ORGANIC LETTERS

2013
Vol. 15, No. 14
3666–3669

Enantioselective Total Syntheses of Pygmaeocins B and C

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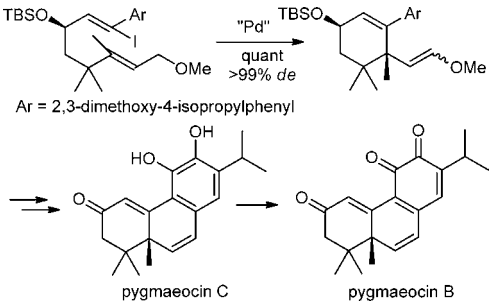
Received June 1, 2013

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 *Pygmaeopremna herbacea*.[1] 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.[1b] 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.[1b] Consequently, they are expected to be promising leads for drug discovery in these areas. To date, although the racemic syntheses of pygmaeocins B[2] and C[3] have been reported, no enantioselective synthesis has been completed. Herein,

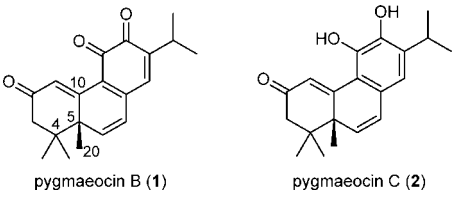


Figure 1. Pygmaeocins B and C.

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[4,5] 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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10.1021/ol401543b
Published on Web 06/28/2013

construction of chiral building blocks for the synthesis of indole alkaloids.[5o] We envisioned a sequential oxocarbenium ion-mediated Friedel–Crafts type cyclization, desilylation, oxidation and demethylation of **3** to give pygmaeocin C (**2**), which can be converted to pygmaeocin 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).

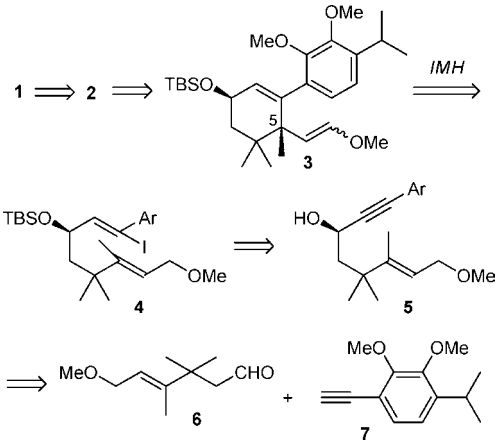
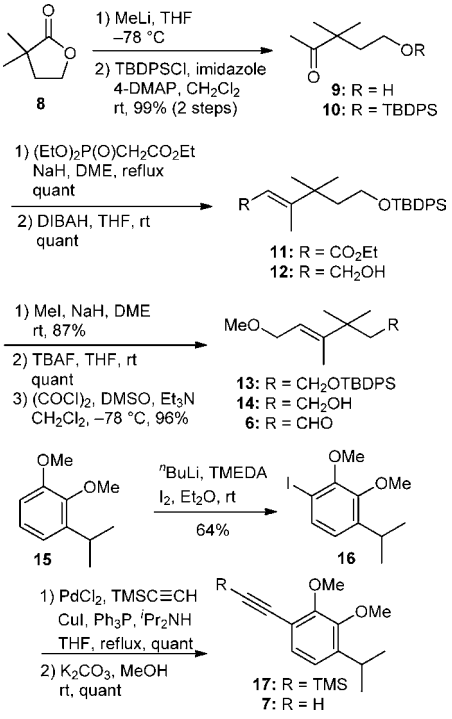


