Synthesis of Briarane Diterpenoids: Biomimetic Transannular Oxa-6π electrocyclization Induced by a UVA/UVC Photoswitch

Andrew J. Hall, Stéphane P. Roche,*,‡ and Lyndon M. West*,‡

Department of Chemistry and Biochemistry, Florida Atlantic University, Boca Raton, Florida 33431, United States

S Supporting Information

ABSTRACT: A biomimetic synthesis of briareolate ester B (**3**) from briareolate ester L (**1**) via the intermediate briareolate ester G (**2**) has been achieved through a unique transannular oxa-6π electrocyclization induced by UVA light. UVC irradiation of **3** triggered a rapid retro-6π electrocyclization to establish an unprecedented photochromic switch. In the ground state, reaction of **1** led to the formation of a polycyclic γ-spiroketal γ-lactone **5**, architecturally related to the ether-bridged cembranoids of the cladiellin class.
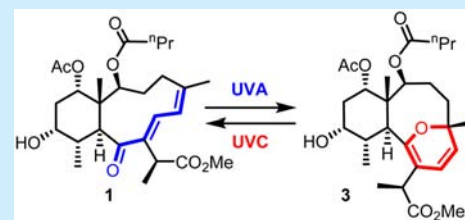
The synthesis of natural products by terrestrial and marine organisms often requires light-induced transformations such as isomerizations, fragmentation, and pericyclic reactions.[1] Pericyclic reactions represent an important body of chemical transformations that enable skeletal rearrangements and facile ring formation (e.g., electrocyclizations, cycloadditions, and sigmatropic rearrangements).[2] Electrocyclic reactions,[3] which often occur in Nature, have been largely explored in biomimetic syntheses of complex natural products.[4] An important subset of these are transannular reactions and are an extremely efficient synthetic approach to prepare complex polycyclic molecules. A large number of impressive examples exist for transannular Diels–Alder[5] and hetero-Diels–Alder[5,6] reactions with electron-poor enone dienophiles to synthesize complex molecules. However, examples of transannular electrocyclization (6π, 8π, or 12π) are extremely rare due to their innate reversibility.[7]

Briareolate ester L (**1**), G (**2**), and B (**3**), briarane-type cembranoids, were isolated from the octocoral *Briarium asbestinum* and have been postulated to be related through a transannular oxa-6π electrocyclic reaction (Figure 1).[4a] The biogenic relationship between these compounds was attractive to us for two reasons: (1) oxa-6π electrocyclization reactions are known for being fast and reversible,[9] and therefore, generating a steady equilibrium between **1**, **2**, and **3** may be challenging; (2) transannular oxa-6π electrocyclizations have been rarely studied. Only one example of transannular oxa-6π electrocyclization has been previously reported.[10]

With our ability to access these rare natural products, we became interested in testing a plausible biosynthetic pathway from **1** to **3** via the intermediacy of **6** to establish an unprecedented transannular oxa-6π electrocyclization (Figure 2). The proposed reaction involves isomerization of the (E,Z)-dienone in **1** to the corresponding (Z,Z)-dienone (**2**) and hinges on the ability of the carbonyl moiety in **2** to undergo rotation (s-trans to s-cis) and overcome the constraints imposed by the macrocycle to reach the sterically hindered inside space.[11]

Given the pivotal importance of rotation of the carbonyl group of the conjugated enone moiety to undergo an oxa-6π
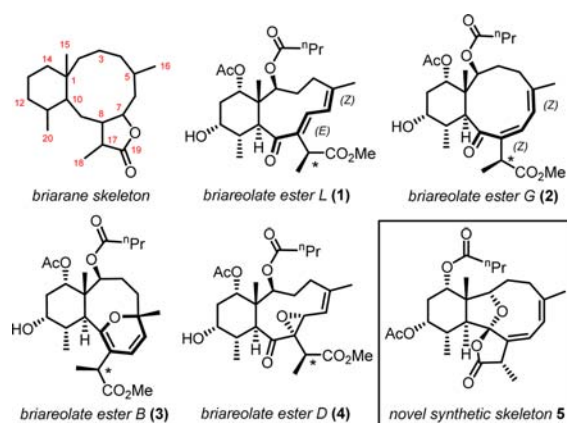
Figure 1. Natural and synthetic briarane diterpenoids with revised structures of briareolate esters showing a (S)-configuration (*) for C-17.

