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Letter

Synthesis of Daucane Natural Products Enabled by a Gold(I)-Catalyzed Tandem Cycloisomerization/(4 + 3) Cycloaddition

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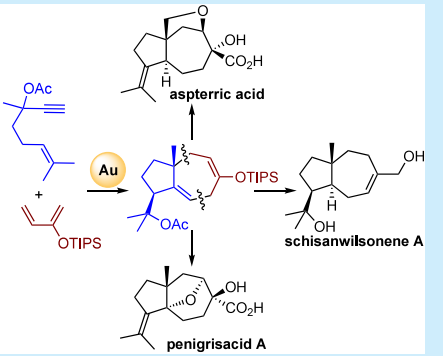
ABSTRACT: A divergent synthesis of three members of the daucane family of natural products is reported, enabled by a gold(I)-catalyzed cycloisomerization/formal (4 + 3) cycloaddition as the key step. The synthesis of penigrisacid A features a vanadium-catalyzed tandem epoxidation/S_N2' cyclization, whereas a Suárez radical cyclization enables the synthesis of aspterric acid. This work has also led to the reassignment of the structure of penigrisacid A as well as a short formal synthesis of schisanwilsonene A.



Daucanes are a family of sesquiterpenes that, for a long time, seemed to be restricted to compounds isolated from Umbelliferae plants. However, new natural products with the same hydroazulene structure were later isolated from fungal and marine origins.[1] All members of this family share a bicyclo[5.3.0]decane core with the carbon skeleton of daucene (**1**), which is naturally occurring in both enantiomeric forms[1b] (Scheme 1A), with diverse functionality and varied degrees of oxidation, and have been shown to exhibit diverse biological activities.[2] For example, aspterric acid (**2**)[3] has been found to inhibit *Arbidopsis* pollen development at meiosis[4] as well as to have other potent herbicide properties.[5] Among the simpler carotene-like natural products, schisanwilsonene A (**3**)[6] has strong antiviral activity and has been synthesized first by our group[7] and later by the group of Xiang.[8] Other naturally occurring daucanes were recently isolated from deep-sea-derived fungi, including penigrisacid A and C and piltunine C, whose structures were proposed as compounds **4**, **5**, and **6**, respectively.[9,10] Interestingly, thus far, among all reported daucanes, only peniterester (**7**),[11] obtained from an artificially mutated *Penicillium* sp. T2-8 strain, presents an *anti* configuration between angular C-15 and the CO_2R moiety at C-14.

In recent work, we reported the synthesis of the core skeleton of daucanes by a gold(I)-catalyzed cycloisomerization/formal (4 + 3) cycloaddition of 1,6-enynes **8** with 1,3-dienes **9** (Scheme 1B).[12] On the basis of experimental and computational work, we proposed that this multistep transformation proceeds by a 5-*exo*-dig gold(I)-catalyzed cyclization to form cyclopropyl gold(I) carbene **int1**, which undergoes a 1,5-OR-migration to form *α*,*β*-unsaturated gold(I) carbene **int2**. Intermolecular reaction of intermediate **int2** with 1,3-dienes **9**, in a non-concerted (4 + 3) cycloaddition, gives rise to hydroazulene **10**. We envisioned that a functionalized derivative of compound **10** could be a common building block for the synthesis of aspterric acid (**2**) and compound **4**. The first one, product **2**, was previously synthesized by Harayama and Inubishi shortly after its isolation in 27 steps and 1.2% overall yield, featuring a Robinson annulation and PCl_5-mediated ring contraction as key steps.[13] On the other hand, to date, penigrisacid A has never been synthetically prepared nor has its biological activity been studied. Here, we report a new synthesis of compounds **2** and **4**, the reassignment of the structure of penigrisacid A as compound **4a**, the C3 epimer of acid **4**, and a formal synthesis of schisanwilsonene A (**3**).

