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Regiodivergent Photocyclization of Dearomatized Acylphloroglucinols: Asymmetric Syntheses of (–)-Nemorosone and (–)-6-*epi*-Garcimultiflorone A

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Abstract

Regiodivergent photocyclization of dearomatized acylphloroglucinol substrates has been developed to produce type A polycyclic polyprenylated acylphloroglucinol (PPAP) derivatives using an excited-state intramolecular proton transfer (ESIPT) process. Using this strategy, we achieved the enantioselective total syntheses of the type A PPAPs (–)-nemorosone and (–)-6-*epi*-garcimultiflorone A. Diverse photocyclization substrates have been investigated leading to divergent photocyclization processes as a function of tether length. Photophysical studies were performed and photocyclization mechanisms were proposed based on investigation of various substrates as well as deuterium-labeling experiments.

Graphical Abstract

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Supporting Information

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Experimental procedures, flow system set-ups, characterization data and NMR spectra for reported products (PDF)

X-ray crystallographic data for (–)-**12** (CIF)

X-ray crystallographic data for (–)-**21** (CIF)

We declare no competing financial interests.

INTRODUCTION

Polycyclic polyprenylated acylphloroglucinols (PPAPs) are a large family of natural products primarily isolated from the plants of *genera Hypericum* and *Garcinia*.¹ More than 500 related members have been identified since the first report of hyperforin (**1**, Figure 1) in 1971.^{1b, 2} Two major types of PPAPs are known: type A PPAPs (*e.g.* hyperforin (**1**), nemorosone (**2**), and garcimultiflorone A (**3**), Figure 1) which have a quaternary center α to the bridgehead acyl group³; and type B PPAPs (*e.g.* clusianone (**4**), Figure 1) that possess an α -acyl- β -hydroxyenone motif. More complex PPAP natural products have been identified that cannot simply be categorized into these two types.^{1b} Based on their highly oxygenated and densely functionalized bicyclo[3.3.1]nonane frameworks and broad range of biological activities, both types of PPAPs have drawn significant synthetic attention in organic synthesis.^{1,4} Hyperforin (**1**), a transient receptor potential cation channel 6 (TRPC6) agonist,⁵ is also the main constituent of St. John's wort responsible for its antidepressant activity.⁶ Nemorosone (**2**)^{3a,7} has been another attractive target⁸ owing to its complex structure and antimicrobial,⁹ anticancer,¹⁰ anti-oxidant,¹⁰ and anti-HIV¹¹ activities. Further mechanistic studies indicated that anticancer activity of hyperforin and nemorosone may arise from the inhibition of protonophoric mitochondrial uncoupling activity.¹² Recent studies of type B PPAPs by Plietker and coworkers have revealed impressive antibiotic activity against multiresistant *S. aureus* and vancomycin-resistant *Enterococci*.¹³

Biomimetic syntheses of several PPAP natural products and non-natural derivatives have been reported from our laboratory using dearomatization of acylphloroglucinols.¹⁴ In particular, (-)-clusianone (**4**), a type B PPAP natural product, was synthesized employing a biomimetic, acid-promoted cyclization of the homoallyl-tethered, dearomatized acylphloroglucinol (-)-**5** *via* carbocation intermediate **6** (Scheme 1a).^{14f} In our continuing studies, we aimed to apply an alternative cyclization strategy to **5** to construct the type A PPAP framework. Previous studies by Wan and coworkers have demonstrated excited-state intramolecular proton transfer (ESIPT) processes¹⁵ from phenolic groups to the carbon atoms of arenes leading to cyclization products, as well as alkenes (Scheme 1b).^{16,17} Inspired by these precedents, we envisioned that an oxygen-to-carbon (enol-to-alkene) ESIPT process may convert **5** to the photoexcited intermediate **7** followed by C₁ cyclization

to the type A PPAP core **8** (Scheme 1c). The proposed photocyclization (**5** $\rightarrow$ **8**) represents a chemical alternative to enzymatic reactions employing prenyl diphosphate to generate related carbocation intermediates enroute to type A PPAPs.^{3a,18} The length and nature of the tethered alkene was also of interest as part of our investigation. Herein, we report photocyclization of homoallyl-tethered, dearomatized substrates to construct type A PPAP scaffolds which has enabled the shortest synthesis of nemorosone (**2**) to date along with the first synthesis of (–)-6-*epi*-garcimultiflorone A, a non-natural diastereomer of garcimultiflorone A (**3**). Detailed mechanistic and photophysical studies are also described.

