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Total synthesis and structural revision of engelhardione

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ABSTRACT

The total synthesis of the macrocyclic natural product engelhardione is reported. This effort led to the structural revision of the published structure of engelhardione to that of pterocarine. The revision reflects the change of the substitution pattern of one phenyl ether ring from the *meta* to the *para* position. To confirm, pterocarine (**2**) and its close regioisomer **3** were subsequently synthesized for comparison. Moreover, to the best of our knowledge, our synthesis of **1** represents the first example of a 14-membered macrocyclic diarylheptanoid with a *meta–meta* substitution pattern at the diphenyl ether moiety.

Engelhardione was originally isolated from the roots of *Engelhardia roxburghiana* (Juglandaceae).[1] It belongs to a broad family of natural plant metabolites called diarylheptanoids, which are characterized by two phenolic aromatic rings linked by a linear seven-carbon aliphatic ketone chain to form a macrocyclic architecture.[2] The macrocyclic diphenyl ether moiety is widely present in many naturally occurring molecules, including vancomycin, K-13, aceroside IV, piperazinomycin, and engelhardione (Fig. 1), which are important medicinal molecules with antibacterial and anticancer properties.[3–5] Several plant species containing diarylheptanoids are widely used in traditional medicine.[2]

Our interest in the synthesis of engelhardione arose from the following: engelhardione was reported to have potent in vitro activity against the *Mycobacterium tuberculosis* strain H37Rv (MIC = 0.2 μg/mL)[1]; and, despite its potent antituberculosis activity, no synthetic efforts toward engelhardione have been reported to date. Although several total syntheses of engelhardione-related natural products, including acerogenins, galeon, and pterocarine were reported,[6–10] none of these analogs has been systematically evaluated for antituberculosis activity. Furthermore, engelhardione has desirable and druglike Lipinski's rule of five properties,[11] including a low molecular weight of 312.36, four hydrogen bond acceptors, two hydrogen bond donors, and calculated log *P* 3.18.[12] Compared to the other members of diaryl ether natural products (Fig. 1), engelhardione possesses a relatively simple structure, and we envisioned that the synthesis should be quite achievable by adapting available synthetic schemes. To this end, engelhardione represents a valuable natural product lead for further investigation and evaluation.

Herein, we report the first total synthesis of engelhardione. Ultimately, our synthesis led to the structural revision of the proposed (published) structure **1** of engelhardione.

There are basically three different synthetic strategies to construct a macrocyclic diarylheptanoid bearing a diphenyl ether skeleton: (i) the dianion chemistry of methyl acetoacetate and the S_NAr reaction for the diaryl ether formation reported by the Zhu group[6,7]; (ii) the modified Ullmann reaction and the Wittig reaction reported by the Nógrádi group[13]; and, (iii) the classical Ullmann coupling using a Cu(II) catalyst and aldol condensation reported by the Natarajan[8] and Jahng[9,10] groups. We chose to adapt the scheme of Jahng et al. for the synthesis of **1** because this classical macrocyclization procedure employing Cu(II) oxide and potassium carbonate has also been successfully used to synthesize the other members of naturally occurring macrocyclic ethers,[14] and also, mild reaction conditions were used in the aldol and Claisen–Schmidt condensation reactions. More importantly, from a medicinal chemistry point of view, a range of diversified engelhardione analogs, such as benzylated and methylated engelhardione derivatives, can be sequentially generated. These analogs would be invaluable compounds for subsequent structure–activity relationships (SAR) studies.

The retrosynthesis of **1** is shown in Scheme 1. Initial disconnection of the diphenyl ether bond generated the linear diarylheptanoid intermediate, and this macrocyclization would be achieved via intramolecular Ullmann coupling between the corresponding

