

## Total Synthesis of Hoiamide C

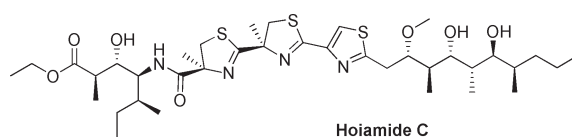
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## ABSTRACT



Hoiamide C was synthesized in 16 steps with an overall yield of 1.8% starting from homoallylic alcohol 18, unambiguously confirming its structure.

Hoiamides (Figure 1) are a new class of marine secondary metabolites recently isolated from cyanobacteria collected in Papua New Guinea.<sup>1</sup> Their structures were determined by NMR, mass, and HPLC techniques. Relative and absolute stereochemistry assignments were based on extensive NMR studies and chemical degradation including modified Mosher ester analysis. Both hoiamides A and B are 26-membered cyclodepsipeptides. Hoiamide C is the linear analogue of hoiamide A, and it can also be obtained from hoiamide A via hydrolysis of both ester bonds.<sup>1</sup> Hoiamides A and B stimulated sodium influx with EC<sub>50</sub> values of 1.7 and 3.9 μM, respectively, in mouse neocortical neurons.<sup>1b</sup> However, hoiamide C showed

no significant activity in the same assay. Hoiamide C (**1**) is composed of a modified isoleucine moiety, a triheterocyclic fragment bearing two α-methylated thiazolines and one thiazole, and a highly oxygenated and methylated polyketide substructure. In addition, a total of 12 stereogenic centers are present in the carbon backbone of hoiamide C.<sup>1b</sup> As part of our program on the synthesis of marine secondary metabolites<sup>2</sup> we were interested in synthetic approaches toward the total synthesis of hoiamides and selected hoiamide C (**1**) as an initial entry into this interesting class of natural products. Herein, we disclose the first total synthesis of hoiamide C by utilizing a highly efficient and convergent approach.

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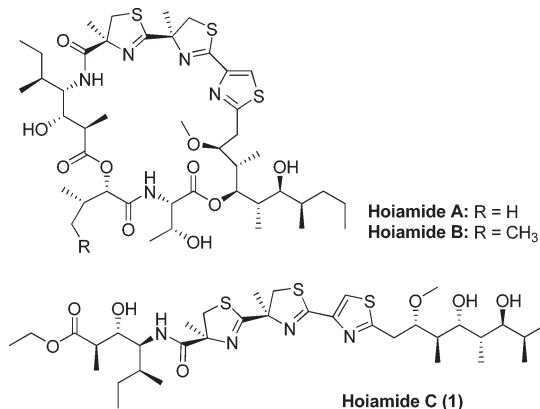
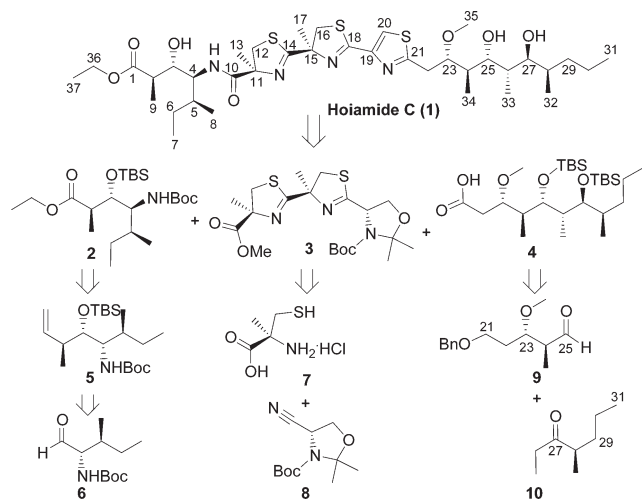


Figure 1. Structures of hoiamides A–C.

