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Concise Formal Synthesis of the Pseudopterins via Anionic Oxy-Cope/Transannular Michael Addition Cascade

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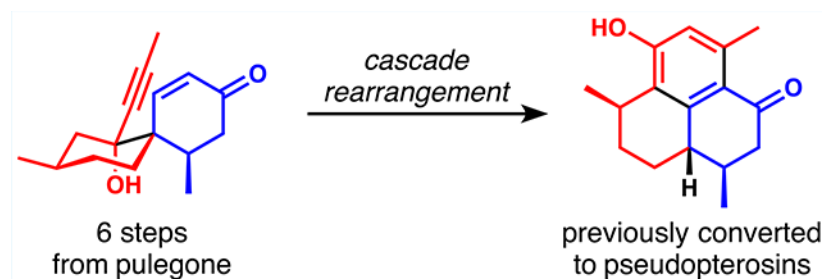
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Abstract

An anionic oxy-Cope/transannular Michael addition cascade converts a spirocyclic architecture—readily available by Diels–Alder cycloaddition—into the hydrophenalene carbon skeleton of the pseudopterins aglycons. Oxidation of the resulting cyclohexenone ring to the catechol that is characteristic of the targets completes a short formal synthesis.

Graphical Abstract



The pseudopterins family of diterpenoid glycosides includes over 30 members.^{1,2} Their diversity arises from only three stereoisomeric aglycons and the identity of the sugar attached via the C9 or C10 phenolic oxygen (Figure 1). These secondary metabolites have been of significant interest to the scientific community since the initial discovery of pseudopterins A–D in 1986,³ due in part to their structures and especially to their wide

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Supporting Information

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Experimental protocols for the preparation of, and characterization data for, all new compounds (PDF)

Accession Codes

CCDC 1982473–1982478 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

range of biological activities. Members of the pseudopterosin family show anticancer,⁴ antimalarial,⁵ antibacterial,⁵ and anti-inflammatory⁶ properties. For example, pseudopterosin A (**1**) is a significantly more potent anti-inflammatory and analgesic agent than the clinically used indomethacin.^{3,6} These natural products are still under active investigation, and recent studies have found new anticancer^{7,8} and neuroprotective properties,^{9,10} while an extract containing pseudopterosins is a key component in Resilience, Estee Lauder's cosmetic skin care product.¹¹

The pseudopterosins have been targeted by many synthetic chemists over the past 30 years, resulting in a large body of work on their total synthesis and the preparation of their aglycons, starting with the first synthesis of pseudopterosin A by Broka in 1988.¹² As clearly articulated by Sherburn in the 2015 report of his group's outstanding synthesis,¹³ all of the syntheses that preceded theirs were based on "structure-goal strategies".¹⁴ These syntheses start from commercially available terpene or aromatic building blocks that overlap with a portion of the tricyclic scaffold; the target is synthesized by sequential chain elongations and ring closures.² On the other hand, the synthesis by Sherburn¹³ and a later one by Luo¹⁵ are transformation-based, focusing on the Diels–Alder reaction and the Cope rearrangement, respectively. These approaches allow for a quick increase in molecular complexity, in both cases ultimately arriving at the target aglycons in fewer than a dozen steps. In this communication, we report a formal synthesis of the pseudopterosins that starts from the chiralpool precursor pulegone, but whose carbocyclic ring is not featured in the final product.

Our research group has been involved in the synthesis of isocyanoterpenes for several years.^{16–19} One of our early, but unsuccessful, approaches to the flagship member 7,20-diisocyanoadociane (DICA, **5**) was predicated on the cascade reaction shown in Scheme 1A. ¹⁶ anionic oxy-Cope/transannular Michael addition sequence was reported by Swaminathan and co-workers, who indicated that this reaction type provided the all-*trans*, all-chair arrangement of hydro-phenalene-type products (**6** to **7**).^{20,21} During our efforts to apply this interesting spiro-to-fused scaffold interchange to DICA, we noted that the stereochemical outcome was not as originally reported, and we offered a stereochemical revision of the product of this otherwise highly productive rearrangement to diastereomer **8**.^{16,22}

