HHS Public Access

Author manuscript

Org Lett. Author manuscript; available in PMC 2021 April 17.

Published in final edited form as:

Org Lett. 2020 April 17; 22(8): 2883–2886. doi:10.1021/acs.orglett.0c00486.

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

Vincenzo Ramella,
Department of Chemistry, University of California, Irvine, California 92697-2025, United States

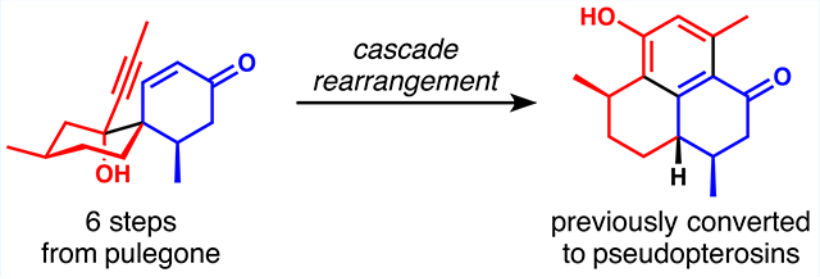
Philipp C. Roosen,
Department of Chemistry, University of California, Irvine, California 92697-2025, United States

Christopher D. Vanderwal
Department of Chemistry and Department of Pharmaceutical Sciences, University of California, Irvine, California 92697-2025, United States

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 pseudopterosin aglycones. Oxidation of the resulting cyclohexenone ring to the catechol that is characteristic of the targets completes a short formal synthesis.

Graphical Abstarct



T he pseudopterosin 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 pseudopter-osins A–D in 1986,[3] due in part to their structures and especially to their wide

Corresponding Author: Christopher D. Vanderwal cdv@uci.edu.

The authors declare no competing financial interest.

■ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00486.
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-inflammatory[6] 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 Sherburn[13] and a later one by Luo[15] 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 conditions[25] provides **13**, the dienophile for the

subsequent Diels–Alder reaction. $SnCl_4$-catalyzed cycloaddition with 2-triethylsilyloxybutadiene forms the spirocyclic products in high yields, favoring the desired diasteromer **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 Corey[31]). 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 Sherburn[13] 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

This work was funded by a DFG fellowship (RA 3139/1–1; 1–2 to V.R.) and the NIH (AI-138139 to C.D.V.). We thank Dr. Joe Ziller for expert assistance with X-ray crystallographic structure determination.

■ REFERENCES

(1). Berrué F; McCulloch MWB; Kerr RG Marine Diterpene Glycosides. Bioorg. Med. Chem. 2011, 19, 6702–6719. [PubMed: 21783368]

(2). Newton CG; Sherburn MS Total Synthesis of the Pseudopterosin Aglycones. Nat. Prod. Rep. 2015, 32, 865–876. [PubMed: 25882677]

(3). Look SA; Fenical W; Matsumoto GK; Clardy J The Pseudopterosins: A New Class of Antiinflammatory and Analgesic Diterpene Pentosides from the Marine Sea Whip Pseudopterogorgia Elisabethae (Octocorallia). J. Org. Chem. 1986, 51, 5140–5145.

(4). Rodríguez II; Shi Y-P; García OJ; Rodríguez AD; Mayer AMS; Sánchez JA; Ortega-Barria E; González J New Pseudopterosin and Seco-Pseudopterosin Diterpene Glycosides from Two Colombian Isolates of Pseudopterogorgia Elisabethae and Their Diverse Biological Activities. J. Nat. Prod. 2004, 67, 1672–1680. [PubMed: 15497938]

(5). Ata A; Win HY; Holt D; Holloway P; Segstro EP; Jayatilake GS New Antibacterial Diterpenes from Pseudopter- ogorgia Elisabethae. Helv. Chim. Acta 2004, 87, 1090–1098.