Our retrosynthetic plan for 3-*epi*-penigrisacid A (**4**) and aspterric acid (**2**) is summarized in Scheme 1C. In the case of 3-*epi*-penigrisacid A (**4**), acetate elimination from compound **11** would lead to the formation of *exo* alkene. We envision that, given the right configuration at C2, we could perform an oxa-Michael addition to the double bond C5−C6 and then perform hydration of the double bond conjugated to the ester. Diene **12** could arise from manipulation of silylenol ether **13**, which is the product of the gold(I)-catalyzed cyclization/cycloaddition of 1,3-diene **14** with enyne **15**. On the other hand, for aspterric acid

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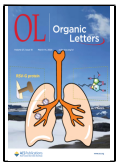
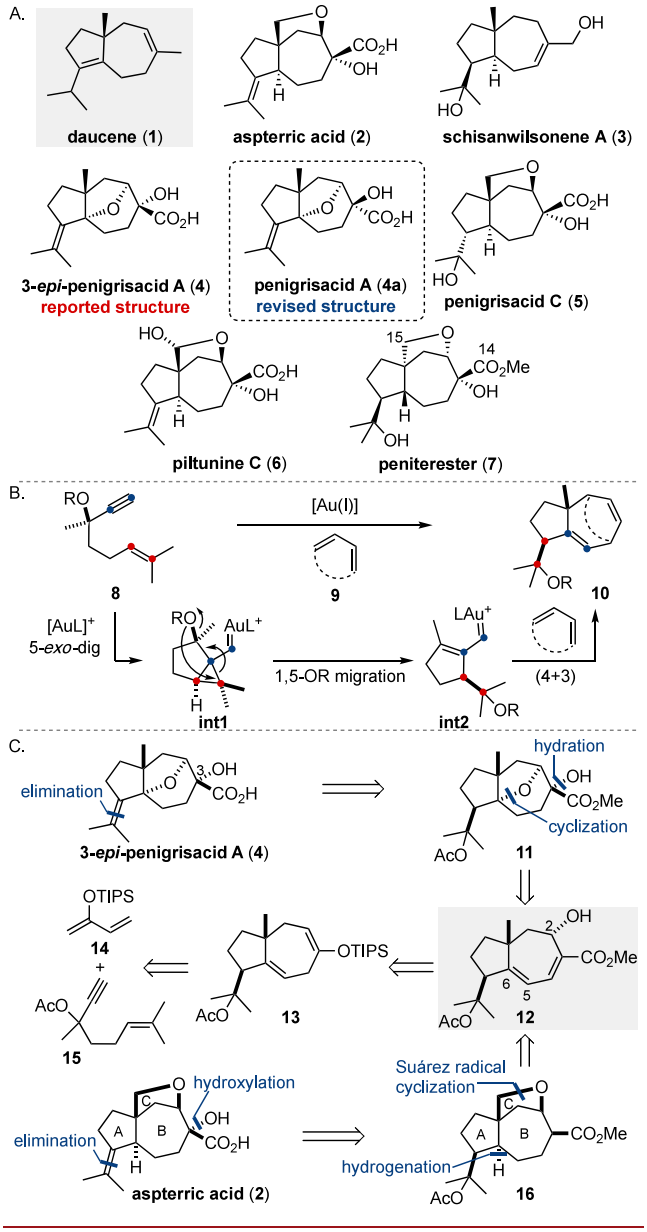


Scheme 1. (A) Selected Daucane Natural Products, (B) Mechanism of the Gold(I)-Catalyzed Cycloisomerization/ Formal (4 + 3) Cycloaddition, and (C) Retrosynthetic Plan for the Synthesis of Penigrisacid A and Aspterric Acid



(**2**), we envision a similar acetate elimination and α-hydroxylation of the ester of intermediate **16**. Then, the closing of ring C would be performed by a Suárez radical cyclization given the right configuration of the alcohol in intermediate **12**. Finally, double hydrogenation would afford the desired *trans* configuration between rings A and B.

