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Formal Synthesis of (±)-Aplykurodinone-1 through a Hetero-Pauson−Khand Cycloaddition Approach

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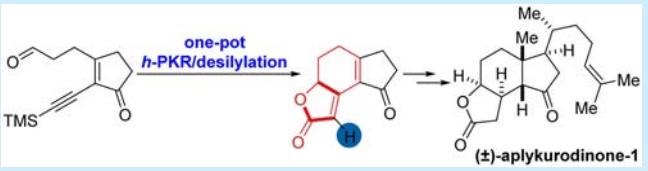
Supporting Information

ABSTRACT: The tricyclic intermediate **2** has been synthesized in eight steps from known compound **6** in 20% overall yield. As such, this constitutes a highly efficient formal synthesis of (±)-aplykurodinone-1. This synthesis features a unique, one-pot, intramolecular hetero-Pauson-Khand reaction (*h*-PKR)/desilylation sequence to expeditiously construct the tricyclic framework, providing valuable insights for expanding the scope and boundaries of *h*-PKR.



The synthesis of steroids has long served to inspire many research groups to design and execute powerful reactions and efficient synthetic strategies.[1] (±)-Aplykurodinone-1 (**1**) is a highly degraded steroidal natural product first isolated from the sea hare *Syphonota geographica* by Gavagnin and co-workers in 2005.[2] The intriguing molecular architecture of (±)-aplykurodinone-1 (**1**) is characterized by the peculiar *cis*-fused hydrindane moiety emanating from a strained γ-lactone ring at C3−C4 and the unsaturated side chain with its stereocenter at C13 connecting to the tricyclic core at C11. Moreover, five contiguous stereocenters including one quaternary stereocenter are concentrated in this highly fused tricyclic framework (Figure 1). Notably, the highly congested stereochemical

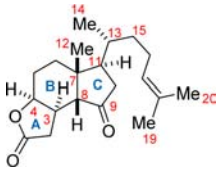


Figure 1. Structure of (±)-aplykurodinone-1.

complexity of this seemingly small molecule poses a particular synthetic challenge, rendering aplykurodinone-1 (**1**) attractive as a synthetic target.

In recent years, aplykurodinone-1 (**1**) has garnered considerable attention from a synthetic perspective. In 2010, Danishefsky and co-workers accomplished the first total synthesis of (±)-**1** via an elegant anionic Diels−Alder cycloaddition.[3a] Their pattern-recognition approach[4] led to the rational installation of all the stereocenters and provided a valuable basis for subsequent synthetic work. In 2013, De Paolis and co-workers reported a concise formal synthesis of (+)-**1** featuring a Hajos−Parrish methodology to assemble the chiral *cis*-hydrindane framework.[3b] In 2014, Yang and co-workers took advantage of a unique SmI_2-mediated intramolecular cascade cyclization to establish the A/C rings and a direct Michael addition of an organocuprate reagent to efficiently install the C11 side chain;[3c] in the same year, Tang and co-workers developed a protecting-group-free strategy toward the total synthesis of (+)-aplykurodinone-1 (**1**),[3d] utilizing a novel aerobic allylic oxidation/elimination sequence and a stereoselective intramolecular radical cyclization to construct the A ring. Recently, Chakraborty and co-workers[3e] realized a formal synthesis of (+)-**1** employing a Ti(III)-mediated radical cyclization to assemble the *cis*-fused ring junction (C7−C8), an RCM reaction to construct the B ring, and a Claisen rearrangement/iodolactonization sequence to install the A ring.

Each of these works employed novel strategies and methodologies to ensure the synthetic efficacy (Figure 2). However, the highly congested stereochemical complexity concentrated in the tricyclic core of aplykurodinone-1 (**1**) has impeded efficient access to this compound, and an abundant synthetic supply remains necessary to facilitate biological investigations[2] of aplykurodinone-1 (**1**), which motivated us to develop a more convergent and efficient route to this appealing molecule.

The Pauson−Khand reaction (PKR) is considered to be a powerful and convergent method for constructing cyclo-

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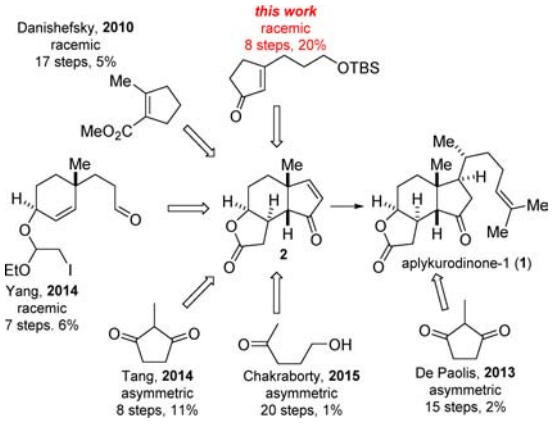


Figure 2. Schematic summary of the previous syntheses of (±)-aplykurodinone-1.

