The total synthesis of (−)-crispatene

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The total synthesis of the molluscan polypropionate (−)-crispatene is described. The synthesis features a palladium-catalyzed cross-coupling to establish a sensitive conjugated tetraene and its Lewis acid-catalyzed cycloisomerization to yield the bicyclo[3.1.0]hexene core of the natural product. The absolute configuration of (−)-crispatene and related molecules is established.

Polypropionate natural products are biosynthetically assembled by a series of Claisen-type condensations involving enzyme-bound thioesters (1). The (formally) resulting polycarbonyl compounds can undergo further condensations, reductions, and dehydrations to yield a range of structural motifs, some of which are shown in Fig. 1. For instance, direct cyclization of the tricarbonyl moiety in **A** yields pyrone **B**, a representative of the "condensed" pattern. NADPH-dependent reduction of carbonyl groups leads to the "aldol" or "polyol" type **C**, which is arguably the most commonly found structural motif in polypropionates. The stereoselective assembly of compounds of this type through directed aldol reactions has captivated the synthetic community for decades. Elimination of secondary hydroxy groups leads to trisubstituted double bonds found in the "partially eliminated" **D** or "fully eliminated" type **E**. Finally, further reduction of the olefinic double bonds affords the "fully reduced" motif **F**. Of course, this structural diversity can be further increased by incorporation of acetate units and starter units other than propionate and additional methyl groups delivered by *S*-adenosylmethionine.

Polypropionates featuring the fully eliminated motif **E** are relatively rare, presumably because of the inherent instability of the conjugated polyene system. In many cases, the polyene moiety is obscured by its tendency to undergo isomerizations and cyclizations resulting in complex ring systems. Some representative natural products that fall into this category are shown in Fig. 2.

The immunosuppressant SNF4435 C (**2**) (2, 3), for instance, is presumably formed from an isomer of the antibiotic spectinabilin (**1**) (4) through an 8π–6π electrocyclization cascade (5). Both compounds have been isolated from *Streptomyces spectabilis* strains. The molluscan polypropionates tridachiahydropyrone (**3**) (6), 9,10-deoxytridachione (**4**) (7), and tridachiapyrone A (**5**) (8) appear to be formed by 6π electrocyclizations from polyene precursors. Photodeoxytridachione (**6**) (9) and crispatene (**7**) (7), isomers of **4** and **5**, respectively, feature a bicyclo[3.1.0]hexene skeleton instead of a cyclohexadiene and presumably stem from the same polyene precursors (see below). Note that these compounds also feature the "condensed" structural motif in the form of an α-methoxy-γ-pyrone ring.

Until recently, relatively little attention has been given to these compounds by synthetic chemists. The lack of attention may in part be due to the difficulties encountered (or anticipated) in assembling conjugated polyenes consisting of trisubstituted double bonds, some of which are (*Z*)-substituted. Even with modern transition metal-catalyzed cross-coupling reactions at hand, this is a difficult task. During past years, however, several groups, including ours, have become interested in the synthesis of the highly unsaturated polypropionates shown in Fig. 2 (5, 10–13).

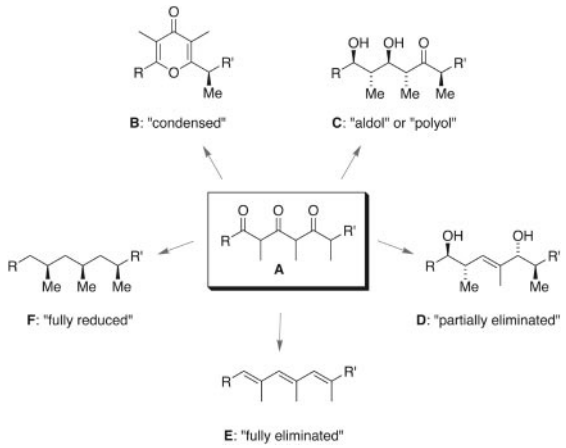

Fig. 1. Polypropionate structural motifs.