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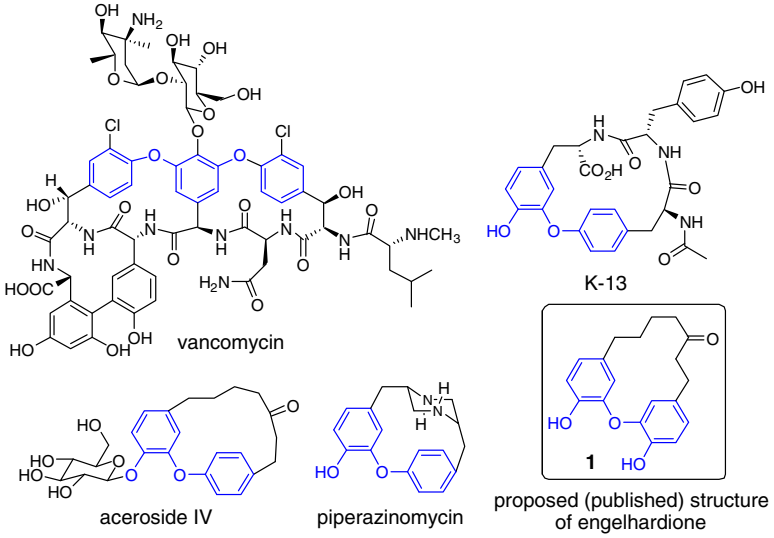
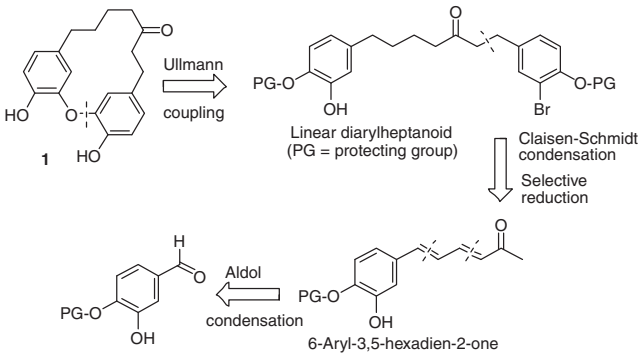


Figure 1. Selected examples of macrocyclic natural products displaying a diaryl ether moiety.

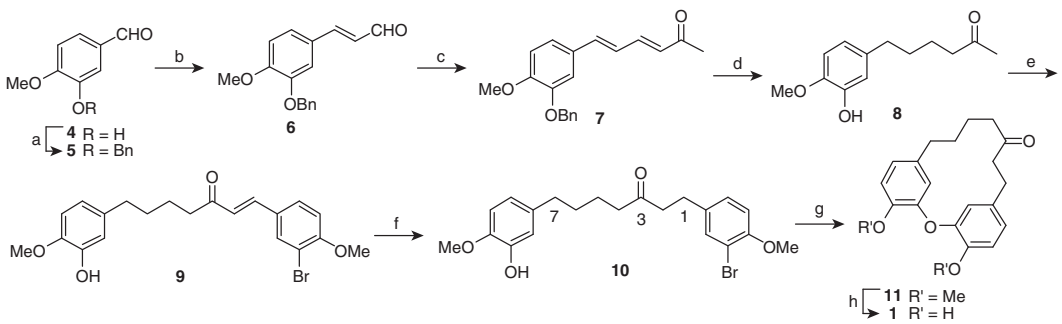


Scheme 1. Retrosynthesis of **1**.

suitably protected phenol derivative and the aryl bromide. The overall synthetic strategy of the key linear 1,7-diaryl-3-ketone can be implemented using a series of cross aldol condensation reactions. The resulting diarylheptanoid would be further disconnected to the unsaturated α,β-conjugated olefin ketone 6-aryl-3,5-hexadien-2-one derivative following selective reduction and Claisen–Schmidt condensation, which can be further derived from the suitably substituted benzaldehyde.