The total synthesis of the common building block **12** commenced with the construction of the hydroazulene core by the gold(I)-catalyzed reaction between 1,3-diene **14** and enyne **15**, which were synthesized from commercially available materials in two steps[14] and one step,[15] respectively (Scheme 2). To favor intermolecular reaction between enyne and diene over unproductive self-cyclization of compound **15**, we performed a slow addition of a solution of compound **15** into a cold solution of compound **14** and cationic JohnPhosAu(MeCN)SbF_6 in CH_2Cl_2. Under these conditions, we could reduce the amount of diene to 1.1 equiv and the gold(I) catalyst loading to 0.5 mol %. Following the cycloaddition, a Rubottom-type oxidation[16] was performed with *m*CPBA. To prevent the unwanted acid-catalyzed isomerization of alkene to conjugated diene in silyl enol ether **13**, $NaHCO_3$ was added to quench any residual acid.[17] Epoxidation of silyl-enol ether and ring opening with MeOH yielded the corresponding acetal intermediate **17**, which, after acid hydrolysis, led to α-hydroxy ketone **18** as a single diastereomer in 36% yield over three steps. Nuclear Overhauser effect spectroscopy (NOESY) experiments as well as the characterization by X-ray diffraction of a *m*CBA adduct of the product[18] confirmed the relative configuration of product **18**. Protection of the secondary alcohol in product **18** with TBSCl, followed by triflation using LiHMDS and Comins' reagent, gave triflate **20** in 93 and 73% yields, respectively. Finally, the palladium-catalyzed methoxycarbonylation of compound **20** and subsequent *tert*-butyldimethylsilyl (TBS) removal afforded common intermediate **12** in an excellent yield. Hydrogenation of diene **12** with catalytic Pd/C resulted in partially reduced intermediates that could not be further hydrogenated. Performing the reaction with 20 mol % Adams' catalyst[19] in EtOAc with traces of HOAc gave fully hydrogenated product **22** in 82% yield.

To close ring C in aspterric acid, the configuration of the alcohol in C2 had to be inverted. After several attempts using Mitsunobu conditions, we decided to switch to an oxidation/reduction sequence with Dess−Martin periodinane (DMP) and $NaBH_4$/MeOH, giving rise to compound **25** in 70% yield over two steps, together with compound **24** (1:1 mixture with compound **22**), which could be recycled back with DMP to compound **23**. The ring closing was then performed via a Suárez radical cyclization.[20] First a C−H activation of the methyl group was achieved with $PhI(OAc)_2$ (1.5 equiv) and I_2 (1 equiv) in deoxygenated cyclohexane and using a desk lamp (35 W). The formation of lactone byproduct **26** was observed when the reaction time was extended, presumably by activation of the other two methyl C−H bonds, leading to an iodoform intermediate, which undergoes ring closure and hydrolysis of the resulting cyclic diiodomethylene in the aqueous work up. To minimize the formation of compound **26**, the reaction was stopped at ca. 50% conversion of compound **25** [monitored by ultra-high-performance liquid chromatography (UHPLC)]. Then, the ether ring was closed quantitatively with $AgNO_3$ in *N*,*N*-dimethylformamide (DMF). The structures of compounds **23**, **25**, and **16** were determined by X-ray diffraction, confirming the relative configuration of the stereocenters at C2 and C6 and the formation of ring C from the desired face of the molecule. α-Hydroxylation of the ester in compound **16** was performed by trapping the potassium enolate with oxygen and reducing the resulting hydroperoxide with triethylphosphite, giving compound **27** in 90% yield as a single diastereomer.