(−)-Crispatene has been isolated by Ireland and Faulkner (7) from the saccoglossan mollusc *Elysia crispata* (the sea slug formerly known as *Tridachia crispata*, Fig. 3). This unusual organism, aptly named the "lettuce slug," lives in shallow waters and harvests functional chloroplasts from algae, which enables it to live autotrophically. *E. crispata*, and numerous related saccoglossans, produces a range of defensive natural products featuring α-methoxy-γ-pyrone moieties, which have also been proposed to act as a sunscreen because of their UV-light-absorbent properties (9). Not surprisingly, some of these natural products have been suspected to arise by means of photochemical reactions.

Biosynthetic investigations on photodeoxytridachione (**6**), a close congener of crispatene, indeed point to a photochemical origin of the bicyclo[3.1.0]hexene skeleton. Ireland and Scheuer (9) demonstrated that 9,10-deoxytridachione (**4**) could be photochemically converted *in vivo* and *in vitro* into photodeoxytridachione (**6**). Since no racemization occurred, the authors concluded that this reaction proceeds as a concerted $[_\sigma 2_a + _\pi 2_a]$ isomerization (Scheme 1). In principle, however, the bicyclo[3.1.0]hexene system could also arise from photochemical $[_\pi 4_a + _\pi 2_s]$ or $[_\pi 4_s + _\pi 2_a]$ cycloadditions involving tetraene precursors **8a**,**b** and **9a**,**b**, respectively. Reactions of this type have been dubbed the "photochemical Diels–Alder reaction" (14). Note that **8a**,**b** and **9a**,**b** are the products of photochemical conrotatory ring opening of the cyclohexadienes **4** and **5**.

Although the photochemical biosynthetic origin of the bicyclo[3.1.0]hexene natural products appears to have been established, at least in the case of photodeoxytridachione, we have been intrigued by the possibility that these compounds could also arise from a thermal $[_\pi 4_a + _\pi 2_a]$ cycloaddition involv-

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Abbreviations: THF, tetrahydrofuran; HF-pyridine, hydrofluoride pyridine.

Data deposition: Crystallographic data (excluding structure factors) for compound **30** has been deposited with the Cambridge Crystallographic Data Centre, Cambridge CB2 1EZ, United Kingdom (CDC reference no. 233526).

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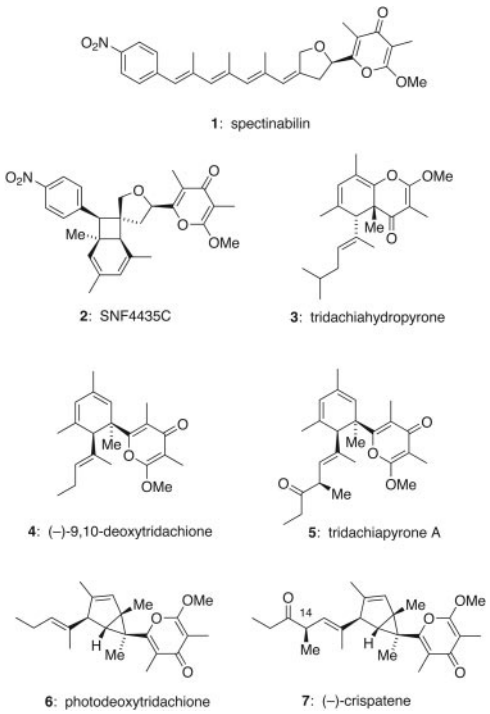


Fig. 2. Highly unsaturated polypropionates.

