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Biomimetic Synthesis of Pyrone-Derived Natural Products: Exploring Chemical Pathways from a Unique Polyketide Precursor

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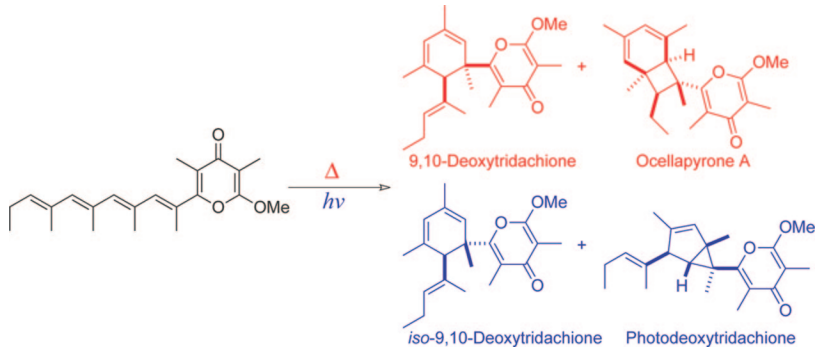

Our biomimetic hypothesis proposes that families of diverse natural products with complex core structures such as 9,10-deoxytridachione, photodeoxytridachione and ocellapyrone A are derived in nature from a linear and conformationally strained all-(*E*) tetraene−pyrone precursor. We therefore synthesized such a precursor and investigated its biomimetic transformation under a variety of reaction conditions, both to the above natural products as well as to diverse isomers which we propose to be natural products "yet to be discovered". We also report herein the first synthesis of the natural product iso-9,10-deoxytridachione.

Introduction

In recent years, a number of pyrone-containing polypropionate derived natural products have been isolated from a restricted group of marine mollusks of the order *Sacoglossan*.[1] These compounds are believed to have evolved as part of a chemical defense strategy against predators, since the producing species are devoid of a hard protective shell.[2] The impressive breadth of biological activities associated with these class of compounds, mirrors their diverse and impressive molecular architectures. These metabolites often comprise a pyrone "head group" appended to a range of complex cyclic cores and unsaturated side chains. Figure 1 illustrates several examples including the unsaturated conjugated polyene cyercene A (**1**),[3] 1,3-cyclohexadiene core units such as (−)−9,10-deoxytridachione (**2**),[4] (+)-iso-9,10-deoxytridachione (**5**)[5] and tridachiahydropyrone (**6**),[6] bicyclo[3.1.0]hexane structures including (−)-photodeoxytridachione (**7**),[7] bicyclo[4.2.0]octadiene such as (+)-ocellapyrone A (**10**),[8] and oxidized derivatives tridachione (**3**),[9] tridachiapyrone I (**4**),[10] tridachiapyrone E (**8**),[11] tridachiapyrone F (**9**),[11]

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[‡] Eli Lilly and Company Ltd.
[§] University of Nottingham.

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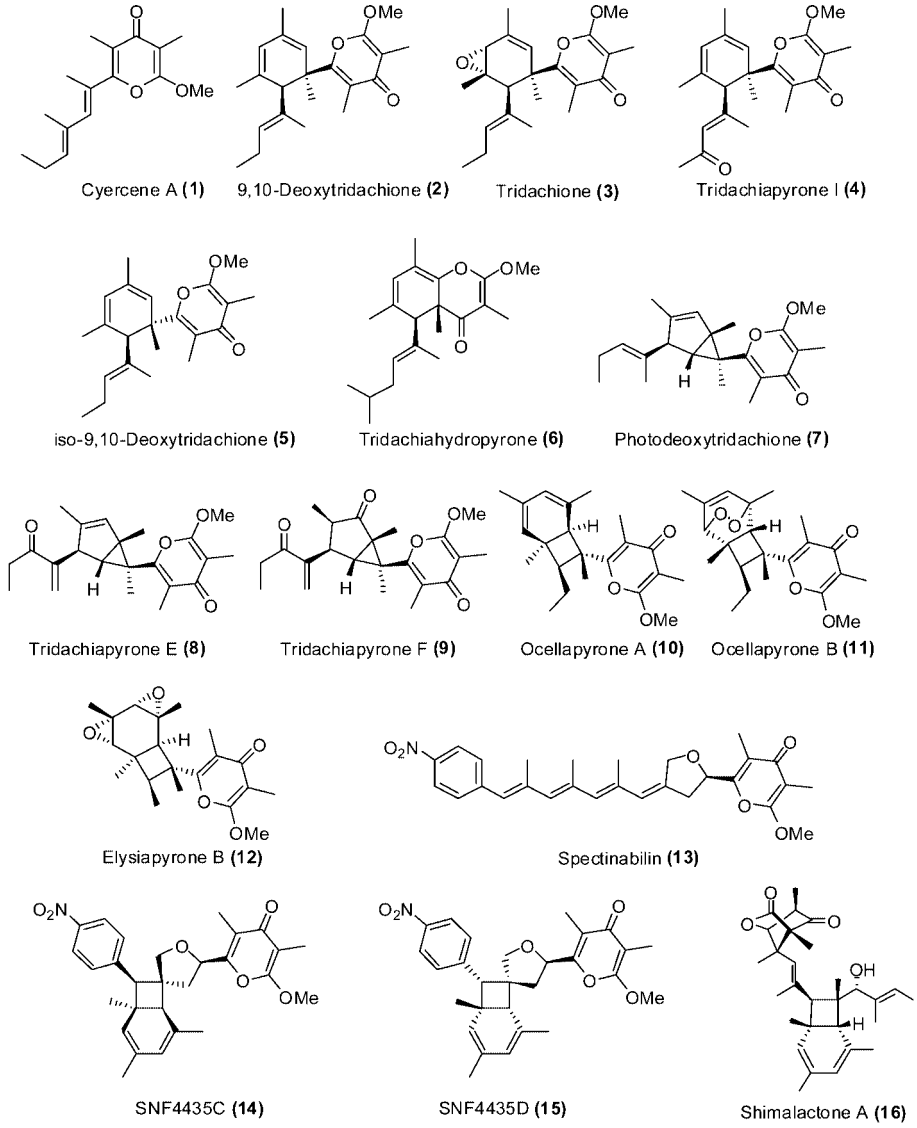
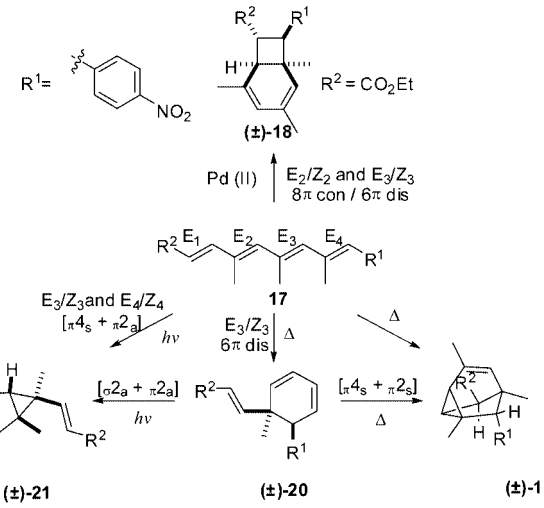


FIGURE 1. Representative structural diversity of polypropionate metabolites.

ocellapyrone B (**11**),[8a,c] and elysiapyrone B (**12**).[12] Whereas the majority of these compounds have been isolated from mollusks, the polypropionate nitrophenyl pyrone spectinabilin (**13**),[13] and the SNF compounds[14] **14** and **15** have been isolated from the actinomycete *Streptomyces spectabilis*. Given the structural similarities of these compounds, it is possible that microorganisms living within the mollusks are the source of these natural products. However, the occurrence of shimalactone A (**16**), a structurally distinct polyketide isolated from a marine-derived fungus bearing little biological resemblance to Streptomycetae is at variance with this hypothesis.[15]

In the late 1970s, Ireland and Faulkner pioneered a program of research searching for related metabolites.[4] Several interesting

