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Communication

Concise Synthesis of 9,11-Secosteroids Pinnigorgiols B and E

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ABSTRACT: Pinnigorgiols B and E are 9,11-secosteroids with a unique tricyclic γ-diketone framework. Herein, we report the first synthesis of these natural products from inexpensive, commercially available ergosterol. This synthesis features a semipinacol rearrangement and an acyl radical cyclization/hemiketalization cascade; the latter efficiently assembled the tricyclic γ-diketone skeleton, with two rings and three contiguous stereogenic centers being formed in a single step.

Rearranged steroid natural products, including secosteroids (in which at least one ring is cleaved) and *abeo*-steroids (in which there is at least one migrated C−C bond within the classic tetracyclic framework), have recently received considerable attention from synthetic chemists owing to the structural diversity and biological importance of these compounds.[1,2] Representative naturally occurring rearranged steroids include cyclopamine,[3] glaucogenins,[4] cortistatins,[5−13] nakiterpiosin,[14] strophasterol A,[15] cyclocitrinols,[16−18] pleurocins,[19] swinhoeisterol,[20] bufospirostenin A,[21] dankasterones, and periconiastone A.[20,22] Two particularly challenging examples of such natural products are the 9,11-secosteroids pinnigorgiol B (**1**) and pinnigorgiol E (**2**) (Figure 1),[23−25]

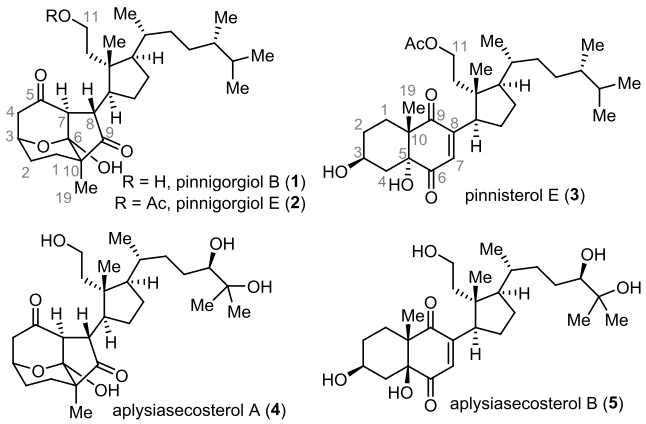

Figure 1. Structures of 9,11-secosteroids.

which possess a unique tricyclo[5,2,1,1]decane framework with an embedded γ-diketone moiety. These compounds were isolated by Sung and co-workers from a *Pinnigorgia* coral species in 2016, along with a biogenetic precursor, pinnisterol E (**3**).[26] Pinnisterol E is a typical secosteroid with one cleaved C−C bond, whereas pinnigorgiol B is both a secosteroid (the C9−C11 bond is cleaved) and an *abeo*-steroid (several bonds of the A/B bicyclic skeleton are migrated) and is among the most heavily rearranged steroid natural products reported so far. Notably, aplysiasecosterol A (**4**) and aplysiasecosterol B (**5**),[27,28] which share the same core skeleton as **1** and **3**, were isolated by Kigoshi and co-workers from the sea hare *Agplysia kurodai*. Importantly, pinnigorgiols have been shown to induce apoptosis of hepatic stellate cells,[29] and aplysiasecosterol A is moderately cytotoxic to human myelocytic leukemia cells (HL-60).[27]

The heavily rearranged scaffolds and intriguing biological activities of these 9,11-secosteroids make them interesting targets for chemical synthesis.[30] In 2018, Li and co-workers reported a remarkable convergent synthesis of **4**,[31] which featured a series of impressive transformations, including a desymmetrizing lactolization, an Aggarwal lithiation−borylation, and a hydrogen-atom-transfer-based radical cyclization. From a synthetic perspective, the development of an efficient semisynthetic approach to **1** and **2** presents a formidable challenge because it requires the identification of an inexpensive steroid precursor that can undergo selective cleavage of the C9−C11 bond, as well as a controllable skeletal rearrangement to transform the common decalin A/B ring system to the tricyclic γ-diketone core framework. Herein, we report the realization of a concise, radical cyclization approach[32] to pinnigorgiols B and E from inexpensive, commercially available ergosterol.

