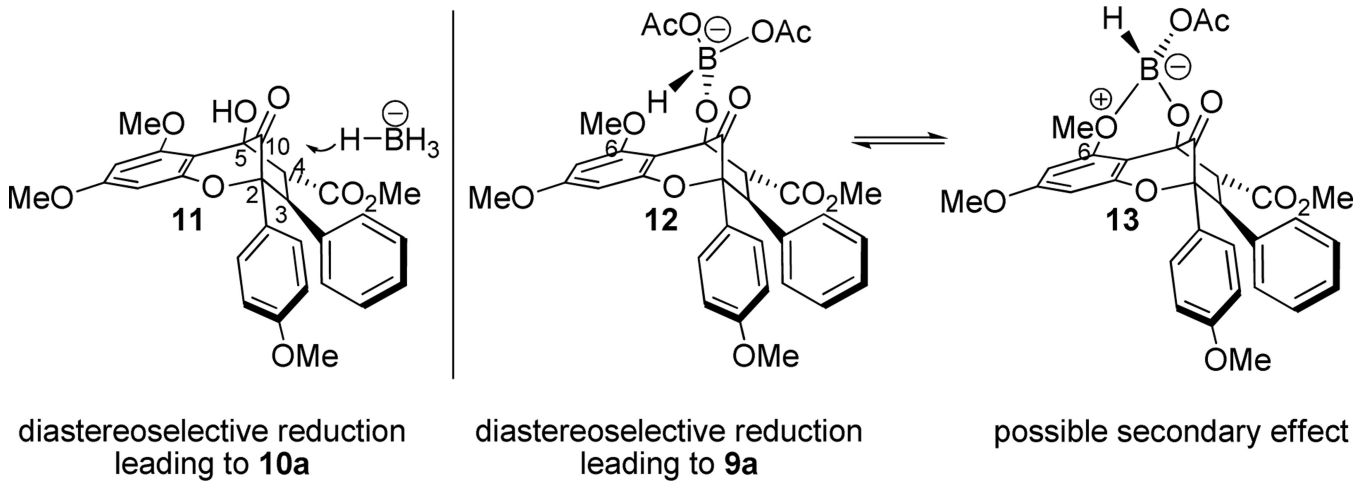


Figure 2.
Proposed assemblies for diastereoselective reduction.

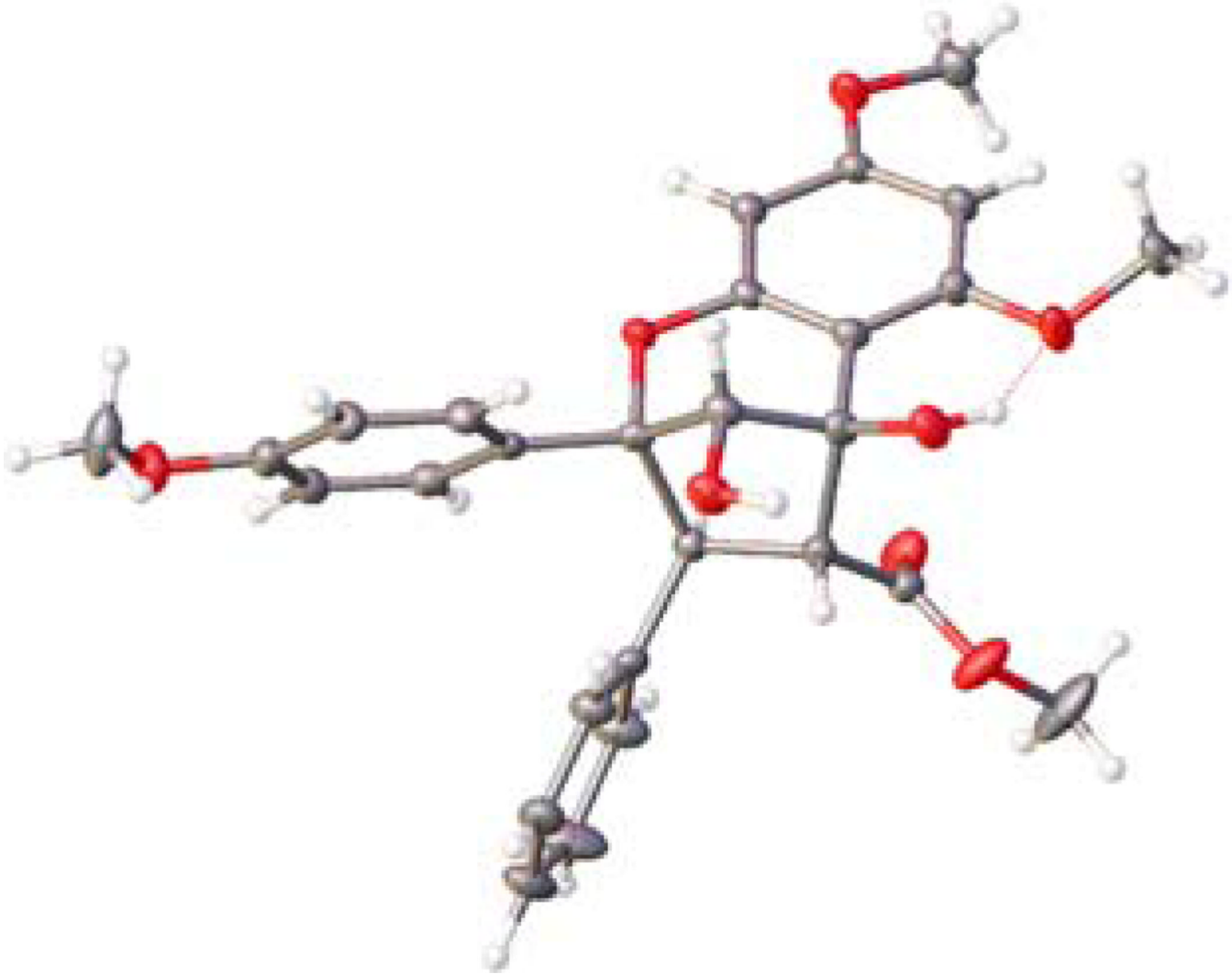


Figure 3.
Determination of the absolute stereochemistry of enantiopure aglain (+)-**9a** using Cu-K_α radiation X-ray analysis.