electrocyclization, a better understanding of the conformation (s-*trans* or s-*cis*) of both dienones in **1** and **2** was necessary. It was previously reported that the diene in **1** was twisted out of plane due to conformational restrictions of the 10-membered macrocycle.[8] This suggests the possibility that the diene in **1** could be in a quasi-s-*cis* conformation, in order to releave ring strain in the macrocycle. This conformation is supported by the presence of a small coupling between H-6 (δ_H 6.21, brs) and H-7 (δ_H 7.68, brs) and an NOE correlation observed between these two protons (Figure 2). The conformation of the carbonyl group of the enone moiety in **1** was determined by comparison with the epoxide briareolate ester D (**4**), whose structure was confirmed by X-ray crystallography (Figure 2).[12] The presence of comparable chemical shifts and coupling constants of protons about the perimeter of the macrocycle between that of **1** and **4** suggests that **1** has a similar puckered conformation of the macrocycle with an s-*trans*-enone conformation. In briareolate ester G (**2**), the
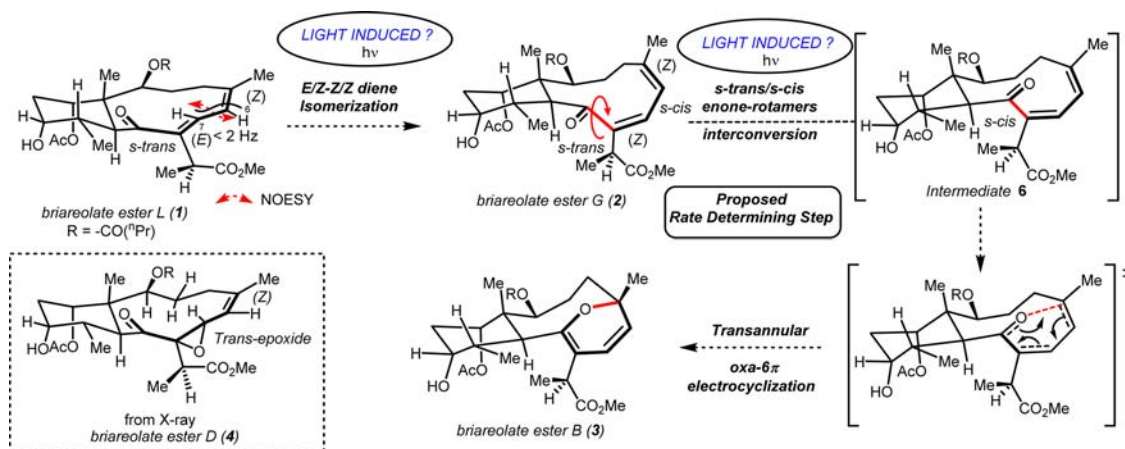
Figure 2. Proposed biosynthetic pathway for conversion of briareolate esters L (**1**) and/or G (**2**) to briareolate ester B (**3**), and 3D drawing of the crystal structure of briareolate ester D (**4**).
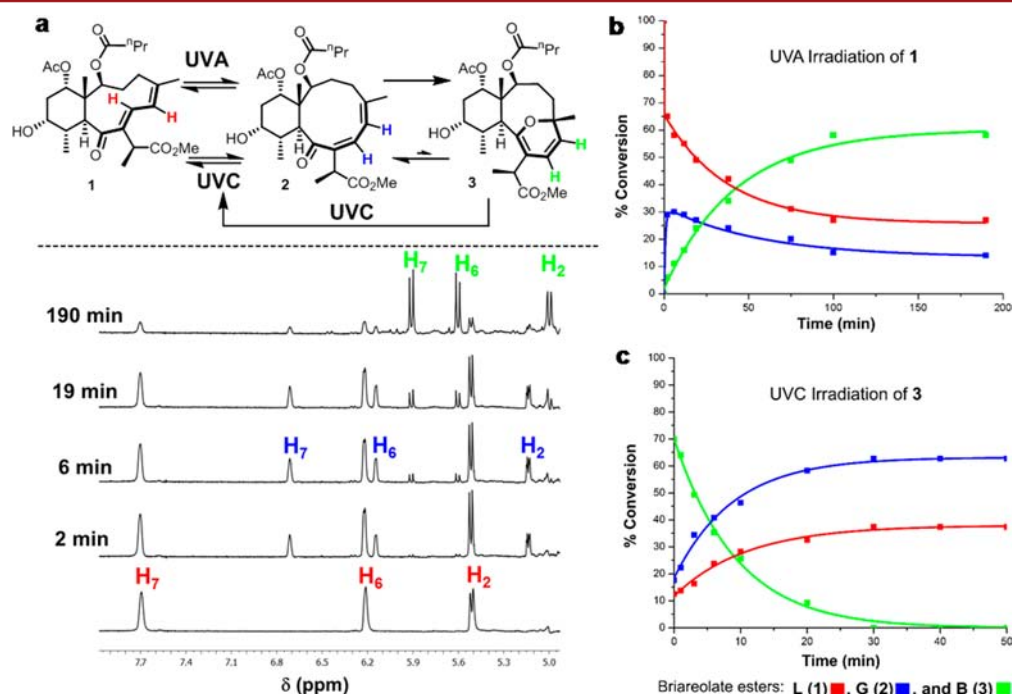
Figure 3. Reaction profiles generated using ^{1}H NMR data for the irradiation of briareolate ester L (**1**) and B (**3**) with UV light. (a) Stacked plot of ^{1}H NMR spectra of the irradiation of briareolate ester L (**1**) with UVA light at different time intervals. (b) Photoirradiation of **1** in MeOH [20 mM] with UVA light. (c) Photoirradiation of **3** in MeOH [20 mM] with UVC light (λ = 254 nm).