RESULTS AND DISCUSSION

We began our study with preparation of the requisite dearomatized scaffold **5**, which can be readily achieved from commercially available 5-methoxyresorcinol in four steps *via* dearomatization of **9** with chiral triflate **10** (Scheme 2a).^{14f, 19} Having previously accessed the type B PPAP core from the cyclization of (–)-**5** (Scheme 1a),^{14f} we directed our investigation to the photocyclization of (+)-**5** to access nemorosone core **8**. Pleasingly, we discovered that photoirradiation of diastomeric mixture **5** with UV light ($\lambda_{\text{max}} = 350$ nm) only afforded the desired product (–)-**8** as a single diastereomer in 16% yield along with 12% of the *O*-cyclized byproduct **11** using a recirculating flow system (Scheme 2b).^{15a,20} Interestingly, the cyclization product derived from (–)-**5** was not observed along with (–)-**8**. A control experiment involving microwave thermolysis of substrate **5** (dioxane, 100 °C)¹⁹ ruled out a thermal Conia-ene reaction²¹ and provided support for photoinduced cyclization of **5** $\rightarrow$ **8**.

In order to further probe photoreactivity, a UV/VIS absorption study of the starting material **5** was conducted. According to the UV/VIS spectra (Figure 2), substrate **5** in 2-methyl tetrahydrofuran (2-MeTHF) features an absorption range of 300–400 nm. To determine the excited state properties of **5** to optimize its photocyclization to **8**, we carried out steady state and time resolved experiments in 2-MeTHF at room temperature. As we observed very weak fluorescence, we next evaluated the emissive properties at low temperature.¹⁹ At 77 K, 2-MeTHF glass was formed and we were able to observe phosphorescence.¹⁹ To validate the observed luminescence, excitation spectra were recorded by monitoring the fluorescence signal that matched the absorption profile, indicating the origin of emission and absorption were from the same chromophore. The triplet energy of **5** was determined from the phosphorescence spectra to be ~56 kcal/mol. Based on the phosphorescence signal, we observed three distinct lifetimes *i.e.* 4.4, 23.4, and 69.9 ms. These distinct lifetimes are not surprising as we had employed a mixture of diastereomers [(+)-**5** and (–)-**5**] in the photophysical experiments combined with the matrix anisotropy expected at 77 K. Deciphering the nature of the excited state provided an avenue to rationalize the mechanistic details for the photocyclization (*vide infra*).

Our photophysical studies led us to anticipate that a light source with wavelength slightly longer than 350 nm may be beneficial to improve the photocyclization yield. Indeed, after condition optimization,¹⁹ use of a purple LED lamp ($\lambda_{\text{max}} = 390$ nm, 370–420 nm) in CH₃CN at 38 °C for 4 h (residence time) improved the yield of (–)-**8** to 29% (67% from (+)-**5** using a continuous flow reactor (Scheme 3).¹⁹ In contrast to the original conditions,

only a trace amount of byproduct **11** was observed. Several triplet sensitizers with a triplet energy above 56 kcal/mol were also tested for the cyclization. Unfortunately, the presence of the sensitizers only accelerated decomposition of substrate **5**.¹⁹ The structure and stereochemistry of (–)-**8** was unambiguously determined from X-ray analysis of the crystalline dicyclohexylammonium salt (–)-**12**.¹⁹ With the type A core structure confirmed, (–)-*O*-methylnemorosone [(–)-**13**] was accessed in good yield following global olefin cross metathesis with the Grubbs 2nd generation catalyst and isobutylene. Demethylation with LiCl/DMSO-*d*₆ was achieved in 67% yield which completed a 7-step total synthesis of (–)-nemorosone [(–)-**2**], the shortest synthesis of this natural product to date.