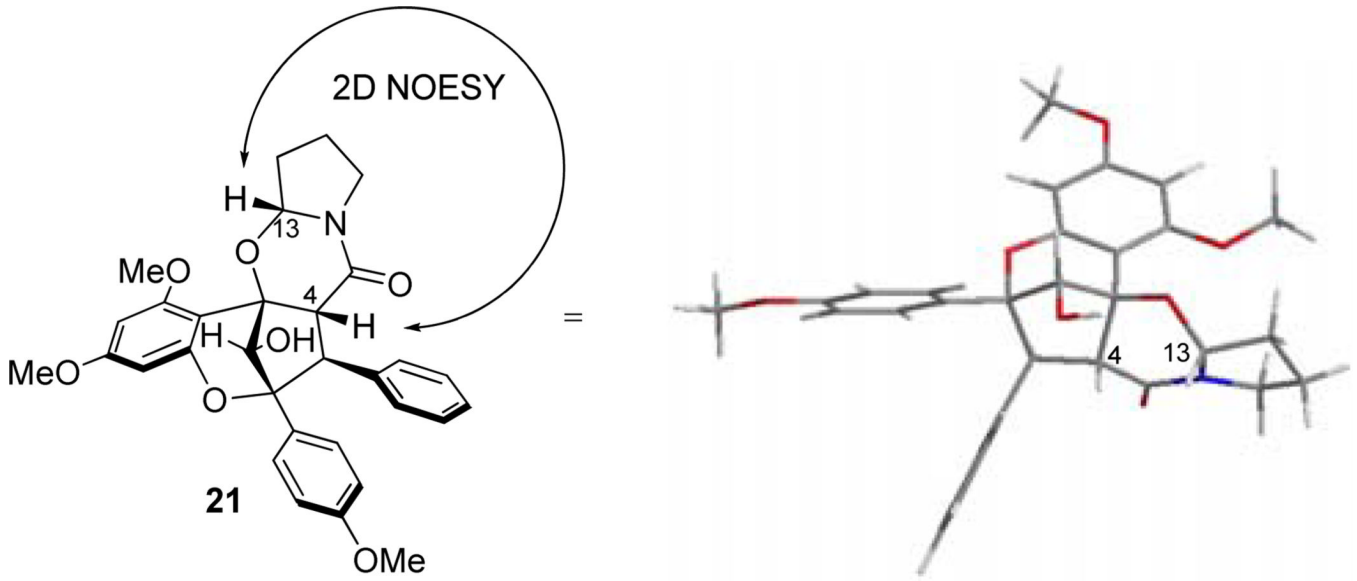


Figure 4.
B3LYP/6-31G* ground state conformer of cyclic aminal **21** and assigned relative configuration based on the observed 2D NOESY

