

# Communications

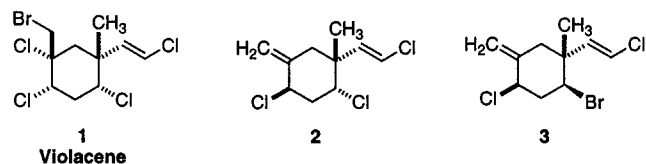
## Total Synthesis of a *Plocamium* Monoterpene Marine Natural Product. Synthetic Applications of Bridgehead Allylsilanes

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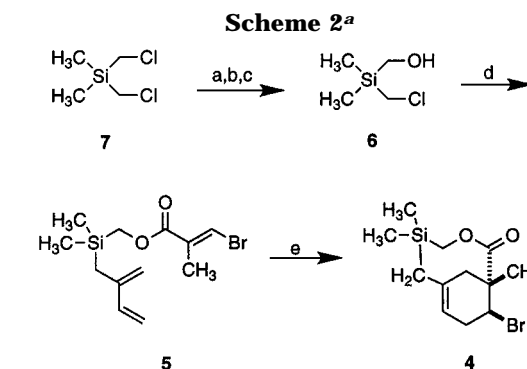
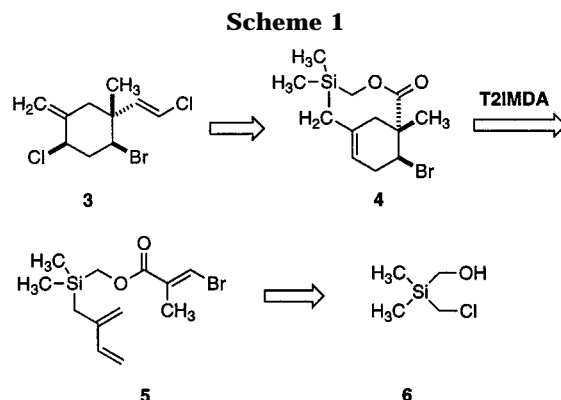
A variety of polyhalogenated monoterpene natural products have been isolated from the red marine algae *Plocamium* sp. Violacene (**1**) and a related metabolite **2** are representatives of this class of molecules.<sup>1</sup> These monoterpenes have been postulated to be involved in the chemical defense of the algae and possess insect anti-feedant properties.<sup>1,2</sup>



The complex pattern of halogenation apparent on the cyclohexane core and the requirement for their regio- and stereoselective introduction presents an interesting synthetic challenge. In 1985, Willard and de Lazslo reported<sup>3</sup> an attempted synthesis of violacene, along with a related *Plocamium* metabolite, **2**.<sup>4</sup>

Their Diels–Alder approach employed a  $\beta$ -halomethacrolein as dienophile for the synthesis of the halogenated six-membered ring. However, since cycloaddition with monosubstituted dienes such as isoprene gave inseparable mixtures of regioisomers, a straightforward construction of the terpenoid skeleton was not feasible, and an alternative, less direct approach was adopted.

Recent advances in controlling both regio- and stereochemistry in Diels–Alder reactions offered a potential solution to these problems.<sup>5</sup> In this paper, we describe the application of type 2 intramolecular Diels–Alder (T2IMDA) chemistry to the synthesis of a *Plocamium*



<sup>a</sup> Reagents: (a) KOAc, DMF (99%); (b) HCl, CH<sub>3</sub>OH (99%); (c) *t*-BuOCl, Ph<sub>3</sub>P, CHCl<sub>3</sub> (98%); (d) (i) CH<sub>3</sub>MgBr, THF, (ii) Mg, (iii) chloroprene, cat. NiCl<sub>2</sub>dppp, (iv) *E*-2-bromo-3-methylacryl chloride, **8**; (e) toluene, cat. proton sponge and BHT, 0.65 mM, 185 °C (74%).

natural product, **3**.<sup>6</sup> Our synthetic plan incorporates a differentiated organosilane, **6**, as a disposable tether between the diene and dienophile, as seen in triene **5**. Notably, cycloadduct **4** contains a bridgehead allylsilane, which was subsequently elaborated in a stereospecific chlorination of the bridgehead double bond.