Synthesis of **1** is illustrated in Scheme 2. First, in the presence of potassium carbonate, the hydroxyl group of the commercially available 3-hydroxy-4-methoxybenzaldehyde **4** reacted with benzyl bromide in methanol to give the benzyl protected ether derivative **5** in quantitative yield. The successive aldol condensations with acetaldehyde and then acetone yielded the substituted cinnamaldehyde derivative **6** and 3,5-hexadien-2-one **7**, respectively. Next, the α,β-conjugated olefin ketone **7** underwent selective palladium/carbon (Pd/C)-catalyzed hydrogenation in methanol to afford the debenzylated and saturated 2-ketone intermediate **8** in 94% yield.[15] Claisen–Schmidt condensation of **8** with 3-bromo-4-methoxybenzaldehyde was performed to generate the conjugated diarylhepten-3-one **9**. Final chemoselective reduction of the olefin **9** was achieved using 10% Pd/C in the presence of diphenylsulfide[16] to yield the desired 1,7-diphenylheptan-3-one derivative **10** in 90% yield.[17]

With the linear building block **10** in hand, Ullmann macrocyclization was subsequently performed to generate the 14-membered macrocyclic diphenyl ether product **11**. To screen the experimental conditions, conversion of **10** to **11** was examined using a variety of Cu reagents, bases, and solvent systems and the results are shown in Table 1. According to the procedure reported by Jahng and coworkers,[10] when CuO was used and the reaction was conducted in pyridine using K_2CO_3 as base, the macrocyclic product **11** was first provided in 25% yield after 20 h (Table 1, entry 1). It should be noted, by comparing entries 1 and 2, that the same reaction without N_2 yielded a similar result. Further inspired by the work of the Natarajan group,[8] a sealed pressure tube was then employed in an attempt to accelerate the reaction and to improve the yield.



Scheme 2. Synthesis of **1**. Reagents and conditions: (a) $PhCH_2Br$, K_2CO_3, MeOH, reflux, 4 h, 100%; (b) CH_3CHO, 10% NaOH, EtOH, rt, 3 h, 18%; (c) acetone, 10% NaOH, rt, overnight, 95%; (d) 10% Pd/C, H_2, MeOH, rt, 4 h, 94%; (e) 3-Br-4-$MeOC_6H_3CHO$, 10% NaOH, EtOH, rt, overnight, 64%; (f) 10% Pd/C, H_2, Ph_2S (0.05 equiv), $CHCl_3$, 7 h, 90%; (g) CuO, K_2CO_3, pyridine, 175 °C, 4.5 h, 52%; (h) $AlCl_3$, CH_2Cl_2, reflux, 20 h, 31%.

Table 1
Optimization of intramolecular macrocyclic Ullmann reaction of **10** to **11**[a]

Entry	Cu reagent (equiv)	Base (equiv)	Solvent	Reaction condition[b]	*T* (°C)	Concn (M)	Time (h)	Yield[c,d] (%)
1	CuO (2.5)	K_2CO_3 (1.0)	Pyridine	Reflux under N_2	130	0.02	20	25
2	CuO (2.5)	K_2CO_3 (1.0)	Pyridine	Reflux	130	0.02	25	25
3	CuO (2.5)	K_2CO_3 (1.0)	Pyridine	Reflux	150	0.02	20	33
4	CuO (2.5)	K_2CO_3 (1.0)	Pyridine	Sealed tube	130	0.02	20	NR
5	CuO (2.5)	K_2CO_3 (1.0)	Pyridine	Sealed tube	150	0.02	12	71
6	CuO (2.5)	K_2CO_3 (1.0)	Pyridine	Sealed tube	175	0.02	4.5	52
7	CuO (2.5)	K_2CO_3 (1.0)	Pyridine	Sealed tube under N_2	175	0.02	4.5	51
8	CuO (2.5)	K_2CO_3 (1.0)	Pyridine	Sealed tube under N_2	200	0.02	1	44
9	CuO (2.5)	K_2CO_3 (1.0)	Pyridine	Sealed tube	175	0.004	50	59
10	CuBr-SMe_2 (10)	NaH (2.0)	1,4-Dioxane	Reflux under N_2	130	0.004	46	NR[e]
11[f]	CuI (0.2)	$CsCO_3$ (2.0)	1,4-Dioxane	Reflux under N_2	100	0.05	16.5	NR