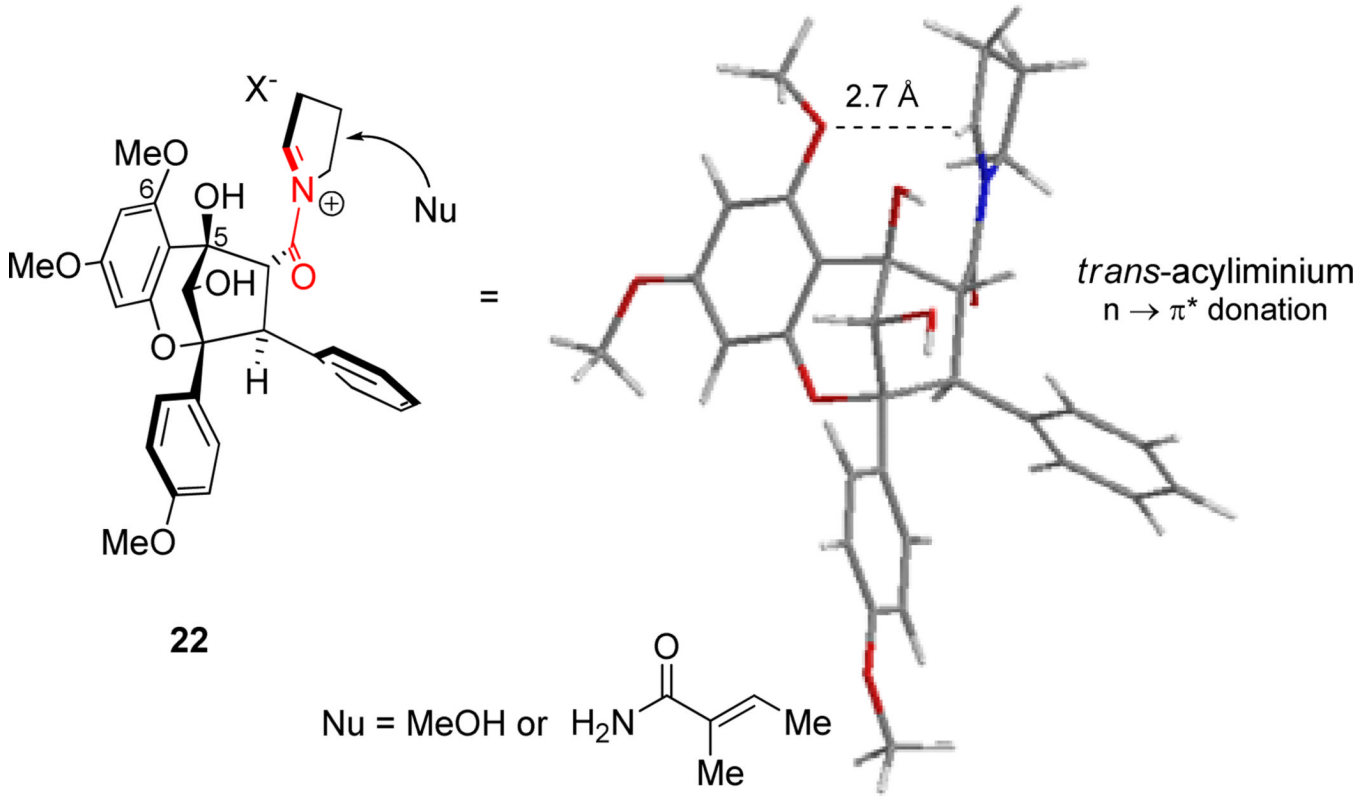


Figure 5.
B3LYP/6-31G** ground state conformer of acyliminium **22** and stereoselective approach of the nucleophile.

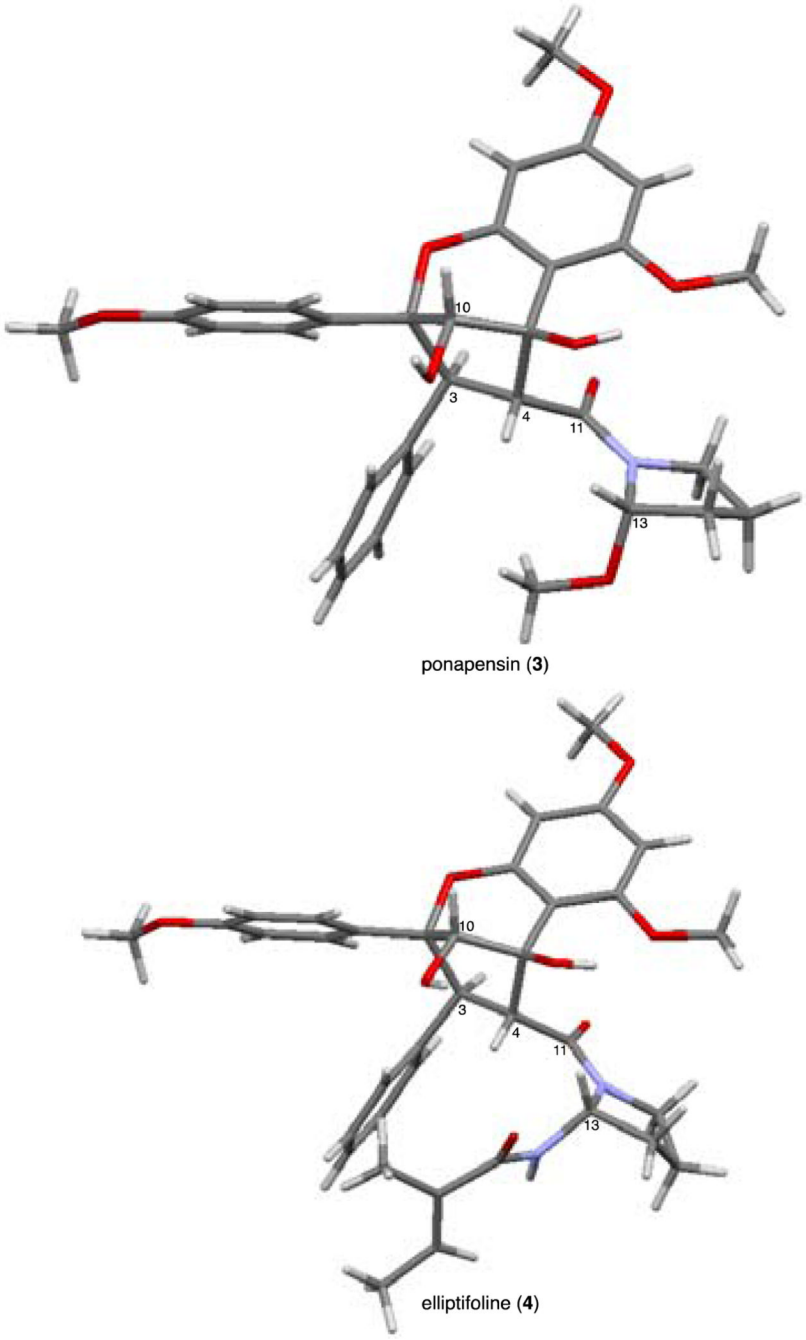


Figure 6.
X-ray crystal structures of the racemic natural products. The structures shown have the absolute configuration of (+)-ponapensin (**3**) and (+)-elliptifoline (**4**), enantiomers of the natural products.