While of no service to a synthesis of DICA, we noted that the hydrophenalene scaffold that results from the Swaminathan rearrangement is well-represented in terpenoid natural products and considered featuring this chemistry in an approach to the pseudopterosins (Scheme 1B). Phenol **9** and its enantiomer are known precursors of the pseudopterosin aglycons.²³ **9** can be generated by oxidation of cyclohexenone **10**,²⁴ which is the projected product of the anionic oxy-Cope/transannular Michael addition cascade of spirocyclic yne/enone **11**. The attractiveness of this route rests in the rapid access to spirocycle **11**. In this communication, we demonstrate the feasibility of this approach with a short formal synthesis of the pseudopterosins starting from pulegone.

Scheme 2 describes the conversion of 3-methylcyclohexanone to the late-stage pseudopterosin aglycon intermediate **9** in only seven steps. Aldol condensation of **12** with acetaldehyde under carefully optimized conditions²⁵ provides **13**, the dienophile for the

subsequent Diels–Alder reaction. SnCl₄-catalyzed cycloaddition with 2-triethylsilyloxybutadiene forms the spirocyclic products in high yields, favoring the desired diastereomer **15** (2:1 dr). Significant attempts were made to bias the diastereoselectivity further; while it was possible to increase the **15:14** ratio with the application of chiral Lewis acids, the efficiency of these reactions was low. Fortunately, the diastereomers can easily be separated at this stage. Oxidation of the desired silyl enol ether to enone **16** proceeds smoothly. Attempts to selectively add propynyl organometallic reagents to the ketone over the enone were unsuccessful, so the enone was transiently protected as its cross-conjugated silyl enol ether. Propynylmagnesium bromide then adds cleanly to provide **11** with a diastereoselectivity of 5.8:1 (major isomer shown, minor isomer characterized by X-ray crystallography) after the silyl enol ether is removed in the workup.²⁶ In our previous efforts toward DICA, we showed that both diastereomers at the alcohol undergo the oxy-Cope rearrangement to give the same product,¹⁶ and that proved true in this case as well.

With propargylic alcohol **11** in hand, we investigated the critical anionic oxy-Cope/transannular Michael cascade. Initial attempts to effect a one-pot transformation of **11** to tricyclic products via the full cascade resulted in decomposition. Therefore, we examined a stepwise version of the process (Scheme 3). Anionic oxy-Cope rearrangement of the diastereomeric mixture of alcohols **11** induced with KH at low temperature gives the bicyclo[7.3.1] system **19** in nearly quantitative yield as a single diastereomer.²⁷ Investigation of the double-bond isomerization and transannular Michael addition steps eventually led to clean isomerization using DBU in carefully degassed THF to give **20**, which unfortunately has the undesired configuration at C4. Without careful removal of oxygen, oxygenated products such as **21** and **22** were observed during attempted transannular bond formation; they presumably arise in part from strain-induced reactivity of the various conjugate base forms of **19**. Treatment of **20** with methanolic base led to efficient transannular ring closure to give **17**; however, this product retains the undesired configuration at C4.^{28,29} Adapting the knowledge gained from the stepwise rearrangement studies, we were able to induce formation of the desired compound **18** in a one-pot process by treating alcohol **11** with potassium methoxide at 85 °C in DMF for a short time (Scheme 2). This procedure affords the desired tricyclic core in good yield, slightly favoring the undesired diastereomer (**17** again) at C4 (1:1.5 dr). Further attempts to bias the selectivity toward the desired stereoisomer were unsuccessful; however, the reaction is noteworthy for forming only two diastereomers of a possible 16.³⁰ The cascade reaction is subject to fluctuations in the isolated product yield because competitive decomposition of the products occurs under the reaction conditions. Finally, oxidation of the enone to the phenol completes a very brief formal synthesis of the pseudopterosins.²⁴ This approach shortens the synthesis of phenol **9** to eight steps (from 13 steps by Corey³¹). Conversion of the phenol to the pseudopterosin aglycon can be achieved in seven further steps, and therefore, a total synthesis using this approach would be only slightly longer than those reported by Sherburn¹³ and Luo.¹⁵

We also investigated the reactivity of **14**, the minor diastereomeric product of the Diels–Alder reaction (Scheme 4). Addition of propynylmagnesium bromide followed by IBX oxidation provided the cascade precursor **23**.³² In contrast to the reaction of the desired diastereomer **11**, the one-pot anionic oxy-Cope/transannular Michael cascade of **23** proceeds

quickly and in nearly quantitative yield at 0 °C, giving a single diastereomer of tricyclic cascade product **24**, which bears the desired C3/C4 vicinal relationship. Oxidation of **24** affords phenol **25**. In principle, the C7 stereogenic center might be equilibrated to the natural pseudopterosin configuration via *o*-quinone methide intermediates, though we have not investigated this possibility by experiment.

