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Total synthesis of Hirtellanine A

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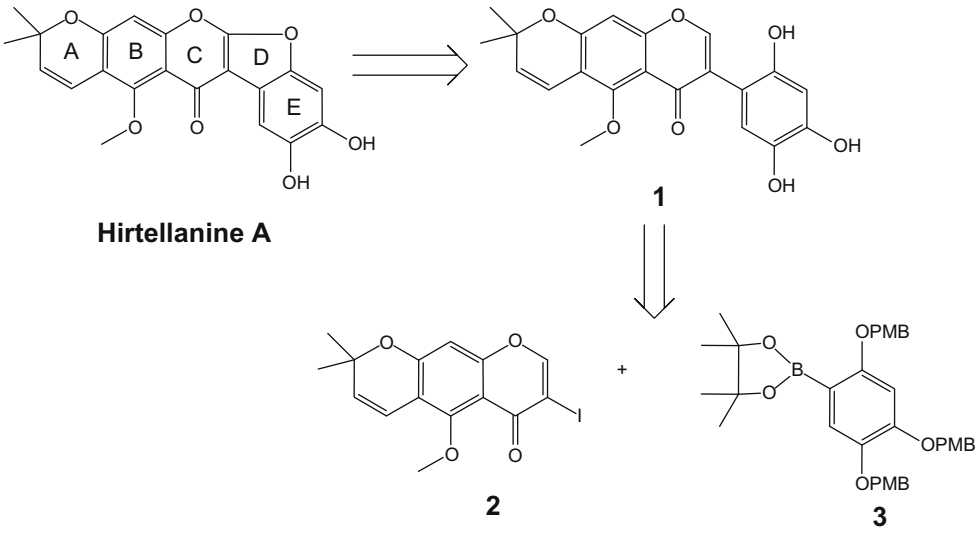
ABSTRACT

The first total synthesis of hirtellanines A is described. The key transformations include (i) base-mediated regioselective pyran ring formation, (ii) one-pot sequential boronation and Suzuki–Miyaura cross-coupling, and (iii) a tandem acid-induced deprotection and subsequent tautomerizations.

Hirtellanine A is a coumaronochromone derivative isolated from the roots of *Campylotropis hirtella* (Franch.) Schindl.[1] In vitro assay indicates that hirtellanine A has strong B lymphocyte suppression activity (IC50: 0.06 μM) and T lymphocyte suppression activity (IC50: 0.92 μM). Compared with cyclosporin A, hirtellanine A displays stronger B lymphocyte suppression activity and lower cytotoxicity, thus there is extreme interest in developing a concise synthetic strategy for this compound. Herein, we describe the first total synthesis of hirtellanine A, which could be useful for structure–activity relationship study.

Our retrosynthetic analysis of hirtellanine A was depicted in Scheme 1. The ordinary approaches toward the synthesis of coumaronochromone derivatives involved oxidative cyclization of 2′-hydroxy isoflavones.[2] Various oxidants were used such as $K_3Fe(CN)_6$, Ag_2CO_3, $Pb(OAc)_4$, SeO_2, usually with relatively lower yields.[3] More recently, a mild oxidative cyclization method had been developed for the synthesis of alkylpolyhydroxy- and alkoxy-coumaronoc-hromones from 2′-hydroxyisoflavones.[4] The mechanism of the reaction was assumed to be an oxy-michael addition followed by dehydrogenation. However, it was still unclear



Scheme 1. Restrosynthetic analysis of hirtellanine A.

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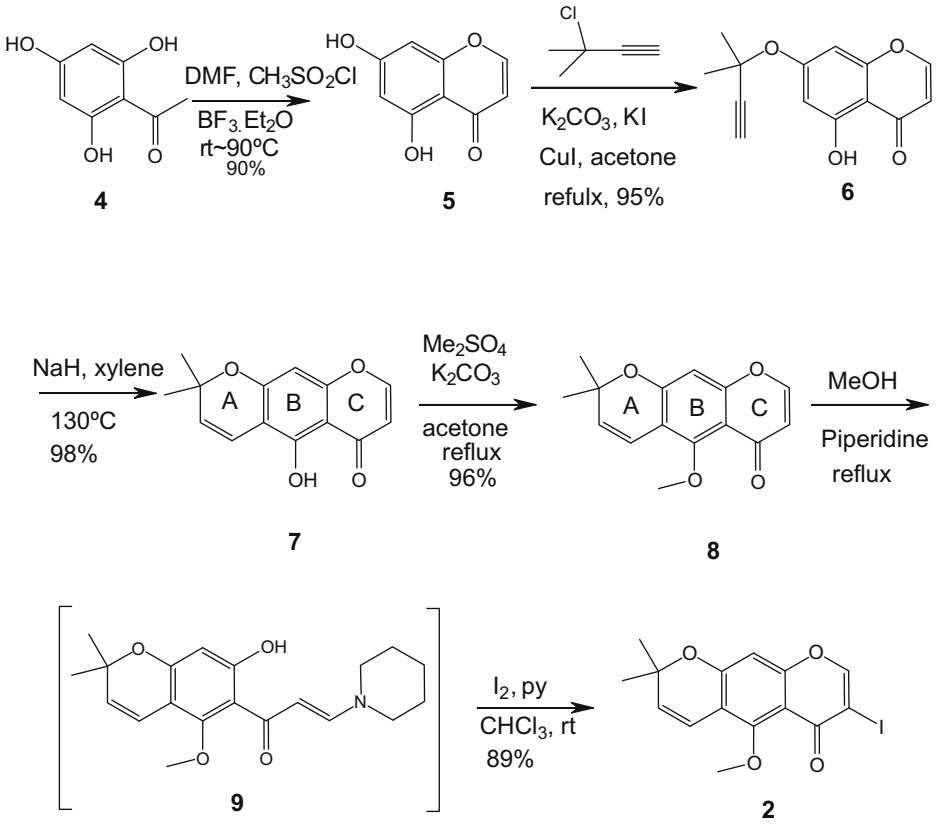