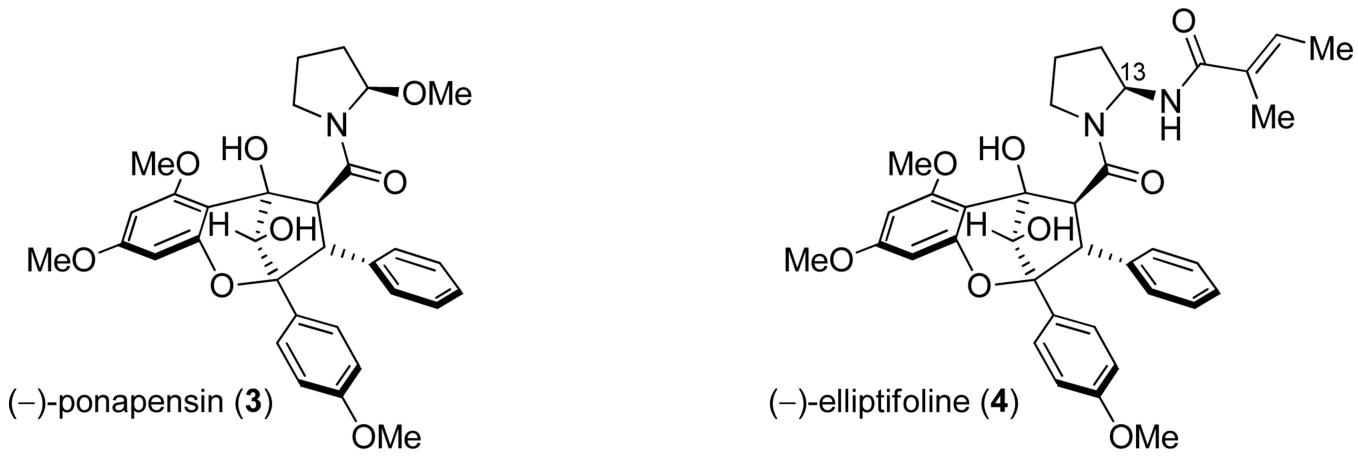


Figure 7.