In conclusion, we have developed a concise formal synthesis of the pseudopterosins using a transformation-based approach. We have demonstrated that the key anionic oxy-Cope/transannular Michael cascade can be both efficient and remarkably selective and therefore might prove useful in the stereocontrolled synthesis of other polycyclic natural products. Although selectivity in the key step was not quite in our favor, the related case of substrate **23** is highly efficient and perfectly stereoselective. These results frame the need for further investigations into the impact of the structural features and reaction conditions on the diastereoselectivity of this cascade rearrangement. Overall, as a result of the rapid synthesis of the spirocyclic cascade precursor and the efficiency of the key step, our synthesis competes favorably with much of the work on the pseudopterosins that has gone before.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

■ ACKNOWLEDGMENTS

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 - (28). The relative configuration of 17 could not be ascertained; however, the configuration at C4 was determined by structural analysis of its oxidation product to a phenol that was epimeric to 9 at C4.
 - (29). Of course, the transannular Michael addition of 20 could equally be characterized as a 6π - electrocyclic ring closure.
 - (30). In principle, the undesired diastereomer 17 could be salvaged for a synthesis of the target molecules. Oxidation to the phenol and epimerization of C4, which is activated by the o-ketone,

could provide the desired relative configuration. Initial attempts to do so were unsuccessful, likely because deprotonation of the phenol greatly reduces the acidity of the C4 proton.

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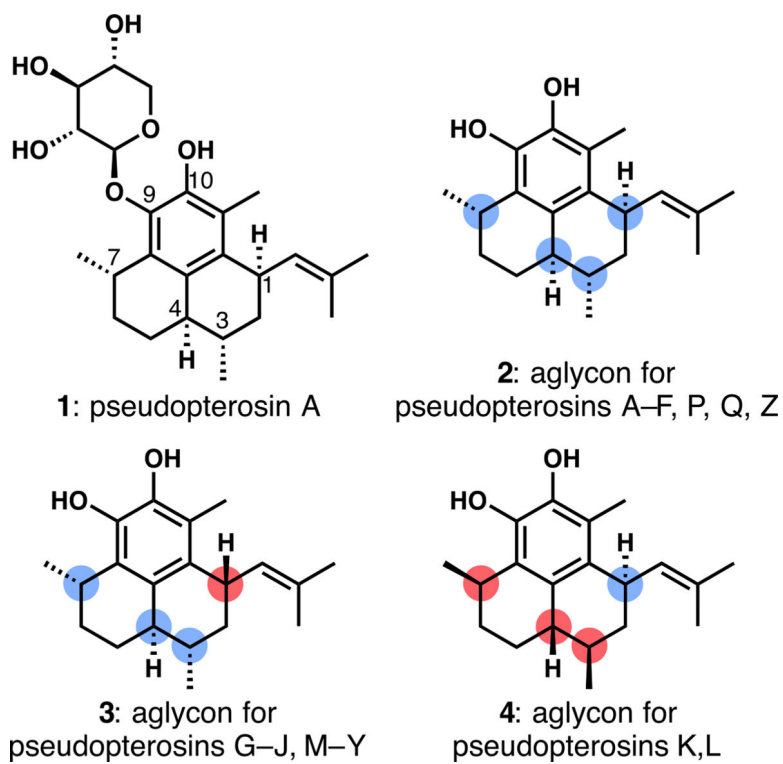
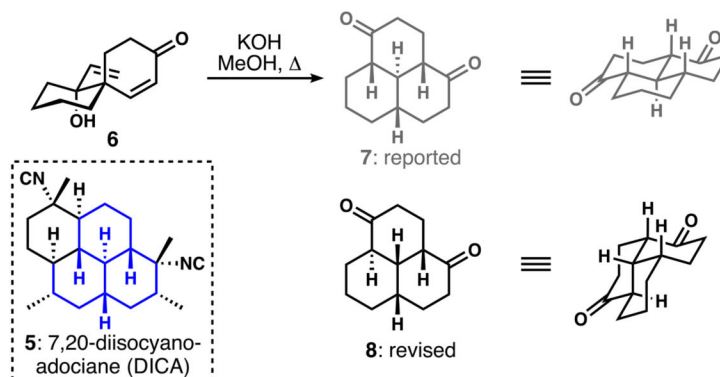
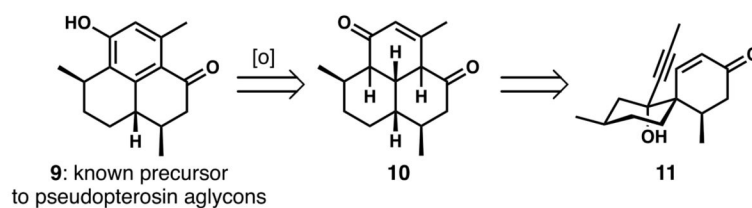