[a] Experiments were performed using 0.08 mmol of **10** except entry 9 (0.016 mmol of **10** was used) and monitored by HPLC of the reaction mixture.
[b] Experiments were performed under N_2 atmosphere except entries 2–6 and 9.
[c] Isolated yield based on flash column chromatography.
[d] NR indicates that no product **11** was detected by HPLC at the end of the experiment.
[e] 79% of **10** was recovered after column chromatography.
[f] 0.3 equiv of *N*,*N*-dimethyl glycine was used as additive, which has been reported to promote the intermolecular diphenyl ether reaction.[19]

In addition, a systematic optimization was performed to evaluate the effect of temperature on the reaction yield. When the experiment was conducted at 130 °C in a sealed tube, no reaction occurred after 20 h based on HPLC analysis of the reaction mixture (entry 4). A more encouraging result was obtained after the temperature was increased to 150 °C, when the reaction was complete in 12 h, affording the macrocyclic product **11** in 71% yield (entry 5). As expected, when the temperature was raised to 175 °C, a significant decrease in reaction time was observed; after 4.5 h the reaction went to completion to afford **11** in 52% yield. Under the same reaction conditions with N_2 atmosphere, a comparable yield of 51% was obtained (entries 6 and 7). Increasing the reaction temperature further to 200 °C resulted in a much shorter reaction time (1 h), nevertheless, a lower yield (44%) was also observed due to the formation of polymeric by-products.

The effect of concentration was then evaluated. A 59% yield was obtained in a dilute solution in pyridine (0.004 M) in notably prolonged time (50 h) (entry 9). Finally, attempts to conduct the experiment in milder conditions by employing alternative Cu reagents, including CuBr-SMe_2[18] (entry 10) or CuI and *N*,*N*-dimethyl glycine as an additive[19] (entry 11) failed to afford the cyclic product **11** in our experiments. Overall, considering the reaction time and yield, we chose the conditions (CuO, K_2CO_3, 0.02 M, sealed tube, 175 °C, 4.5 h; entry 6) as the optimum experimental conditions for the macrocyclization step. Final O-demethylation of **11** by $AlCl_3$ in CH_2Cl_2 at reflux afforded **1** in 31% yield.[20]

After completing the synthesis of **1**, we were surprised to find that both ^1H and ^{13}C NMR data of our synthetic engelhardione were not consistent with those of the reported engelhardione, although the ^1H and ^{13}C NMR spectra of both samples were recorded in $CDCl_3$ at 400 and 100 MHz, respectively. In particular, we did not observe the previously reported aromatic proton peak at 5.57 ppm (1H, d, J = 2.0 Hz)[1] in the ^1H NMR spectrum of our synthetic sample (Fig. 2a). After further reviewing the literature, it became evident that this characteristic signal appeared to indicate that the diphenyl ether moiety of the macrocyclic diarylheptanoid was connected at *meta* and *para* positions, respectively. The mass spectra of **1** and reported engelhardione showed the two compounds had the same molecular weight. Therefore, instead of the *meta*–*meta* linked diphenyl ether core structure as originally proposed, we hypothesized that the published structure of engelhardione should possess the *meta* and *para*-linked macrocyclic architecture, which could be compound **2** or **3**, as illustrated in Scheme 3. Compound **2** was originally reported as pterocarine[21] and its total synthesis has been published.[9] After comparing the published ^1H and ^{13}C NMR data of engelhardione and pterocarine, we found that the reported spectroscopic data of engelhardione were, indeed, consistent with those of pterocarine. To further confirm our hypothesis, pterocarine (**2**) and its close regioisomer **3** were next synthesized following the same synthetic strategy (Scheme 3). Synthesis of **2** was achieved starting from 3-methoxy-4-hydroxybenzaldehyde **12**, followed by benzylation, aldol