Our synthetic strategy to pinnigorgiols was largely guided by a biosynthetic pathway proposed by Kigoshi and Kita (Scheme 1A).[27,28] They suggested that the tricyclic γ-diketone structure of **2** might be derived from **3** by means of an α-ketol rearrangement[33] to generate **6**, followed by a vinylogous α-ketol rearrangement[15,34,35] to generate **7**. Protonation of **7** and subsequent hemiketal formation would afford **2**. The brevity of this proposed biosynthetic pathway inspired us to attempt to design a practical, efficient route to these unique 9,11-secosteroids. Because the ketol intermediate structurally similar to **6** was reported to undergo facile C10 migration from C6 to C5,[36] and achieving the desired vinylogous α-ketol rearrange-

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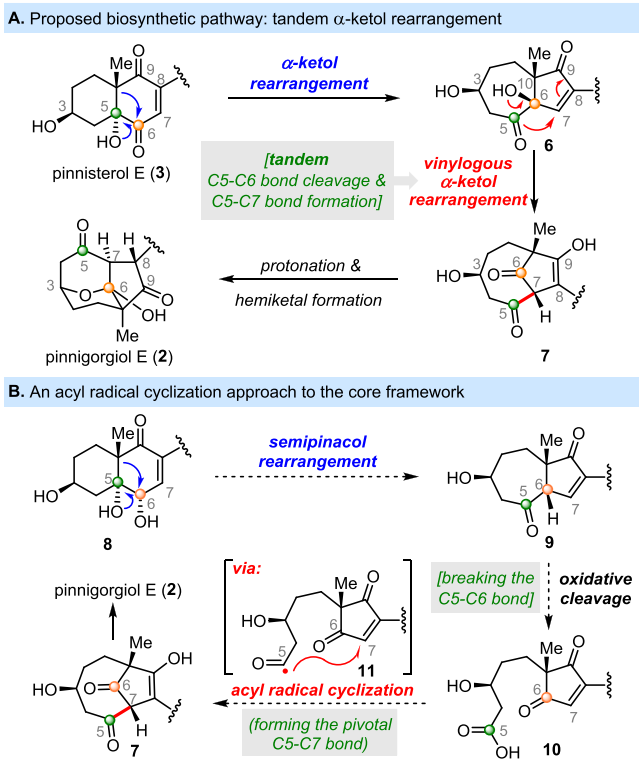
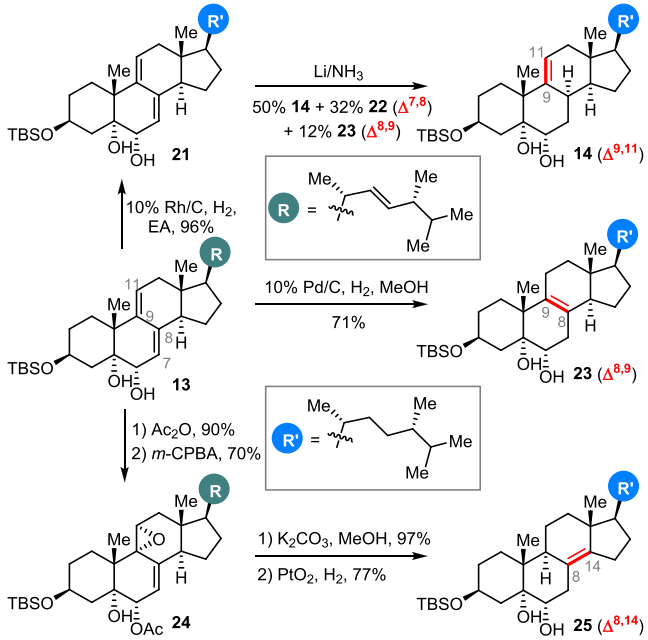
Scheme 1. (A) Proposed Biosynthetic, Polar Framework Rearrangement and (B) Design of an Alternative, Radical Cyclization Approach



