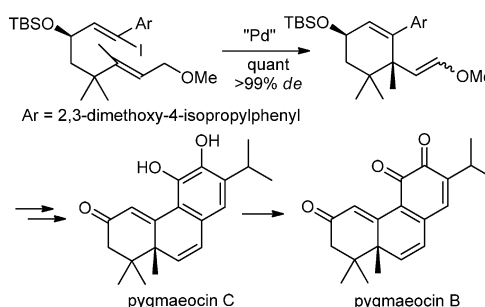


Enantioselective Total Syntheses  
of Pygmaeocins B and CAkiko Obase, Akihito Kageyama, Yuki Manabe, Tsukasa Ozawa, Takaaki Araki,  
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## ABSTRACT



The first enantioselective total syntheses of pygmaeocins B and C have been accomplished using an efficient and highly diastereoselective intramolecular Heck cyclization for the construction of a quaternary stereogenic center and the functionalized A-ring of the natural products as the key step.

The pygmaeocins B (**1**) and C (**2**) comprise a novel class of irregular abietane diterpenoids that were isolated by Hesse and Meng from the roots of *Pygmaopremna herbacea*.<sup>1</sup> Their structures were elucidated by extensive spectroscopic studies and their absolute configurations, while not determined directly, were deduced to be *R* on the basis of the likely biogenetic pathway.<sup>1b</sup> These compounds contain one quaternary stereogenic center at C5 and a densely functionalized hydrophenanthrene skeleton with a high oxidation state. The outstanding characteristic structural feature of these molecules is the C20-Me migration from C10 to C5 with an intact C4–C5 bond. Although their biological activities have never been reported, the plant is used in the Yunnan province of China as a folk medicine against inflammation and malaria.<sup>1b</sup> Consequently, they are expected to be promising leads for drug discovery in these areas. To date, although the racemic syntheses of pygmaeocins B<sup>2</sup> and C<sup>3</sup> have been reported, no enantioselective synthesis has been completed. Herein,

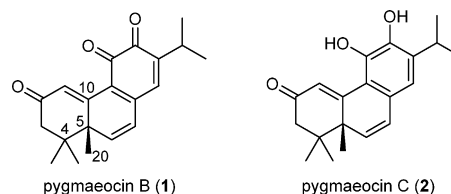


Figure 1. Pygmaeocins B and C.

we report the first enantioselective total syntheses of pygmaeocins B (**1**) and C (**2**), thereby establishing their absolute stereochemistries, via a diastereoselective intramolecular Heck (IMH) reaction<sup>4,5</sup> for the construction of the functionalized A-ring of the natural products with a quaternary stereogenic center as the key step (Figure 1).

Our retrosynthetic strategy is illustrated in Figure 2. The preparation of pygmaeocins B (**1**) and C (**2**) was based on chemistry we developed recently for the diastereoselective

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construction of chiral building blocks for the synthesis of indole alkaloids.<sup>5o</sup> We envisioned a sequential oxo-carbenium ion-mediated Friedel–Crafts type cyclization, desilylation, oxidation and demethylation of **3** to give pygmaecocin C (**2**), which can be converted to pygmaecocin B (**1**) by oxidation of the catechol functionality. The fully functionalized cyclohexene **3** would be constructed by an IMH reaction of **4**, which has a tertiary stereogenic center with the *R* configuration, via a 1,4-chirality transfer for assembling a quaternary stereogenic center at C5 with the *R* configuration. The vinyl iodide **4** would be derived from the corresponding optically active acetylenic alcohol (*R*)-**5**, which in turn would be prepared from the aldehyde **6** and the aryl acetylene **7** (Figure 2).