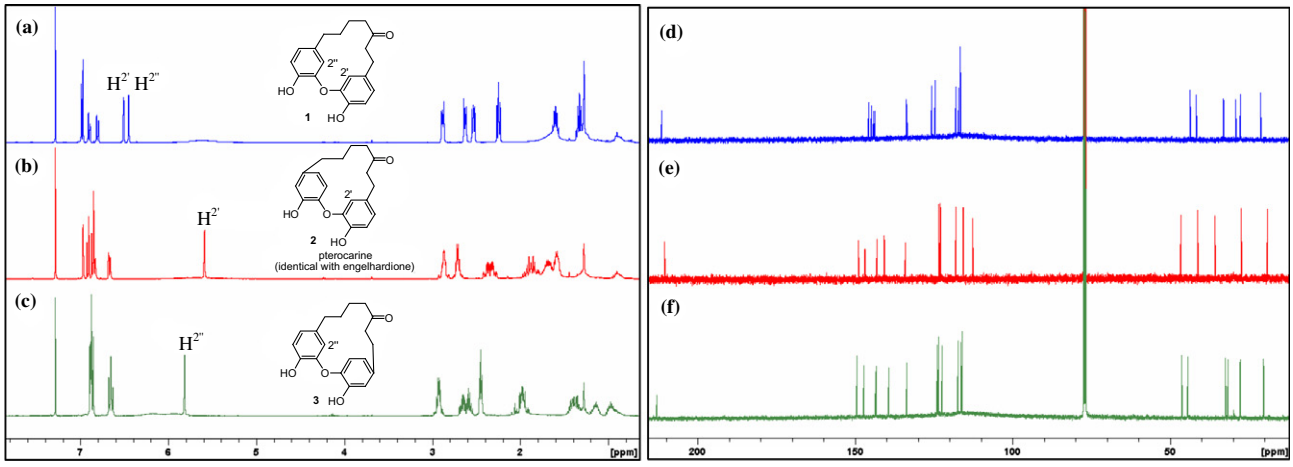
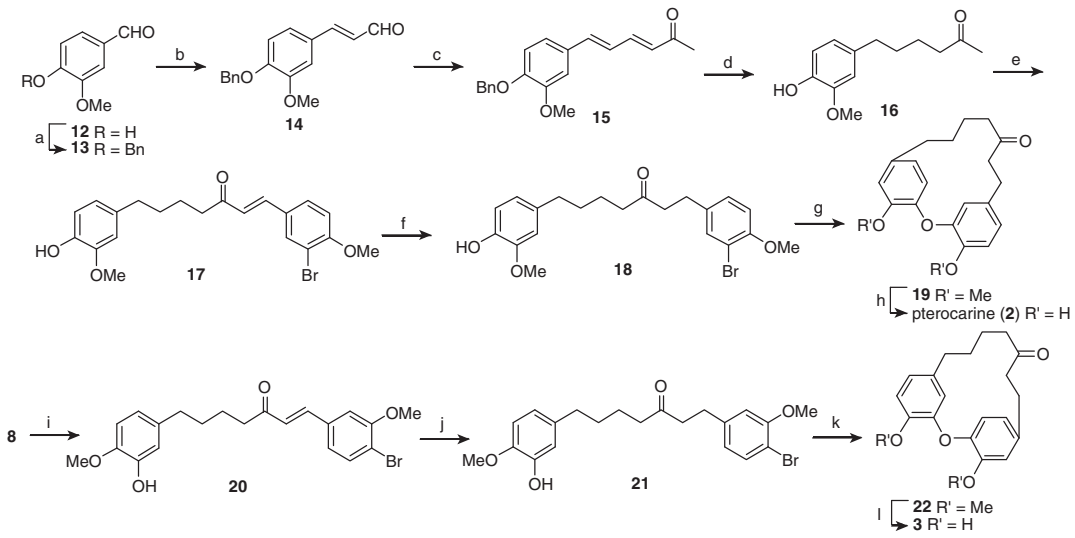


Figure 2. ^1H and ^{13}C NMR spectra (recorded at 400 and 100 MHz in $CDCl_3$, respectively) of **1**, pterocarine (**2**), and **3**.