ment was challenging, we opted to design an alternative, stepwise strategy for accessing **2** (Scheme 1B). We envisaged that diol **8** would undergo a semipinacol rearrangement[37] to afford ketone **9**, which would likely be much more stable than **6** and could thus be isolated. In contrast to the vinylogous α-ketol rearrangement of **6**, which involved tandem C5−C6 bond cleavage and C5−C7 bond formation, we speculated that oxidative cleavage of **9** would break the C5−C6 bond to afford **10**, and the pivotal C5−C7 bond formation reaction to access **7** could be accomplished by means of an acyl radical cyclization.[38,39]

As depicted in Scheme 3, our work on the synthesis of **1** and **2** commenced with the preparation of the known compound dehydroergosterol (**12**) from ergosterol.[40] Protection of the C3 hydroxyl group of **12** as a *tert*-butyldimethylsilyl ether, followed by asymmetric dihydroxylation[41] of the C5−C6 olefin generated triene **13**. Hydrogenation of the C7−C8 and C22−C23 double bonds of **13** regioselectively over the C9−C11 double bond proved to be nontrivial and necessitated extensive experimentation. Intriguingly, we were able to identify three sets of optimal conditions for divergently accessing regioisomeric olefins **14**, **23**, and **25**, which have C9−C11, C8−C9, and C8−C14 double bonds, respectively (Scheme 2). Treatment of **13** with 10% Rh/C in ethyl acetate enabled selective hydrogenation of the C22−C23 olefin, providing diene **21** in 96% yield. Li/NH_3 reduction of **21** gave rise to desired olefin **14** as the major product, along with the C7−C8 olefin (**22**) and **23** as minor products. Alternatively, hydrogenation of **13** over 10% Pd/C in MeOH furnished **23** in 71% yield. Interestingly, acetylation of the C6 hydroxyl group of **13** enabled regioselective epoxidation of the C9−C11 double bond, giving rise to epoxide **24**. Removal of the C6 acetyl

Scheme 2. Regioselective-Hydrogenation-Enabled Divergent Access to Regioisomeric Olefins



group and subsequent hydrogenation over PtO_2 provided **25** exclusively. The structures of **23** and **25** were confirmed by X-ray crystallographic analysis of their corresponding semipinacol rearrangement products (see Supporting Information for details). The development of conditions for efficient access to these three regioisomeric olefins can be expected to greatly facilitate the selective redox and C−C bond reorganization reactions of the tetracyclic skeleton, and thus, these conditions are likely to find utility for the synthesis of other steroid natural products. For example, intermediates bearing a C8−C9 or C8−C14 olefin might find potential application in the synthesis of 8,9-secosteroid jereisterol A or 8,14-secosteroid jereisterol B.[42]

Having established a reliable method for preparing **14**, we were poised to attempt the first bond migration within the decalin A/B ring system to generate the 7,5-bicyclic scaffold by means of the semipinacol rearrangement. Selective mesylation of **14** afforded the desired C6 mesylate, which was heated in DMF in the presence of $CaCO_3$ and NEt_3 to furnish ketone **15** in 92% yield (Scheme 3).[43] The stereochemistry at C6 for **15** was determined through X-ray crystallographic analysis of the semipinacol rearrangement products of structurally similar olefins **23** and **25** (see the Supporting Information for details). Notably, this stereochemical result was in good agreement with Newhouse's recent elegant study of a cationic rearrangement to access the triterpenoid justicioside E aglycone.[44] Ozonolysis of **15** and subsequent reduction with $NaBH_4$ gave a 5,11-diol intermediate, which was converted to **16** by selective acetylation and in situ Dess−Martin oxidation. The conditions for oxidative cleavage of the C5−C6 bond of **16** and introduction of the C7−C8 double bond to produce acid **18** were investigated next. First, regioselective formation of a C5−C6 silyl enol ether by reaction with trimethylsilyl iodide[45] and subsequent ozonolysis delivered the C5 carboxylic acid **17**. Dehydrogenation of the resulting 1,3-cyclopentanedione of **17** was achieved through bromination of the C6−C7 silyl enol ether, which gave rise to **18** in 58% yield over four steps.