Figure 1. Structures of pseudopterosin A and the three stereoisomeric pseudopterosin aglycons.

A. Reported anionic oxy-Cope/transannular Michael addition cascade and structure revision that resulted from our attempts to apply it to DICA

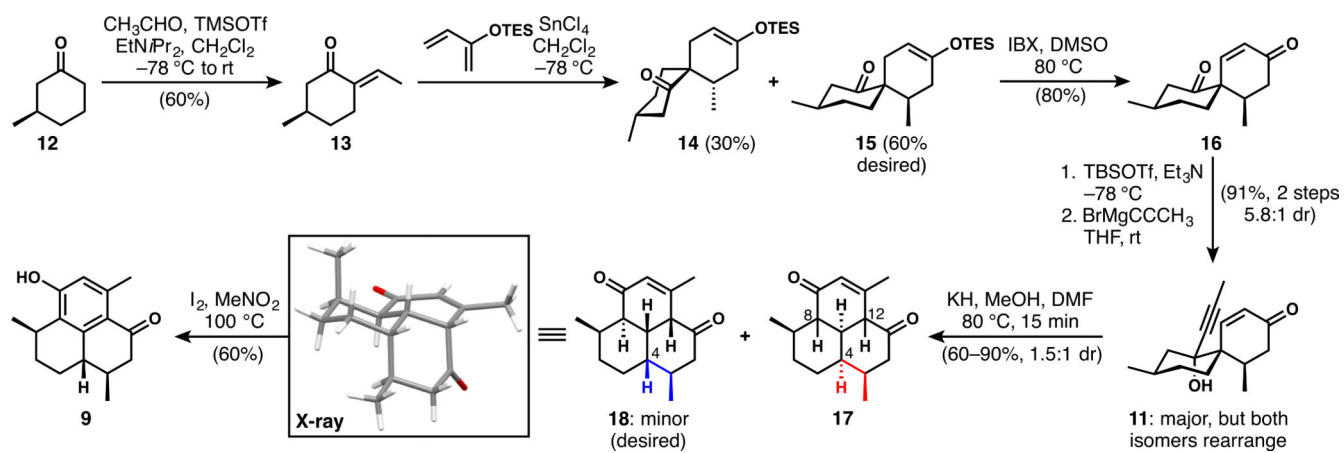


B. Anionic oxy-Cope/transannular Michael addition cascade application to the pseudopterosin substructure

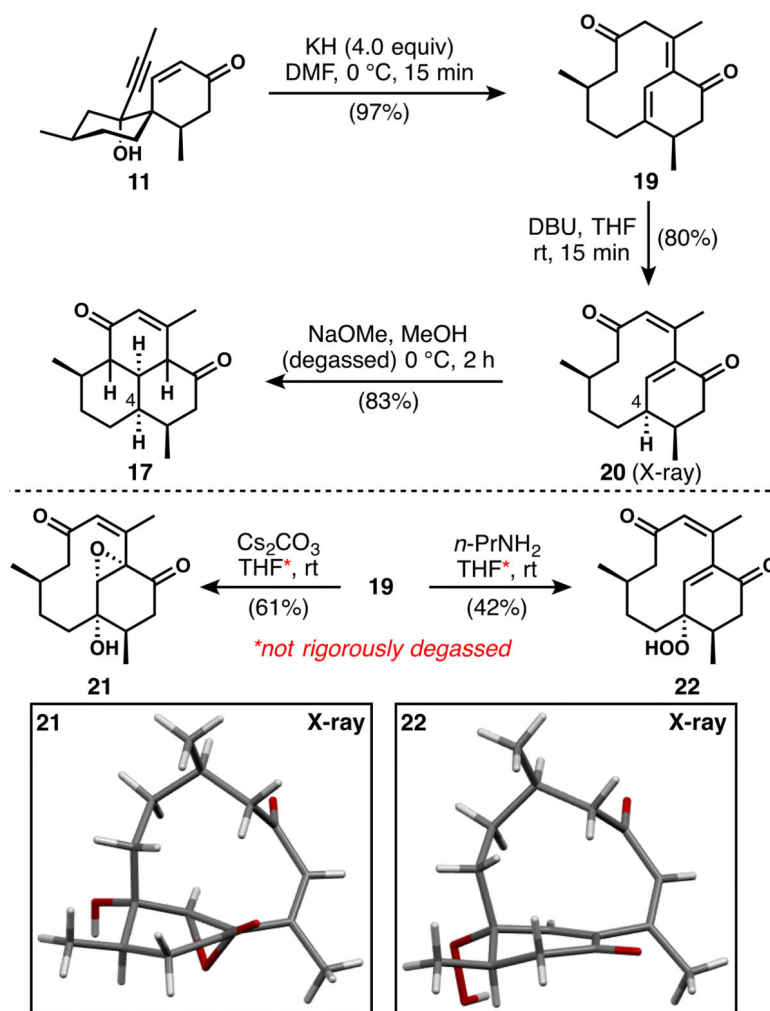


Scheme 1.