similarity in the chemical shifts of the methylene protons in the macrocycle indicates the (Z,Z)-dienone imposes less conformational restriction and allows opening of the macrocycle while retaining an s-*trans* orientation of the enone moiety. Support for an s-*trans*-enone conformation in both **1** and **2** was provided by the observation of diagnostic C=O stretching bands at 1650 and 1640 cm^{-1}, respectively, in the IR spectra and is consistent with a single conformation of the carbonyl in an s-*trans* conformation.[13] This suggests that the carbonyl of **2** would be required to undergo an unfavorable rotation to the inside of the macrocycle in order to achieve the desired oxa-6π electrocyclization.

The fact that the ^{1}H NMR spectra of all three isomers **1**, **2**, and **3** contain a number of signals that do not overlap suggested it would be possible to follow the course of the photoreactions by using standard ^{1}H NMR to enable a relatively precise measurement of isomer ratios over time (Figure 3a). Under the typical conditions

promoting photoinduced oxa-6π electrocyclization with UVC (λ < 260 nm),[9] irradiation of a methanolic solution of **1** in a Quartz reaction vessel was unable to achieve the desired transannular electrocyclization (see Figure S8, Supporting Information (SI)). Instead, **1** readily underwent isomerization to **2** and gave a mixture of the (E,Z)-dienone (**1**) and (Z,Z)-dienone (**2**) which reached a steady state equilibrium after 15 min without any obvious formation of **3** (photostationary state ratio for **1**:**2**:**3** of 37:63:0). Upon UVC irradiation, it is likely that the triplet excited state of **2** undergoes isomerization of the dienone moiety followed by the actual electrocyclization to generate the 2H-pyran product **3**.[9] As shown previously, the retro-6π electrocyclization of **3** may occur more rapidly than the forward reaction[14] which could explain why briareolate ester B (**3**) is not observed. The strongly absorbent dienol ether chromophore may be easily photoexcited (π−π* transition) thus enabling the facile retro-electrocyclization