(6). Look SA; Fenical W; Jacobs RS; Clardy J The Pseudopterosins: Anti-Inflammatory and Analgesic Natural Products from the Sea Whip Pseudopterogorgia Elisabethae. Proc. Natl. Acad. Sci. U. S. A. 1986, 83, 6238–6240. [PubMed: 2875457]

(7). Sperlich J; Teusch N Pseudopterosin Inhibits Proliferation and 3D Invasion in Triple-Negative Breast Cancer by Agonizing Glucocorticoid Receptor Alpha. Molecules 2018, 23, 1992.

(8). Sperlich J; Kerr R; Teusch N The Marine Natural Product Pseudopterosin Blocks Cytokine Release of Triple-Negative Breast Cancer and Monocytic Leukemia Cells by Inhibiting NF-κB Signaling. Mar. Drugs 2017, 15, 262.

(9). Niu X; Yu C; Jiang G; Wu J; Tan X; Zhang W; Hou L Pseudopterosin A Ameliorates Ischaemia-Induced Brain Injury by Acting on Akt Signalling Pathway. Folia Neuropathol. 2018, 56, 104–111. [PubMed: 30509030]

(10). Caplan LS; Zheng B; Dawson-Scully K; White AC; West ML Pseudopterosin A: Protection of Synaptic Function and Potential as a Neuromodulatory Agent. Mar. Drugs 2016, 14, 55.

(11). Kijjoa A; Sawangwong P Drugs and Cosmetics from the Sea. Mar. Drugs 2004, 2, 73–82.

(12). Broka CA; Chan S; Peterson B Total Synthesis of (−)-Pseudopterosin A. J. Org. Chem. 1988, 53, 1584–1586.

(13). Newton CG; Drew SL; Lawrence AL; Willis AC; Paddon-Row MN; Sherburn MS Pseudopterosin Synthesis from a Chiral Cross-Conjugated Hydrocarbon through a Series of Cycloadditions. Nat. Chem. 2015, 7, 82–86. [PubMed: 25515894]

(14). Corey EJ Retrosynthetic Thinking—Essentials and Examples. Chem. Soc. Rev. 1988, 17, 111–133.

(15). Yu X; Su F; Liu C; Yuan H; Zhao S; Zhou Z; Quan T; Luo T Enantioselective Total Syntheses of Various Amphilectane and Serrulatane Diterpenoids via Cope Rearrangements. J. Am. Chem. Soc. 2016, 138, 6261–6270. [PubMed: 27115064]

(16). Roosen PC; Vanderwal CD Investigations into an Anionic Oxy-Cope/Transannular Conjugate Addition Approach to 7,20-Diisocyanoadociane. Org. Lett. 2014, 16, 4368–4371. [PubMed: 25105694]

(17). Daub ME; Prudhomme J; Le Roch K; Vanderwal CD Synthesis and Potent Antimalarial Activity of Kalihinol B. J. Am. Chem. Soc. 2015, 137, 4912–4915. [PubMed: 25815413]

(18). Roosen PC; Vanderwal CD A Formal Enantiospecific Synthesis of 7,20-Diisocyanoadociane. Angew. Chem., Int. Ed. 2016, 55, 7180–7183.

(19). Karns AS; Ellis BD; Roosen PC; Chahine Z; Le Roch KG; Vanderwal CD Concise Synthesis of the Antiplasmodial Isocyanoterpene 7,20-Diisocyanoadociane. Angew. Chem., Int. Ed. 2019, 58, 13749–13752.

(20). Rao CSS; Kumar G; Rajagopalan K; Swaminathan S Base Catalysed Rearrangement of a Spiro Oxy-Cope System and Related Studies: A New Entry into Perhydrophenalene and Perhydroacenaphthylene Systems. Tetrahedron 1982, 38, 2195–2199.

(21). Ravikumar VT; Rajagopalan K; Swaminathan S Anionic Oxycope Rearrangements in Acetylenic Spiro Systems. Tetrahedron Lett. 1985, 26, 6137–6138.

(22). Although 8 was the major diastereomer of this reaction, a minor stereoisomer was also observed, but no evidence of 7 was seen.