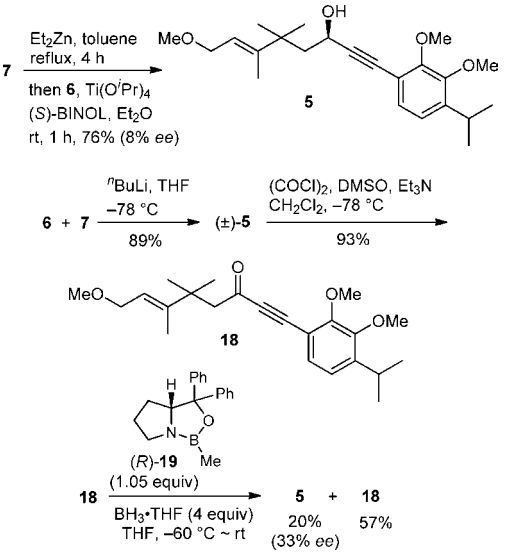
Figure 2. Retrosynthetic analysis.

The starting aldehyde **6** and the aryl acetylene **7** were prepared as shown in Scheme 1. Treatment of the lactone **8**[6] 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**



was prepared from **15**[7] 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_2CO_3 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

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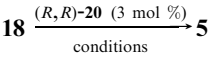
reported by Pu et al.[8] provided only the adduct **5**. Thus, treatment of **7** with Et_2Zn in refluxing toluene resulted in the zinc acetylide, which was reacted with **6** in the presence of (*S*)-BINOL and titanium tetraisopropoxide in Et_2O at room temperature to give **5** in 76% yield; however, 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 (±)-**5**, generated from **6** and the lithium acetylide of **7**. Treatment of **18** with (*R*)-methyl-CBS-oxazaborolidine **19**[9] and BH_3•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).

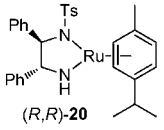
We next examined the asymmetric transfer hydrogenation of the acetylenic ketone **18** using a chiral Ru (II) catalyst.[10] The results are shown in Table 1. Treatment of **18** with 3 mol % of (*R*,*R*)-**20** in isopropanol at room temperature for 19 h provided the alcohol **5** in 46% yield with 92% *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_3N in THF at room temperature for 5 h,[11] **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



entry	conditions	product 5	
		yield (%)	*ee* (%)[a]
1	^{i}PrOH, rt, 19 h	46	92
2	^{i}PrOH, MeCN, rt, 18 h	88	93
3	formic acid, Et_3N, THF, rt, 5 h	90	94

[a] determined by HPLC analysis



(*R*,*R*)-**20**

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[12] 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_3N (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**[5g,13] in 46 and 21% yield, respectively (entry 1). The reaction that

Scheme 3. Preparation of Substrate **4**

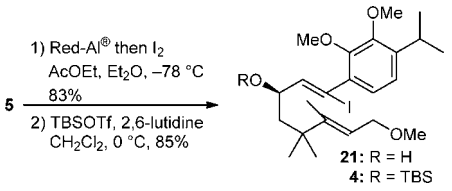
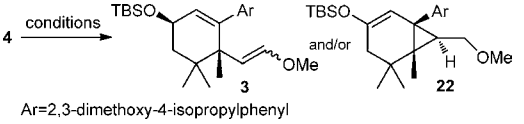


Table 2. Intramolecular Heck Reaction



entry	conditions	product(s)	yield (%) **3** (*E*:*Z*)[a]	yield (%) **22** (ratio)[a]
1	$(Ph_3P)_2PdCl_2$ (20 mol %) Et_3N, DMF, H_2O 80 °C, 30 h	**3** + **22**	46 (5.6:1)	21 (3:1)
2	$Pd(OAc)_2$ (30 mol %) Ph_3P (60 mol %) Ag_2CO_3, THF, 65 °C, 19 h	**3** + **22**	33 (1.8:1)	22 (3:1)
3	$Pd(OAc)_2$ (10 mol %) (*o*-tol)$_3$P (20 mol %), Et_3N MeCN, H_2O, reflux, 30 h	**3**	quant (1:2.3)	