### Scheme 1. Retrosynthetic Analysis of Hoiamide C (3)

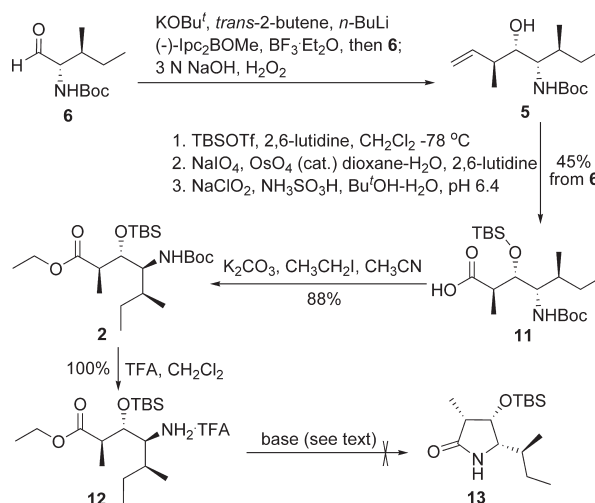


As outlined retrosynthetically in Scheme 1, our synthetic approach relies on the assembly of three main building blocks of comparable complexity, that is, **2**, **3**, and **4**. The thiazole moiety was planned to arise from the masked amino alcohol **3** and acid **4**, while condensation of an acid derived from **3** with a free amine derived from **2** was envisioned to deliver the required amide. Further retrosynthetic analysis of the individual subunits revealed that they can be assembled from alkene **5**, aldehyde **6**, amino acid **7**, nitrile **8**, aldehyde **9**, and ketone **10**.

The synthesis of fragment **2** started with the reaction of the known aldehyde **6**<sup>3</sup> with (-)-*B-E*-crotyldiisopinocampheylborane<sup>4</sup> to afford the desired *anti* homologated allylic alcohol **5**, which is inseparable with the pinocampheol (Scheme 2). After conversion of **5** to its TBS ether, the terminal alkene was oxidatively cleaved through the action of OsO<sub>4</sub>-NaIO<sub>4</sub> in the presence of 2,6-lutidine<sup>5</sup> to yield the corresponding aldehyde, which was immediately oxidized to the carboxylic acid **11** using Pinnick oxidation conditions;<sup>6</sup> the carboxylic acid was obtained in 45% yield in four steps from aldehyde **6**. Esterification of acid **11** with ethyl iodide under basic conditions afforded the corresponding ester **2** in 88% yield. The removal of the Boc protecting group in **2** under acidic conditions afforded **12** in quantitative yield. In principle, the free amine, derived from a base treatment of **12**, might be poised to undergo *O,N*-acyl migration to afford  $\gamma$ -lactam **13**. To our delight, this side reaction did not occur when **12** was treated with *N*-methylmorpholine to afford the corresponding free amine (*vide infra*). This might be attributed to

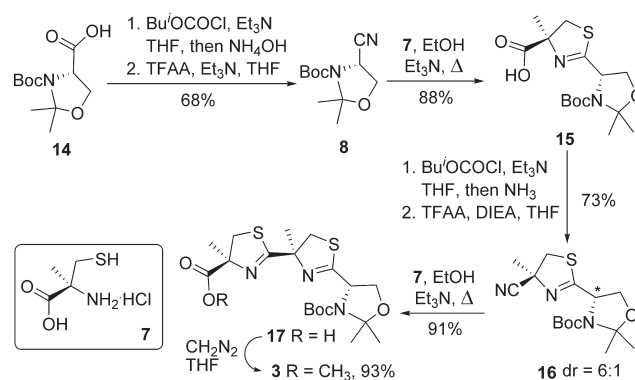
the fact that the formation of **13** requires all three substituents to lie on the same side of the  $\gamma$ -lactam ring; the high steric hindrance of the transition state suppressed the propensity for the *O,N*-acyl migration process.