Screening of basic and acid conditions for the acetate elimination led to either decomposition of the starting material or elimination and isomerization of the double bond in compound **29** to form the more stable endocyclic alkene **30**. While relatively strong acids, such as MsOH or *p*-toluenesulfonic acid (PTSA), led to the clean formation of byproduct **30**, we discovered that, by performing the reaction in acetone in the presence of I_2 as a catalyst, compound **29** could be obtained in a moderate yield,[21] although as an inseparable 85:15 mixture with its *exo*-alkene isomer.[22] Finally, saponification of the ester afforded aspterric acid (**2**) in good yields as an 85:15 mixture with the *exo*-alkene isomer **31**. The ^1H and ^{13}C nuclear magnetic

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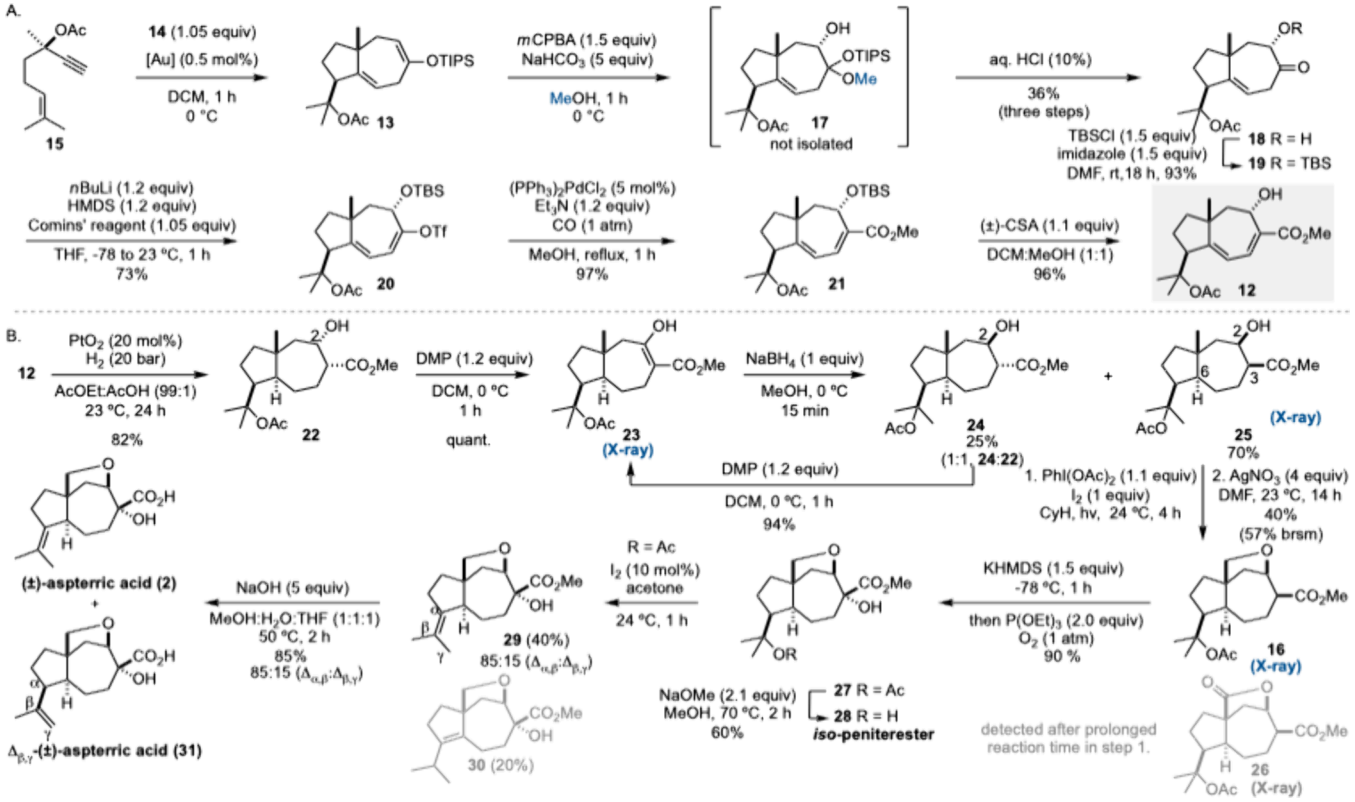
Scheme 2. (A) Synthesis of Common Intermediate 12 and (B) Total Synthesis of (±)-Aspterric Acid[a]



[a][Au] = [JohnPhosAu(MeCN)]SbF_6.