to occur (see Figure S7, SI). In a serendipitous experiment, irradiation of a methanolic solution of **1** in a Pyrex vessel using low energy (UVA) irradiation ($\lambda > 350$ nm) gave a mixture of the (*E,Z*)-dienone (**1**) and (*Z,Z*)-dienone (**2**) as well as the desired 2*H*-pyran **3** as the major product after 3 h (steady state ratio for **1**:**2**:**3** of 23:12:65; Figure 3b). Extended irradiation times did not afford full conversion to **3**, as decomposition occurred over time. The isomerization of **1** to **2** takes place within minutes (Figure 3a), rapidly reaching a photostationary state, thus implying that the rate-determining step of the cascade is most likely the carbonyl C-9 isomerization. Upon rotation of the C-9 carbonyl inside the macrocycle, the final transannular 6π electrocyclization can take place. These results are unique by the fact that a two-photon process is taking place to promote both the enone photoisomerization and transannular oxa-6π electrocyclization via the excited state of n−π* character. As expected, the carbonyl isomerization (s-*trans* to s-*cis* of enone moiety) appeared nontrivial due to the strain imparted by the macrocycle[11] and was achieved by a plausible pyramidalization in the excited state to access the cisoid reactive rotamer **5** (*vide infra*).[15]

To understand the photochemical experiments we recorded the emission spectrum of the lamps and the absorption spectra of the starting materials **1**, **2**, and **3** (see Figure S7, SI). Initial inspection of the absorption spectrum of **1** revealed two intense bands ($\lambda = 237$ and 284 nm) that could be attributed to π−π* transitions associated with the diene and enone moieties. However, deconvolution of the spectrum using Origin software revealed a weak n−π* transition at $\lambda = 315$ nm (see Figure S6a, SI). The overlay of absorption spectrum of **1** with the normalized UVA and UVC emission spectra in a Rayonet photoreactor revealed the UVC emission overlapped mostly with the π−π* transitions of **1**, while the UVA emission has a slight overlap with the n−π* transition of **1**. It is also important that the n−π* transition is more intense for compound **2** (see Figure S6b, SI), as expected from a more conjugated dienone chromophore.

To follow up on these results, irradiation of briareolate ester B (**3**) using UVA light showed neither reaction nor degradation over the course of several hours. We then turned our attention to the photochemistry of **3** under UVC irradiation to evaluate the reversibility of the 6π electrocyclization (Figure 3c). As expected, UVC photoexcitation of **3** triggered a rapid and complete retro-6π electrocyclization in 40 min to reach an identical photostationary state (similar to the forward reaction from **1**) leading to the matching ratio between **1**, **2**, and **3** of 37:63:0 (see Figure S8, SI). These results support our earlier hypothesis that the oxa-6π electrocyclization from **1** occurred under UVC irradiation (via **2** and **6**), while the retro-transformation rate is even faster.[14]

To assess the possibility of a ground-state acid-mediated or thermal isomerization and oxa-6π electrocyclization sequence, we evaluated several conditions (see Table S3, SI).[4a,16] Both **1** and **2** were found to be thermally stable up to 150 °C (sealed tube) as monitored by ¹H NMR. Over time, decomposition was observed before any isomerization took place. 1,4-Conjugated additions can usually be achieved on dienones with various Lewis bases to trigger cascade transformations such as isomerization followed by oxa-6π electrocyclization.[17] Recently, a DABCO-mediated transformation was attempted but did not result in either isomerization or in electrocyclization.[17a] As previously reported, addition of thiophenol to **1** delivered stereoselectively the macrocyclic enol **7** in a quantitative manner (Scheme 1).[8] Unfortunately, additions of Lewis or Brønsted acids to **7** did not promote the isomerization to (*Z,Z*)-isomer **2**. Further under acid-catalyzed conditions with TFA or PTSA, **1** remained untouched, but in the presence of a