SCHEME 1. Complex Structures Derived from 17



and structurally unique compounds were uncovered, and fascinating chemical relationships observed. For example, Faulkner and Scheuer independently observed the photochemical

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(11) Ksebati, M. B.; Schmitz, F. J. *J. Org. Chem.* **1985**, *50*, 5637–5642.
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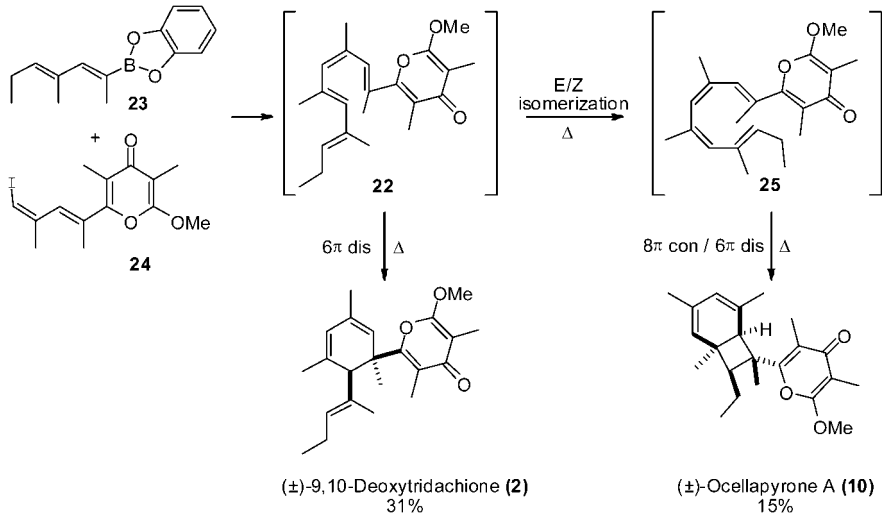
SCHEME 2. Biomimetic Synthesis of (±)-9,10-Deoxytridachione (2) and (±)-Ocellapyrone A (10) from 22



conversion, in vitro[4] and in vivo,[7] respectively, of (−)−9,10-deoxytridachione (**2**) into (−)-photodeoxytridachione (**7**).

The structural diversity, varied biological activities, and novel chemical relationships make this family of compounds very attractive targets for synthesis. In addition to our own investigations,[16] research from the groups of Trauner,[17] Jones,[18] Parker,[19] Perkins,[6b,20] and Nicolaou[21] have resulted in numerous elegant syntheses of unsaturated polyketides and have provided a more detailed understanding of the chemistry of polyenes in general.

We have previously demonstrated that conjugated polyenes with all-(*E*) geometry, under controlled reaction conditions, are able to undergo selective cascade isomerization−pericyclization to form a range of complex structures (Scheme 1). Polyene **17** was encouraged to undergo selective *E*/*Z* double-bond isomerization under a variety of reaction conditions, resulting in the required geometry for cascade electrocyclizations to occur. Core structures (±)-**18**, (±)-**20**, and (±)-**21** all share common structural features with the polypropionate metabolites described above. These observations led us[16] to propose a biosynthetic rationale to explain the origin of such unsaturated pyrone polyketides from polyene precursors.

We surmised that many complex polypropionate metabolites are derived biosynthetically from linear polyenes via *Z*/*E* double bonds isomerization, thermal and/or photochemical electrocyclization,[22] [4 + 2] cycloaddition reactions, or [2 + 2] concerted rearrangement, generating significant structural diversity. We recently provided support for our hypothesis, with the biomimetic synthesis of both (±)-9,10-deoxytridachione (**2**) and (±)-ocellapyrone A (**10**), from the conjugated polyene-pyrone precursor (*E,Z,E,E*)-**22**, via intermediate **25** (Scheme 2).[23] In order to produce the required (*Z*)-double bond, polyene **22** was constructed using a convergent Suzuki coupling approach from the boronic ester **23** and the vinyl iodide **24**. Although providing evidence to support our biosynthetic proposal, we were keen to gain further insights into the biomimetic modes of reactivity that might arise from the corresponding polyene all-(*E*)-**26** (Scheme 3).

Scheme 3 illustrates our proposed hypothesis toward a general biosynthetic pathway for representative polypropionate metabolites containing γ-pyrones and describes possible chemical relationships between them. The all-(*E*)-polyene **26** could, after selective photochemical or thermal double bond isomerizations, lead to the (*E,Z,E,E*)-**22**, (*E,Z,Z,E*)-**25**, and (*Z,Z,E,E*)-**27** polyenes, which could subsequently undergo photochemically or thermally allowed pericyclic processes[24] to provide the natural metabolites **2**, **7**, and **10**, respectively. Furthermore, selective late-stage oxidation could lead to related metabolites including **3**, **4**, **8**, **9**, and **11**. Although several of the natural products of interest were isolated in enantiomerically pure form, in biomimetic terms, we consider that these molecular frameworks would have arisen by intrinsically favorable chemical pathways, and therefore the skeletal complexity could have initially originated by nonenzymatic reactions in the primitive organism. Indeed, if these molecules resulting from such complex chemical processes were beneficial to the organism, enzymes might have

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(22) For an excellent review concerning biosynthetic and biomimetic electrocyclizations, see: Beaudry, C. M.; Malerich, J. P.; Trauner, D. *Chem. Rev.* **2005**, *105*, 4757–4778.

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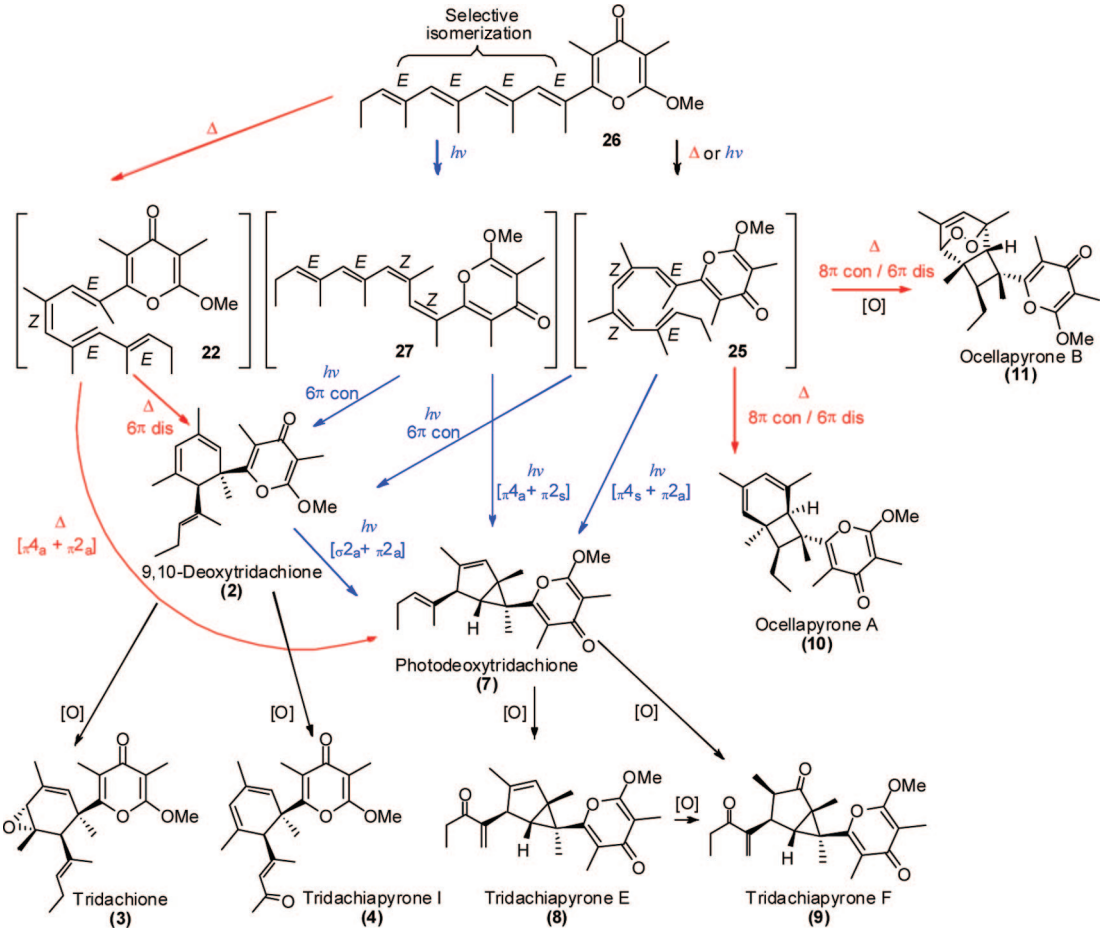
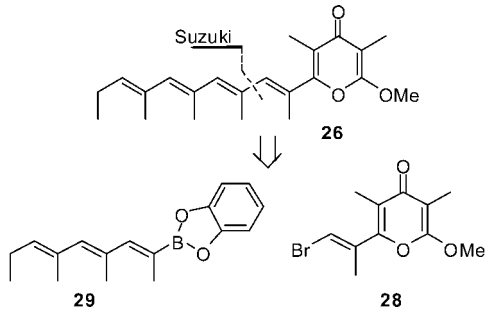
SCHEME 3. Proposed Biosynthetic Pathways from 26