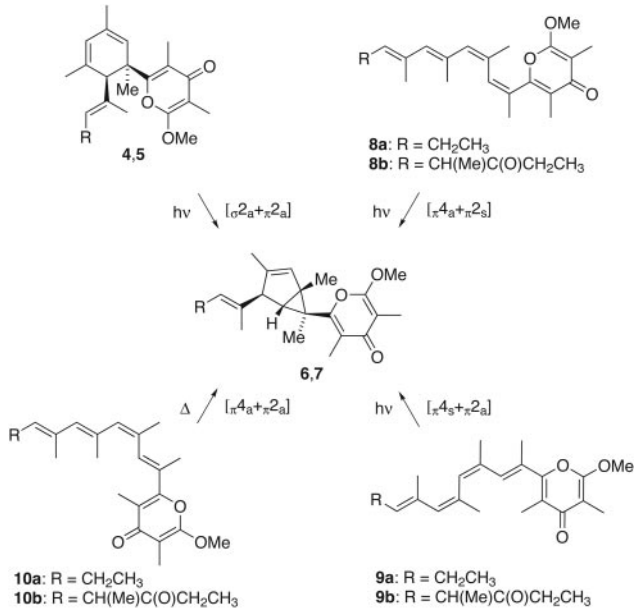
ing precursors of type **10a**,**b** (Scheme 1). Recently, we have reported the Lewis acid-catalyzed cycloisomerization of polyenes related to **10a**,**b** to bicyclo[3.1.0]hexenes and the application of this reaction to the total synthesis of racemic photodeoxytridachione (**6**) (10, 11). This reaction could proceed as a $[\pi 4_a + \pi 2_a]$ cycloaddition or involve a stepwise mechanism. The polyene substrate was assembled by using an iterative strategy that involved Horner–Wadsworth–Emmons and Still–Gennari condensations to install the (*E*)- and (*Z*)-configured double bonds, respectively.

We now report the application of our cyclization to the total synthesis of (−)-crispatene and its stereoisomer 14-*epi*-*ent*-crispatene. Our synthesis allows for the assignment of the absolute stereochemistry of the natural product and confirms the relative stereochemistry proposed. In an improvement of our overall synthetic strategy, the required polyolefin substrates were assembled with modern palladium-catalyzed cross-coupling methods.

Materials and Methods

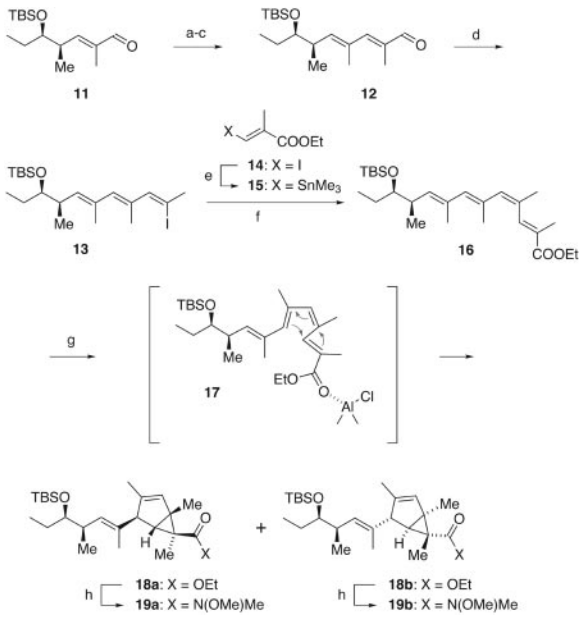
Unless otherwise noted, all reagents were purchased from commercial suppliers and used without further purification.

Fig. 3. *E. crispata*, the ''lettuce slug.''