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

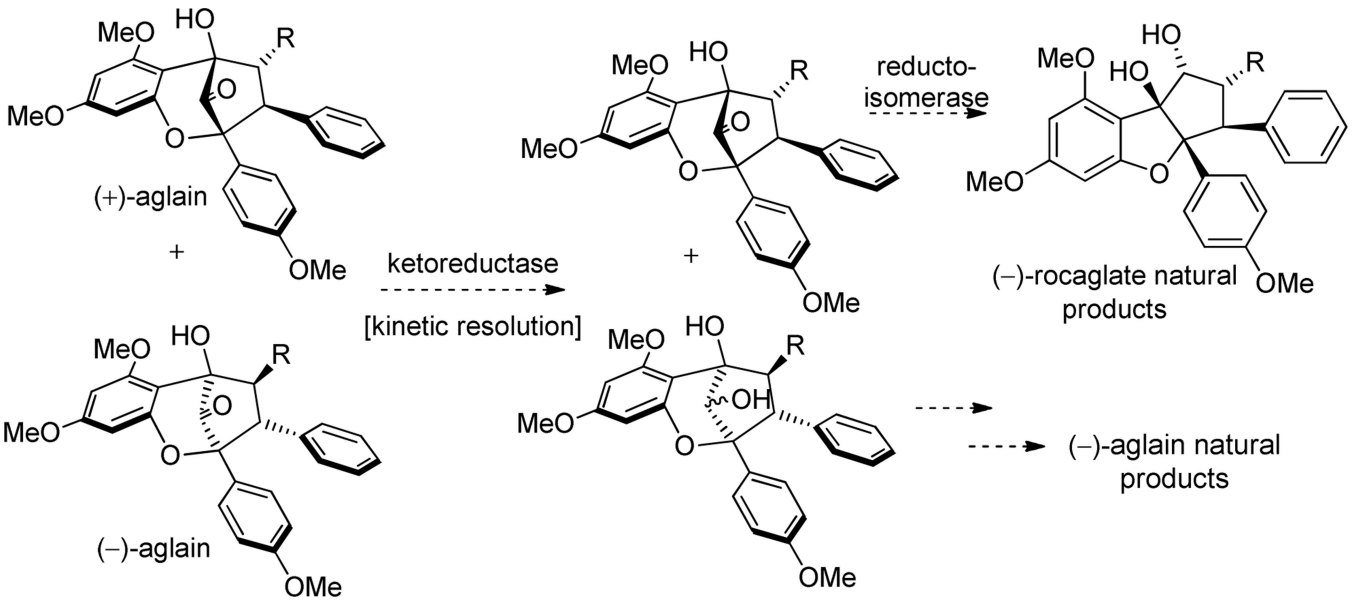
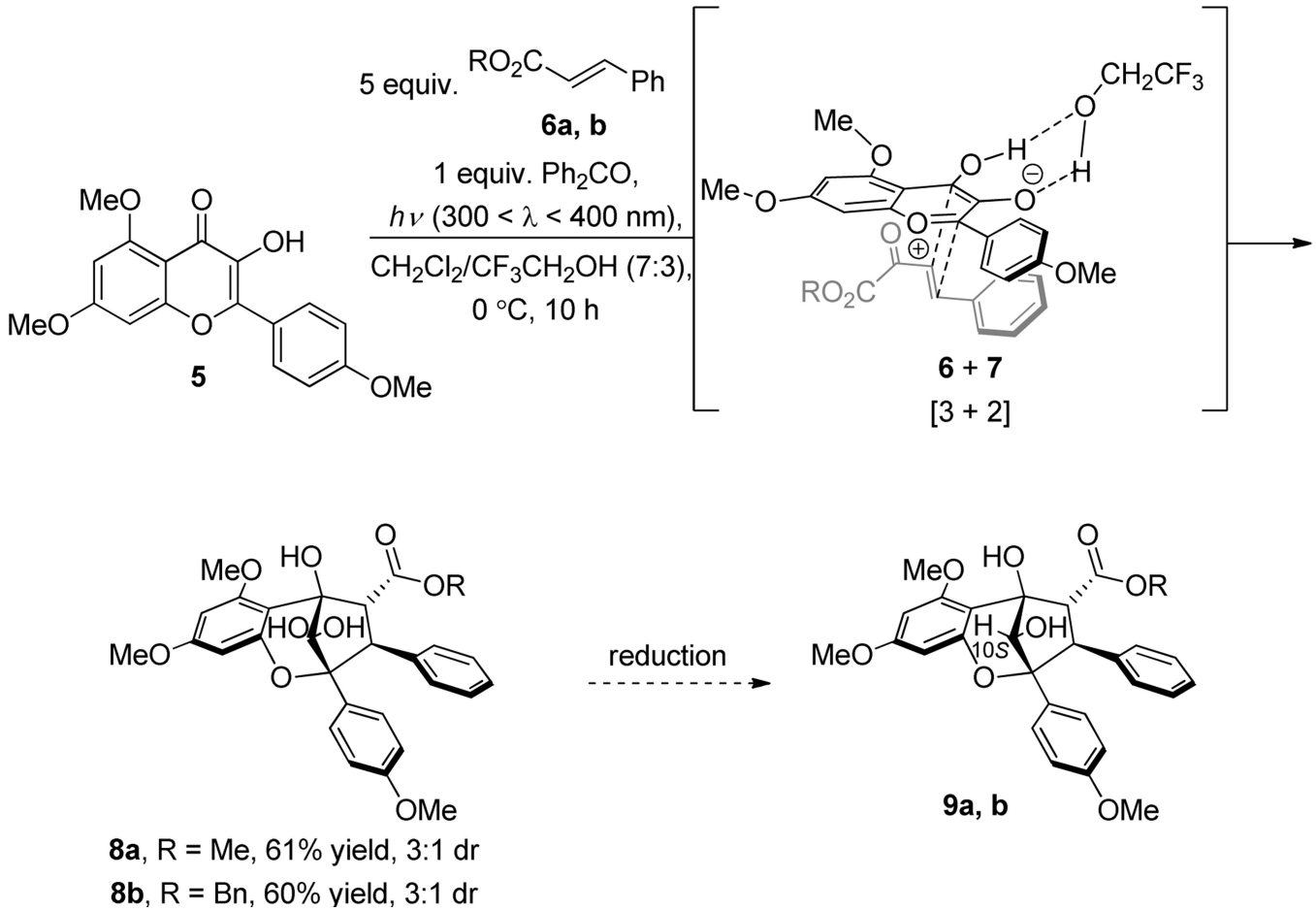
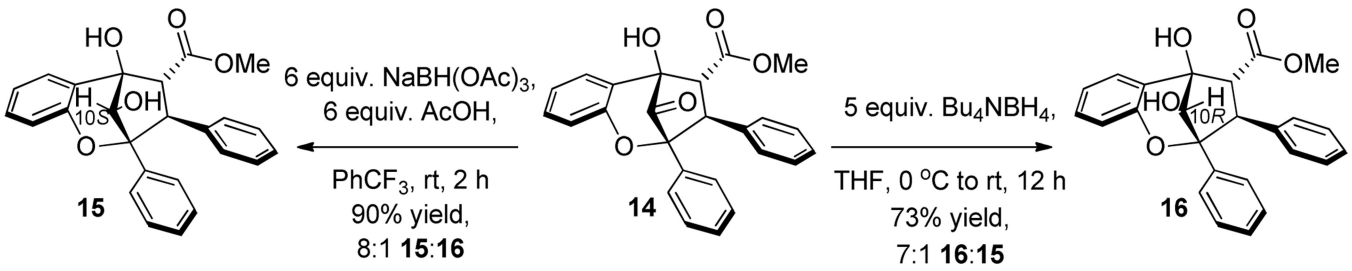