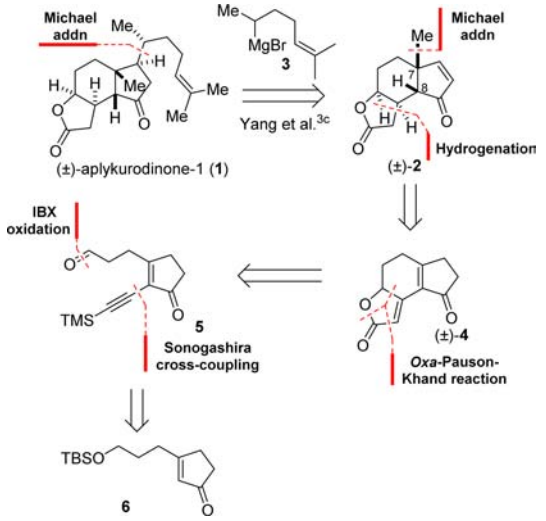
pentenones and is widely utilized in natural product synthesis.[5] In contrast, the hetero-Pauson–Khand reaction (*h*-PKR) variant is much less investigated. Although the *h*-PKR is recognized as a convenient method for constructing butenolides (oxa-Pauson–Khand reaction, *o*-PKR) and α,β-unsaturated lactams (aza-Pauson–Khand reaction, *a*-PKR),[6] its application in natural product synthesis is relatively rare. To date, only five examples of the *h*-PKR have been reported in natural product synthesis.[7] Having successfully employed the *h*-PKR strategy in the rapid construction of the two γ-butyrolactone-containing natural products, i.e., mintlactone[7a] and merrilactone A,[7b] we were encouraged to further explore the scope of the *h*-PKR in the total synthesis of other natural products. Herein, we report a successful implementation of a novel one-pot intramolecular *h*-PKR/desilylation sequence that procures a highly efficient formal synthesis of (±)-aplykurodinone-1 (**1**).

We envisaged that the main synthetic challenge of (±)-aplykurodinone-1 (**1**) would arise from the highly congested stereochemical complexity concentrated in the γ-butyrolactone-containing tricyclic framework and that this could be addressed by utilizing the powerful *o*-PKR to expeditiously assemble the tricyclic core. This would require a late-stage stereoselective reduction of olefins to install the requisite stereocenters. With this strategy in mind, we undertook a retrosynthetic analysis, as depicted in Scheme 1.

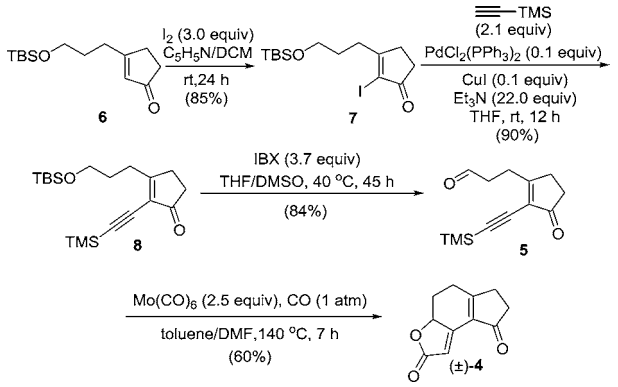
The side chain of (±)-aplykurodinone-1 (**1**) can be introduced in a single step via a direct Michael addition of an organocuprate reagent to α,β-unsaturated ketone **2** developed by Yang's group.[3c] The contiguous C7 and C8 stereocenters could be installed simultaneously through a Michael addition,[8] and the remaining stereocenters could be set via the late-stage reduction of olefins, which traced the origin of α,β-unsaturated ketone **2** to butenolide **4**. The critical intramolecular *o*-PKR would provide rapid access to the tricyclic butenolide **4** from compound **5**, and the cyclization substrate **5** could be prepared from known compound **6**[9] via a Sonogashira cross-coupling[10] followed by IBX-promoted cleavage of the TBS ether and oxidation.[11]

Our synthetic strategy for expeditious access to the tricyclic core commenced with known enone **6**[9] (Scheme 2). Iodination[12] of enone **6**[9] with iodine and pyridine in DCM afforded vinyl halide **7** in 85% yield. Then a Sonogashira cross-coupling of vinyl halide **7** with TMS-acetylene in the presence of triethylamine and a catalytic amount of $PdCl_2(PPh_3)_2$/CuI

