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

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ABSTRACT

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.

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**).

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.

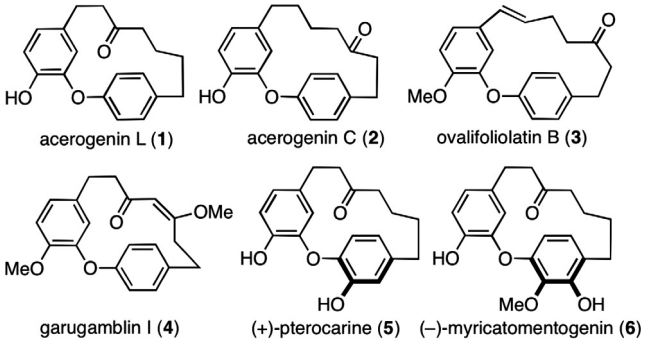

Fig. 1. Selected diaryletherheptanoid natural products.

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

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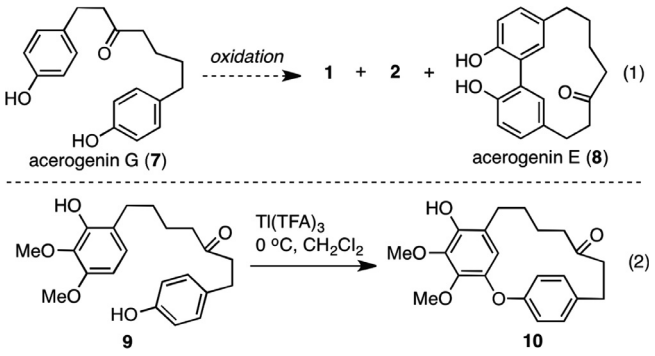
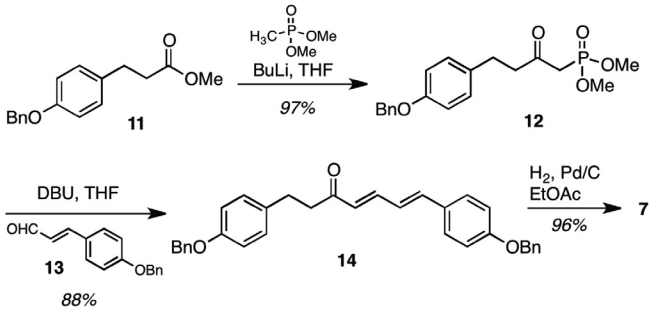


Scheme 1. Biosynthetic considerations of the acerogenins.



Scheme 2. Synthesis of acerogenin G (**7**).

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.

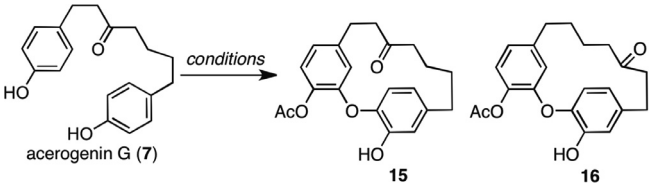
Results and discussion

Preparation of key substrate **7** was accomplished using standard transformations (Scheme 2). Cinnamic acid derivative **11** is a known[9] 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.

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] $K_3Fe(CN)_6$,[18] and CAN[19]) gave complex mixtures of products that did not contain the desired cyclophanes.

Encouragingly, use of $Pb(OAc)_4$[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 pterocarine (**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**.

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

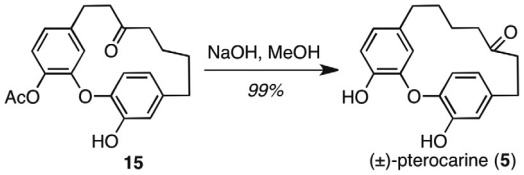


Entry	Conditions	Result/yield (%)
1	$PhI(OAc)_2$, K_2CO_3, CF_3CH_2OH	No rxn
2	$PhI(TFA)_2$, K_2CO_3, CF_3CH_2OH	No rxn
3	SeO_2, K_2CO_3, dioxane, H_2O	No rxn
4	Salcomine (1 equiv.), MeOH, DMF	No rxn
5	$FeCl_3$, O_2, Et_2O, Δ	No rxn
6	$VOCl_3$, CH_2Cl_2	Decomp
7	$KMnO_4$, K_2CO_3, EtOH	Decomp
8	$K_3Fe(CN)_6$, K_2CO_3, EtOH	Decomp
9	$(NH_4)_2Ce(NO_3)_6$, MeCN	Decomp
10	$Pb(OAc)_4$, CH_2Cl_2	**15** (~5%)
11	PbO_2, HOAc	**15** (20%) + **16** (7%) + **7** (40%)

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 acetoxylated 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.

With the successful preparation of **15**, we advanced this material to pterocarine (**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 pterocarine (**5**), which we had previously prepared, and the physical and spectral properties of both samples were a complete match (Scheme 3). 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 pterocarine (**5**).



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

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2017.04.015.

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