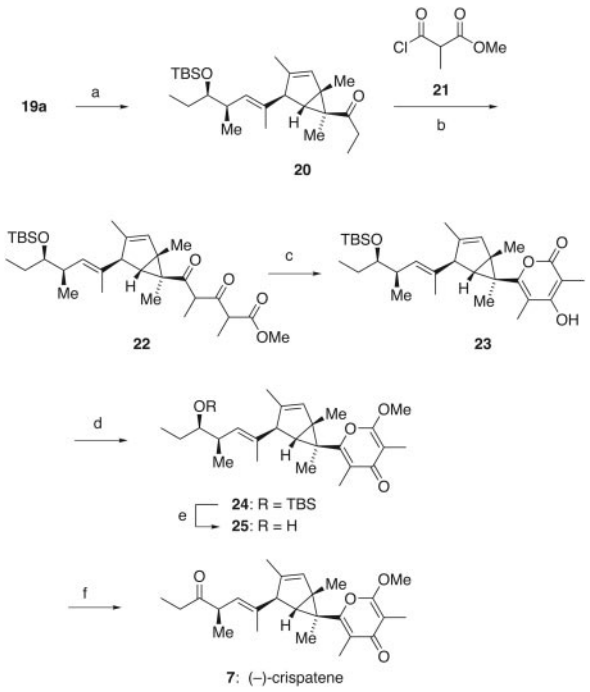


Scheme 1. Biosynthetic origin of the bicyclo[3.1.0]hexene system.

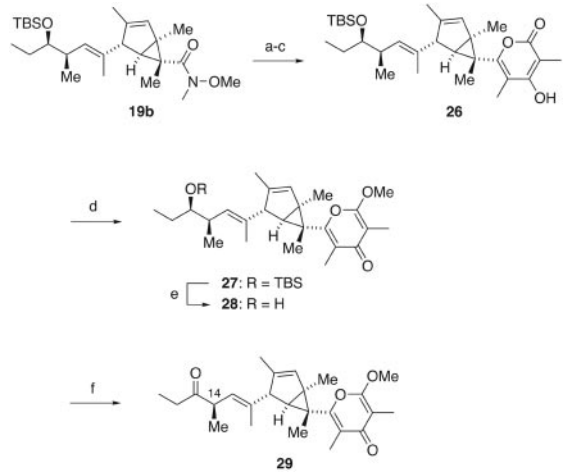
Melting points were measured on a Büchi melting point apparatus (Büchi Labortechnik, Flawil, Switzerland) and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a DRX 500 and a AVB 400 (Bruker, Billerica, MA). Optical rotations were measured on a PerkinElmer 241 polarimeter. Silica gel chromatography was carried out by using ICN SiliTech 32–63 D 60Å. TLC was performed with Merck Silica Gel 60 plates. Mass spectra and elemental analysis were performed by the Micro-



Scheme 2. Total synthesis of (−)-crispatene. Preparation of the bicyclo-[3.1.0]hexene core. Reagents and conditions: (a) $Ph_3P{=}C(Me)COOEt$, THF, rflx., 94%; (b) diisobutylaluminum hydride, CH_2Cl_2, −78°C, 98%; (c) Dess–Martin periodinane, CH_2Cl_2, 88%; (d) $Ph_3P{=}CHCH_3$, I_2, sodium hexamethyldisilazide, −78°C, 86%; (e) $Pd(Ph_3P)_4$, $Me_3SnSnMe_3$, *i*-Pr_2NEt, PhH, rflx., 90%; (f) $Pd_2(dba)_3{\cdot}CHCl_3$, (2-furyl)$_3$P, CuI, 1-methyl-2-pyrrolidinone, 57%; (g) Me_2AlCl (0.2 eq), CH_2Cl_2, 83%; and (h) MeHNOMe·HCl, *i*-PrMgCl, THF, 76% combined yield (93% based on recovered starting material).



Scheme 3. Total synthesis of (−)-crispatene (continued). Reagents and conditions: (a) EtMgBr, THF, 0°C, 87%; (b) **21**, lithium hexamethyldisilazide (3 eq), THF, hexanes, −78°C, 74% (94% based on recovered starting material); (c) 1,8-diazabicyclo[5.4.0]undec-7-ene, PhH, 60°C, 87%; (d) FSO_2OMe, CH_2Cl_2, −5°C, 32% **24**, 17% **25**; (e) HF-pyridine, pyridine, THF, 77%; (f) Dess–Martin periodinane, CH_2Cl_2, 86%.