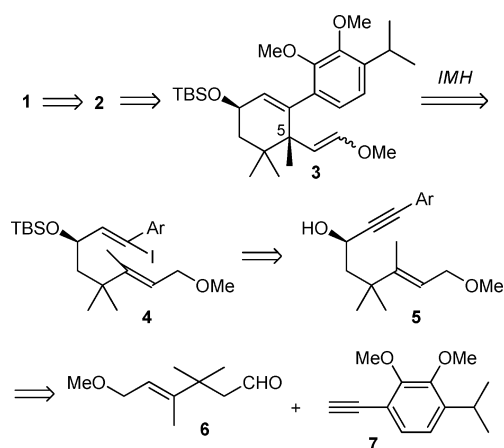
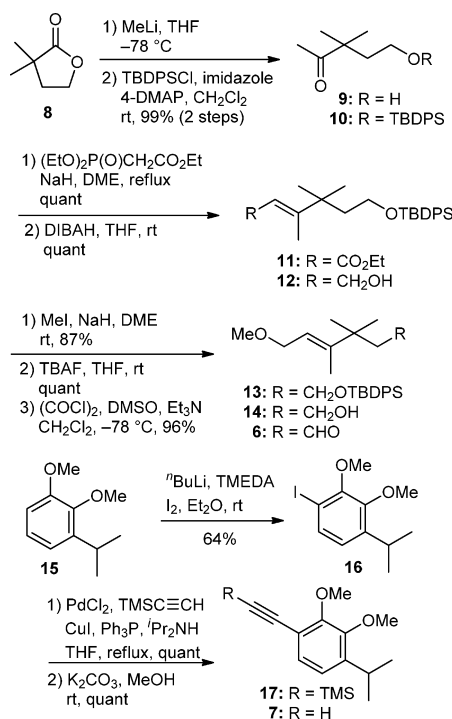


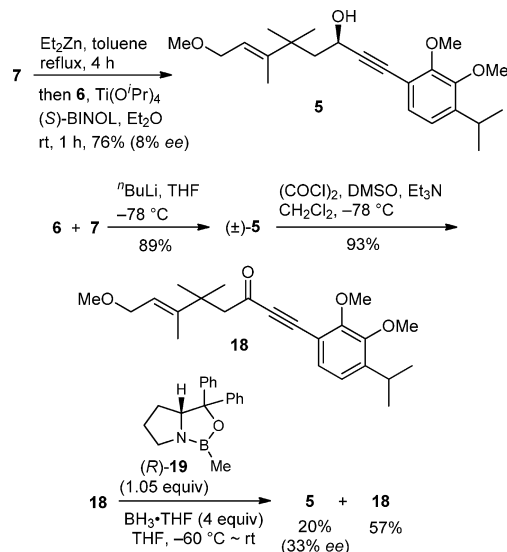
Figure 2. Retrosynthetic analysis.

The starting aldehyde **6** and the aryl acetylene **7** were prepared as shown in Scheme 1. Treatment of the lactone **8**<sup>6</sup> with MeLi followed by silylation provided the ketone **10**, which was subjected to Horner–Wadsworth–Emmons olefination to give the (*E*)-enoate **11**. Sequential DIBAH reduction, methylation, desilylation and Swern oxidation provided the aldehyde **6** in 83% overall yield from **8**. The aryl acetylene, 3-ethynyl-4-isopropyl-1,2-dimethoxybenzene (**7**),

## Scheme 1. Preparation of **6** and **7**



## Scheme 2. Attempted Preparation of (*R*)-**5**



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was prepared from **15**<sup>7</sup> via a three-step sequence. Thus, ortho-lithiation followed by iodination furnished the iodobenzene **16**, which was exposed to the conditions of Sonogashira coupling with trimethylsilylacetylene, and the resulting **17** was desilylated with K<sub>2</sub>CO<sub>3</sub> in methanol to give **7** in 64% yield from **15** (Scheme 1).