evolved to facilitate the production of these useful materials in enantiomerically pure form. Hence, the objective of our synthetic studies was not only the synthetic challenge, but to understand and perhaps replicate, the elegant biomimetic pathways leading to this intriguing family of compounds. Thus, we now report full details of our study on the synthesis of the all-(*E*) tetraene **26,** and its subsequent biomimetic conversion to a range of pyrone-derived natural products

SCHEME 4. Retrosynthetic Analysis for 26



Results

Our experience with polyketide-derived polyenes led us to a Suzuki disconnection of the target **26** requiring the vinyl halide **28** and the boronic ester **29** (Scheme 4). The synthesis of the key vinyl bromide **28** from the known pyrone **30**[25] began with deprotonation using lithium hexamethyldisilazide at −78 °C in THF, followed by quenching the resulting carbanion with Davis oxaziridine[26] to produce the functionalized hydroxypyrone **31** (Scheme 5). Swern oxidation[27] of **31** next afforded ketone **32**, which underwent a Wittig reaction[28] to give the (*E*)-vinyl bromide **28** together with a minor quantity of the corresponding (*Z*)-isomer **33**. The stereochemistry of **28** was corroborated by X-ray crystallography (Figure 2).[29]

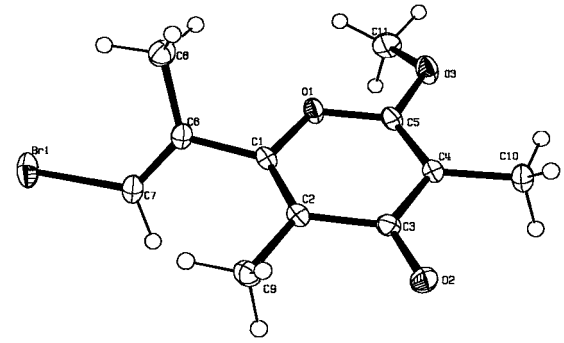
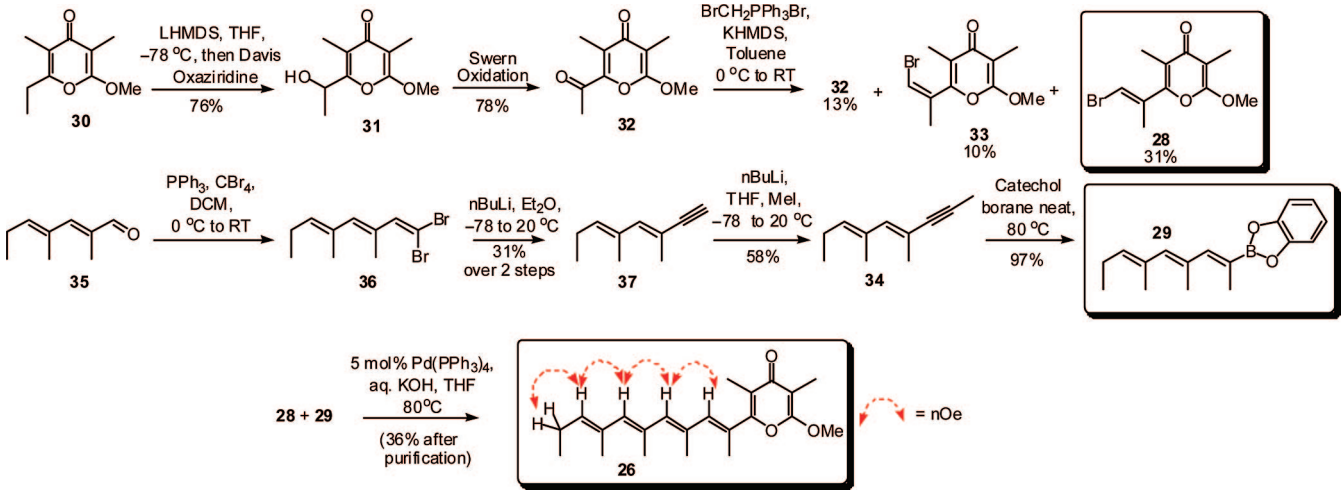


FIGURE 2. X-ray crystal structure of **28**.

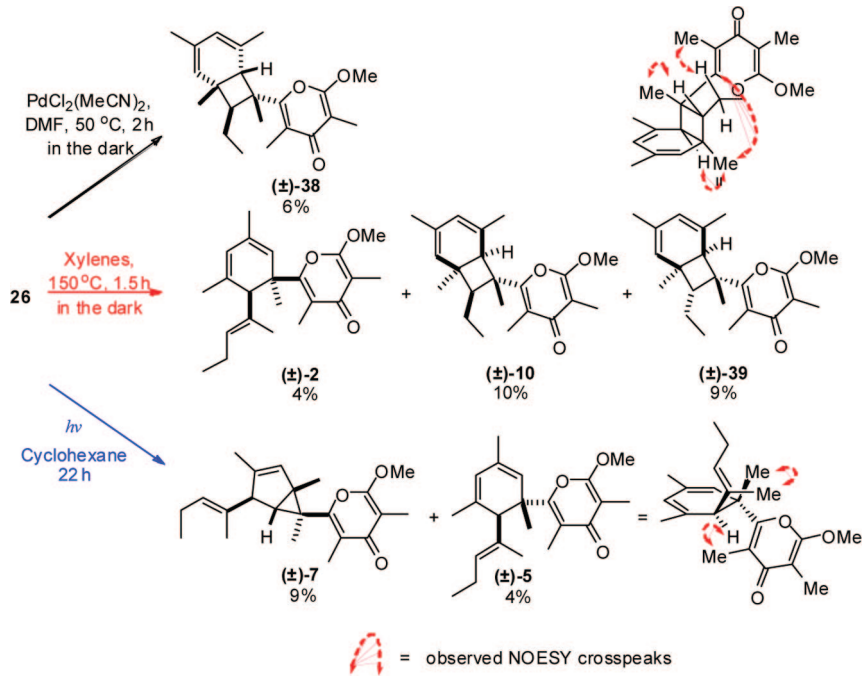
Boronic ester **29** was obtained from a chemoselective and regioselective hydroboration of the alkyne **34** using catecholborane.[30] The alkyne **34** was generated from the known aldehyde

(25) Hatakeyama, S.; Ochi, N.; Takano, S. *Chem. Pharm. Bull.* **1993**, *41*, 1358–1361.
(26) Davis, F. A.; Stringer, O. D. *J. Org. Chem.* **1982**, *47*, 1774–1775.
(27) Huang, S. L.; Omura, K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 3329–3331.