Scheme 3. Synthesis of pterocarine (**2**) and regioisomer **3**. Reagents and conditions: (a) $PhCH_2Br$, K_2CO_3, MeOH, reflux, 4 h, 100%; (b) CH_3CHO, 10% NaOH, EtOH, rt, 3 h, 20%; (c) acetone, 10% NaOH, rt, overnight, 81%; (d) 10% Pd/C, H_2, MeOH, rt, 2 h, 92%; (e) 3-Br-4-$MeOC_6H_3CHO$, 10% NaOH, EtOH, rt, 9.5 h, 52%; (f) 5% Pd/C, H_2, Ph_2S (0.05 equiv), $CHCl_3$, 18 h, 78%; (g) CuO, K_2CO_3, pyridine, 175 °C, 5 h, 54%; (h) $AlCl_3$, CH_2Cl_2, reflux, 25 h, 62%; (i) 4-Br-3-$MeOC_6H_3CHO$, 10% NaOH, EtOH, rt, 3.5 h, 41%; (j) 5% Pd/C, H_2, Ph_2S (0.05 equiv), 18 h, 80%; (k) CuO, K_2CO_3, pyridine, 175 °C, 5 h, 58%; (l) $AlCl_3$, CH_2Cl_2, reflux, 11 h, 42%.

condensation reactions, and selective hydrogenations to generate 1,7-diphenylheptan-3-one variant **18**, followed by the macrocyclic Ullmann condensation and O-demethylation to afford pterocarine (**2**). Accordingly, Claisen–Schmidt condensation of **8** with 4-bromo-3-methoxybenzaldehyde followed by chemoselective reduction, macrocyclization, and demethylation gave the regioisomer **3**.

Macrocyclic compounds **1–3** were fully characterized by mass spectrometry, ^1H and ^{13}C NMR, and 2D HSQC, HMBC, and COSY spectroscopy (See Supplementary data). Their complete ^1H and ^{13}C NMR spectra are shown in Figure 2a–f. The spectroscopic data of our synthetic pterocarine (**2**) were identical with those of the originally reported engelhardione[1] as well as natural and synthetic pterocarine.[9,21] Moreover, on the basis of these spectra, interestingly, we noted that minor structural changes in the substitution patterns at the two aromatic rings result in dramatic differences in their respective NMR spectra. Most notably, for *meta* and *para* connected pterocarine (**2**) and regioisomer **3**, high-field shifts of H-2′ (δ = 5.59 ppm, d, J = 1.7 Hz) of **2** (Fig. 2b) and H-2″ (δ = 5.82 ppm, d, J = 2.0 Hz) of **3** (Fig. 2c) were observed due to the anisotropic effect of the adjacent aromatic rings, as previously reported.[6,7,10] In contrast, the resonances of these aromatic protons H-2′ and H-2″ from the *meta–meta* diaryl ether-linked **1** (Fig. 2a) are at 6.51 and 6.45 ppm with a coupling constant value of 1.9 Hz, respectively. Differences of the chemical shifts of the aliphatic protons of the heptan-3-one chain among **1–3** were also observed (Fig. 2a–c). Our data suggest that these macrocyclic molecules display a high degree of conformational flexibility in solution. Further evidence was demonstrated from the ^1H NMR data of **19**, which was recorded in both non-polar $CDCl_3$ and polar DMSO-d_6 for comparison. We noted that the signals of the geminal protons in the heptyl chain of **19** merged together in DMSO-d_6 compared to those signals recorded in $CDCl_3$, additionally, changes of chemical shifts from the aromatic protons were also observed (See Supplementary data).

In conclusion, we report the first synthesis of engelhardione and this effort led to the structural revision of this macrocyclic natural product.[22] The correct structure of the previously reported engelhardione should be that of pterocarine (**2**). To confirm, **2** and its close regioisomer **3** were also synthesized. The published spectroscopic data of engelhardione were in full agreement with those of pterocarine. Biological studies of these macrocyclic compounds and syntheses of their structural analogs are currently ongoing and will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures for the synthesis of compounds **1–22**, copies of ^1H and ^{13}C NMR spectra, HPLC chromatographs for compounds **1–22**, and HSQC, HMBC, and COSY spectra of macrocyclic compounds **1–3**, **11**, **19**, and **22**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.06.112.

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methanol was used as solvent, the over-reduction of the carbonyl group can be sufficiently suppressed for this reaction.
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22. When we contacted Professor Ih-Sheng Chen for advice regarding the structure revision of engelhardione to pterocarine, we were informed that the incorrect structural elucidation has also been found very recently in his laboratory.