(23). Corey EJ; Carpino P Enantiospecific Total Synthesis of Pseudopterosins A and E. J. Am. Chem. Soc. 1989, 111, 5472–5474.

(24). Yadav JS; Bhasker EV; Srihari P Synthesis of a key intermediate for the total synthesis of pseudopteroxazole. Tetrahedron 2010, 66, 1997–2004.

(25). See the Supporting Information for details.

(26). The more direct CeCl3-mediated addition of Grignard reagent to 15 was successful, although after oxidation with IBX, the overall yield of this two-step protocol is significantly lower. Intriguingly, in that situation the diastereoselectivity for the 1,2-addition switches, favoring the other diastereomer than that formed via the three-step sequence shown.

(27). (a)Shanmugam P; Devan B; Srinivasan R; Rajagopalan K Studies in bromoacetylenic oxy-Cope rearrangement: Synthesis of functionalised medium-size, bicyclic and angularly fused tricyclic compounds. Tetrahedron 1997, 53, 12637–12650.(b)Thornton PD; Cameron TS; Burnell DJ Vinylogous anionic processes in the formation and interconversion of tetracyclic ring systems. Org. Biomol. Chem. 2011, 9, 3447–3456. [PubMed: 21424007]

(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.

(31). Corey E; Carpino P A New Enantiospecific Route to the Pseudopterosins. Tetrahedron Lett. 1990, 31, 3857–3858.

(32). The configuration of the propargylic carbinol stereogenic center could not be ascertained spectroscopically.