### Scheme 2. Synthesis of Ester 2



The synthesis of bithiazoline **3** started with the conversion of the known acid **14**<sup>7</sup> into the corresponding amide and then to the nitrile **8**<sup>8</sup> in 68% yield (Scheme 3). A condensation reaction between the nitrile **8** and the (*S*)-2-methylcysteine methyl ester hydrochloride (**7**) prepared according to Pattenden's procedure<sup>9</sup> led to the thiazoline **15** as a viscous oil in 88% yield. Intermediate **15** was then elaborated to the acid **17** in 66% overall yield by an identical strategy as described above, including a conver-

### Scheme 3. Synthesis of Bithiazoline 3



sion of the acid functional group into the corresponding nitrile **16**, followed by a condensation reaction with the

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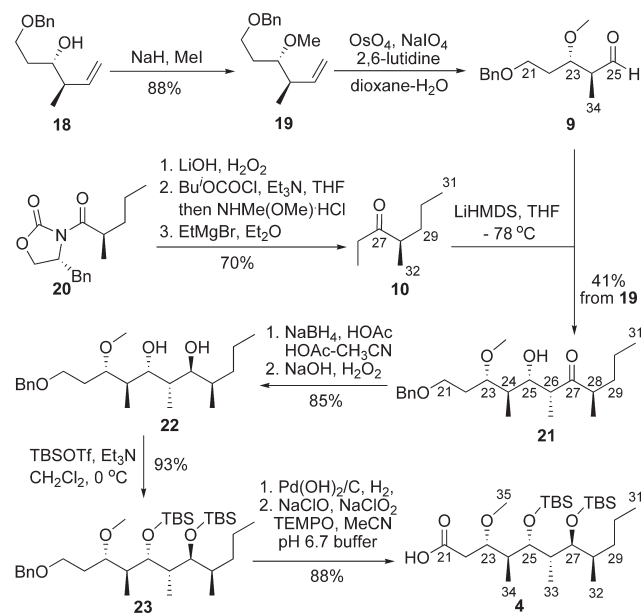
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(*S*)-2-methylcysteine methyl ester hydrochloride (**7**). Acid **17** was treated with ethereal diazomethane to afford methyl ester **3** in 93% yield. It should be mentioned that some degree of epimerization occurred at the secondary amine-containing center during the step involving the reaction of mixed anhydride with ammonia that led to nitrile **16** as a 6:1 mixture of diastereomers. Fortunately, diastereomerically pure **16** could easily be separated from its epimer by column chromatography, and fragment **3** was therefore obtained as a single diastereomer.

The preparation of the polyketide fragment **4** began with methylation of the known homoallylic alcohol **18**<sup>10</sup> to give compound **19** in 85% yield. Oxidative cleavage of the terminal alkene **19** afforded the corresponding aldehyde **9** (Scheme 4). In parallel, oxazolidinone **20**<sup>11</sup> was converted into the corresponding Weinreb amide, followed by Grignard addition of this amide to afford the extended ketone **10** in 70% yield over three steps. With both aldehyde **9** and ketone **10** in hand, it was possible to explore the assembly of the two subunits through a double diastereoselective aldol reaction. In an optimized procedure, lithium hexamethyldisilyl azide (LiHMDS) was employed to generate the enolate of **10**, which smoothly reacted with

**Scheme 4.** Synthesis of Acid **4**



aldehyde **9** at  $-78\text{ }^{\circ}\text{C}$  to give adduct **21** in moderate yield (41% from **19**) as a mixture of two diastereomers (90% de). The dominant isomer was tentatively assigned as the 24,25-*anti*-Felkin-25,26-*syn*-26,28-*anti* product **21** (Scheme 4)