Scheme 1. Retrosynthetic Analysis



Scheme 2. Four-Step Synthesis of the Tricyclic Core (±)-4



efficiently produced the 2-alkynyl-2-cyclopentenone **8** in 90% yield. Treatment of the TBS ether **8** with 2-iodoxybenzoic acid (IBX) in DMSO/THF at 40 °C resulted in a one-pot desilylation/oxidation sequence of the relatively inert TBS ether **8**, delivering aldehyde **5** in 84% yield.[13]

With the precursor **5** in hand, the crucial intramolecular Mo-mediated *o*-PKR was then explored (Table 1). A variety of conditions[6,7] were examined, and many of our efforts were fruitless, leading to no reaction or decomposition under more harsh conditions (entries 1–4). In contrast, cyclization proceeded successfully when operated in an "all-together" manner,[7c] where the highly unstable $Mo(CO)_3(DMF)_3$ was generated in situ in the toluene/DMF system in the presence of $Mo(CO)_6$. Much to our delight, when run at 140 °C for 1.5 h, the cyclization product **9** was forged with retention of the TMS group, but this could be converted into the desilylated product **4** through further treatment with TBAF and AcOH (entry 5). During the reaction condition screening, we found that extending the reaction time to 2.5 h led to a separable mixture of compound **9** and the desilylated product **4** (entry 6), which prompted us to further investigate this cycloaddition reaction. Surprisingly, it was found that the two-step cycloaddition/desilylation procedure could be performed as a tandem one-pot process if the reaction time was extended to 7 h, this delivering the desilylated product **4** as the exclusive product in 60% yield (entry 7).

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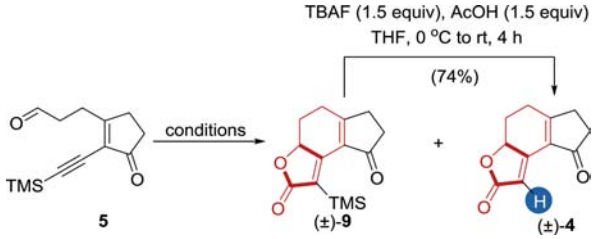
Table 1. One-Pot Mo-Mediated *h*-PKR/Desilylation

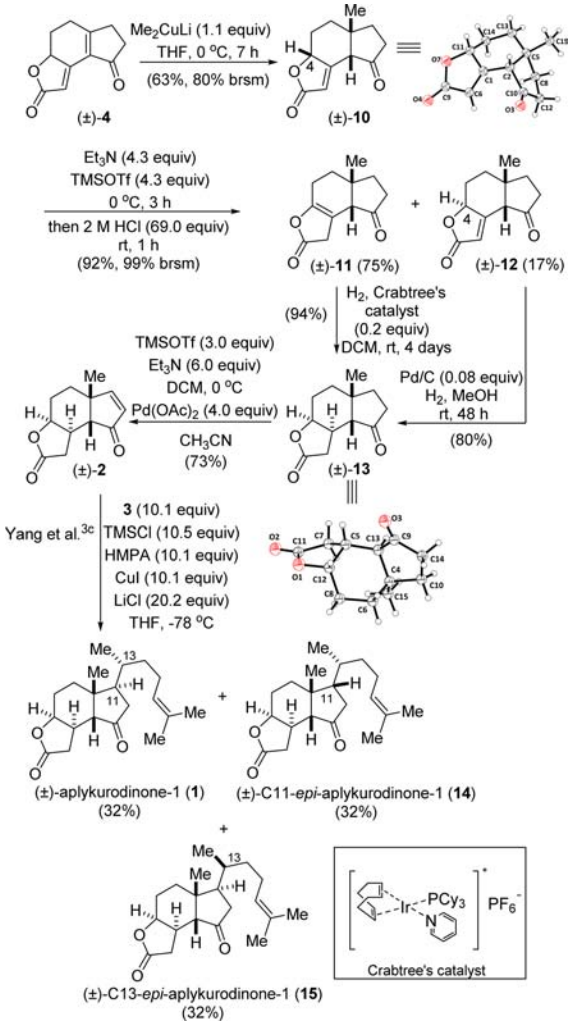


entry	catalyst (equiv)	additive (equiv)	CO (atm)	solvent	temp (°C)	time (h)	**9** (%)	**4** (%)
1	$Mo(CO)_6$ (1.5)	TBAB (10.0)	none	DCE	90	12	0	0
2	$Mo(CO)_6$ (1.5)	TBAI (10.0)	none	DCE	90	12	0	0
3	$Mo(CO)_3(DMF)_3$ (1.1)	none	none	THF	25	24	0	0
4	$Mo(CO)_3(DMF)_3$ (1.1)	none	1	THF	25	24	0	0
5	$Mo(CO)_6$ (2.5)	none	1	toluene/DMF	140	1.5	63	0
6	$Mo(CO)_6$ (2.5)	none	1	toluene/DMF	140	2.5	40	22
7	**$Mo(CO)_6$ (2.5)**	**none**	**1**	**toluene/DMF**	**140**	**7**	**0**	**60**

