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Total Synthesis of (+)-Aplykurodinone-1

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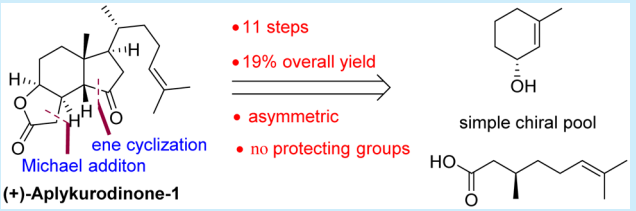
Supporting Information

ABSTRACT: Starting from (*R*)-citronellic acid and (*R*)-seudenol, the total synthesis of (+)-aplykurodinone-1, a highly degraded marine steroid, has been achieved in 11 steps and in 19% overall yield with excellent stereochemical control. In addition to the features such as an Ireland−Claisen rearrangement, an intramolecular carbonyl−ene cyclization, and an intramolecular Michael addition, the present synthetic strategy is accomplished without the use of protecting groups.



The aplykurodins and aplykurodinones,[1] isolated from marine mollusks of the genus *Aplysia*, are a family of highly degraded marine steroids (Figure 1). The structures of

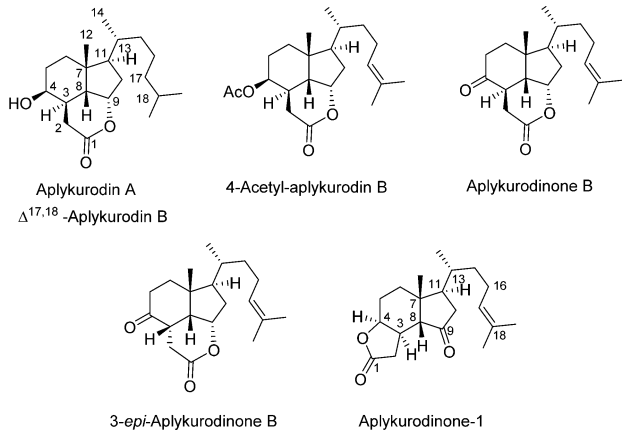
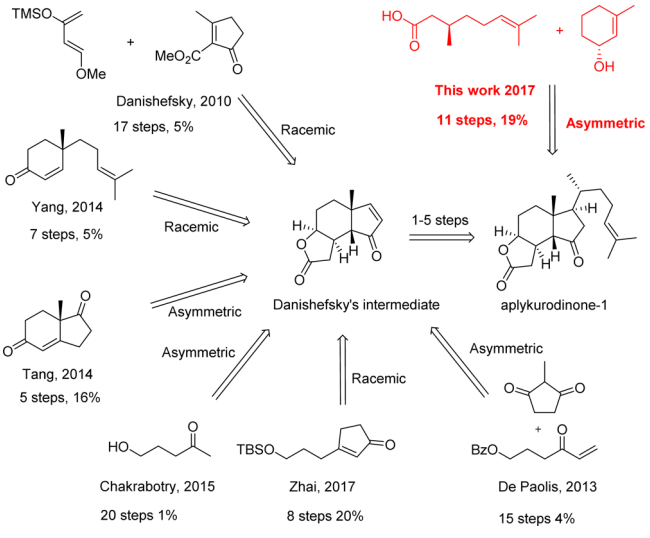


Figure 1. Representative structures of aplykurodins and aplykurodinones.

the first isolated aplykurodins, i.e., aplykurodin A and aplykurodin B, were determined via spectroscopic methods and X-ray crystallographic analysis.[1a] Aplykurodinone-1, isolated from the sea hare *Siphonota geographica* in 2005,[1d] possesses an unusual *cis*-hydrindane moiety and six contiguous stereochemical centers, one of which is quaternary. Although the biological profile of aplykurodinone-1 remains unknown, aplykurodinone B and 4-acetylaplykurodin B have shown strong ichthyo toxicity (10 ppm) to the mosquito fish *Gambusia affinisat*. In addition, 3-*epi*-aplykurodinone B has exhibited mild in vitro cytotoxicity against four tumor cell lines.[1c]

The structural complexity and the potential biological activities of aplykurodinone-1 have attracted considerable attention from the synthetic community.[2] In 2010, Danishefsky and Zhang[2a] reported the first total synthesis of aplykurodines-1 in 22 steps based on an elegant anionic Diels−Alder cycloaddition strategy. After that, five different syntheses by De Paolis,[2b] Yang,[2c] Tang,[2d] Chakrabotry,[2e] and Zhai,[2f] respectively (Scheme 1), were reported. Although novel strategies and methodologies have been employed in these syntheses, all of them have used Danishefsky's intermediate. The major