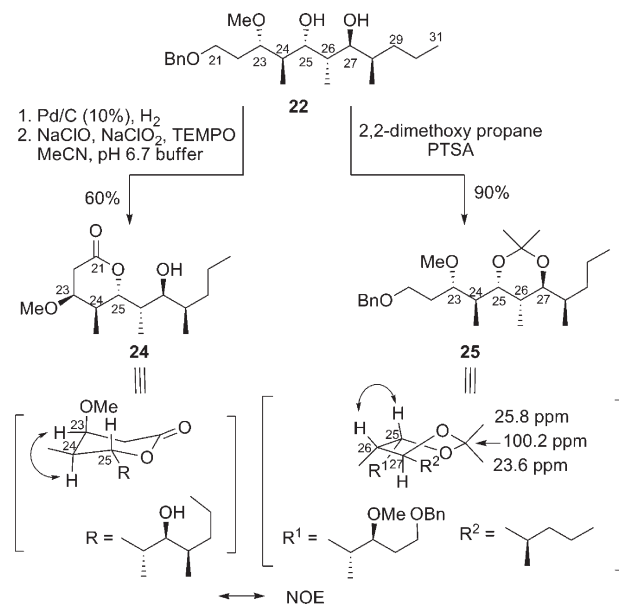
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based on literature precedent for similar double stereo-differentiating lithium aldol reactions.<sup>12</sup> Stereoselective hydroxy-directed 1,3-*anti*-reduction of the ketone group with an Evans–Saksena reagent<sup>13</sup> afforded 1,3-*anti*-diol compound **22** in 85% yield with excellent diastereoselectivity ( $>20:1$  in favor of *anti*). Protection of diol **22** with TBSOTf,  $\text{Et}_3\text{N}$  afforded **23**, which was then converted into acid **4** in 88% yield through a two-step sequence including the hydrogenolysis of the benzyl ether and oxidation of the resultant hydroxyl group by the action of TEMPO/ $\text{NaClO}/\text{NaClO}_2$ .<sup>14</sup>

In order to confirm the relative and absolute stereochemistry at C25, C26, and C27 of fragment **4**, we elected to convert intermediate **22** into lactone **24** and acetonide **25** for NMR analysis. First, the benzyl ether in diol **22** was hydrogenolyzed to give the corresponding primary alcohol, which was subsequently transformed into lactone **24** by the action of a TEMPO-mediated oxidation. The observed relative stereochemistry of **24** was proved by analysis of the coupling constants in the  $^1\text{H}$  NMR spectrum as well as by NOESY experiments. The large vicinal coupling constant for H24–H25 (11.0 Hz), together with the small observed values for H23–H24 (2.2 Hz), unambiguously established the proposed 23,24-*anti*, 24,25-*anti* relative stereochemistry of **22** (Scheme 5). Second, treatment of diol **22** with dimethoxypropane in the presence of *p*-toluenesulfonic acid (PTSA) afforded acetonide **25** in

**Scheme 5.** Assignment of Stereochemistry of **22**



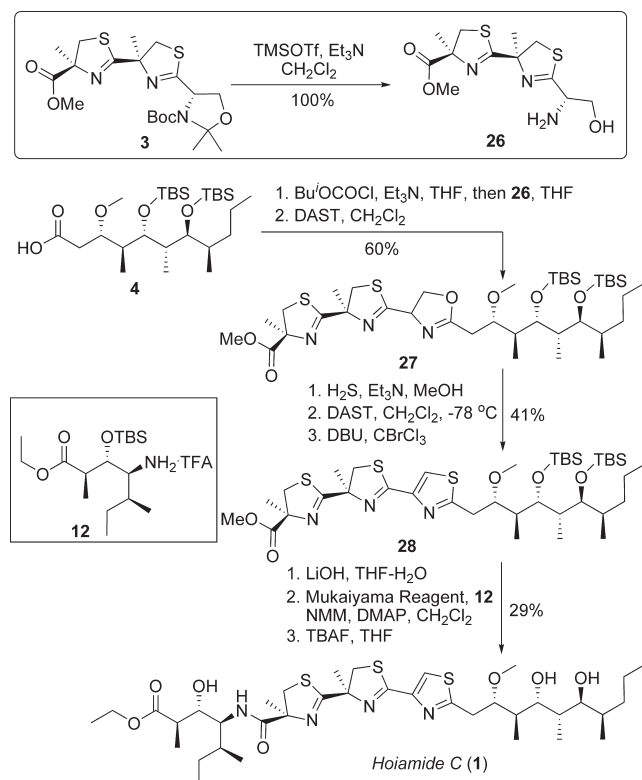
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90% yield. The C25–C27 stereochemistry of diol **22** was confirmed by examining the spectral properties of acetonide **25**. The acetonide methyl groups ( $\delta$  23.6, 25.8) and ketal carbon ( $\delta$  100.2) of **25** exhibited  $^{13}\text{C}$  NMR chemical shifts ( $\text{CDCl}_3$ , 125 MHz) characteristic of *anti*-1,3-diol acetonides ( $\delta$  23.6–25.6 and 100.2–101.0) and distinct from those observed for *syn*-1,3-diol acetonides ( $\delta$  18.6–19.9/29.8–30.2 and 98.0–99.3).<sup>15</sup> Furthermore, the correlation for H25–H26 by NOESY experiment confirmed the expected 25,26-*syn*, 26,27-*anti* stereochemistry.