Scheme 4. Total synthesis of 14-*epi*-*ent*-crispatene **29**. Reagents and conditions: (a) EtMgBr, THF, 0°C, 97%; (b) lithium hexamethyldisilazide (3 eq), **21**, THF, hexanes, −78°C, 74%; (c) 1,8-diazabicyclo[5.4.0]undec-7-ene, PhH, 60°C, 96%; (d) FSO_2OMe, CH_2Cl_2, −5°C, 25% **27**, 64% **28**; (e) HF-pyridine, pyridine, THF, 94%; (f) Dess–Martin periodinane, CH_2Cl_2, 97%.

analytical Laboratory operated by the UCB College of Chemistry. X-ray analysis was performed on a Bruker SMART CCD area-detector diffractometer. All reactions were carried out under an atmosphere of Ar or N_2 in oven-dried glassware. Tetrahydrofuran (THF) and methylene chloride (CH_2Cl_2) were dried by passing through activated alumina columns. Benzene, hexanes, and *i*-Pr_2NEt were distilled from calcium hydride. *n*-Butyl lithium was titrated by using diphenylacetic acid in THF. CuI was purified by precipitation from hot aqueous NaI. $Pd_2(dba)_3{\cdot}CHCl_3$ was synthesized according to a procedure in the literature (15). Methyl fluorosulfonate (FSO_2OMe) was vacuum-distilled before use. Full experimental details and characterization data for selected compounds, including vinyl iodide **13**, tetraene **16**, bicyclo[3.1.0]hexenes **19a** and **19b**, crispatene (**7**), and 14-*epi*-*ent*-crispatene **29**, are included in the supporting information, which is published on the PNAS web site.

Results and Discussion

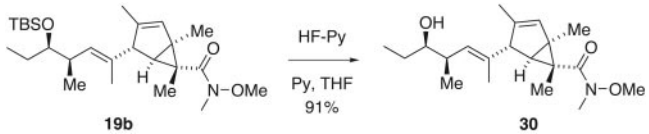
The synthesis of (−)-crispatene started with the known aldehyde **11** (16), easily available from the corresponding Evans *syn*-aldol adduct (Scheme 2). Elongation using standard methodology gave the doubly unsaturated aldehyde **12**. A highly stereoselective Stork–Zhao olefination (17) yielded (*Z*)-vinyl iodide **13**. The tetraene system was assembled by Stille-coupling (18) of **13** with stannane **15**, which was obtained by halogen–tin exchange from the corresponding known iodide **14** (19).

With the sensitive tetraene **16** at hand, we explored its Lewis acid-catalyzed cyclization to a bicyclo[3.1.0]hexene derivative. Gratifyingly, in the presence of 20 mol% of dimethylaluminum chloride, **16** underwent clean cycloisomerization, via Lewis acid adduct **17**, to afford an inseparable 1:1.5 mixture of diastereomers **18a** and **18b** in good overall yield. Only after conversion to the corresponding Weinreb amides **19a** and **19b** could the two isomers be separated.

Although the cycloisomerization showed little inherent diastereoselectivity, we were satisfied with its outcome. At this time, we had no way of knowing which of our compounds corresponded to which diastereomeric series. The ^1H and ^{13}C NMR spectra of **18a** and **18b**, and **19a** and **19b**, respectively, proved to be virtually identical, pointing to little stereochemical communication between the bicyclic nucleus of the molecules and their side chains. In addition, we felt that the stereochemical assignment of the methyl group at C-14 was less than secure (C-14 was assigned in analogy to the related natural product crispatone, whose structure was secured by x-ray crystal structure analysis) (7). It was therefore decided to carry on both diastereomers **19a** and **19b** to crispatene and 14-*epi*-crispatene, or their enantiomers.

