Bio-inspired oxidative phenolic coupling: Total synthesis of the diarylether heptanoid ($\pm$)-pterocarine

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ABSTRACT

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The diaryletherheptanoid natural product, pterocarine, is expeditiously synthesized using a bioinspired intramolecular oxidative phenolic coupling of acerogenin G. The cyclization precursor is prepared from a simple cinnamic acid derivative in three high yielding synthetic operations. The key oxidative coupling is inspired by biosynthetic hypotheses; however, the oxidative coupling proceeds with concomitant hydroxylation of the diphenyl ether motif.

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1. Introduction

The diaryletherheptanoids (DAEHs) are a family of more than two dozen natural products isolated from woody plants (Fig. 1).¹ Their cyclophanic molecular architecture is characterized by a medium sized ring made of a diphenylether and a heptanoid ansa bridge, exemplified by the relatively simple DAEHs acerogenins L (1) and C (2).

Figure 1. Selected diaryletherheptanoid natural products.

Individual DAEH family members are distinguished by a higher oxidation state of the ansa bridge (e.g. 3 and 4) or by alkoxy groups that decorate the diphenylether motif (e.g. 5 and 6). Perhaps the most interesting aspect of the DAEH structure is that some family members (e.g. 5 and 6) are chiral non-racemic molecules that exist in stable enantiomeric conformations that racemize only slowly at high temperatures (e.g. >200 °C).² As a result of these observations, the DAEHs have attracted the attention of several synthetic groups,³ including our own.^{2,4}

DAEH biosynthesis has long been postulated to involve an intramolecular oxidative phenolic coupling of a linear precursor (Scheme 1).^{5,6} Specifically, oxidative coupling of acerogenin G (7) could lead to 1, 2, or to biphenylheptanoid acerogenin E (8). Furthermore, experimental evidence from feeding experiments with isotopically enriched primary metabolites in *Acer nikoense* supports such a cyclization in the biosynthesis of the acerogenins.⁷ Attempts to affect such a cyclization in the laboratory have met little success. Whiting and Wood attempted to oxidize 9 to a biphenyl; however, unexpected byproduct 10 was observed.⁸ Note that in this cyclization, the *para*-substituted phenyl ring of the cyclophane bears fewer oxygen substituents, which is *not* the pattern seen in DAEH natural products such as 5 and 6. To the best of our knowledge, no DAEH has been prepared using an oxidative phenolic coupling of this type.

Scheme 1. Biosynthetic considerations of the acerogenins.

A bio-inspired oxidative coupling reaction would represent an expeditious synthetic strategy to DAEH natural products from relatively simple cyclization substrates. If successful, such a reaction could be used to rapidly prepare DAEH natural products and congeners for subsequent studies (i.e. racemization

measurements, cytotoxicity studies, etc.). We decided to investigate such a cyclization in a relatively uncomplicated DAEH system, and we elected to investigate the cyclization of 7 to 1, 2, or biarylheptanoid 8. We speculated that control of the regio- and chemoselectivity could be possible through judicious choice of the oxidant.

2. Results and Discussion

Preparation of key substrate 7 was accomplished using standard transformations. Cinnamic acid derivative 11 is a known⁹ commercially available molecule that was converted to the corresponding phosphonate (12) following standard conditions.¹⁰ Horner–Wadsworth–Emmons reaction with aldehyde 13 gave dienone 14 in high yield. Reduction of 14 resulted in hydrogenation of both carbon-carbon double bonds and hydrogenolysis of the benzyl ethers to give cyclization substrate 7 in near quantitative yield.

Scheme 2. Synthesis of acerogenin G (7).