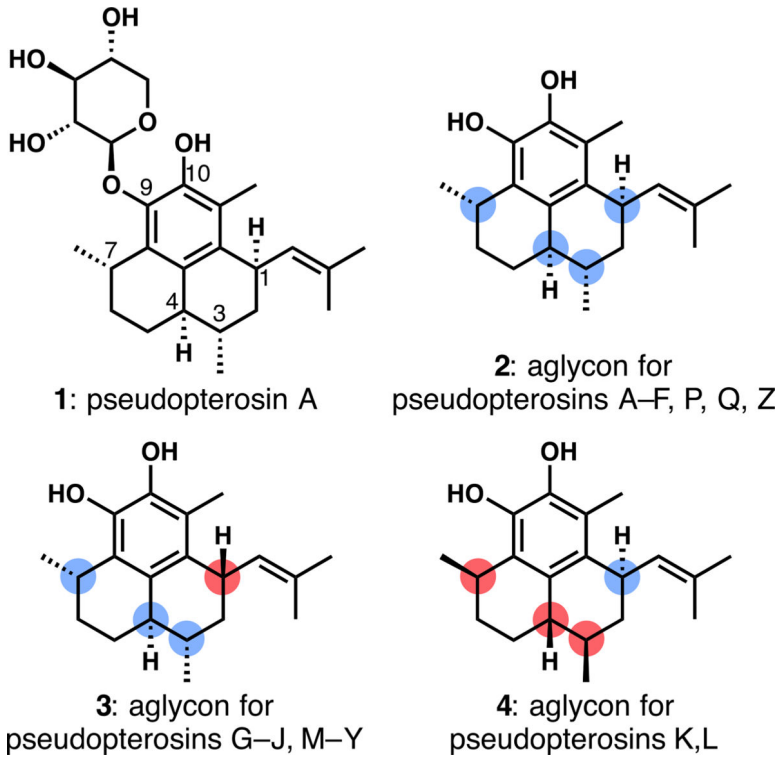
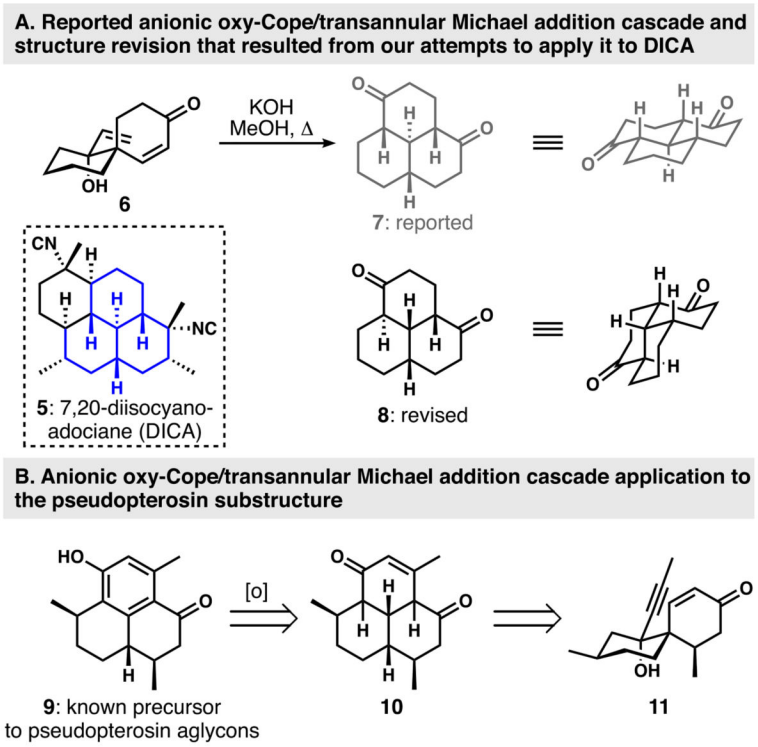
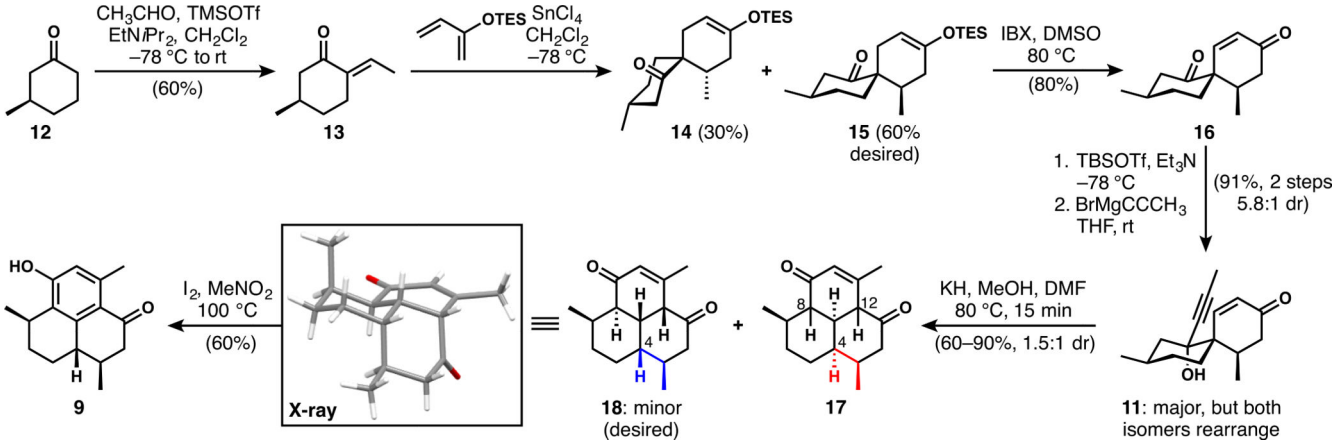


Figure 1.
Structures of pseudopterosin A and the three stereoisomeric pseudopterosin aglycons.