Scheme 1. Acid-Mediated Synthesis of γ-Spiroketal γ-Lactone (5)
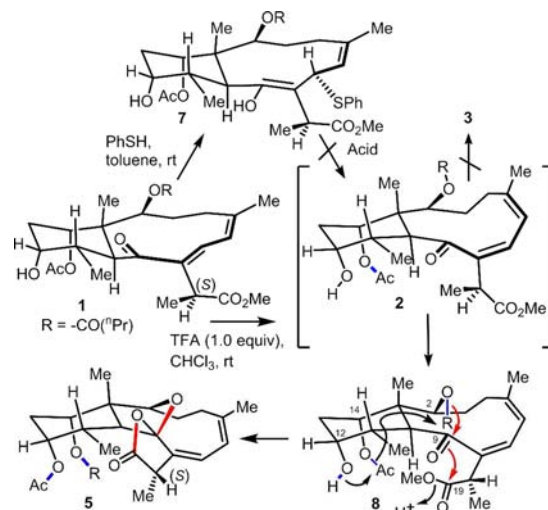
stoichiometric amount of these acids, **1** was slowly converted to **2** without ever affording the 2*H*-pyran product **3** (Scheme 1). Instead, **2** was transformed through an elaborate orchestration of acyl transfers (two successive transesterifications) followed by the C-2 alcohol undergoing a transannular cyclization into the C-9 ketone, which further cyclized to form the γ-spiroketal γ-lactone **5** in 92% yield. The structure of compound **5** was established through interpretation of spectroscopic data including detailed NMR analysis (see Figure S4, SI). NOE correlations observed from H-6 to H₃-16 and between H-7 and H₃-18, together with a small scalar coupling observed between H-6 and H-7, established a (*Z,Z*)-diene arising from the isomerization of **1**. In addition, a distinctive correlation observed between H₃-18 on the γ-lactone ring and H₃-20 indicated that the two methyl groups are spatially proximate. This suggested the configuration at C-17 was *S*, opposite of what was reported for **1**, and other reported briareolate esters and briaranes.[18] Interestingly, inspection of the X-ray data previously reported for briareolate esters A[19] and D (**4**)[12] revealed that the configuration of C-17 in both compounds was also *S* and indicated the structures were incorrectly drawn in the original publications. Therefore, we propose that the C-17 configuration of briareolate esters **1**−**3** all have an (*S*)-configuration at C-17. We also note the structural similarity of **5** to that of the cladiellin skeleton, a structurally related cembranoid-derived class of natural products. Cladiellin diterpenoids, precursor to the briarellin and asbestinin classes, are found in a variety of soft corals and possess a wide range of biological activities.[20]

In summary, the synthesis of briareolate ester B (**3**) from briareolate ester L (**1**) has been achieved through a set of isomerization/oxa-6π electrocyclization using UVA light. Furthermore, UVC irradiation of **3** triggered a rapid retro-6π electrocyclization to give a mixture of **1** and **2** to establish a unique photochromic switch that are of interest to the scientific community.[21] This molecular switch offers insight into trans-annular oxa-6π-electrocyclic reactions of macrocyclic dienone systems via a two-photon process and is likely to find numerous applications in the synthesis of medium-sized macrocycles.[22] The study also confirms the hypothesis that the briareolate esters (**1**−**3**) are genuinely produced photochemically in their natural habitat. Finally, the reaction of **1** under acidic conditions led to the synthesis of γ-spiroketal γ-lactone **5**, related to the ether-bridged

Cladiellin class of natural products, and led to revision of the configuration at C-17 as *S* for the briareolate esters.

ASSOCIATED CONTENT

ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03689.

> General experimental procedures, isolation and structural elucidation of briareolate esters (**1−3**), ^{1}H NMR spectra of briareolate esters (**1−3**), photochemical and ground state procedures, structural elucidation of **5**, NMR spectra of **5** including ^{1}H, ^{13}C, COSY, HSQC, HMBC, and ROESY, photochemical reaction procedures, and kinetic reaction profiling (PDF)

AUTHOR INFORMATION

Corresponding Authors
*E-mail: lwest@fau.edu.
*E-mail: sroche2@fau.edu.

ORCID ⓘ
Lyndon M. West: 0000-0003-0909-830X

Author Contributions
‡S.P.R. and L.M.W. contributed equally.

Notes
The authors declare no competing financial interest.