Our attempts to realize an oxidative cyclization of 7 began using standard oxidants with literature precedent for similar oxidative transformations of phenols (Table 1). Reagents containing hypervalent iodine (BAIB, PIFA)¹¹ gave no reaction and forcing conditions (i.e. elevated temperatures) led to decomposition. Other oxidants (SeO_2 ,¹² salcomine,¹³ FeCl_3 ¹⁴) did not lead to oxidation of the substrate. Some transition metal oxidants (VOCl_3 ,¹⁵ KMnO_4 ,¹⁶ MnO_2 ,¹⁷ $\text{K}_3\text{Fe}(\text{CN})_6$,¹⁸ and CAN)¹⁹ gave complex mixtures of products that did not contain the desired cyclophanes.

entry	conditions	result / yield
1	$\text{PhI}(\text{OAc})_2$, K_2CO_3 , $\text{CF}_3\text{CH}_2\text{OH}$	no rxn
2	$\text{PhI}(\text{TFA})_2$, K_2CO_3 , $\text{CF}_3\text{CH}_2\text{OH}$	no rxn
3	SeO_2 , K_2CO_3 , dioxane, H_2O	no rxn
4	salcomine (1 equiv), MeOH , DMF	no rxn
5	FeCl_3 , O_2 , Et_2O , Δ	no rxn
6	VOCl_3 , CH_2Cl_2	decomp
7	KMnO_4 , K_2CO_3 , EtOH	decomp
8	$\text{K}_3\text{Fe}(\text{CN})_6$, K_2CO_3 , EtOH	decomp
9	$(\text{NH}_4)_2\text{Ce}(\text{NO}_3)_6$, MeCN	decomp
10	$\text{Pb}(\text{OAc})_4$, CH_2Cl_2	15 (~5%)
11	PbO_2 , HOAc , RT	15 (20%) + 16 (7%) + 7 (40%)

Table 1. Oxidative cyclization of acerogenin G (7).

Encouragingly, use of $\text{Pb}(\text{OAc})_4$ ²⁰ as an oxidant gave trace amounts of cyclophane products that we tentatively assigned as **15**; however, attempts to optimize the transformation with this oxidant were unsuccessful. We next evaluated PbO_2 as a reagent for the oxidative cyclization, as it is an oxidant that has been used for the conversion of phenols to phenoxyl radicals.^{21,22} Gratifyingly, this oxidant affected the oxidation of **7** to **15** and **16**. The reaction is quite clean (no by products) and is moderately high yielding based on recovery of 40% of the starting material.²³ Surprisingly, the cyclization occurs with concomitant oxidative hydroxylation of the diphenylether, and with esterification of a resident phenol, leading to acetyl pterocarane (**15**) and its regioisomer (**16**). The regiochemistry of the reaction was relatively modest, favoring **15** in an approximate 3:1 ratio. Interestingly, the reaction was completely chemoselective, and we found no evidence of formation of any biphenylheptanoid such as **8**.

We know of no other reported oxidative phenolic coupling (inter- or intramolecular) that occurs with concomitant oxidation of the diphenylether motif.²⁴ In the oxidation of **7**, the mechanistic order of oxidation steps is unclear; we did not detect any uncyclized acetoxyated intermediates or any acerogenins (i.e. **1** or **2**) in the product mixture. However, it is possible that once formed, the cyclophane ring strain renders the phenyl group more prone to oxidative hydroxylation. Whether or not such a cyclophane hydroxylation has biosynthetic relevance for hydroxylated or methoxylated DAEHs such as **5** or **6** is unclear.

Scheme 3. Synthesis of (±)-pterocarane (**5**).

With the successful preparation of **15**, we advanced this material to pterocarane (**5**). Separation of **15** and **16** was possible using standard chromatography. Although chemical shift considerations suggested the major product was properly assigned as structure **15**, establishing the structure of **15** and **16** was not straightforward. However, hydrolysis of **15** gave pterocarane (**5**), which we had previously prepared, and the physical and spectral properties of both samples were a complete match. To the best of our knowledge, this represents the first synthesis of a DAEH natural product by a bio-inspired cyclization reaction.

In summary, we have discovered conditions that promote a bio-inspired oxidative cyclization of a simple diarylheptanoid, acerogenin G, to give a diaryletherheptanoid. This cyclization proceeds with concomitant oxidative hydroxylation of the diphenylether group and with esterification of a resident phenol. Saponification of the cyclization product gives pterocarane (**5**).

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