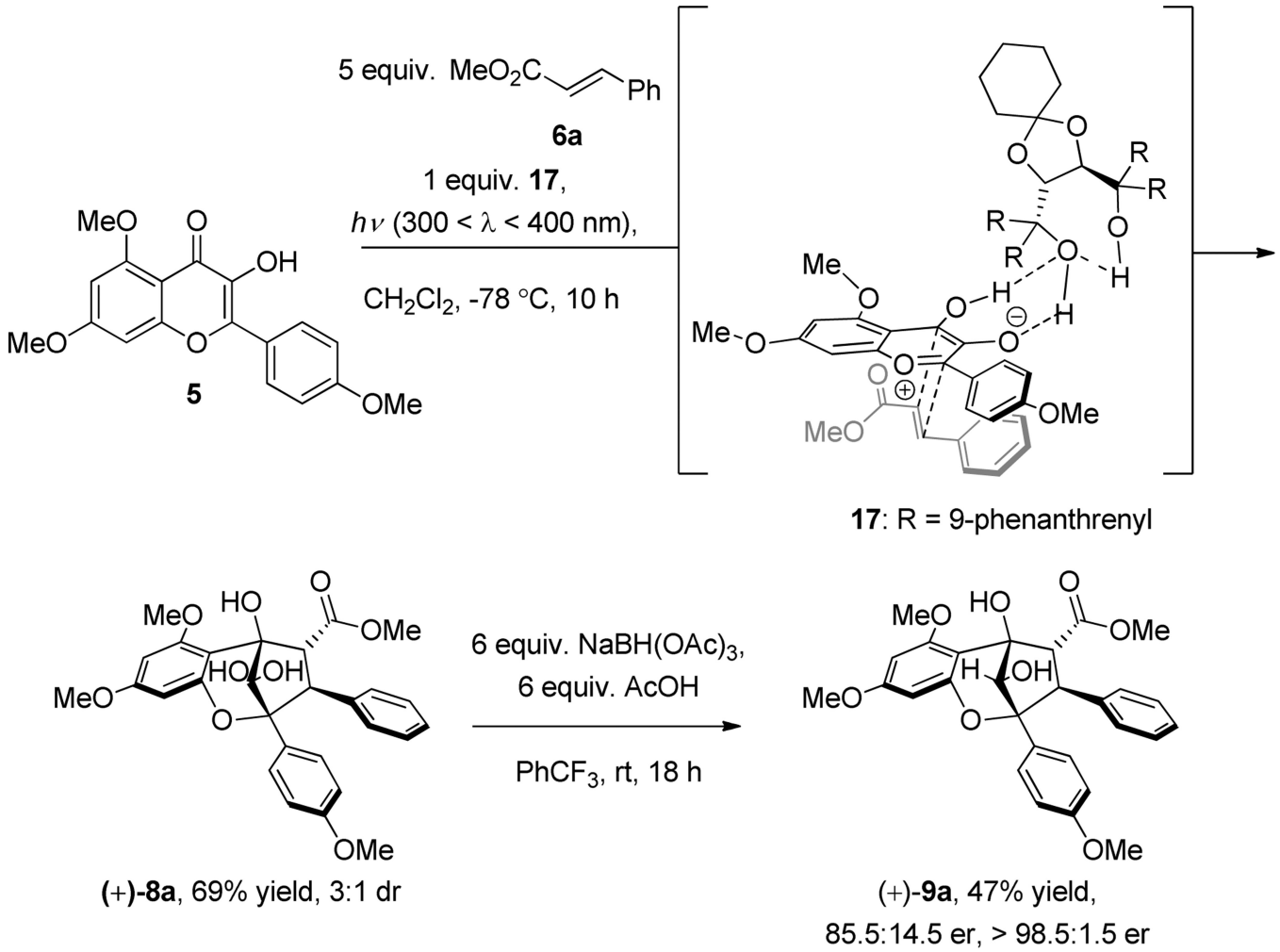
Figure 8.
Proposed kinetic resolution of racemic aglains.



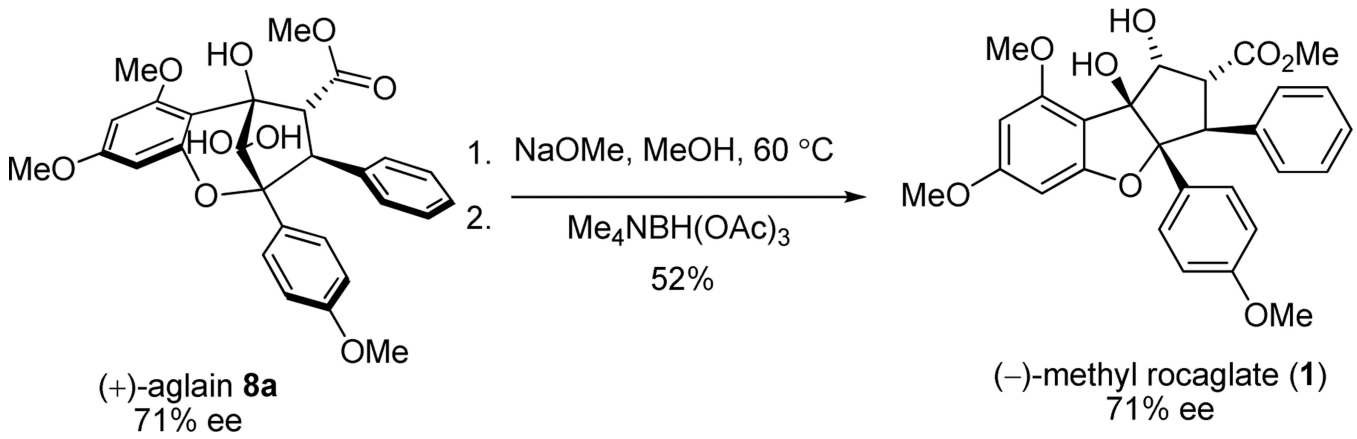
Scheme 1.
Cycloaddition of 3-HF **5** and Cinnamic Esters **6**