For the preparation of optically active acetylenic alcohol (*R*)-**5**, we initially examined the asymmetric alkynylation of **6** with **7**. After several attempts, we found that the procedure

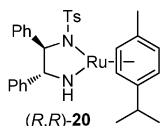
reported by Pu et al.<sup>8</sup> provided only the adduct **5**. Thus, treatment of **7** with Et<sub>2</sub>Zn in refluxing toluene resulted in the zinc acetylide, which was reacted with **6** in the presence of (*S*)-BINOL and titanium tetrakisopropoxide in Et<sub>2</sub>O at room temperature to give **5** in 76% yield; however, the enantiomeric excess was only 8% (HPLC analysis). We then attempted asymmetric reduction of the acetylenic ketone **18**, which was prepared by Swern oxidation of ( $\pm$ )-**5**, generated from **6** and the lithium acetylide of **7**. Treatment of **18** with (*R*)-methyl-CBS-oxazaborolidine **19**<sup>9</sup> and BH<sub>3</sub>•THF provided **5** and the recovered **18** in 20 and 57% yield, respectively. However, the enantiomeric excess of **5** still remained low (33% *ee*) (Scheme 2).

We next examined the asymmetric transfer hydrogenation of the acetylenic ketone **18** using a chiral Ru (II) catalyst.<sup>10</sup> The results are shown in Table 1. Treatment of **18** with 3 mol % of (*R,R*)-**20** in isopropanol at room temperature for 19 h provided the alcohol **5** in 46% yield with 92% *ee* (entry 1). Addition of acetonitrile as the solvent resulted in a higher yield with comparable enantioselectivity (88%, 93% *ee*) (entry 2). When the reaction was conducted with 3 mol % of **20** in the presence of formic acid and Et<sub>3</sub>N in THF at room temperature for 5 h,<sup>11</sup> **5** was obtained in 90% yield with 94% *ee* (entry 3). The absolute configuration of **5** was deduced to be *R* from a mechanistic point of view and it was firmly established by the following conversions (Table 1).

**Table 1.** Asymmetric Transfer Hydrogenation

<b>18</b> $\xrightarrow[\text{conditions}]{(R,R)\text{-}\mathbf{20} \text{ (3 mol \%)}}$ <b>5</b>			
entry	conditions	product <b>5</b>	
		yield (%)	<i>ee</i> (%) <sup>a</sup>
1	<i>i</i> PrOH, rt, 19 h	46	92
2	<i>i</i> PrOH, MeCN, rt, 18 h	88	93
3	formic acid, Et <sub>3</sub> N, THF, rt, 5 h	90	94

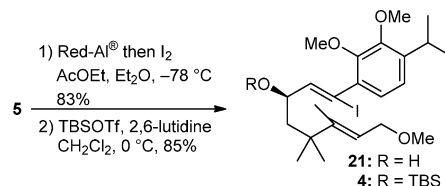
<sup>a</sup> determined by HPLC analysis



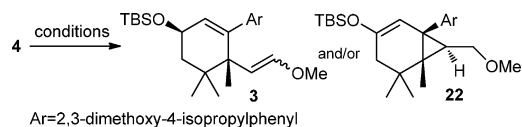
The optically active acetylenic alcohol **5** was then sequentially treated with Red-Al and iodine in one pot to give the *Z*-vinyl iodide **21** in 83% yield. At this stage, the absolute configuration was determined to be *R* by the Kusumi–Mosher method<sup>12</sup> of the MTPA ester of **21**.

For the key IMH reaction, we treated the substrate **4**, obtained by silylation of **21** (Scheme 3), with 20 mol % of bis(triphenylphosphine)palladium(II) dichloride and Et<sub>3</sub>N (3 equiv) in a mixture of DMF and water to give a chromatographically separable mixture of the requisite cyclized product **3** (an inseparable 5.6:1 mixture of *E* and *Z* olefinic isomers) and the bicycle[4.1.0]heptane **22**<sup>5g,13</sup> in 46 and 21% yield, respectively (entry 1). The reaction that