SCHEME 5. Synthesis of 26



SCHEME 6. Biomimetic Conversion of 26



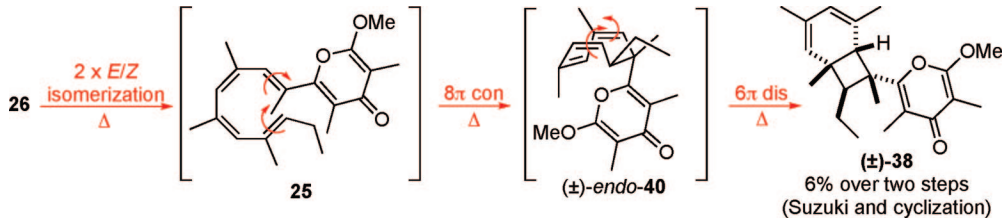
35[31] using Corey−Fuchs methodology[32] to afford the terminal alkyne **37**, followed by methylation to **34**. Subsequent Suzuki cross-coupling[33] of **28** and **29** furnished the desired highly sensitive polyene−pyrone **26**, which was used directly to avoid decomposition.[34] The stereochemistry of **26** was further confirmed by NOE correlation of the four alkenyl hydrogens.

We had previously demonstrated that polyene isomerizations could be facilitated by transition-metal catalysis and by thermal or photochemical means, and we were curious to investigate these different modes of activation on **26**. To the best of our knowledge, no previous study had been carried out using an all-(*E*) tetraene−pyrone unit, and we were intrigued to determine whether or not this "key building block" would indeed yield any trace of the described natural products or not.

Thus, isomerization studies with **26** were carried out in the dark under palladium-catalyzed conditions previously described by Moses et al.[16a] Under these conditions, a complex mixture of products was obtained. However, chromatographic separation afforded a reasonable quantity of the racemic bicycle[4.2.0]octadiene **38**, corresponding to the *endo*-isomer of ocellapyrone A (**10**), for which the spectroscopic data were in agreement with those previously reported by Trauner and co-workers (Scheme 6).[8c] LCMS analysis did not reveal any detectable trace of **2**, **7**, or **10** in the crude material from which (±)-**38** was isolated. Interestingly, compound (±)-**38** was incorrectly proposed as the original structure of **10**,[8a] before revision and confirmation of the correct structure by synthesis.[8b,c] It is noteworthy that (±)-**38** could be the precursor for the biosynthesis of ocellapyrone

(28) O'Donnell, M. J.; Arasappan, A.; Hornback, W. J.; Huffman, J. C. *Tetrahedron Lett.* **1990**, *31*, 157–160.
(29) CCDC 619001 contains the supplementary crystallographic data for this article. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.
(30) (a) Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1975**, *97*, 5249–5255. (b) Paterson, I.; Perkins, M. V. *J. Am. Chem. Soc.* **1993**, *115*, 1608–1610.
(31) Dahmann, G.; Hoffmann, R. W. *Liebigs Ann. Chem.* **1994**, *5*, 837–345.
(32) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *36*, 3769–3772.

SCHEME 7. Proposed Mechanism for the Formation of (±)-38



B (**11**). However, this intermediate has not yet been isolated from a natural source.

Thermal cyclization of **26** was carried out in xylene at 150 °C in the dark for 1.5 h. These reaction conditions afforded multiple products, from which we were able to isolate (±)-ocellapyrone A (**10**), along with the related diastereoisomer (±)-**39** and (±)-9,10-deoxytridachione (**2**) (Scheme 6). Natural products (±)-**2** and (±)-**10** have been synthesized independently within the Baldwin[8b] and Trauner[8c] laboratories from the corresponding precursor **22**. The ^{1}H and ^{13}C NMR data for (±)-ocellapyrone A (**10**) and (±)-9,10-deoxytridachione (**2**) matched the literature data,[8] whereas the ^{1}H NMR spectrum for compound (±)-**39** clearly indicated two new characteristic vinylic protons. There were significant similarities between (±)-**10**, (±)-**38**, and (±)-**39** in their ^{1}H NMR [for example, the coupling constant for 5-CH_3 (d, 1.5 Hz) and the unusual chemical shifts of the two protons directly substituting the cyclobutane ring, between δ 2.0 and δ 3.3 ppm]. The structure of compound (±)-**39** was further supported by NOE experiments.

Photolysis of **26** was carried out in a Rayonet reactor equipped with lamps that had optimum emission at 350 and 419 nm. These reaction conditions again afforded a complex mixture of products from which (±)-photodeoxytridachione (**7**) was isolated, where spectral data were in all respects identical to literature data (Scheme 6).[4,7,35] We were agreeably surprised to isolate another compound for which spectroscopic data were in all respects identical to those of the natural product (+)-iso-9,10-deoxytridachione (**5**).[5] The ^{1}H NMR spectrum of (±)-**5** clearly indicated three characteristic vinylic protons. There were significant spectral similarities between (±)-**5** and (±)-**2** [for example, the ^{13}C signals at 45.1 ppm for (±)-**5** and 47.5 ppm for (±)-**2** corresponding to the pyrone-substituted carbon of the cyclohexadiene ring and the ^{1}H signals for the vinylic protons between 5.1 ppm and 5.7 ppm]. The identity of (±)-**5** was further supported by NOE experiments. This unique total synthesis of (±)-**5** along with full spectroscopic analysis allowed us to support the previously reported structure of (+)-iso-9,10-deoxytridachione.

In each set of reaction conditions attempted, complex mixtures of degradation and unidentified side-products were observed, and it was difficult to be conclusive about the exact product ratios. Nevertheless, we had successfully identified four natural products and two related isomers which could be natural products "yet to be isolated".

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(34) Due to its sensitivity, crude **26** was used directly in the isomerization/cyclization studies. For analytical purposes, a separate batch of **26** was prepared and purified using flash silica gel chromatography to give a 36% isolated yield.

(35) Miller, A. K.; Trauner, D. *Angew. Chem., Int. Ed.* **2003**, *42*, 549–552.

Discussion

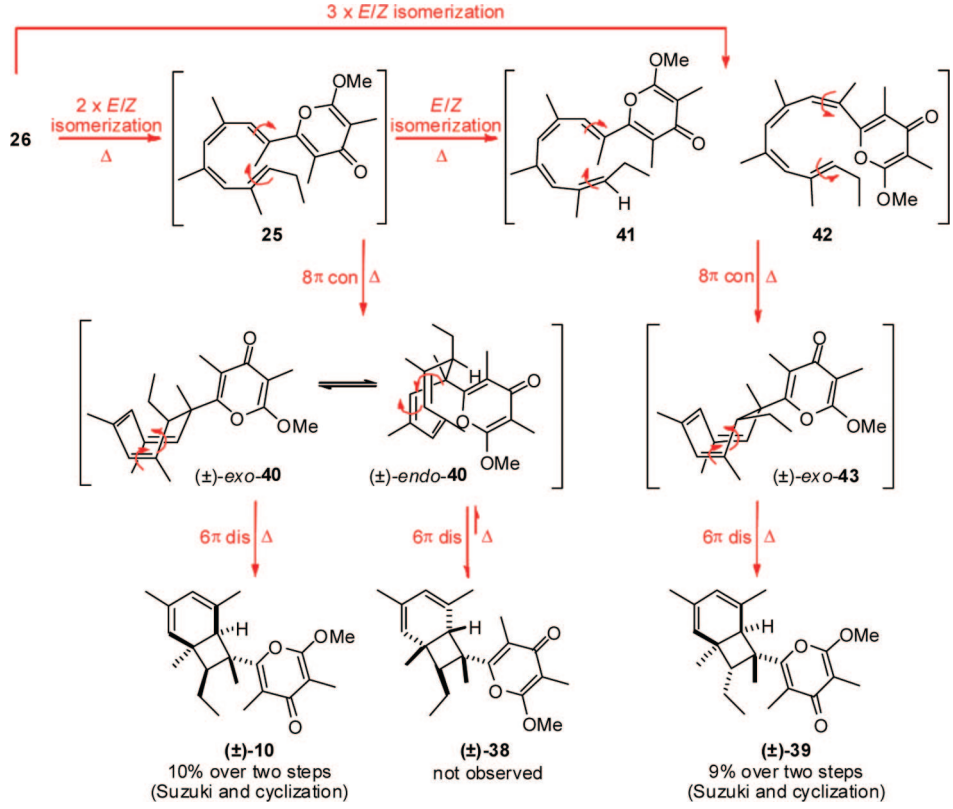
A proposed mechanism for the formation of **38** from the corresponding tetraene−pyrone precursor **22** has been described by Trauner and co-workers.[8c,17] In the present study, it is proposed that the all-(*E*)-polyene **26** first undergoes two palladium(II)-catalyzed double-bond isomerizations leading to **25**. Compound **25** can then undergo a thermal 8π conrotatory electrocyclization to form the cyclooctatriene (±)-**40** followed by a thermal 6π disrotatory electrocyclization of the endo[36] conformation of (±)-**40** producing the bicyclo[4.2.0]octadiene product (±)-**38** (Scheme 7).