In the event, the minor diastereomer **19a** was converted into synthetic (−)-crispatene (Scheme 3). Reaction of **19a** with ethylmagnesium bromide afforded ethyl ketone **20**. Deprotonation with excess base and addition of malonyl chloride **21** gave **22** in good yield. Subsequent cyclization of **22** under basic conditions gave γ-hydroxy-α-pyrone **23**. Regioselective methylation under Beak's conditions (20) was accompanied by significant desilylation to afford a 2:1 mixture of α-methoxy-γ-pyrones **24** and **25**. The former could be converted into the latter by treatment with hydrofluoride pyridine (HF-pyridine). Finally, oxidation of the secondary alcohol function to the ketone afforded synthetic (−)-crispatene (**7**).

The ^1H and ^{13}C NMR, IR, and mass spectra of synthetic **7** were in full agreement with the spectra obtained from authentic natural product (see supporting information). In addition to this, the optical rotation of the synthetic material, $[\alpha]_D = -112°$ (c = 1.2, $CHCl_3$), matched the reported value for (−)-crispatene, $[\alpha]_D = -92.8°$ (c = 0.12, $CHCl_3$). We therefore conclude that naturally occurring (−)-crispatene has the absolute configuration shown in Fig. 2 and Scheme 3.



Scheme 5. Preparation of compound **30**.

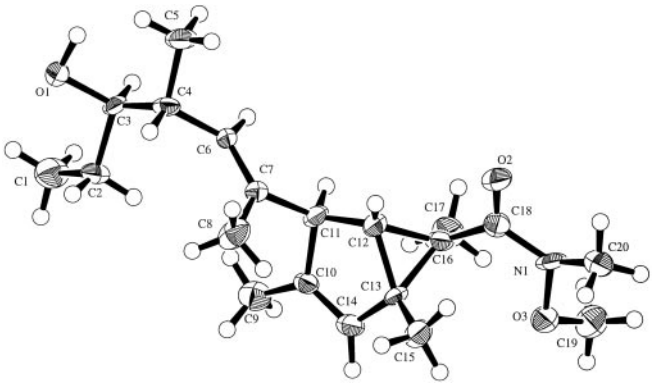
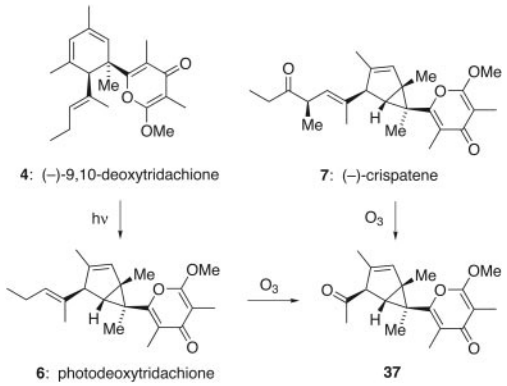


Fig. 4. X-ray structure of compound **30**.

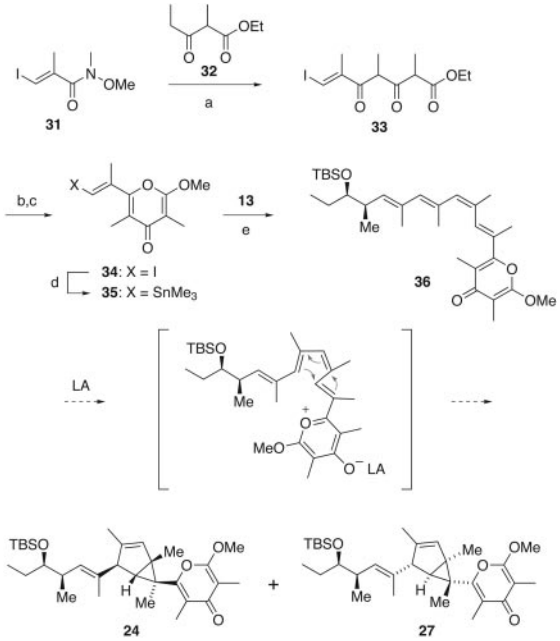


Scheme 7. Stereochemical correlations.

