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A Biomimetic Synthesis Elucidates the Origin of Preisolactone A

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Abstract

A short, biomimetic synthesis of the fungal metabolite preisolactone A is described. Its key steps are a purpurogallin-type (5+2)-cycloaddition, followed by fragmentation, vinylogous aldol addition, oxidative lactonization and a final benzilic acid rearrangement. Our work explains why preisolactone A has been isolated as a racemate and suggests that the natural product is not a sesquiterpene but a phenolic polyketide.

Graphical Abstract

Natural products that feature multiple stereocenters and complex molecular topologies, yet occur as racemates, hold a special fascination to chemists. A surprisingly large number of such compounds has been isolated from almost all realms of Nature (Fig. 1). Classic examples are carpanone¹ and the endiandric acids,² whereas more recent members of this category include kingianin A,³ santalin Y,⁴ epicolactone,^{5,6} incarvilleatone,⁷ rubioncolin B,⁸ nitramine,⁹ and paraseolide A.¹⁰

Natural racemates can stem from compounds that were initially formed asymmetrically and then gradually undergo racemization.¹¹ Alternatively, they can result from reactions that do not require enzymatic catalysis and involve achiral precursors, such as electrocyclizations

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

CIF file for compound **12** (Deposition Number 1946496).

Experimental procedures, spectroscopic data and copies of NMR-spectra. The CIF files are also available free from charge on <https://www.ccdc.cam.ac.uk/structures/>.

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and cycloadditions. Incorporation of these reactions into cascades can further increase the stereochemical complexity of the racemates. Indeed, cascades have been implicated in all of the natural products shown in Fig. 1 and have been validated through biomimetic total synthesis in each case.^{12–22}

Preisolactone A is another racemic natural product which was recently isolated from the endophytic fungus *Preussia isomera*.²³ The caged compound has a very attractive molecular structure marked by a tricyclo[4.4.0^{1,6}.0^{2,8}]decane skeleton which contains seven adjacent stereocenters, two of which are quaternary. It also features two butyrolactones, a vinylogous methyl ester, and a tertiary alcohol. Preisolactone A showed activity against the gram-positive bacterium *Micrococcus luteus*, with an MIC value of 10.2 μ M, but was inactive against human cancer cell lines.

Biosynthetically, preisolactone A was proposed to stem from farnesyl pyrophosphate via a complex pathway that involves a terpene cyclase and several oxidative editing steps. This scenario seemed implausible to us since it implies that several enzymatic hydroxylations and other oxidative transformations occur with equal efficiency on both enantiomers in a series of intermediates. Although terpene cyclases that generate either enantiomer are well-documented,^{24–26} such parallel oxidative pathways have never been demonstrated, to the best of our knowledge, within the same organism.

We now present an alternative biosynthetic hypothesis and provide experimental evidence to support it. It states that preisolactone A is not a terpenoid, but a polyketide and is formed through oxidative dimerization of catechol **1** with pyrogallol **2** (Scheme 1). The latter is a known fungal metabolite that is biosynthetically formed via decarboxylation and oxidation of orsellinic acid.²⁷ Although this parentage has not been proven for catechol **1**, it is likely that **1** also stems from this archetypical polyketide. Oxidation of **1** and **2** yields *o*-quinone **3** and hydroxy-*o*-quinone **4**, respectively, which undergo a (5+2) cycloaddition to furnish tricyclic intermediate **5**. Reactions of this type are well-precedented in the chemistry of benzotropolones²⁸ and have recently found an application in our biomimetic total synthesis of epicolactone.¹⁷ They have also been implicated in the biosynthesis of the merocytochalasans. Attack of water onto the carbonyl bridge of **5**, followed by a retro-Dieckmann type fragmentation yields ene-dione **6**, which is normally prone to further oxidation and tautomerization. Intermediate **6**, however, bears a quaternary carbon, cannot aromatize, and rather undergoes a vinylogous aldol addition. The resulting tricyclic diosphenol **7** engages in an oxidative lactonization, possibly through an oxa-Michael reaction or a Prins-type mechanism. Oxidation of the resultant ene-diol **8** then affords diketolactone **9**, which cannot enolize due to ring strain. In the final key step of the cascade, **9** undergoes a benzylic acid type rearrangement with ring-contraction via oxetane **10** to simultaneously form one of the butyrolactones and the adjacent tertiary alcohol of preisolactone A.

To provide support for this hypothesis, we decided to probe it with a biomimetic synthesis (Scheme 2). It started with the known²⁹ resorcinol ether **11**, which underwent Dakin-oxidation to afford the catechol **1**. Incubation of **1** with the known³⁰ symmetric pyrogallol **2** in the presence of potassium ferricyanide triggered the first phase of the cascade and gave a

mixture of interconverting isomers that presumably contain the diosphenol **7**, its 1,2-diketo form, and the acetal **12**. From this mixture, we were able to obtain single crystals of **12** suitable for X-ray analysis. The X-ray structure of **12** is shown in Fig. 2. The presence of **7** was supported by treatment of the mixture with potassium carbonate and methyl iodide and isolation of the methyl ester and methyl enol ether **14** (Scheme 2, bottom). We also found that the ratio of **7** to **12** could be transiently altered in favor of **7** by treatment with aqueous base followed by acidification (see Supporting Information).

In the second phase of our synthesis, we used Koser's reagent to oxidize **7**.³¹ This presumably led to the formation of a lactone via activation of the enolized 1,2-diketone as iodine(III)-species **13**. The resultant product **9**, however, was not isolated since it underwent the proposed benzilic acid rearrangement upon workup with aqueous phosphate buffer (pH = 8). This afforded preisolactone A in 57% overall yield from the mixture of **7** and **12**. Our synthetic material was identical in all respects with the natural product (see Supporting Information).

Attempts to carry out both oxidative cascades in one step under a variety of conditions have failed so far. For instance, exposure of **7** and **12** to horse radish peroxidase and hydrogen peroxide,³⁰ or air, failed to produce noticeable amounts of preisolactone A. This raises the interesting question which oxidant is used in Nature and whether a dedicated oxidizing enzyme is required for each phase of the pathway.

In conclusion, we have developed a short biomimetic synthesis that creates a complex, polycyclic natural product in three oxidative steps. Its initial phase resembles the epicolactone/purpurogallin cascade, whereas the endgame involves oxidative lactonization, followed by a ring contraction through a benzilic acid-type rearrangement. Our work demonstrates, once again, that biomimetic synthesis can contribute to the elucidation of biosynthetic pathways as it strongly suggests that preisolactone A is a polyketide. Based on our results, it seems likely that catechol **1**, pyrogallol **2**, and perhaps acetal **12** can be isolated from *Preussia isomera* as well. We believe that many caged compounds resembling preisolactone A and epicolactone will be identified as natural products in the future. Pyrogallols and catechols abound in nature and many have substitution patterns that would prevent rearomatization to flat, purpurogallin-like colorants, such as the theaflavins.³² The systematic exploitation of this chemistry to produce molecules with precisely positioned functional groups and the biological evaluation of these molecules is currently under active investigation in our laboratory. The oxidative lactonization of diosphenols, which – to the best of our knowledge – is not a known reaction, will also be studied in more detail.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1:
Complex natural products that occur as racemates.

Figure 2:
X-ray structure of isomer **12**.

Scheme 1:
Proposed biosynthetic origin of preisolactone A.

Scheme 2:
Biomimetic synthesis of preisolactone A.