Under thermal conditions, **26** is considered to undergo two thermally induced double-bond isomerizations, leading to formation of the intermediate polyene **25**, followed by a thermal 8π conrotatory electrocyclization leading to the cyclooctatriene (±)-**40** (Scheme 8). A thermal 6π conrotatory electrocyclization of the exo isomer of (±)-**40** then affords (±)-ocellapyrone A (**10**).[17,23] In a recent report, Trauner and co-workers observed the formation of (±)-**38** as the major isomer along with smaller quantities of (±)-**10** starting from the polyene **25** at the lower temperature of 45 °C.[8c] The higher temperature (150 °C) used during our thermal experiment allowed us to isolate compound (±)-**10** as the major product without any observable trace of (±)-**38**. However, if formed, the thermally unstable product (±)-**38** could, in principle, convert into the (±)-*endo*-**40** intermediate at high temperature via a retro-electrocyclization and subsequently displace the equilibrium toward the more stable exo conformer **40**, the latter yielding the natural product (±)-**10**. This explanation is consistent with the results of our palladium(II)-catalyzed experiment, in which case a lower temperature was employed and no trace of (±)-**10** was observed. To explain the formation of the previously unidentified diastereoisomer (±)-**39**, it can be reasoned that the polyene **26** undergoes three double bonds isomerizations to form either the tetraene-pyrones (*E*,*Z*,*Z*,*Z*)-**41** and/or (*Z*,*Z*,*Z*,*E*)-**42**. It is reasonable that compound (*E*,*Z*,*Z*,*E*)-**25** could be an intermediate in this process considering the coisolation of (±)-**10**. A thermal 8π conrotatory electrocyclization of **41** and/or **42** next affords cyclooctatriene (±)-**43**, which then undergoes an exo-thermal 6π disrotatory electrocyclization to give the product (±)-**39**.

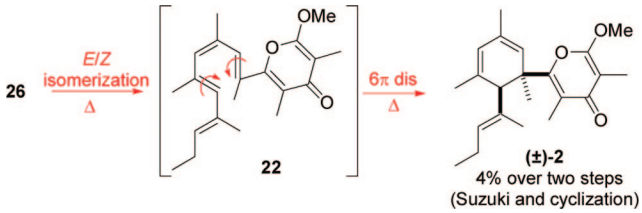
The formation of (±)-9,10-deoxytridachione (**2**) may occur through double-bond isomerization of **26**, leading to **22**, followed by a thermal 6π disrotatory electrocyclization (Scheme 9).

Under photochemical conditions, it is possible that (±)-photodeoxytridachione (**7**) is formed via a pathway consistent with our biomimetic hypothesis (Scheme 3). The precursor **26** could undergo two double-bond isomerizations leading to tetraene **25**. A photochemical 6π conrotatory electrocyclization of **25** would then afford (±)-**2**, which is able to undergo a further photochemical [$_{\sigma}2_a + {}_{\pi}2_a$] rearrangement leading to (±)-photodeoxytridachione (**7**) (Scheme 10). This pathway is in

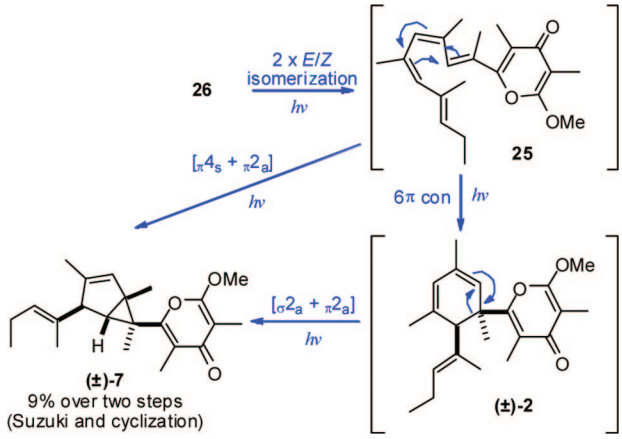
SCHEME 8. Proposed Mechanism for the Formation of (±)-Ocellapyrone A (10) and Isomer (±)-39



SCHEME 9. Proposed Mechanism for the Formation of (±)-9,10-Deoxytridachione (2)

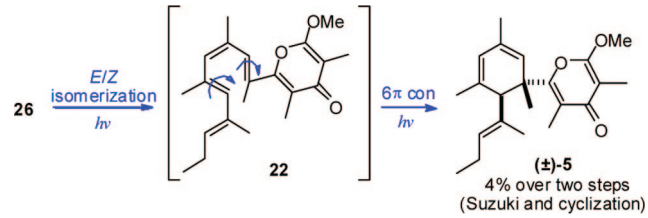


SCHEME 10. Proposed Mechanism for the Formation of (±)-Photodeoxytridachione (7)



agreement with the observations of Ireland et al.[4,7] Alternatively, it may be possible that (±)-**7** is formed by an intramolecular $[\pi 4_s + \pi 2_a]$ Diels−Alder photocycloaddition of the tetraene−pyrone **25**. Similarly, it could be envisaged that an analogous pericyclic process starting from the polyene **27** would lead to the same

SCHEME 11. Proposed Mechanism for the Formation of (±)-iso-9,10-deoxytridachione (5)



products (Scheme 3). However, recent evidence provided by Jones and Trauner[18b] suggests that (±)-**7** is formed by a highly selective diradical process.

Since the proposed mechanism of formation of (±)-9,10-deoxytridachione (**2**) under thermal conditions proceeds via a 6π disrotatory electrocyclization of **22** (Scheme 2), it is conceivable that the formation of (±)-**5** also proceeds via a double-bond isomerization of **26** to provide **22**. Under photochemical conditions, however, **22** undergoes a 6π conrotatory electrocyclization to afford the natural product (±)-iso-9,10-deoxytridachione (**5**), a diastereoisomer of (±)-**2** (Scheme 11).

In each of the proposed mechanisms, it is likely that isomerization of the all-(*E*)-polyene **26** into the isomer **22** is the first key step. Intermediate **22** may then undergo further double-bond isomerization followed by electrocylization or may directly undergo pericyclization processes. This hypothesis is supported by our previous observations with the model tetraene **17**.[16] The crystal structure of **17** revealed a significant lack of planarity in the polyene backbone, due to strong 1,3-steric interactions between the methyl substituents along the polyene chain. We believe that such a highly strained tetraene, as demonstrated by the presence of $\alpha > 130°$ dihedral angle of the

key internal double bond, would provide the necessary driving force for selective isomerization.