REFERENCES

(1) For reviews on photochemical reactions as key steps in natural products' synthesis, see: (a) Hoffmann, N. *Chem. Rev.* **2008**, *108*, 1052. (b) Bach, T.; Hehn, J. P. *Angew. Chem., Int. Ed.* **2011**, *50*, 1000. (c) Glusac, K. *Nat. Chem.* **2016**, *8*, 734.

(2) (a) Houk, K. N. *Top. Curr. Chem.* **1996**, *183*, 1. (b) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668.

(3) (a) Marvell, E. N. *Thermal Electrocyclic Reactions*; Academic Press: New York, 1980; Vol. *43*. (b) Ansari, F. L.; Qureshi, R.; Qureshi, M. L. *Electrocyclic Reactions*; Wiley: Weinheim, Germany, 1999.

(4) (a) Beaudry, C. M.; Malerich, J. P.; Trauner, D. *Chem. Rev.* **2005**, *105*, 4757. (b) Thompson, S.; Coyne, A. G.; Knipe, P. C.; Smith, M. D. *Chem. Soc. Rev.* **2011**, *40*, 4217.

(5) (a) Layton, M. E.; Morales, C. A.; Shair, M. D. *J. Am. Chem. Soc.* **2002**, *124*, 773. (b) Balskus, E. P.; Jacobsen, E. N. *Science* **2007**, *317*, 1736. For a review on the early development of the transannular Diels−Alder strategy in organic synthesis, see: (c) Marsault, E.; Toró, A.; Nowak, P.; Deslongchamps, P. *Tetrahedron* **2001**, *57*, 4243.

(6) For a selected list of natural product syntheses featuring transannular Diels−Alder reactions, see: (a) Vosburg, D. A.; Vanderwal, C. D.; Sorensen, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 4552. (b) Evans, D. A.; Starr, J. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1787. (c) Vanderwal, C. D.; Weiler, S.; Sorensen, E. J.; Vosburg, D. A. *J. Am. Chem. Soc.* **2003**, *125*, 5393.

(7) For selected examples of transannular 6π electrocyclization, see: (a) Sun, H. H.; Waraszkiewicz, S. M.; Erickson, K. L.; Finer, J.; Clardy, J. *J. Am. Chem. Soc.* **1977**, *99*, 3516. (b) Pohnert, G.; Boland, W. *Nat. Prod. Rep.* **2002**, *19*, 108. For a selected example of transannular 8π electrocyclization, see: (c) Nicolaou, K. C.; Petasis, N. A.; Zipkin, R. E.; Uenishi, J. *J. Am. Chem. Soc.* **1982**, *104*, 5555. For a unique example of transannular 12π electrocyclization, see: (d) Derewacz, D. K.; Covington, B. C.; McLean, J. A.; Bachmann, B. O. *ACS Chem. Biol.* **2015**, *10*, 1998.

(8) Gupta, P.; Sharma, U.; Schulz, T. C.; Sherrer, E. S.; McLean, A. B.; Robins, A. J.; West, L. M. *Org. Lett.* **2011**, *13*, 3920.

(9) For a selected list of oxa-6π electrocyclization and corresponding (2*H*)-pyran product syntheses, see: (a) Büchi, G.; Yang, N. *J. Am. Chem. Soc.* **1957**, *79*, 2318. (b) Marvell, E. N.; Caple, G.; Gosink, T. A.; Zimmer, G. *J. Am. Chem. Soc.* **1966**, *88*, 619. (c) Marvell, E. N.; Chadwick, T.; Caple, G.; Gosink, T.; Zimmer, G. *J. Org. Chem.* **1972**, *37*, 2992. (d) Gaudiana, R. A.; Graf, J. F.; Lillya, C. P. *J. Org. Chem.* **1979**, *44*, 646. (e) Krasnaya, Z. A. *Chem. Heterocycl. Compd.* **1999**, *35*, 1255.

(10) Olson, B. S.; Trauner, D. *Synlett* **2005**, 700.