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

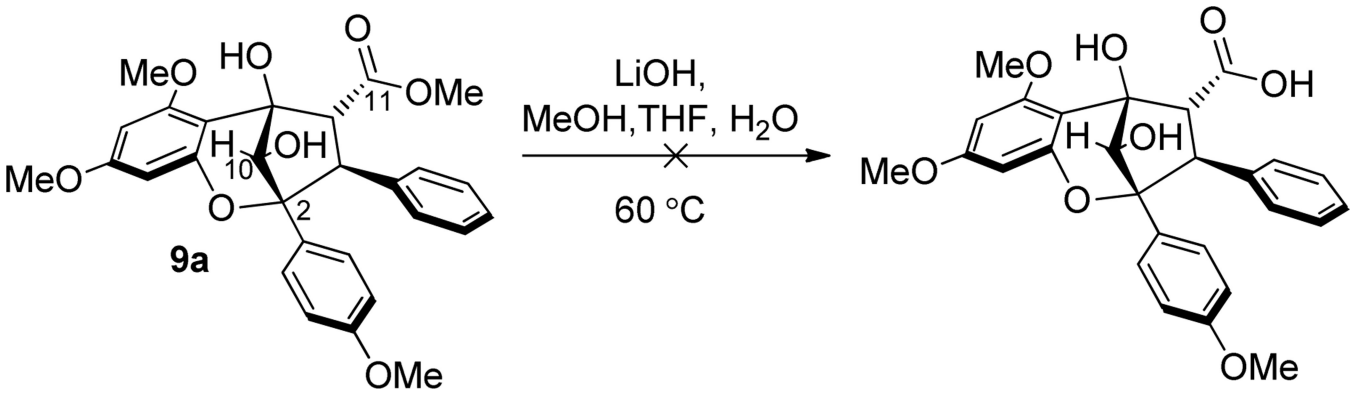


Scheme 3.
Enantioselective Photocycloaddition and Subsequent Reduction

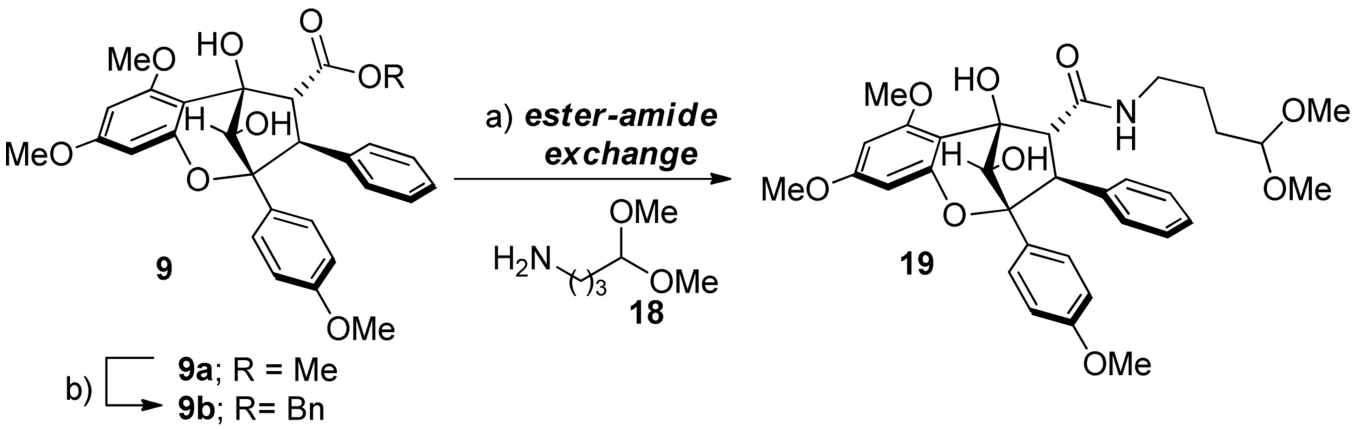


Scheme 4.

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



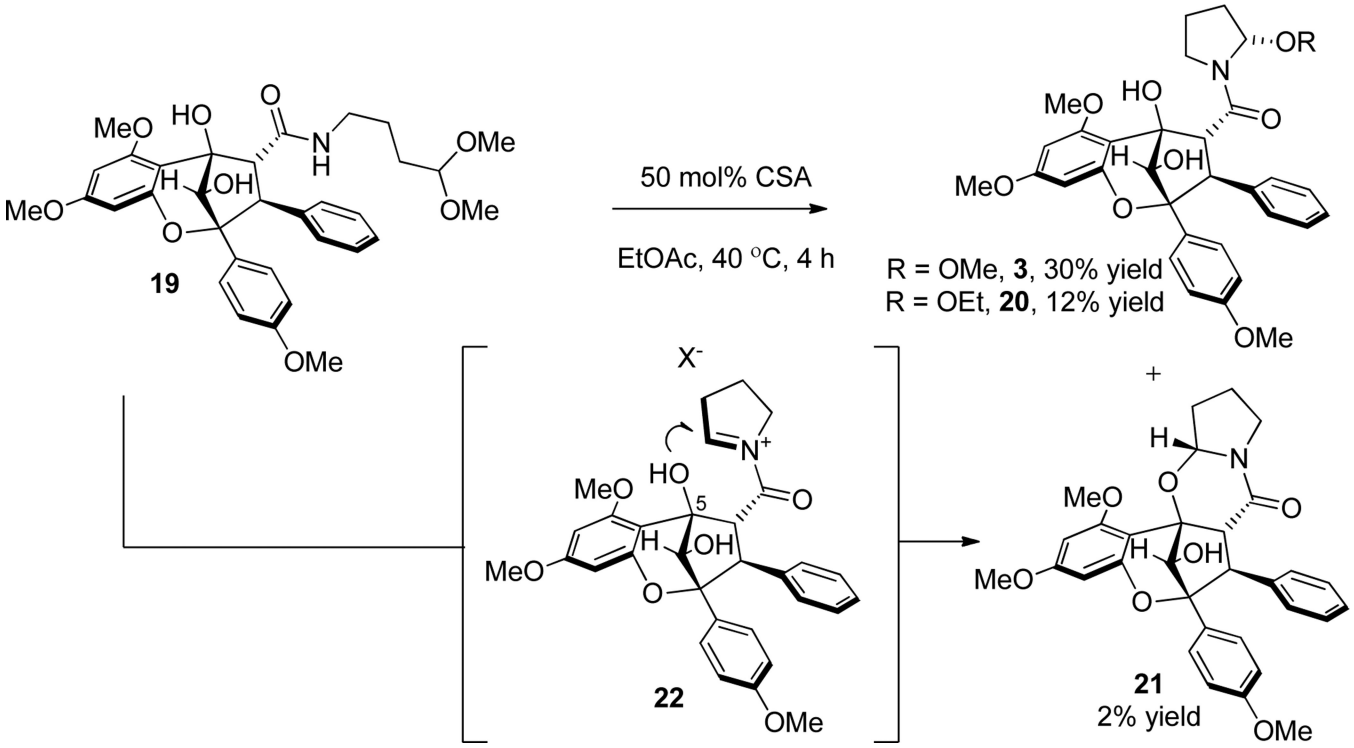
Scheme 5.
Attempted Hydrolysis of **9a**