From a synthetic viewpoint, we have discovered a novel one-pot *h*-PKR/desilylation sequence that avoids deprotective manipulation and therefore remarkably shortens the synthesis. Moreover, the intramolecular *o*-PKR uses the unsaturated ketones (such as **5**), where the alkyne and aldehyde moieties have been connected via their α and β positions. Such cyclization substrates have been rarely reported[6] because the relatively strained structures and the functional group compatibility challenge such cycloadditions. Our work has thus provided a significant extension of the existing *h*-PKR strategy.

With the four-step access to tricyclic carbon skeleton (±)-**4** realized, we next turned our attention to establishment of the requisite stereocenters and the completion of the formal synthesis of (±)-aplykurodinone-1 (**1**) (Scheme 3). The contiguous C7 and C8 stereocenters were simultaneously installed by a Michael addition of lithium dimethylcuprate, delivering (±)-**10** as a single stereoisomer. The structure of (±)-**10** was confirmed through X-ray crystallographic analysis.[14] The stereochemical outcome of this reaction possibly arises from a kinetically controlled lithium dialkylcuprate addition. That is, the lithium dimethylcuprate approaches enone **4** from the less hindered convex face, providing the kinetically favorable product (±)-**10**.[8] Establishment of the correct C4 stereochemistry was then explored. Treatment of lactone (±)-**10** with TMSOTf and triethylamine followed by protonation afforded (±)-**11** (major) via a double-bond isomerization, along with the thermodynamic product (±)-**12** (minor).[15] Compounds **11** and **12** were separately converted into the desired product (±)-**13** in excellent yields, the structure of which was confirmed by single-crystal X-ray diffraction.[16] Gratifyingly, the desired product **13** was obtained as a single stereoisomer, and this complete facial selectivity of these two hydrogenation transformations may arise from the different steric environments of **11** and **12**. Specifically, the coordination effects between the oxygen and iridium made the hydrogenation of **11** stereospecifically occur at the concave face. In contrast, reduction with Pd/C resulted in the opposite stereochemical outcome with hydrogenation occurring from the less hindered convex face of **12**.[17] Finally, compound **13** underwent Ito–Saegusa oxidation[3a,c] to give desired enone (±)-**2**, which completed the formal synthesis of (±)-aplykurodinone-1 (**1**), since the final Michael addition step has been previously reported by Yang et al.[3c,18] It should be noted that, in terms of atom economy,[19] we have developed an efficient synthetic route that proceeds with high stereoselectivity.

Scheme 3. Formal Synthesis of (±)-Aplykurodinone-1



In conclusion, we have completed a highly efficient formal synthesis of (±)-aplykurodinone-1 (**1**) by showcasing a novel, one-pot intramolecular *h*-PKR/desilylation sequence to rapidly construct the tricyclic framework. This represents the highest

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yield route to the advanced intermediate (±)-**2** (eight steps, 20% overall yield, from known compound **6**[9]). Other features of the synthesis include a stereoselective Michael addition to simultaneously install the contiguous C7 and C8 stereocenters and a late-stage rational establishment of the stereocenters at C3 and C4 through stereospecific hydrogenation, all of which highlight the high stereoselectivity and the atom economy of the present route. This concise strategy offers an efficient protocol for the synthesis of other aplykurodines[20] and other butenolide-containing bioactive compounds. On the basis of the current work, the investigation of enantioselective versions and application of *h*-PKR to the synthesis of other analogs is ongoing in the laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00068.

Experimental details; NMR data (PDF)
Crystallographic data for **10** (CIF)
Crystallographic data for **13** (CIF)

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Notes

The authors declare no competing financial interest.

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(14) CCDC 1515244 (**10**) contains the supplementary crystallographic data for this paper. These data are available free of charge from the Cambridge Crystallographic Data Centre.

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(18) Yang and co-workers reported that the final attachment of the C11 side chain provided (±)-aplykurodinone-1 (**1**) as well as (±)-C11-*epi*-aplykurodinone-1 (**14**) and (±)-C13-*epi*-aplykurodinone-1 (**15**) in excellent combined yields.[3c]

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