**Scheme 3.** Preparation of Substrate **4**



**Table 2.** Intramolecular Heck Reaction



entry	conditions	product(s)	yield (%)	
			<b>3</b> ( <i>E:Z</i> ) <sup>a</sup>	<b>22</b> (ratio) <sup>a</sup>
1	(Ph <sub>3</sub> P) <sub>2</sub> PdCl <sub>2</sub> (20 mol %) Et <sub>3</sub> N, DMF, H <sub>2</sub> O 80 °C, 30 h	<b>3</b> + <b>22</b>	46 (5.6:1)	21 (3:1)
2	Pd(OAc) <sub>2</sub> (30 mol %) Ph <sub>3</sub> P (60 mol %) Ag <sub>2</sub> CO <sub>3</sub> , THF, 65 °C, 19 h	<b>3</b> + <b>22</b>	33 (1.8:1)	22 (3:1)
3	Pd(OAc) <sub>2</sub> (10 mol %) ( <i>o</i> -tol) <sub>3</sub> P (20 mol %), Et <sub>3</sub> N MeCN, H <sub>2</sub> O, reflux, 30 h	<b>3</b>	quant (1:2.3)	

<sup>a</sup> determined by <sup>1</sup>H NMR

produced **3** took place with perfect diastereoselectivity and was confirmed by the <sup>1</sup>H and <sup>13</sup>C NMR spectra, in which only two sets of resonances corresponding to the *E/Z* isomers were observed. The stereostructure of **3** was confirmed by the NOESY spectroscopy<sup>14</sup> and the configuration of a newly generated quaternary stereogenic center at C5 proved to be the requisite *R* as shown in Figure 3. The cyclopropane derivative **22**, which would be generated via a double Heck cyclization, was obtained as an inseparable 3:1 mixture of the rotational isomers, the NOESY spectra of which showed the presence of two conformers (Figure 3). That the minor isomer converged to the major

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(14) Both *E* and *Z* isomers showed the same NOESY correlations as indicated in Figure 3.

one upon heating was confirmed by the measurement of  $^1\text{H}$  NMR spectrum at 100 °C in  $\text{DMSO}-d_6$ .<sup>15</sup> The reaction using 30 mol % of  $\text{Pd}(\text{OAc})_2$ , 60 mol % of  $\text{Ph}_3\text{P}$  and  $\text{Ag}_2\text{CO}_3$  in THF at 65 °C<sup>5a</sup> provided a mixture of **3** and **22** in 33 and 22% yield, respectively (entry 2). When the reaction was conducted using 10 mol % of  $\text{Pd}(\text{OAc})_2$ , 20 mol % of (*o*-tol) $_3\text{P}$  and  $\text{Et}_3\text{N}$  in refluxing aqueous acetonitrile, **3** was produced as the sole product in a dramatic improvement in the yield to quantitative (*E:Z* = 1:2.3) (entry 3) (Table 2).

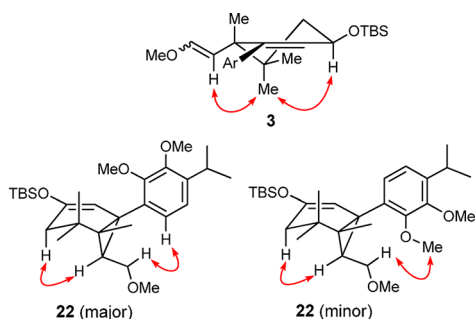


Figure 3. NOESY of **3** and **22**.

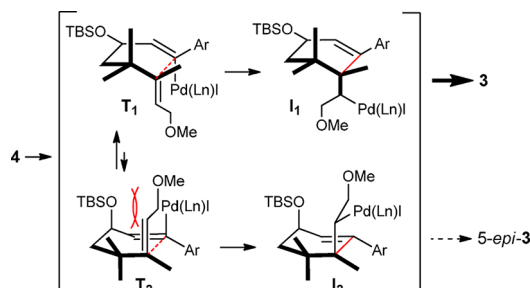
One plausible mechanism for the diastereoselective formation of **3** is outlined in Scheme 4. The cyclization would proceed predominantly through the intermediate **I**<sub>1</sub>, derived from the boat-like transition state **T**<sub>1</sub>, which has an equatorially disposed TBS-oxy substituent and an eclipsed orientation of the Pd–C  $\sigma$  and alkene  $\pi$  bonds,<sup>5b</sup> to afford **3** exclusively via reductive elimination of the palladium hydride species. The diastereoselection achieved in the Heck-cyclization step can be attributed to an unfavorable allylic strain in **T**<sub>2</sub> (leading to 5-*epi*-**3** via **I**<sub>2</sub>) as shown (Scheme 4).