[a] determined by ^{1}H NMR

produced **3** took place with perfect diastereoselectivity and was confirmed by the ^{1}H and ^{13}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[14] 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}H NMR spectrum at 100 °C in DMSO-d_6.[15] The reaction using 30 mol % of $Pd(OAc)_2$, 60 mol % of Ph_3P and Ag_2CO_3 in THF at 65 °C[5a] provided a mixture of **3** and **22** in 33 and 22% yield, respectively (entry 2). When the reaction was conducted using 10 mol % of $Pd(OAc)_2$, 20 mol % of $(o\text{-tol})_3P$ and Et_3N 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).

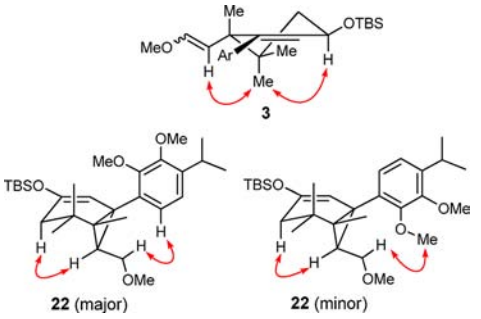


Figure 3. NOESY of **3** and **22**.

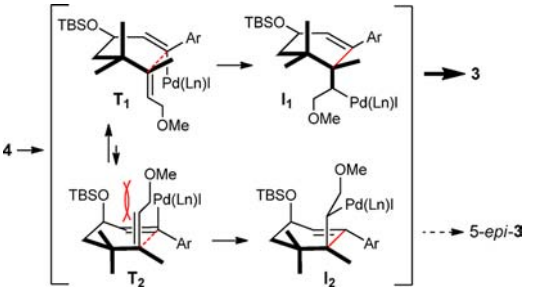
One plausible mechanism for the diastereoselective formation of **3** is outlined in Scheme 4. The cyclization would proceed predominantly through the intermediate $\mathbf{I_1}$, derived from the boat-like transition state $\mathbf{T_1}$, which has an equatorially disposed TBS-oxy substituent and an eclipsed orientation of the Pd−C σ and alkene π bonds,[5b] 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 $\mathbf{T_2}$ (leading to 5-*epi*-**3** via $\mathbf{I_2}$) 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 BBr_3 in dichloromethane to give pygmaeocin 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 pygmaeocin 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}H and ^{13}C NMR, IR and HRMS) of the synthetic materials **1**, **2** and **26** were identical with those reported in the literature[1b] and the completion of the total syntheses of pygmaeocins B and C was accomplished. Since the CD spectra of **1** and **2** were also identical with those for the natural products,[16] the absolute configuration at C5 was established to be *R* (Scheme 5).

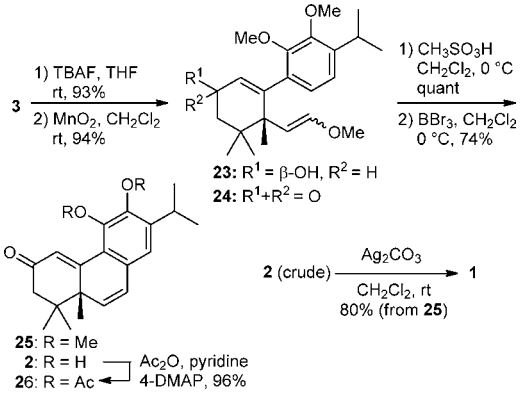
(15) On heating a solution of the corresponding ketone, which was prepared from **22** by treatment with TBAF, in C_6D_6 in an NMR tube at 70 °C, the minor rotational isomer also converged cleanly to the major one.

(16) See Supporting Information.

Scheme 4. Plausible Mechanism for the Diastereoselection



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



In summary, we have completed the first enantioselective total syntheses of pygmaeocins 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.[1] 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}H and ^{13}C NMR, IR, MS) of pygmaeocins 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.