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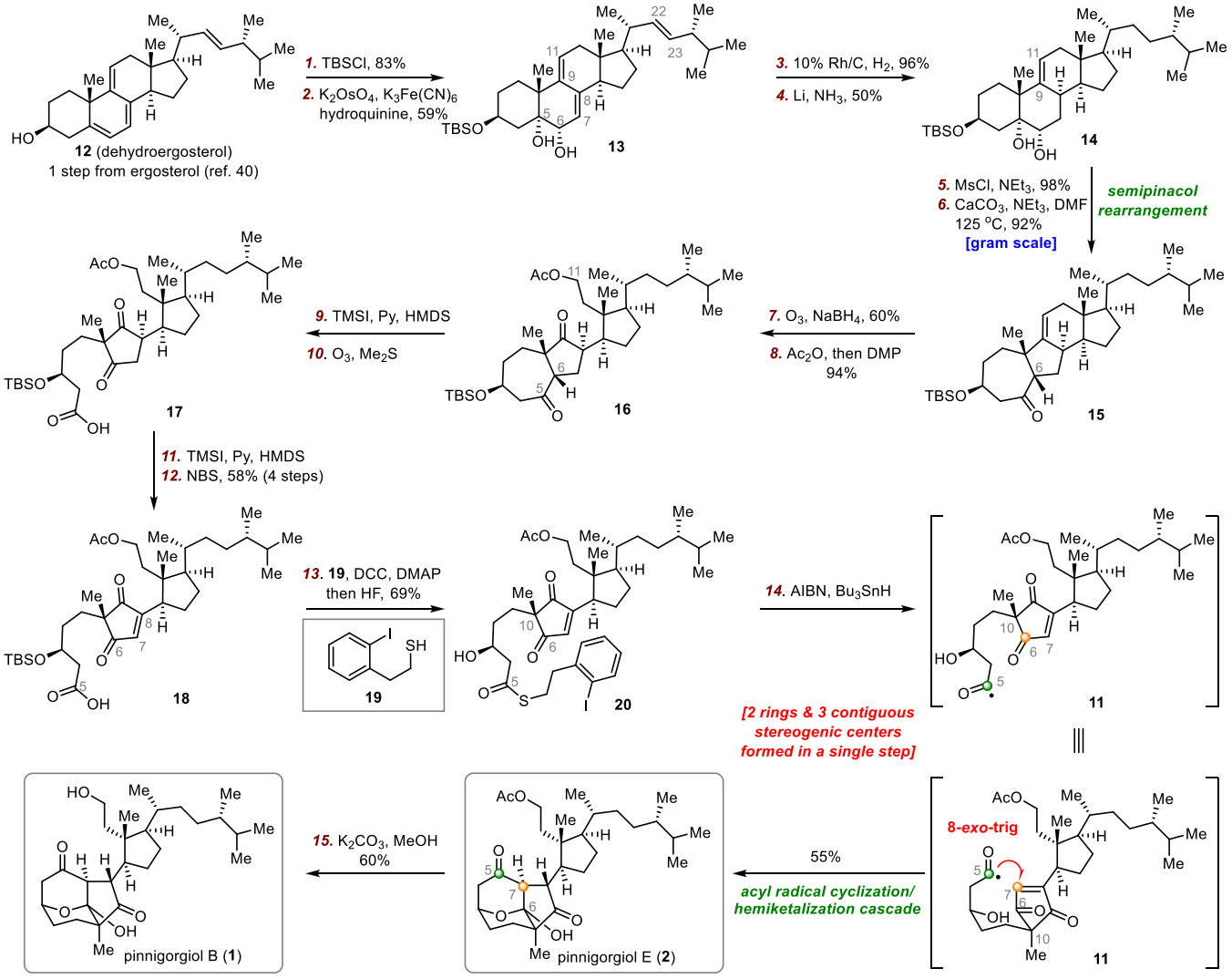
Scheme 3. Acyl Radical Cyclization Approach to Pinnigorgiols B and E[a]