In the final phase of the synthesis, treatment of **3** with TBAF in THF, followed by oxidation of the resulting allylic alcohol **23** with manganese dioxide provided the enone **24**, which was exposed to methanesulfonic acid in dichloromethane at 0 °C to give the tricyclic enone **25** quantitatively. The methyl ethers in **25** were cleaved with  $\text{BBr}_3$  in dichloromethane to give pygmaecocin C (**2**) in 74% yield. Due to the less stable character of **2**, its catechol moiety was acetylated to give the diacetate **26** in 96% yield. On the other hand, for the synthesis of pygmaecocin B (**1**), the crude **2** was immediately oxidized with silver carbonate in dichloromethane at room temperature to produce **1** in 80% yield from **25**. The spectral properties ( $^1\text{H}$  and  $^{13}\text{C}$  NMR, IR and HRMS) of the synthetic materials **1**, **2** and **26** were identical with those reported in the literature<sup>1b</sup> and the completion of the total syntheses of pygmaecocins B and C was accomplished. Since the CD spectra of **1** and **2** were also identical with those for the natural products,<sup>16</sup> the absolute configuration at C5 was established to be *R* (Scheme 5).

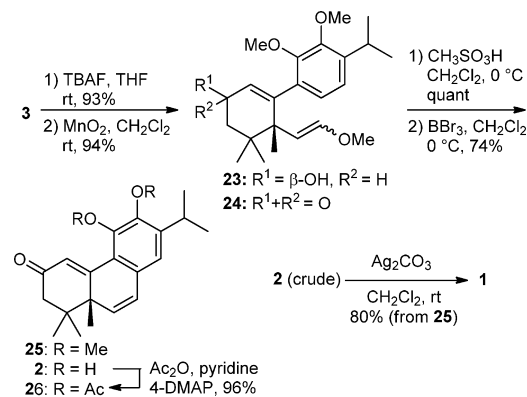
(15) On heating a solution of the corresponding ketone, which was prepared from **22** by treatment with TBAF, in  $\text{C}_6\text{D}_6$  in an NMR tube at 70 °C, the minor rotational isomer also converged cleanly to the major one.

(16) See Supporting Information.

Scheme 4. Plausible Mechanism for the Diastereoselection



Scheme 5. Syntheses of Pygmaecocins B (**1**) and C (**2**)



In summary, we have completed the first enantioselective total syntheses of pygmaecocins B and C using, as the key step, a 1,4-chirality transfer that occurred with high diastereoselectivity during the IMH reaction for the construction of the sole quaternary stereogenic center at C5 and the functionalized A-ring of the natural products in a longest linear sequence of eighteen and seventeen steps, respectively, from the lactone **8** with overall yields of 30 and 28%. In addition, the absolute configuration at the C5 quaternary stereogenic center was firmly established by the total synthesis to be *R*, which had been proposed by Hesse and Meng.<sup>1</sup> The synthetic route developed here is general and efficient and could also be applied to the syntheses of other related natural products.

**Acknowledgment.** We are grateful to Dr. Meng, AtheroGenics, Inc., for providing spectral data ( $^1\text{H}$  and  $^{13}\text{C}$  NMR, IR, MS) of pygmaecocins B and C. This work was supported by a Grant-in-Aid from the Program for the Promotion of Basic and Applied Research for Innovation in the Bio-oriented Industry (BRAIN).

**Supporting Information Available.** Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.