Conclusion

In accord with our biomimetic hypothesis, we have shown that a number of novel and diverse natural products, such as (±)-**2**, (±)-**5**, (±)-**7**, and (±)-**10**, are indeed accessible from a common all-(*E*) tetraene−pyrone precursor **26**. For the first time, the natural products (±)-**5** and (±)-**7** have been obtained by biomimetic pericyclic processes and we have achieved the first synthesis of (±)-iso-9,10-deoxytridachione (**5**). The related diastereisomers (±)-**38** and (±)-**39** were also obtained from **26**, and it is conceivable that these compounds might be natural products, yet to be discovered and characterized.

Experimental Section

Ketone (32). To a dry flask containing DCM (50 mL) under N_2 at −78 °C was added oxalyl chloride (1.9 mL, 22 mmol). After the solution was stirred for 5 min, a solution of dimethyl sulfoxide (3.35 mL, 43 mmol) in dry DCM (5 mL) was added dropwise via syringe and stirring was continued for a further 15 min. A solution of alcohol **31** (2.66 g, 13.5 mmol) in dry DCM (50 mL) was then added dropwise, and after 25 min, triethylamine (12 mL, 87 mmol) was added. The reaction mixture was allowed to warm to rt, and after 1 h, the reaction was quenched by addition of H_2O (50 mL). The organic layer was washed with satd ammonium chloride (150 mL) followed by brine (3 × 150 mL). The organic fraction was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash silica gel chromatography (30−40 petroleum ether/EtOAc 7:3) to yield the title compound ketone **32** (2.08 g, 78%) as a white solid: R_f 0.10 (30−40 petroleum ether/EtOAc 7:3); mp 145−147 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ_H 1.90 (3H, s), 2.30 (3H, s), 2.54 (3H, s), 4.08 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 7.2, 10.0, 28.0, 55.7, 101.8, 126.5, 148.5, 161.3, 180.3, 193.4; IR ν_{max}/cm^{-1} (KBr disk) 2925 (m), 1710 (s), 1629 (s), 1578 (s), 1474 (m), 1409 (m), 1372 (m), 1324 (s), 1266 (m), 1203 (m), 1168 (s); HRMS [ESI] calcd for $C_{10}H_{13}O_4$ $[M + H]^+$ 197.0814, found 197.0813.

(*E*)-Vinyl Bromide (28) and (*Z*)-Vinyl Bromide (33). Adapted from the method of O'Donnell et al.[28] Potassium bis(trimethylsilyl)amide (10.42 mL of a 0.5 M solution in toluene 5.21 mmol) was added to a stirred solution of (bromomethyl)triphenylphosphonium bromide (2.32 g, 5.21 mmol) in dry toluene (65 mL) at rt. A bright yellow suspension was immediately obtained, and after 30 min, by which time the suspension had turned dark red, the reaction mixture was cooled to 0 °C and ketone **32** (1.02 g, 5.21 mmol) was added as a solution in toluene (60 mL). The reaction mixture was warmed to rt over 10 min and stirred overnight at rt. The reaction mixture was concentrated under reduced pressure to yield a crude mixture of products as a brown solid. The crude mixture was triturated with Et_2O (80 mL) and then filtered. The filtrate was concentrated under reduced pressure to give a crude brown solid. Purification by flash silica gel chromatography (30−40 petroleum ether/EtOAc 17:3) gave the (*E*)-isomer **28** (437 mg, 31%) as a white solid: R_f 0.50 (30−40 petroleum ether/EtOAc 1:1); mp 78−80 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ_H 1.87 (3H, s), 1.99 (3H, s), 2.11 (3H, d, *J* 1.5 Hz), 3.96 (3H, s), 6.59 (1H, q, *J* 1.5 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 6.9, 11.6, 18.1, 55.4, 99.8, 114.4, 119.3, 133.7, 154.5, 162.9, 180.8; IR ν_{max}/cm^{-1} (KBr disk) 3089 (w), 3032 (w), 3000 (m), 2956 (m), 2923 (w), 2853 (w), 1655 (s), 1621 (s), 1592 (s), 1458 (m), 1410 (m), 1374 (m), 1326 (m), 1286 (m), 1251 (m), 1160 (s), 1119 (m), 1049 (w); HRMS [ESI$^+$] calcd for $C_{11}H_{14}O_3Br$ $[M + H]^+$ 273.0126, found 273.0124.

Further elution yielded the (*Z*)-isomer **33** (148 mg, 10%) as a white solid: R_f 0.40 (30−40 petroleum ether/EtOAc 1:1); mp 76−78 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ_H 1.88 (3H, s), 1.91 (3H, s), 2.05 (3H, d, *J* 1.5 Hz), 3.96 (3H, s), 6.44 (1H, q, *J* 1.5 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 6.9, 10.6, 21.5, 55.5, 100.0, 109.3, 119.7, 133.8, 153.6, 162.5, 180.7; IR ν_{max}/cm^{-1} (KBr disk) 3061 (w), 3029 (w), 2958 (m), 2920 (s), 2850 (m), 1666 (s), 1629 (s), 1613 (s), 1586 (s), 1465 (m), 1437 (m), 1413 (m), 1376 (m), 1335 (m), 1282 (m), 1263 (m), 1244 (m), 1183 (m), 1159 (m), 1120 (m), 1034 (m); HRMS [ESI] calcd for $C_{11}H_{14}O_3Br$ $[M + H]^+$ 273.0126, found 273.0122.

Further elution afforded some recovered starting material **32** as a white solid (138 mg, 13%).

(3*E*,5*E*)-3,5-Dimethylocta-3,5-dien-1-yne (37). To a solution of triphenylphosphine (22.4 g, 85.2 mmol) in dry DCM (100 mL) was added carbon tetrabromide (14.13 g, 42.6 mmol) in portions. After being stirred for 5 min, the reaction mixture had become a red/brown solution. The reaction mixture was cooled to 0 °C before dropwise addition of aldehyde **35** (3.92 g, 28.4 mmol) as a solution in DCM (10 mL). The reaction was allowed to warm to rt and stirred for 2 h before being quenched by addition of H_2O (100 mL). The layers were separated, and the aqueous layer was extracted with DCM (3 × 100 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash silica gel chromatography (30−40 petroleum ether) to give the dibromide **36** (6.21 g) as a yellow oil. The dibromide was unstable and was used immediately in the next reaction.

To a stirred solution of dibromide **36** (6.21 g, 21.1 mmol) in Et_2O (75 mL) at −78 °C was added ^{n}BuLi (17.8 mL of a 2.5 M solution in hexanes, 44.4 mmol), dropwise. The reaction mixture was allowed to warm to rt over 2 h and then quenched by addition of satd aq ammonium chloride (5 mL). H_2O (100 mL) was added, and the aqueous layer was extracted with Et_2O (2 × 100 mL). The combined organic layers were then dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by distillation [bp (25 mb) 75−76 °C] gave the title compound **37** (1.18 g, 31% from **35**) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ_H 1.00 (3H, t, *J* 7.5 Hz), 1.77 (3H, s), 1.97 (3H, s), 2.11 (2H, dq, *J* 7.5, 7.5 Hz), 2.85 (1H, s), 5.42 (1H, t, *J* 7.5 Hz), 6.34 (1H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 13.9, 16.2, 18.8, 21.5, 74.4, 88.2, 115.2, 131.4, 135.4, 141.7; IR ν_{max}/cm^{-1} (film) 3311 (s), 2965 (s), 2933 (m), 2874 (m), 2089 (w), 1643 (w), 1619 (w), 1444 (m), 1379 (m), 1344 (w), 1304 (w), 1181 (w), 1119 (w), 1067 (w), 1009 (w); HRMS [FI] calcd for $C_{10}H_{14}$ $[M]^{\bullet+}$ 134.1096, found 134.1092.