[a]Abbreviations: TBS, *t*-butyldimethylsilyl; Ms, mesyl; DMP, Dess−Martin periodinane; TMS, trimethylsilyl; HMDS, 1,1,1,3,3,3-hexamethyldisilazane; NBS, *N*-bromosuccinimide; DCC, dicyclohexylcarbodiimide; DMAP, *N*,*N*-4-dimethylaminopyridine; AIBN, 2,2′-azobis(isobutyronitrile).

All that remained to complete the synthesis of **2** was connection of the pivotal C5−C7 bond, which we envisioned could be accomplished through an intramolecular acyl radical cyclization approach.[46−49] However, because this approach would involve an 8-*exo*-trig cyclization to generate a bicyclo[5.2.1] bridged ring system, the transformation presented a considerable challenge.[30] Therefore, we decided to search for a suitable acyl radical precursor to investigate the feasibility of the approach. Attempted preparation of the corresponding acyl telluride[39] of carboxylic acid **18** were unsuccessful. Conversion of the carboxyl group of **18** to the corresponding phenyl selenoester by reaction with $(PhSe)_2$ and *n*-Bu_3P in DMF proceeded smoothly.[50] However, treatment of the selenoester with azobis(isobutyronitrile) (AIBN) and Bu_3SnH led to a mixture of unidentified products, and formation of the desired C5−C7 bond was not observed. We speculated that the bulky *tert*-butyldimethylsilyl (TBS) group at C3 was detrimental because its proximity to the acyl radical at C5 hampered the approach of C5 to C7, thus hindering formation of the desired bond. Attempts to remove the TBS group from the phenyl selenoester intermediate resulted in a complex mixture, possibly because of the instability of the phenyl selenoester. Inspired by the generation of an acyl radical from a thiolester by Crich et al.,[51] we prepared thiolester **20** by a coupling reaction between **18** and thiol **19** followed by removal of the TBS group with HF. We were pleased to find that treating **20** with a solution of Bu_3SnH and AIBN in benzene at 100 °C afforded **2** in 55% yield.[51] This process, which likely involved an acyl radical cyclization/hemiketalization cascade, efficiently forged the tricyclic γ-diketone framework, with two rings and three contiguous stereogenic centers being formed in a single step. Hydrolysis of **2** furnished **1** uneventfully, and the spectroscopic data for **1** and **2** were in good agreement with those of the isolated samples.[23−25]

In conclusion, we have achieved the first synthesis of the 9,11-secosteroids pinnigorgiols B and E from inexpensive ergosterol. Our synthesis of the pinnigorgiols features a semipinacol rearrangement and an acyl radical cyclization/hemiketalization cascade, which converts a biogenetic tandem

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polar rearrangement into a stepwise hybrid combination of polar and radical reactions.[52] Our work also demonstrates how inspiration from a putative biosynthesis pathway can be strategically used to develop a practical synthetic approach.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c13426.

Experimental procedures and ^{1}H NMR and ^{13}C NMR spectra for all compounds (PDF)

Accession Codes

CCDC 2058214−2058215 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, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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