After significant experimentation to access (–)-nemorosone, photoirradiation of the dearomatized substrate **14**^{14g, 19} with a purple LED lamp at 38 °C for 4 h (residence time) enabled diastereotopic, group-selective²² photoinduced C-cyclization to provide the garcimultiflorone core (–)-**15** (54%) as a single diastereomer along with the *O*-cyclized byproduct **16** (11%) and the de Mayo cycloaddition²³ product **17** (7%) (Scheme 4). Interestingly, further photoirradiation of **16** in a separate experiment also led to the production of the [2 + 2] photocycloadduct **17** in 80% yield. Vinyl allylation of bicyclic core structure **15** and *O*-cyclization of **18** both proceeded in reasonable yields leading to the production of **19**. Finally, cross metathesis with Grubbs 2nd generation catalyst and isobutylene resulted in the first synthesis of (–)-6-*epi*-garcimultiflorone A [(–)-**20**]. The stereochemistry of cyclized intermediate (–)-**15** was confirmed by 2D NMR experiments and the structure of the derived compound (–)-**21** was unambiguously determined by X-ray crystal structure analysis.¹⁹

Having developed a photocyclization method to access (–)-nemorosone (**2**) and (–)-6-*epi*-garcimultiflorone A (**20**), we aimed to further investigate targeted examples of the process to access [3.3.1]-bicyclic systems. Under the optimized conditions used to access type A PPAP core, dearomatized scaffold **22** cyclized to provide the type A PPAP scaffold **23** in 27% yield (Scheme 5a). In this case, its corresponding *O*-cyclized byproduct was not produced. To evaluate the importance of the enol functionality to facilitate photocyclization to access [3.3.1]-bicyclic PPAP core structures, we also discovered that the *bis-O*-methylated substrate **24/24'** did not cyclize under the reaction conditions suggesting that an unprotected enol functionality is necessary (Scheme 5b).

To further understand the hydrogen atom/proton transfer process pathway in the photocyclization of **5**, we conducted a deuterium-labeling study. Photocyclization of deuterated substrate **5-*d*** was accomplished in CD₃CN:D₂O (v/v 50:1) at 10 °C over 6 h (residence time) in flow using 390 nm light (Figure 3A). The geminal methyl groups *a* and *b* of photocyclization product (–)-**8** have well defined chemical shifts as shown in Figure 3B.^{3a,19} To our surprise, only the diastereotopic methyl group *a* was deuterated as determined by ¹H NMR analysis. Inspection of the ¹H NMR spectra revealed that a small amount of non-deuterated product (–)-**8** was also formed, along with a new triplet resonance (*a'*) appearing slightly up-field (Figure 3C). We later confirmed that this *a'*-signal was monodeuterated (–CH₂D) by 2D NMR analysis.¹⁹ Deuterium-labeling was also found to only occur with substrate **5** and not with product (–)-**8**.¹⁹ This result indicates that hydrogen

atom/proton transfer with substrate **5** is stereoselective and occurs with a well-defined topology (*vide infra*).