(4*E*,6*E*)-4,6-Dimethylnona-4,6-dien-2-yne (34). To a stirred solution of **37** (1.82 g, 13.6 mmol) in THF (30 mL) at −78 °C was added ^{n}BuLi (6.5 mL of a 2.5 M solution in hexanes, 16.3 mmol) dropwise. The reaction mixture was allowed to warm to rt over 2 h and then recooled to −78 °C. MeI (1.7 mL, 27 mmol) was added dropwise and the reaction mixture allowed to warm to rt. After being stirred overnight, the reaction was quenched by addition of satd aq ammonium chloride (3 mL). H_2O (20 mL) was added, and the aqueous layer was extracted with Et_2O (2 × 30 mL). The combined organic layers were then dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification by distillation [bp (15mb) 89−90 °C] gave the title compound **34** (1.17 g, 58%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ_H 0.98 (3H, t, *J* 7.5 Hz), 1.73 (3H, s), 1.92 (3H, s), 1.94 (3H, s), 2.09 (2H, dq, *J* 7.5, 7.5 Hz), 5.35 (1H, t, *J* 7.5 Hz), 6.15 (1H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 4.2, 14.1, 16.3, 19.3, 21.5, 83.1, 84.0, 116.9, 131.6, 134.0, 138.9;IR ν_{max}/cm^{-1} (film) 2964 (s), 2933 (s), 2917 (s), 2856 (s), 2734 (m), 1442 (m), 1378 (m), 1303 (w), 1240 (w), 1199 (w), 1067 (w), 1034 (m), 1007 (w), 958 (w); HRMS [FI] calcd for $C_{11}H_{16}$ $[M]^{\bullet+}$ 148.1252, found 148.1252.

Boronic Ester (29). Freshly distilled catechol borane (105 mg, 0.88 mmol) and alkyne **34** (132 mg, 0.88 mmol) were heated in a dry flask under N_2 at 80 °C for 2 h in the absence of solvent. The mixture was then cooled to rt. Product **29** was obtained as a yellow oil (231 mg, 97%) without further purification: ^{1}H NMR (400 MHz,

$CDCl_3$, TMS) δ_H 1.04 (3H, t, *J* 7.5 Hz), 1.82 (3H, s), 2.08 (3H, s), 2.15 (3H, s), 2.16 (2H, dq, *J* 7.5, 7.0 Hz), 5.48 (1H, t, *J* 7.0 Hz), 6.10 (1H, s), 7.05−7.10 (2H, m), 7.13 (1H, s), 7.21−7.26 (2H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 14.0, 15.5, 16.8, 18.4, 21.7, 112.3, 122.4, 131.8, 132.7, 134.2, 138.3, 148.6, 150.7; IR ν_{max}/cm^{-1} (film) 3216 (m), 2962 (m), 2932 (m), 2872 (m), 1604 (m), 1510 (m), 1473 (s), 1410 (m), 1380 (m), 1312 (m), 1274 (m), 1237 (s), 1198 (m), 1130 (m), 1096 (m), 1031 (m), 1006 (w); HRMS [FI] calcd for $C_{17}H_{21}BO_2$ $[M]^{\bullet+}$ 268.1635, found 268.1640.

(*E*,*E*,*E*,*E*)-Polyene−Pyrone (26). A mixture of **28** (231 mg, 0.84 mmol), tetrakis(triphenylphosphine)palladium(0) (49 mg, 5 mol %), and degassed THF (10 mL) was stirred for 10 min at rt under N_2. Borane **29** (249 mg, 0.93 mmol) in degassed THF (5 mL) was added, and the reaction mixture heated to 80 °C. After 5 min, degassed potassium hydroxide (1 M, 0.67 mL) was added. The reaction was heated at 80 °C for 2 h and then cooled to rt. The mixture was extracted with Et_2O (3 × 10 mL), and then the combined organic layers were extracted with brine (40 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to afford the crude title compound **26** as a brown oil (523 mg). Purification by flash silica gel chromatography (30−40 petroleum ether/EtOAc 17:3) gave the title compound **26** (102 mg, 36%) as a yellow oil: R_f 0.20 (30−40 petroleum ether/EtOAc 17:3); ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ_H 1.03 (3H, t, *J* 7.5 Hz), 1.80 (3H, s), 1.90 (3H, s), 1.98 (3H, s), 2.06 (3H, s), 2.07 (3H, s), 2.12 (3H, s), 2.09−2.19 (2H, m), 4.00 (3H, s), 5.43 (1H, t, *J* 7.5 Hz), 5.90 (1H, s), 6.02 (1H, s), 6.19 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 6.9, 12.0, 14.1, 16.4, 16.9, 18.7, 18.9, 21.6, 55.3, 99.3, 115.6, 117.8, 120.2, 126.0, 131.5, 133.6, 135.7, 138.2, 140.6, 159.2, 162.0, 181.7; IR ν_{max}/cm^{-1} (film) 2960 (m), 2928 (m), 2872 (m), 2729 (m), 1728 (m), 1657 (s), 1614 (m), 1598 (s), 1538 (w), 1496 (w), 1462 (m), 1406 (m), 1376 (m), 1322 (m), 1255 (m), 1165 (s), 1116 (w), 1071 (w), 1051 (w); HRMS [ESI] calcd for $C_{22}H_{31}O_3$ $[M + H]^+$ 343.2268, found 343.2265.

Palladium-Catalyzed Studies. (±)-Endo Diastereomer (38). Crude **26** (327 mg, 0.917 mmol) and $(MeCN)_2PdCl_2$ (74 mg, 0.29 mmol) were placed in a dry Schlenk tube. The Schlenk tube was then purged with N_2, and DMF (10 mL) was added. The reaction mixture was stirred at 50 °C in the dark for 2 h and then cooled to rt. Water (15 mL) was added, and the aqueous layer was extracted with DCM (3 × 20 mL). The combined organic fractions were washed with brine (2 × 40 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material contained a mixture of products. The products were separated by reversed-phase HPLC using a PrincetonSPHER C18 100 × 30 mm column. The title compound 38 [water/acetonitrile 2:3, run time 41 min, retention time 15.87 min] was obtained a yellow oil (11 mg, 6% over two steps (Suzuki and cyclization)): R_f 0.45 (30−40 petroleum ether/EtOAc 3:1); ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ_H 0.86 (3H, t, J 7.5 Hz), 1.16 (3H, s), 1.44 (1H, ddq, J 7.5, 7.5, 6.5 Hz), 1.54 (3H, s), 1.56−1.60 (1H, m), 1.60 (3H, d, J 1.5 Hz), 1.64 (3H, s), 1.84 (3H, s), 2.06 (3H, s), 2.59 (1H, s), 3.23 (1H, dd, J 9.0, 6.5 Hz), 3.96 (3H, s), 5.03 (1H, s), 5.40 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 7.0, 12.1, 13.3, 19.2, 21.6, 22.9, 23.4, 23.6, 36.6, 51.9, 53.9, 55.7, 56.6, 98.9, 119.2, 124.3, 126.8, 127.6, 131.9, 160.1, 161.8, 181.7; IR ν_{max}/cm^{-1} (film) 2960 (s), 2930 (s), 2873 (m), 2860 (m), 1728 (s), 1658 (s), 1610 (s), 1542 (w), 1463 (m), 1406 (m), 1377 (m), 1321 (m), 1288 (s), 1215 (w), 1167 (m), 1124 (m), 1073 (w), 1039 (w), 986 (w); HRMS [ESI] calcd for $C_{22}H_{31}O_3$ $[M + H]^+$ 343.2268, found 343.2268.

Thermal Studies. (±)-9,10-Deoxytridachione (2). Crude **26** (288 mg, 0.808 mmol) was dissolved in xylenes (10 mL) and heated in a sealed tube for 1 h 30 min at 150 °C in the dark. The solvent was then removed under reduced pressure to give the crude mixture of cyclization products including **2**, **10**, and **39** as a brown oil. The products were separated by reversed-phase HPLC using a PrincetonSPHER C18 100 × 30 mm column.