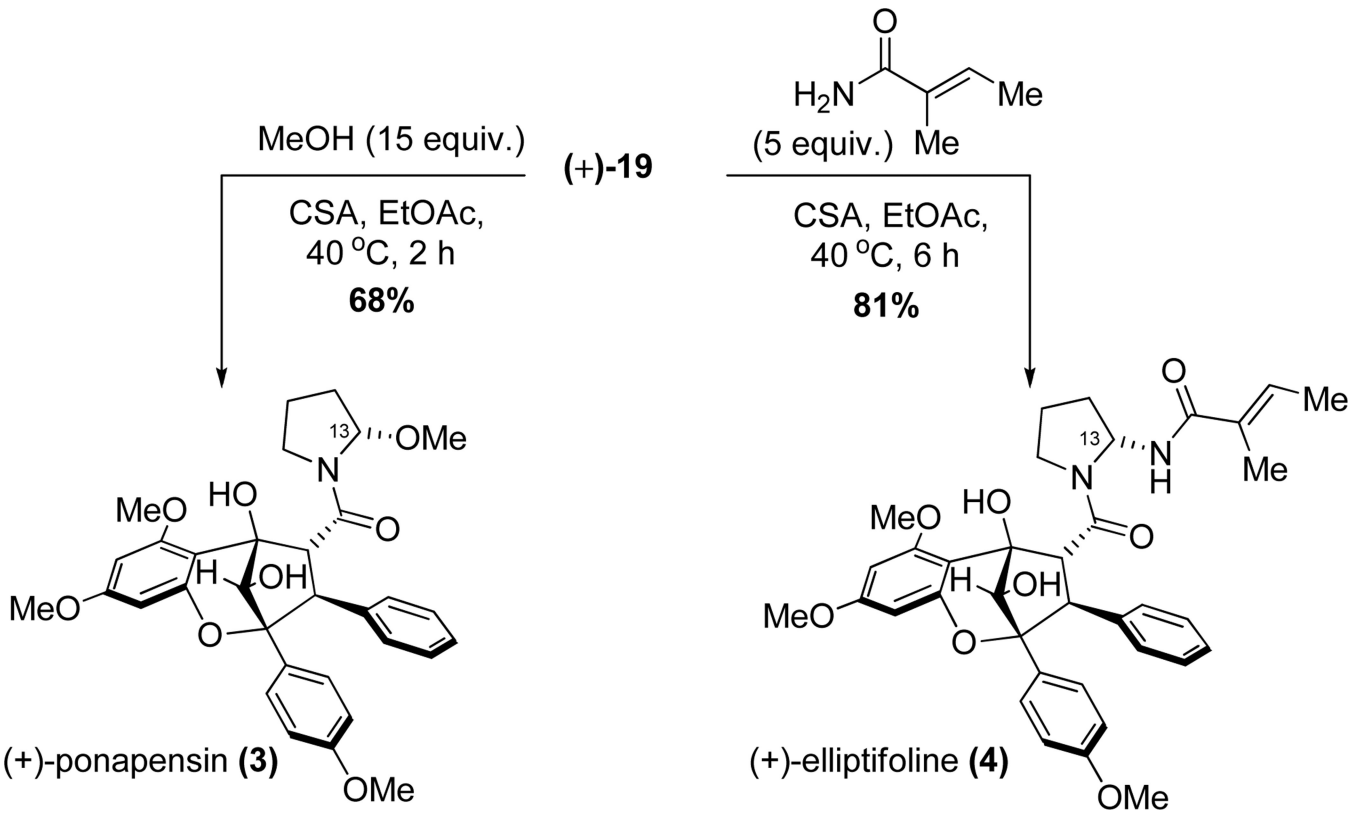
Scheme 6.

Transesterification/ Ester-Amide Exchange toward Ponapensin and Elliptifoline

a) From **9a**: Me_3Al (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%, recovery 28% **9b**).



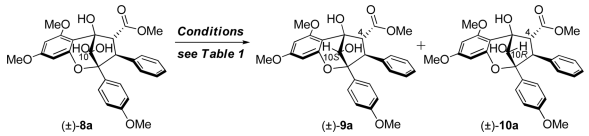
Scheme 7.
Acid-Catalyzed Cyclization without Additional Methanol



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

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_4NBH_4	THF	-	1:5	98
4	$Me_4NBH(OAc)_3$	benzene	AcOH	3:1	95
5	$Me_4NBH(OAc)_3$	$PhCF_3$	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 ^1H NMR analysis of the crude reaction mixture.

[c] Isolated after purification by silica gel chromatography.