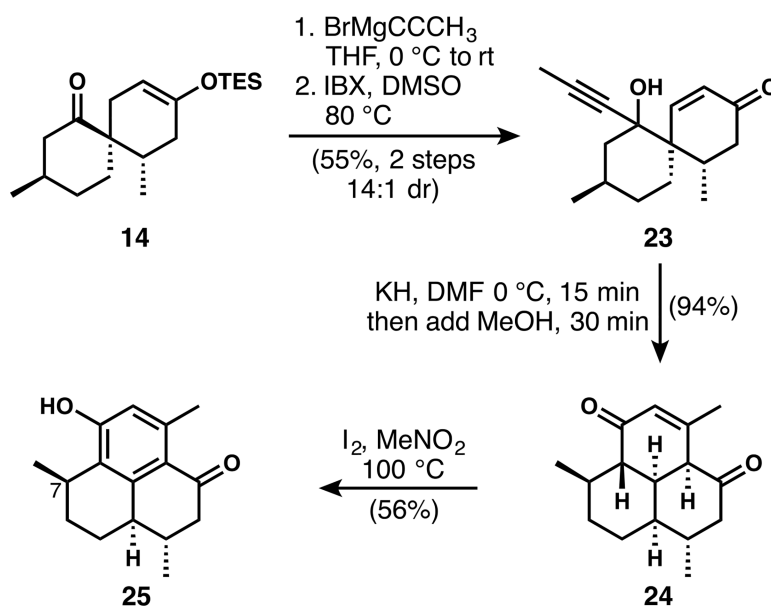
(A) Anionic Oxy-Cope/Transannular Michael Addition Cascade as Initially Reported by Swaminathan²⁰ and the Revised Structure; (B) Strategic Application of the Cascade Reaction for a Formal Synthesis of the Pseudopterosins



Scheme 2.
Formal Synthesis of the Pseudopterosins



Scheme 3.
 Results of Attempted Stepwise Protocols for the Anionic Oxy-Cope/Transannular Michael Process



Scheme 4.
Reactivity of Diels–Alder Side Product 14