Scheme 1. Schematic Summary of the Previous Total Syntheses of Aplukurodinone-1



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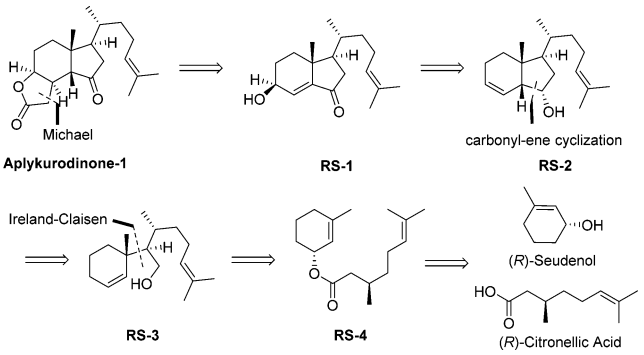
drawback of using this intermediate is the poor control of the stereochemistry of the 13-methyl group, while the 13-epimer is difficult to separate. So far, this seemingly simple molecule has presented significant synthetic challenges. Herein, we report a new, convergent, yet protecting-group-free total synthesis of aplykurodinone-1 from simple starting materials.

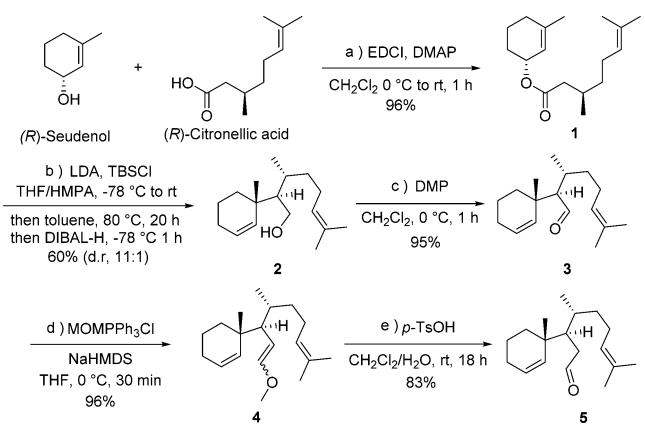
Since all of the previous work has witnessed difficulty with the stereocontrolled introduction of the unsaturated side chain in the later stage, we plan to install the C_{11} side chain prior to the construction of the tricyclic core skeleton. The retrosynthetic analysis (Scheme 2) shows that an Ireland–Claisen rearrangement combined with a carbonyl–ene cyclization may be efficient for the construction of the core structure. The lactone ring of aplykurodinone-1 may be introduced via an intramolecular Michael addition. The advanced intermediate **RS-2** may be converted into **RS-1** by using an epoxidation–oxidation and epoxide ring-opening reaction sequence. The bicyclic core structure of **RS-2** may be constructed via an intramolecular carbonyl–ene cyclization, while the quaternary stereochemical center in **RS-3** may be constructed via an Ireland–Claisen rearrangement. Intermediate **RS-4** may be generated from the coupling of (*R*)-citronellic acid and (*R*)-seudenol, which can be readily prepared from pulegone and 3-methylcyclohexenone, respectively.[3]