The title compound **2** [water/acetonitrile 2:3, run time 41 min, retention time 17.70 min] was obtained as a yellow oil (6 mg, 4% over two steps (Suzuki and cyclization)): R_f 0.60 (30−40 petroleum ether/EtOAc 3:1); ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ_H 0.71 (3H, t, *J* 7.5 Hz), 1.33 (3H, s), 1.44 (3H, s), 1.73 (3H, s), 1.74−1.80 (2H, m), 1.79 (3H, d, *J* 1.5 Hz), 1.83 (3H, s), 2.06 (3H, s), 2.72 (1H, s), 3.99 (3H, s), 5.06 (1H, t, *J* 7.0 Hz), 5.59 (1H, s), 5.68 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 6.8, 12.2, 13.7, 14.1, 21.0, 21.5, 22.3, 26.8, 47.5, 55.3, 59.4, 98.6, 119.9, 122.3, 124.2, 127.7, 130.8, 132.0, 134.8, 161.0, 161.6, 181.1; IR ν_{max}/cm^{-1} (film) 2960 (s), 2929 (s), 2873 (m), 2859 (m), 1729 (s), 1662 (m), 1616 (m), 1599 (w), 1462 (m), 1404 (w), 1378 (w), 1274 (m), 1166 (w), 1123 (w), 1072 (m), 1040 (m), 984 (w); HRMS [ESI] calcd for $C_{22}H_{31}O_3$ $[M + H]^+$ 343.2268, found 343.2268.

(±)-Exo Diastereomer (39). The title compound **39** [water/acetonitrile 2:3, run time 41 min, retention time 18.90 min] was obtained as a yellow oil (14 mg, 9% over two steps (Suzuki and cyclization)): R_f 0.55 (30−40 petroleum ether/EtOAc 3:1); ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ_H 0.84 (3H, t, *J* 7.5 Hz), 1.00 (3H, s), 1.17−1.32 (2H, m), 1.48 (3H, s), 1.72 (3H, d, *J* 1.5 Hz), 1.72 (3H, s), 1.87 (3H, s), 1.88 (3H, s), 2.05−2.08 (1H, m), 3.26 (1H, s), 4.05 (3H, s), 5.19 (1H, s), 5.66 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C7.0, 12.3, 13.6, 21.6, 21.8, 22.0, 22.9, 23.6, 35.9, 45.1, 48.1, 56.4, 58.0, 100.1, 118.3, 125.6, 127.2, 128.4, 130.0, 161.0, 162.0, 181.7; IR ν_{max}/cm^{-1} (film) 2959 (w), 2929 (s), 2875 (m), 2730 (w), 1728 (m), 1659 (s), 1616 (s), 1461 (m), 1408 (m), 1377 (m), 1321 (m), 1284 (m), 1245 (m), 1164 (m), 1123 (m), 1072 (w), 1038 (w); HRMS [ESI] calcd for $C_{22}H_{31}O_3$ $[M + H]^+$ 343.2268, found 343.2268.

(±)-Ocellapyrone A (10). The title compound **10** [water/acetonitrile 2:3, run time 41 min, retention time 21.50 min] was obtained as a yellow oil (16 mg, 10% over two steps (Suzuki and cyclization)): R_f 0.55 (30−40 petroleum ether/EtOAc 3:1); ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ_H 0.89 (3H, t, *J* 7.5 Hz), 1.15 (3H, s), 1.25 (3H, s), 1.55−1.61 (1H, m), 1.70−1.81 (1H, m), 1.74 (3H, d, *J* 1.5 Hz), 1.77 (3H, s), 1.88 (3H, s), 1.97 (3H, s), 2.41 (1H, dd, *J* 11.5, 3.0 Hz), 3.12 (1H, s), 4.01 (3H, s), 5.07 (1H, s), 5.62 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 7.2, 9.8, 13.3, 15.5, 18.9, 22.2, 23.5, 32.5, 38.1, 47.3, 49.2, 57.2, 57.3, 100.6, 116.7, 122.9, 125.4, 129.9, 130.2, 162.2, 164.9, 182.0; IR ν_{max}/cm^{-1} (film) 2959 (m), 2929 (m), 2874 (w), 2857 (w), 1728 (w), 1661 (s), 1616 (s), 1459 (m), 1405 (m), 1375 (m), 1317 (m), 1290 (m), 1246 (m), 1168 (m), 1129 (w), 1036 (w); HRMS [ESI] calcd for $C_{22}H_{31}O_3$ $[M + H]^+$ 343.2268, found 343.2266.

Photochemical Studies. (±)-Photodeoxytridachione (7). Crude **26** (435 mg, 1.22 mmol) was dissolved in cyclohexane (10 mL) and irradiated at 419 nm at rt. After 24 h, no reaction had taken place. The precursor **26** was then irradiated for 22 h at 350 nm and 419 nm, after which the reaction mixture was concentrated under reduced pressure to afford a crude mixture of cyclization products including **7** and **5**. The products were separated by reversed-phase HPLC using a PrincetonSPHER C18 100 × 30 mm column.

The title compound **7** [water/acetonitrile 2:3, run time 41 min, retention time 25.40 min] was obtained as a yellow oil (21 mg, 9% over two steps (Suzuki and cyclization)): R_f 0.60 (30−40 petroleum ether/EtOAc 3:1); ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ_H 0.97 (3H, t, *J* 7.5 Hz), 1.10 (3H, s), 1.20 (3H, s), 1.42 (1H, s), 1.49 (3H, s), 1.57 (3H, s), 1.84 (3H, s), 1.97 (3H, s), 2.05 (2H, dq, *J* 7.5, 7.5 Hz), 2.73 (1H, s), 3.96 (3H, s), 5.30 (1H, t, *J* 7.5 Hz), 5.33 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 6.9, 10.8, 12.7, 13.1, 13.7, 14.3, 17.1, 21.2, 31.7, 36.7, 40.7, 55.3, 58.3, 99.4, 120.4, 128.5, 128.8, 133.9, 144.0, 160.4, 162.3, 181.7; IR ν_{max}/cm^{-1} (film) 3029 (w), 2960 (s), 2928 (s), 2871 (s), 2731 (w), 1729 (m), 1662 (s), 1602 (s), 1541 (w), 1462 (s), 1408 (m), 1377 (m), 1330 (m),

1305 (m), 1165 (m), 1122 (m), 1073 (w), 1041 (w), 987 (w); HRMS [ESI] calcd for $C_{22}H_{31}O_3$ $[M + H]^+$ 343.2268, found 343.2268.

(±)-Iso-9,10-deoxytridachione (5). The title compound **2** [water/acetonitrile 2:3, run time 41 min, retention time 22.44 min] was obtained as a yellow oil (11 mg, 4% over two steps (Suzuki and cyclization)): R_f 0.55 (30−40 petroleum ether/EtOAc 3:1); ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ_H 0.94 (3H, t, *J* 7.5 Hz), 1.31 (3H, s), 1.54 (3H, s), 1.67 (3H, s), 1.77 (3H, d, *J* 1.5 Hz), 1.83 (3H, s), 2.02 (2H, dq, *J* 7.5, 7.5 Hz), 2.09 (3H, s), 3.19 (1H, s), 3.92 (3H, s), 5.15 (1H, s), 5.26 (1H, t, *J* 7.5 Hz), 5.62 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 6.9, 11.4, 14.0, 14.1, 21.0, 21.2, 21.7, 22.4, 45.1, 55.4, 56.4, 98.7, 118.8, 123.7, 124.3, 131.4, 131.7, 133.1, 136.9, 161.6, 163.5, 181.9; IR ν_{max}/cm^{-1} (film) 2962 (m), 2929 (m), 2872 (w), 1728 (w), 1660 (s), 1613 (s), 1539 (w), 1461 (m), 1404 (m), 1374 (m), 1310 (m), 1245 (w), 1166 (m), 1072 (w), 1039 (w); HRMS [ESI] calcd for $C_{22}H_{31}O_3$ $[M + H]^+$ 343.2268, found 343.2269.

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Supporting Information Available: Spectroscopic data for all new compounds and CIF for compound **28**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(36) In the ocellapyrone system described, the endo/exo terminology corresponds to the position of the pyrone group relative to the cyclooctatriene in the transition state during the 6π electrocyclization.