With the three key fragments in hand, the stage was now set for their assembly and elaboration into hoiamide C (Scheme 6). Our fragment assembly began with coupling of fragments **3** and **4**. Thus, the Boc and acetonide protecting

**Scheme 6.** Synthesis of Hoiamide C



groups of bisthiazoline **3** were removed under mild conditions (TMSOTf, triethyl amine) to afford hydroxyl amine **26**. Acid **4** was activated as a mixed anhydride first and then condensed with hydroxyl amine **26** to provide the corresponding  $\beta$ -hydroxy amide, which was then converted into the oxazoline **27** by the action of diethylaminosulfur trifluoride (DAST).<sup>16</sup> Thiolytic of the oxazoline

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**27** with hydrogen sulfide in a solution of methanol/triethylamine (2:1) provided the thioamide intermediate,<sup>17</sup> which was then converted into **28** through a two-step sequence including a second cyclodehydration of the  $\beta$ -hydroxy thioamide with DAST to produce a thiazoline followed by further dehydrogenation by the use of DBU and bromotrichloromethane.<sup>18</sup> Saponification of the methyl ester **28** followed by coupling with amine **12** in the presence of a Mukaiyama reagent<sup>19</sup> provided the corresponding amide in 57% yield, which was then treated with tetrabutylammonium fluoride (TBAF) to afford hoiamide C in 51% yield. The optical rotation of the synthetic product,  $[\alpha]_{\text{D}}^{20} +12$  ( $c$  0.2,  $\text{CHCl}_3$ ), was in close agreement with the value reported in the literature for natural hoiamide C,  $[\alpha]_{\text{D}}^{23} +16$  ( $c$  0.2,  $\text{CHCl}_3$ ). The  $^1\text{H}$  NMR (500 MHz, pyridine- $d_5$ ) and  $^{13}\text{C}$  NMR (125 MHz, pyridine- $d_5$ ) spectra for this compound exactly matched the data reported for naturally derived hoiamide C. Thus, the original assignment of the relative and absolute configuration of hoiamide C had been corroborated via unambiguous total synthesis.

In summary, we have accomplished the total synthesis of hoiamide C from homoallylic alcohol **18** in 1.8% overall yield with the longest linear sequence of 16 steps. This synthesis confirmed the structure of hoiamide C. The extension of this chemistry toward the total synthesis of hoiamide A and novel hoiamide analogues for biological evaluation is underway and will be reported in due course.

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**Supporting Information Available.** Full details for experimental procedures for compounds **1–5**, **5a**, **8–12**, **14a**, **15a**, **15–17**, **19**, **20a**, **21–28**, **27'**, **28a** and  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for compounds **1–4**, **5a**, **8**, **10–12**, **14a**, **15–17**, **19**, **20a**, **21–25**, **27'**, **27**, **28**, and **28a**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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