The silane tether, **6**, was synthesized from the commercially available bis(chloromethyl)dimethylsilane, **7**,<sup>7</sup> in three steps (Scheme 2).<sup>8</sup> Using this tether, chloroprene and dienophile (*E*)-2-bromo-3-methylacryl chloride **8**<sup>9</sup> were joined in a multiple-step, one-pot procedure. This sequence of reactions involved the formation of a Normant–Grignard reagent<sup>10</sup> from **6**, followed by a nickel(0)-catalyzed sp<sup>3</sup>–sp<sup>2</sup> coupling reaction<sup>11</sup> and finally addition of **8** to form triene **5**. The T2IMDA reaction of **5** was performed in an externally heated sealed tube in toluene. The additives (proton sponge and BHT) were found to enhance the yield of cycloadduct **4**. The cycloaddition provides complete regiochemical control.

The bridgehead allylsilane in cycloadduct **4** was then chlorinated with iodobenzene dichloride to give the

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polyhalogenated cyclohexane **9**, structurally verified by X-ray crystallography.<sup>12</sup> Addition to bridgehead double bonds occurs in the *exo-syn* mode to establish the cis relative configuration between chlorine and bromine. The chlorination reaction also produced an allylic chloride side product characteristic of an  $S_E2'$  addition of chlorine to the bridgehead allylsilane. In practice, the mixture of chlorinated products was used in the next reaction without purification. The ester functionality was reduced with DIBAL to obtain alcohol **10**. Concomitant with this reaction, the exocyclic methylene was formed by elimination of the bridgehead chloride.

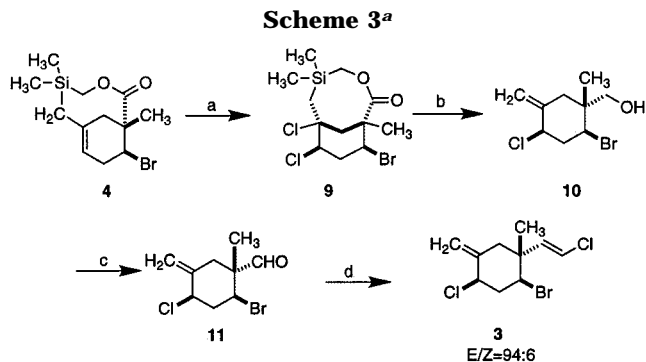
Alcohol **10** was efficiently oxidized to aldehyde **11** using tetrapropylammonium perruthenate (TPAP) (Scheme 3).<sup>13</sup> The remaining step required a chloro-olefination of this aldehyde. Initial attempts using Wittig chemistry resulted in complex product mixtures.<sup>14</sup> Therefore, a more selective reagent was desired. To this end, we employed the Takai reaction,<sup>15</sup> which utilizes in situ generated chromium(III) dichloromethyl species to affect the desired olefination with good stereospecificity (*E/Z* = 94:6). The spectral properties of synthetic **3** were

(12) Compound **9** crystallizes from pentane and a minimal amount of methylene chloride in space group  $P2_1/c$  with  $a = 13.3690(11)$  Å,  $b = 9.9799(9)$  Å,  $c = 12.1109(10)$  Å,  $V = 1509.9(2)$  Å<sup>3</sup>, and  $D_{\text{calc}} = 1.646$  mg/m<sup>3</sup> for  $Z = 4$ . Least-squares refinement of the model based on 2554 reflections ( $F > 4.0\sigma(F)$ ) converged to a final  $R_1 = 3.1\%$ ,  $wR_2 = 6.4\%$ .

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<sup>a</sup> Reagents: (a) iodobenzene dichloride (61%); (b) DIBAL (85%); (c) TPAP, NMO (89%); (d)  $\text{CrCl}_2$ ,  $\text{CHCl}_3$  (58%).

entirely consistent with the assigned structure and those reported in the literature.<sup>6</sup>

In conclusion, a type 2 intramolecular Diels–Alder reaction, utilizing a disposable allyl silane tether, permitted an efficient total synthesis of the novel polyhalogenated monoterpene marine natural product **3**. The generality of this synthetic approach is under further investigation into alternative monoterpene synthetic targets.

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**Supporting Information Available:** Experimental details for the synthesis and characterization of all compounds and X-ray crystallographic data for compound **9** (32 pages).

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