Scheme 2. Retrosynthetic Analysis of Aplykurodinone-1

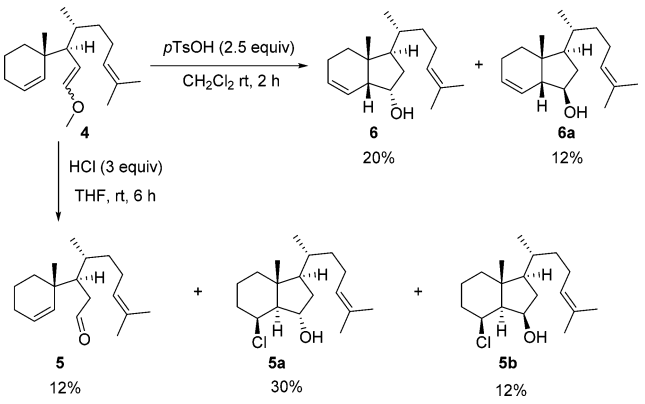


On the basis of the above analysis, the synthetic strategy seemed feasible. Thus, esterification of (*R*)-citronellic acid (98% ee) with (*R*)-seudenol (96% ee) provided intermediate **1** in 96% yield (Scheme 3). Since the configuration of C_{11} is controlled by the geometry of the enolate carbon–carbon double bond, the (*Z*)-enol ether is required for the Ireland–Claisen rearrangement, which was obtained from **1** (LDA, THF–HMPA) according to Bouillon's procedure.[4] It was found that the amount of HMPA was critical for achieving high diastereomeric selectivity. Under the optimized conditions, the Ireland–Claisen rearrangement of the ketene silyl acetal was followed by reduction of the resulting silyl ester with diisobutylaluminum hydride to provide alcohol **2** (dr 11:1 at C_{11}) in 60% combined yield.[5] Dess–Martin oxidation of alcohol **2** was straightforward to afford aldehyde **3** in 95% yield. The requisite one-carbon elongation was achieved by using a Wittig olefination of the aldehyde with methoxymethyltriphenylphosphonium chloride and NaHMDS (96%), and the product was obtained as a 5:1 mixture of the olefin geometric isomers. Surprisingly, hydrolysis of the terminal methoxy vinyl ether **4** with hydrochloric acid yielded aldehyde **5** along with the undesired carbonyl–ene cyclization products **5a** and **5b**, in which a chlorine atom was added instead of the formation of the desired carbon–carbon double bond (Scheme 4). After many unfruitful attempts, we hoped that when treated with 2.5 equiv of *p*-toluenesulfonic acid in freshly distilled methylene chloride at room temperature intermediate **4** would undergo the carbonyl–ene cyclization, and intermediate **6** was obtained in 20% yield and its C_9 epimer **6a** in 12% yield. After extensive optimization, it was found that, to our delight, when a small amount of water was added to the reaction mixture, aldehyde **5** was obtained as the major product (83%), which, when heated in toluene at 160 °C for 17 h in a sealed tube, provided the desired cyclization product **6** in 90% yield[6] (Scheme 5). Other Lewis acids (Me_2AlCl, Et_2AlCl, $SnCl_4$, $Sc(OTf)_3$) also induced the carbonyl–ene cyclization[7] but in moderate yields, along with the formation of considerable amounts of epimer **6a**. Stereoselective epoxidation of **6** using a catalytic amount of $VO(acac)_2$ afforded epoxide **7** (92%) with complete diastereocontrol. Dess–Martin oxidation[8] afforded the unstable epoxyketone, the epoxide of which was partially cleaved to furnish hydroxyenone **8** on silica gel during chromatography. Thus, DBU was added to the reaction mixture after the oxidation, and the epoxide was completely cleaved in one pot (81%). Since the stereochemistry of the hydroxyl group in **8** was different from that of the natural product, a Mitsunobu esterification of monomethyl malonate with alcohol **8** was used to furnish **9** with the desired stereochemistry of the malonate in 89% yield.[9] When treated with cesium carbonate in acetonitrile, intermediate **9** underwent an intramolecular Michael addition in 87% yield to produce the desired lactone **10**, the Krapcho dealkoxycarbonylation of which furnished the final product

Scheme 3. Synthesis of Aldehyde 5



Scheme 4. Carbonyl-Ene Cyclization of 4



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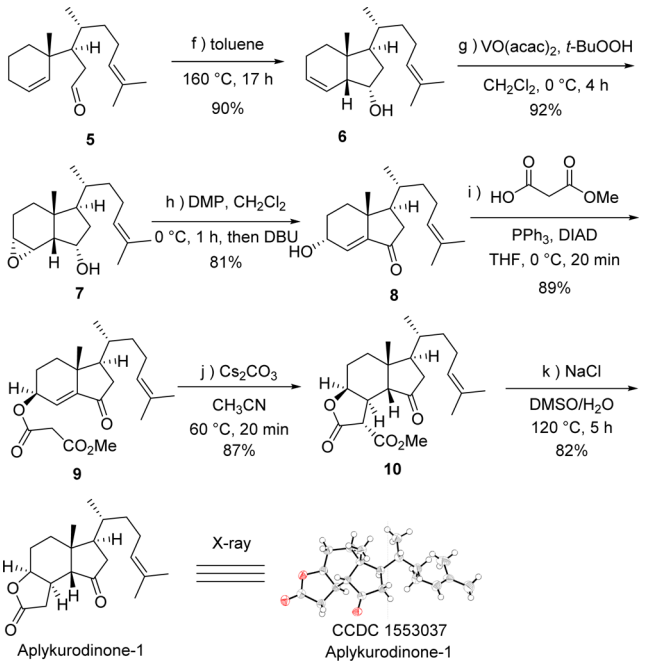
Scheme 5. Total Synthesis of (+)-Aplykurodinone-1



aplykurodinone-1 in 82% yield,[10] whose structure was confirmed via X-ray crystallographic analysis and by comparison of the spectroscopic data with those reported in the literature.

In summary, an asymmetric total synthesis of aplykurodinone-1 has been accomplished with full stereochemical control. The key elements that have enhanced the strategic efficiency include an Ireland−Claisen rearrangement, an intramolecular carbonyl−ene cyclization, and an intramolecular Michael addition. In addition, this synthesis was accomplished without the use of protecting groups.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02350.

Detailed experimental procedures and NMR data (PDF)
Crystallographic data for aplykurodinone-1 (CIF)

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Notes

The authors declare no competing financial interest.

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