(11) For examples of conformational constraints in medium-sized ring macrocycles and relative reactivity, see: (a) Takahashi, T.; Yokoyama, H.; Haino, T.; Yamada, H. *J. Org. Chem.* **1992**, *57*, 3521. (b) Bogdan, A. R.; Jerome, S. V.; Houk, K. N.; James, K. *J. Am. Chem. Soc.* **2012**, *134*, 2127. (c) Zhang, H.; Yu, E. C.; Torker, S.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2014**, *136*, 16493. The equilibrium shift between the dienone (or dienal) and their 2*H*-pyran counterparts does not usually depend on conformational restrictions, but rather depends on electronic factors to stabilize or destabilize the 6π electron conjugation; see: (d) Delbaere, S.; Micheau, J.-C.; Frigoli, M.; Vermeersch, G. *J. Org. Chem.* **2005**, *70*, 5302. (e) Peng, W.; Hirabaru, T.; Kawafuchi, H.; Inokuchi, T. *Eur. J. Org. Chem.* **2011**, *2011*, 5469.

(12) (a) Mootoo, B.; Ramsewak, R.; Sharma, R.; Tinto, W.; Lough, A. *Tetrahedron* **1996**, *52*, 9953. (b) The X-ray data for briareolate ester D (**4**) can be obtained free of charge from the Cambridge Crystallographic Data center via www.ccdc.cam.ac.uk/data_request/cif [CCDC 1274377].

(13) Lillya, C. P.; Kluge, A. F. *J. Org. Chem.* **1971**, *36*, 1977.

(14) Cerfontain, H.; Geenevasen, J. A. J.; van Noort, P. C. M. *J. Chem. Soc., Perkin Trans. 2* **1980**, *7*, 1057.

(15) (a) Diau, E. W. G.; Kotting, C.; Solling, T. I.; Zewail, A. H. *ChemPhysChem* **2002**, *3*, 57. (b) Wang, Y.; Liu, Z.; Xu, Y.; Zhang, B. *J. Chem. Phys.* **2015**, *143*, 064304. (c) Turro, N. *Modern molecular photochemistry*; University Science Books: 1991, pp 11−12.

(16) Malerich, J. P.; Trauner, D. *J. Am. Chem. Soc.* **2003**, *125*, 9554.

(17) (a) Jacob, S. D.; Brooks, J. L.; Frontier, A. J. *J. Org. Chem.* **2014**, *79*, 10296. (b) Shang, H.; Liu, J.; Bao, R.; Cao, Y.; Zhao, K.; Xiao, C.; Zhou, B.; Hu, L.; Tang, Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 14494.

(18) Lei, H. *Chem. Biodiversity* **2016**, *13*, 345.

(19) (a) Maharaj, D.; Mootoo, B. S.; Lough, A. J.; McLean, S.; Reynolds, W. F.; Tinto, W. F. *Tetrahedron Lett.* **1992**, *33*, 7761. (b) Dookran, R.; Maharaj, D.; Mootoo, B. S.; Ramsewak, R.; McLean, S.; Reynolds, W. F.; Tinto, W. F. *Tetrahedron* **1994**, *50*, 1983.

(20) Welford, A. J.; Collins, I. *J. Nat. Prod.* **2011**, *74*, 2318.

(21) (a) Kosa, T.; Sukhomlinova, L.; Su, L.; Taheri, B.; White, T. J.; Bunning, T. J. *Nature* **2012**, *485*, 347. (b) Kramer, R. H.; Mourot, A.; Adesnik, H. *Nat. Neurosci.* **2013**, *16*, 816.

(22) (a) Shang, S.; Tan, D. *Curr. Opin. Chem. Biol.* **2005**, *9*, 248. (b) Marcaurelle, L. A.; Comer, E.; Dandapani, S.; Duvall, J. R.; Gerard, B.; Kesavan, S.; Lee, M. D., IV; Liu, H.; Lowe, J. T.; Marie, J. C.; Mulrooney, C. A. *J. Am. Chem. Soc.* **2010**, *132*, 16962. (c) Kitsiou, C.; Hindes, J. J.; I'Anson, P.; Jackson, P.; Wilson, T. C.; Daly, E. K.; Felstead, H. R.; Hearnshaw, P.; Unsworth, W. P. *Angew. Chem., Int. Ed.* **2015**, *54*, 15794.