Based on our combined photochemical and photophysical investigations, we propose the mechanistic pathway shown in Scheme 6. Photoexcitation of the deuterated, dearomatized scaffold tautomer (+)-**5a-d** using a purple LED lamp leads to the reactive excited state **ES***. The presence of the β -hydroxyenone excited state enables a divergent pathway that can either lead to excited-state proton transfer (ESIPT) resulting in a zwitterionic intermediate **ZW-5** or a triplet biradical pathway resulting in **tBR-5** by a hydrogen atom transfer (HAT) process (from an $n-\pi^*$ triplet excited state based on the observed phosphorescence, *cf.* Figure 2²⁷). The zwitterion **ZW-5** and triplet biradical **tBR-5** intermediates may also be inter-converted by intersystem crossing (ISC) process. Ring closure of **ZW-5** or **tBR-5** can both afford the formation of the type A PPAP scaffold (–)-**8-d**. Intramolecular cyclization can also lead to the *O*-cyclized byproduct **11** for non-deuterated substrate (+)-**5** (*not. shown*). For substrate (+)-**5-d** with a homoallyl-tethered sidechain, the interconvertible intermediates **ZW-5** and **tBR-5** can both occupy chair-chair-chair ten-membered assemblies for D^+ or $D^\bullet$ transfer, respectively. This topology may explain the stereoselective deuterium labeling observed (*cf.* Figure 3). In this manner, the C_7 -allyl group is placed in a favorable equatorial position. In contrast, for intermediates of substrate (–)-**5/5a** the C_7 allyl group must instead occupy an axial position to accomplish the cyclization (*vide infra*).

After our investigation of the photocyclization of the homoallyl-tethered substrates, we also evaluated the effect of substrates with allyl tethers. Photophysical investigations of cinnamyl substrate **25** showcased similar profiles to **5**, which indicates that varying the alkenyl chain from isopentenyl in **5** to cinnamyl in **25** did not alter the excited state properties of the reactive chromophore (*i.e.* β -hydroxyenone moiety).¹⁹ However, under the optimized conditions for type A PPAP scaffolds, photocyclization of **25** afforded the de Mayo-type cycloaddition product **26** as a single diastereomer in 24% yield (Scheme 7). We had previously observed **26** to be a product of visible light-mediated photocycloaddition of **25** resulting from triplet energy transfer.²⁵ In a similar manner, photoirradiation of the dearomatized prenyl derivative **27** afforded the related product **28** in 13% yield along with re-aromatized product **29** (17%).

To further explore the differential outcomes of the two dearomatized substrates (**27** vs. **5**), parallel experiments were conducted using argon and oxygen purging.²⁶ Due to the experimental limitation of degassing the reaction mixture in our established flow system, batch reactions were performed for 12 h.¹⁹ We found that oxygen purging prevented photocyclization of **27**, leading only to recovered starting material and de-composition byproducts. Interestingly, oxygen purging of solutions of **5** did not lead to an observable difference in comparison to reactions conducted under argon. These experiments indicated that the de Mayo and rearomatization products from prenylated substrate **27** are obtained through triplet energy transfer, while the type A PPAP core photocyclization may proceed through a different pathway (Scheme 6). It should be noted that the possibility of substrate **5** reacting through a triplet state cannot be completely ruled out, as the intramolecular cyclization may be faster than the intermolecular reaction between the substrate and oxygen.

Based on the results of [2 + 2] photoreactions of allyl-tethered dearomatized substrates, along with the triplet quenching experiments, we herein propose an additional mechanistic pathway shown in Scheme 8 for photocycloaddition of substrates **25** and **27**. Photoexcitation of the dearomatized scaffold tautomers (**25a** and **27a**) using the purple LED lamp leads to the reactive excited states which ultimately afford a triplet state biradical tBR-**a** which can undergo either a 5-*exo*-trig (pathway **A**) or a 6-*endo*-trig (pathway **B**) cyclization to form new biradical intermediates tBR-**b** or -**c**. The triplet biradical tBR-**b** continues to collapse in an intramolecular fashion to afford the tricyclic de Mayo cycloaddition products (**26** and **28**). It should be noted that the cinnamyl substrate **25** selectively undergoes pathway **B** after photoexcitation, and the resulting tBR-**25b** can rotate to a less hindered conformation to afford **26** as a single diastereomer after radical ring closure. The corresponding 6-*endo*-trig-derived biradical tBR-**c** may undergo ring opening (pathway **B**) followed by formal prenyl shift to the γ -position (tBR-**d**). Further transfer of the prenyl fragment *via* an oxygen-centered radical through a six-membered ring transition state affords tBR-**e** which may rearomatize to **29**.