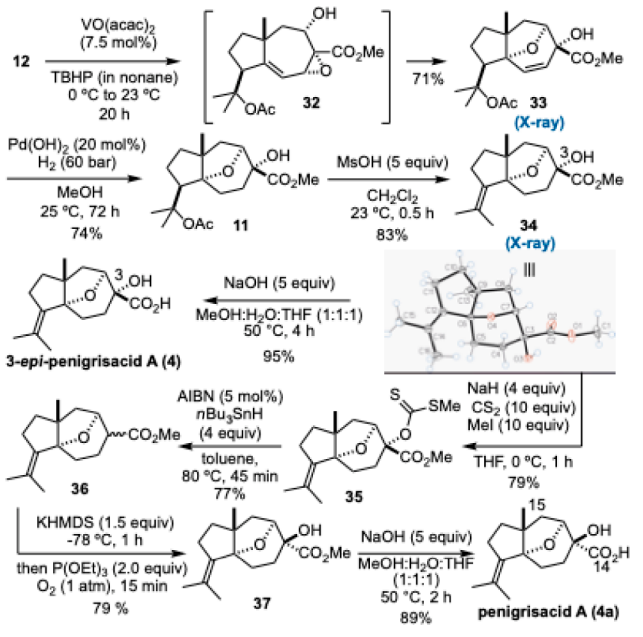
resonance (NMR) spectra of synthesized compound **2** agreed with the spectroscopic data of a sample of the natural product.[23]

The synthesis of analogues of natural products that exhibit biological activity is of importance for the study and development of new potential drugs. On that note, *iso*-peniterester (**28**), a diastereomer of recently isolated peniterester (**7**),[11] which showed potent antibacterial activities,[24] was prepared by methanolysis of compound **27**. On a preliminary screening of the biological activities of some intermediates of the total synthesis of compound **2**, we found that compounds **22**, **23**, and **25** present potent antifungal activities against two fungi (*Cryptococcus neoformans* and *Candida albicans*), with a minimum inhibitory concentration (MIC) of ≤0.25 μg/mL.[22]

For the synthesis of penigrisacid A, a one-pot tandem epoxidation/S_N2' sequence on compound **12** allowed the simultaneous formation of the five-membered ring and α-hydroxylation of the methyl ester (Scheme 3). Initial studies using *m*CPBA led to the formation of desired product **33** in moderate yields. However, the reaction was not easily reproducible, and in some cases, we detected epoxide intermediate **32** by ^{1}H NMR of the crude reaction mixture,[22] which decomposed upon attempted isolation. With the switch to directed epoxidation using $VO(acac)_3$ (7.5 mol %) and *tert*-butyl hydroperoxide (TBHP), the reaction delivered the desired product **33** in 71% yield.

Hydrogenation of compound **33** with catalytic $Pd(OH)_2$ in MeOH and acid-mediated acetate elimination afforded methyl ester **34**, whose structure was confirmed by X-ray diffraction (Scheme 3). Finally, saponification of the ester with NaOH gave the target compound **4**. However, ^{1}H and ^{13}C NMR spectra of synthetic compound **4** did not fully match the reported data,[9]

Scheme 3. Synthesis of 3-*epi*-Penigrisacid A and Revised Penigrisacid A[a]



[a]Oak Ridge Thermal-Ellipsoid Plot (ORTEP) elipsoids of X-ray structures set at 50% probability.

although the NOESY experiments showed similar cross-peaks, pointing to a closely similar structure.[22] The structural assignment of the natural product was based on the assumption that the configuration at C-3 was *R*,[9] as displayed by other