To further support our stereochemical conclusions, the major diastereomer **19b** was advanced in an analogous fashion to afford pyrone **28** (Scheme 4). Oxidation of this material yielded 14-*epi*-*ent*-crispatene **29**. Although the spectra of **29** closely resembled the spectra of synthetic and natural crispatene (**7**), the differences were distinct enough to unequivocally designate their structures.

Independent confirmation of our assignment was finally obtained by deprotecting **19b** to yield a crystalline secondary alcohol, **30**, which was amenable to x-ray structure analysis (Scheme 5). The structure of **30** in the crystal is shown in Fig. 4.

To make our synthesis more convergent, we decided to study the Lewis acid-catalyzed cycloisomerization with the α-methoxy-γ-pyrone moiety already in place (Scheme 6). This approach required the cross-coupling of vinyl stannane **35** with the previously obtained vinyl iodide **13**. The α-methoxy-γ-pyrone building block **35** was obtained from the known iodomethacrylic amide **31** (21) in four straightforward steps.



Scheme 6. Convergent biomimetic approach toward crispatene. Reagents and conditions: (a) **32**, NaH, *n*-BuLi, THF, 0°C, 37%; (b) 1,8-diazabicyclo[5.4.0]undec-7-ene, PhH, 55°C, 46%; (c) FSO_2OMe, CH_2Cl_2, 80%; (d) $Pd(Ph_3P)_4$, $Me_3SnSnMe_3$, *i*-Pr_2NEt, PhH, 60°C, 90%; (e) $Pd_2(dba)_3{\cdot}CHCl_3$, (2-furyl)$_3$P, CuI, 1-methyl-2-pyrrolidinone, 30%.

Condensation of Weinreb amide **31** with the dianion of β-keto ester **32** proceeded smoothly. The resulting tricarbonyl compound **33** underwent cyclization and methylation to afford vinyl iodide **34**. Palladium-catalyzed iodine-tin exchange gave vinyl stannane **35**. Finally, Stille-coupling of **35** and **13**, as previously under Farina–Liebeskind conditions (18), proceeded uneventfully to afford pyranyl tetraene **36** (yield not optimized).

Currently, we are exploring the Lewis or Brønstedt acid-mediated conversion of **36** into a mixture of the previously obtained bicyclo[3.1.0]hexenes **24** and **27**. If successful, this cyclization would have interesting implications for the biosynthesis of the bicyclo[3.1.0]hexene natural products (11). Note that the 6π electrocyclization product of tetraene would form an immediate precursor of tridachiapyrone A (**5**).

Conclusion

In summary, we have demonstrated the usefulness of the Lewis acid-catalyzed isomerization of appropriately substituted polyenes to bicyclo[3.1.0]hexenes in the synthesis of the complex molluscan polypropionate (−)-crispatene. The absolute configuration of the natural product was assigned. Further analysis allows assignment of the absolute stereochemistry of other members of this compound class (Scheme 7). (−)-9,10-Deoxytridachione (**4**) has been photochemically converted to photodeoxytridachione (**6**) and then correlated to (−)-crispatene (**7**) by ozonolytic cleavage of the side chain to yield ketone **37** (7). Similar photochemical $[_\sigma 2_a + _\pi 2_a]$ isomerizations have been shown to proceed with inversion at the quaternary carbon (22). Therefore, the absolute configuration of (−)-9,10-deoxytridachione (**4**) and its photolysis product, photodeoxytridachione (**6**), has been determined and is as depicted in Scheme 7 and Fig. 2. Note that the optical rotation of photochemically synthesized **6** was not reported. Therefore, the absolute configuration of naturally occurring **6** cannot yet be assigned.

Future work should center on the use of chiral Lewis acids to improve the diastereoselectivity of the key cyclization. Lessons learned in this context can be applied to the enantioselective synthesis of (+)-photodeoxytridachione and other members of the series. In addition to this, the potentially biomimetic route shown in Scheme 6 should be further investigated.

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