CONCLUSION

In conclusion, we have successfully synthesized the type A PPAP natural product (–)-nemorosone and a natural product epimer (–)-6-*epi*-garcimultiflorone A by direct photoirradiation of homoallyl-tethered, dearomatized acylphloroglucinol substrates. Photoreactions of allyl-tethered substrates have been shown to provide de Mayo-type products. Accordingly, our investigations have showcased that excited state re-activity can be exploited by use of either a homoallylic or allylic tether which dictates the divergent product outcome by favoring one deactivation pathway (Schemes 6 and 8). Such delicate control of excited state reactivity provides an avenue to build a library of diverse synthetic type A PPAP analogs for further biological investigation which will be the subject of future investigations in our laboratories.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Select examples of type A and B PPAP natural products.

Figure 2. UV/VIS absorption (*blue*), excitation (*red*,) and phosphorescence (*green*) spectra for compound **5** in 2-MeTHF. UV/VIS absorption was recorded at room temperature. Excitation spectra were recorded by monitoring the fluorescence signal at $\lambda_{\text{em}} = 454$ nm at room temperature. Phosphorescence spectra were recorded at 77 K in 2-MeTHF glass.

Figure 3.

(A) Deuterium-labeling study; (B) Methyl groups *a* and *b* (*a* = *b* = -CH₃) in non-deuterated (-)-8; (C) Methyl groups (*a* = *b* = -CH₃; *a'* = -CH₂D) in deuterated (-)-8-d.

Scheme 1.
Regiodivergent Cyclizations to Type A or B PPAP Scaffolds

Scheme 2.

Synthesis and Photocyclization of Dearomatized Substrate 5

Scheme 3.

Total Synthesis of (-)-Nemorosone Utilizing Optimized Conditions for Photocyclization and Structure Confirmation^a

^a *Reagents and Conditions:* a) purple LED (390 nm), FLOW, CH₃CN (1 mM), 38 °C, t_R = 4 h, 29% (67% from (+)-5); b) Grubbs II catalyst (20 mol%), isobutylene, 60 °C, 12 h, 94%; c) LiCl (18.0 equiv), DMSO-*d*₆ 120 °C, 75 min, 61%; d) LiCl (20.0 equiv), DMSO-*d*₆ 120 °C, 75 min; e) dicyclohexylamine (NHCy₂, 1.0 equiv), Et₂O, 58% (2 steps).

Scheme 4.

Synthesis of (-)-6-*epi*-Garcimultiflorone A^a

^a*Reagents and Conditions:* a) purple LED (390 nm), FLOW, CH₃CN (5 mM). 38 °C, t_R = 4 h; b) purple LED (390 nm), FLOW, CH₃CN (5 mM). 38 °C, T_R = 4 h, 80%; c) lithium tetramethylpiperidide (LiTMP, 5.0 equiv), lithium 2-thienylcyanocuprate (Li(2-Th)CuCN, 5.5 equiv), allyl bromide (6.0 equiv), THF. -78 °C. 1 h, 69%; d) TFA/H₂O (v/v 1:1), 60 °C, 3 h. 64%; e) Grubbs II catalyst, isobutylene, 60 °C. 12 h. 79%; f) LiCl (20.0 equiv), DMSO-*d*₆, 120 °C, 75 min; g) NHCy₂ (1.0 equiv), Et₂O. 45%, 2 steps.

Scheme 5.
Additional Photocyclization Examples

Scheme 6.
Proposed Mechanism for Photocyclization

Scheme 7.
Evaluation of Dearomatized Cinnamyl and Prenyl Substrates

Scheme 8.

Proposed Mechanism for [2 + 2] Photocycloaddition of Allyl-Tethered Dearomatized Substrates 25 and 27