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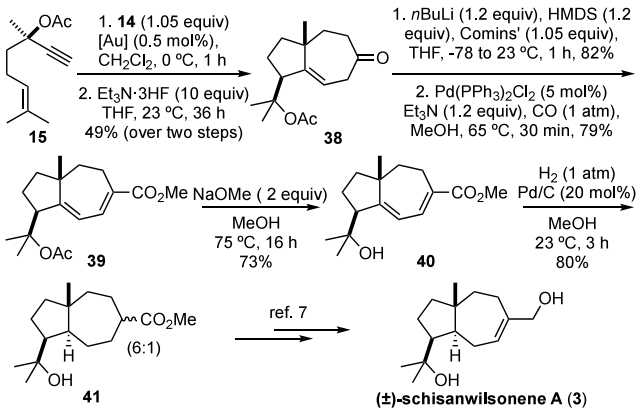
daucanes, including aspterric acid (**2**). This assumption was reasonable, because penigrisacid A was isolated from the same fermentation extract of *Penicillium griseofulvum* together with aspterric acid (**2**), penigrisacid C (**5**), and other metabolites, which have the *R* configuration at C-3.[9] However, because C-3 is the only stereocenter that could not be assigned by NOESY correlations, we decided to synthesize the C-3 epimer of compound **4**. Thus, compound **34** was converted into xanthate **35**, which was deoxygenated under Barton−McCombie conditions to give compound **36** in 60% yield over two steps. Oxidation of the enolate of compound **36** under conditions similar to those employed in the synthesis of aspterric acid (**2**) gave compound **37**, which upon saponification provided penigrisacid A (**4a**), whose NMR spectra matched with those reported for the natural product.[9] Starting from enantioenriched enyne **15** [90:10 enantiomeric ratio (er)], we also completed the asymmetric synthesis of 3-*epi*-penigrisacid A (**4**, 88:12 er) by the same gold(I)-catalyzed reaction.[22]

A formal synthesis of schisanwilsonene A (**3**) was also achieved (Scheme 4), shortening our previous synthetic route.[7]

Scheme 4. Formal Synthesis of (±)-Schisanwilsonene A[a]



[a][Au] = [JohnPhosAu(MeCN)]SbF_6.

After the gold(I)-catalyzed cyclization/cycloaddition, treatment of the silyl enol ether intermediate with $Et_3N{\cdot}3HF$ in THF delivered ketone **38** in 49% yield over two steps. The two-step sequence of triflation/Pd-catalyzed methoxycarbonilation gave methyl ester **39**. Finally, methanolysis of the acetate group gave compound **40** in 73% yield, which was hydrogenated to afford compound **41** in 80% yield. Product **41**, a late intermediate of our previous total synthesis,[7] was obtained as a 6:1 diastereomeric ratio (dr) mixture. Thus, the formal synthesis of schisanwilsonene A (**3**) was achieved in 11 steps (longest linear sequence) and an approximate overall 10% yield.

In conclusion, a divergent total synthesis of three members of the daucane family of natural products was achieved. An efficient gold(I)-catalyzed cycloisomerization/formal (4 + 3) cycloaddition from two readily available starting materials provided the hydroazulene bicyclic skeleton in a single transformation. This enabled the total syntheses of (±)-aspterric acid (**2**) and (±)-schisanwilsonene A (**3**) in 15 and 11 steps and ca. 2 and 10% overall yields, respectively. Furthermore, the reassignment of the structure and the first total synthesis of penigrisacid A (**4a**) have been realized. The enantioselective synthesis of 3-*epi*-penigrisacid A (**4**) was also completed. This work highlights the biosynthetically promiscuous pathways that lead to compounds sharing a similar overall structure but with opposite configurations at different stereocenters.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.4c04542.

Synthetic procedures, characterization data, NMR spectra, and crystallographic data (PDF)

Accession Codes

Deposition numbers 2407063−2407070 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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(22) See the Supporting Information.

(23) Commercially available aspterric acid (5 mg) was bought from Tebubio Spain (catalog number 10-3489).

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