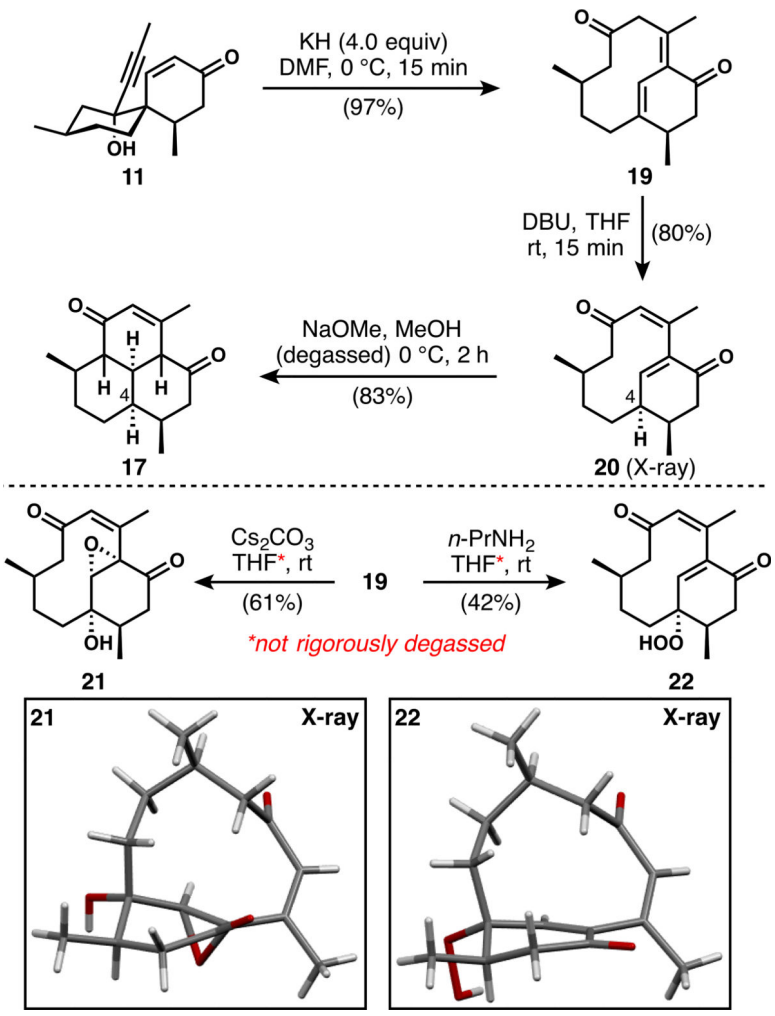


Scheme 1.

(A) Anionic Oxy-Cope/Transannular Michael Addition Cascade as Initially Reported by Swaminathan[20] and the Revised Structure; (B) Strategic Application of the Cascade Reaction for a Formal Synthesis of the Pseudopterosins

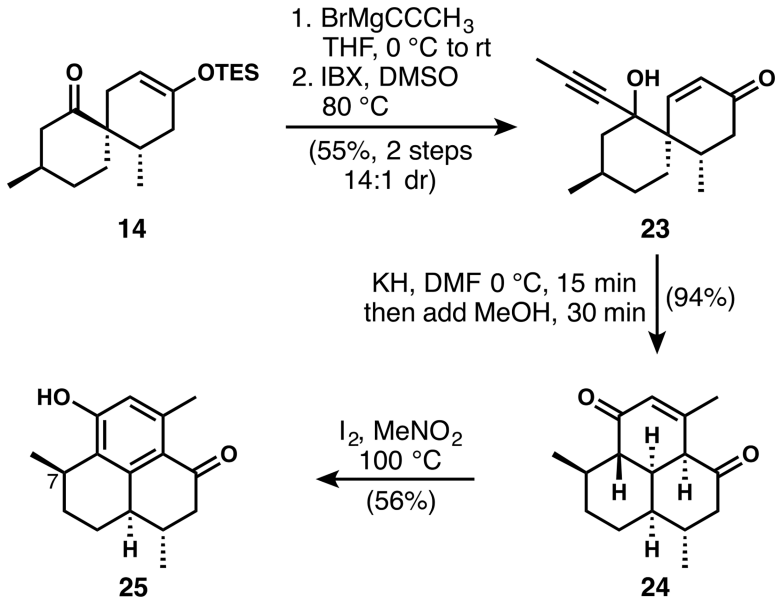


Scheme 2.
Formal Synthesis of the Pseudopterosins



Scheme 3.

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



Scheme 4.
Reactivity of Diels–Alder Side Product 14