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

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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.

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.

Results and discussion

Preparation of key substrate 7 was accomplished using standard transformations (Scheme 2). Cinnamic acid derivative 11 is a known commercially available molecule that was converted to the corresponding phosphonate (12) following standard conditions.10 Horner–Wadsworth–Emmons reaction with aldehyde 13 gave dieneone 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 (SeO₂,12 salcomine,13 FeCl₃(i.e. elevated temperatures) led to decomposition. Other oxidants (K₃Fe(CN)₆,18 and CAN19) gave complex mixtures of products that did not contain the desired cyclophanes. 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 hydroylation 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 biarylheptanoid 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.

Table 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result/yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph(OAc)₃, K₂CO₃, CF₃CH₂OH</td>
<td>No rxn</td>
</tr>
<tr>
<td>2</td>
<td>Ph(TFA)₃, K₂CO₃, CF₃CH₂OH</td>
<td>No rxn</td>
</tr>
<tr>
<td>3</td>
<td>SeO₂, K₂CO₃, dioxane, H₂O</td>
<td>No rxn</td>
</tr>
<tr>
<td>4</td>
<td>Salcomine (1 equiv.), MeOH, DMF</td>
<td>No rxn</td>
</tr>
<tr>
<td>5</td>
<td>FeCl₃, O₂, Et₂O, Δ</td>
<td>No rxn</td>
</tr>
<tr>
<td>6</td>
<td>VOCl₃, CH₂Cl₂</td>
<td>Decomp</td>
</tr>
<tr>
<td>7</td>
<td>KMnO₄, K₂CO₃, EtoH</td>
<td>Decomp</td>
</tr>
<tr>
<td>8</td>
<td>K₃Fe(CN)₆, K₂CO₃, EtoH</td>
<td>Decomp</td>
</tr>
<tr>
<td>9</td>
<td>(NH₄)₂Ce(NO₃)₆, MeCN</td>
<td>Decomp</td>
</tr>
<tr>
<td>10</td>
<td>Pb(OAc)₃, CH₂Cl₂</td>
<td>15 (7%) + 16 (20%)</td>
</tr>
<tr>
<td>11</td>
<td>PbO₂, HOAc</td>
<td>15 (20%) + 16 (7%) + 7 (40%)</td>
</tr>
</tbody>
</table>

Scheme 1. Biosynthetic considerations of the acerogenins.

Scheme 2. Synthesis of acerogenin G (7).

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

Scheme 4. Synthesis of (±)-pterocarine (5).
Acknowledgment

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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.

References and notes


22. PhO2 has been used for oxidation of phenols to quinones. See: Omura K. Synthesis. 1998;1145–1148.

23. Attempts to isolate the remainder of the mass balance of the reaction were unsuccessful.