Scheme 2. Construction of fragment **2**.

whether this method could be applied to the synthesis of polyhydroxy coumaronochromones. In our current studies, the initial design (Scheme 1) was to synthesize the 2′,4′,5′-trihydroxy isoflavone derivative **1**, and hoping to undergo an oxidative cyclization with DDQ to deliver the desired compound hirtellanine A.

Thus, our first attempt was aimed at synthesizing the key intermediate, 3-iodo-5-methoxy-dimethylchromene pyran-4-one **2**, which then underwent Suzuki–Miyaura reaction with 2,4,5-tri(*p*-methoxyphenoxyl)phenylborane **3** to form compound **1**.

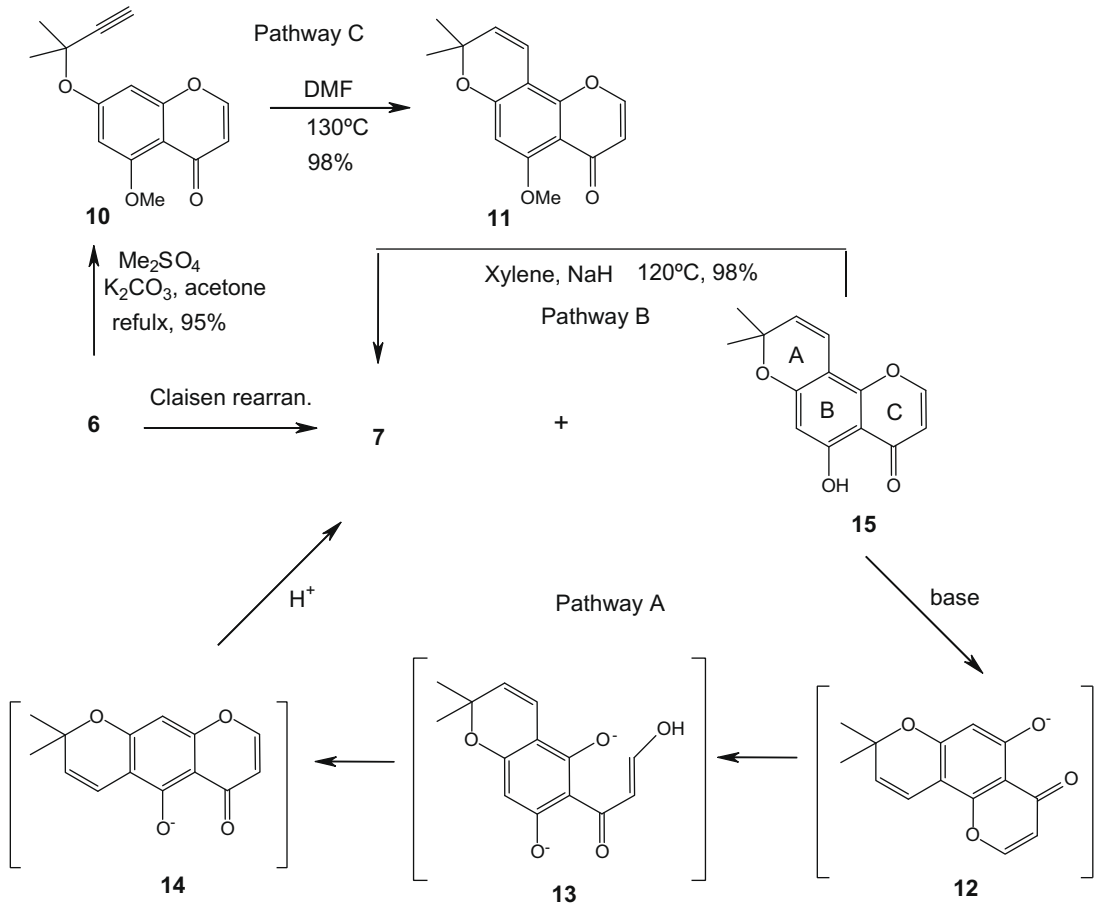
As shown in Scheme 2, the synthesis of the key intermediate **2** started from the commercially available acetylphlorog-lucinol **4**, which underwent Vilsmeier–Haack formylation and cyclization catalyzed by $BF_3{\cdot}Et_2O$ to afford **5** in 90% yield.[5] Subsequently, the regioselective Claisen rearrangement reaction was explored for the construction of the A-ring of **7**. A variety of reaction conditions[6] were attempted, however, none of those reaction conditions gave satisfactory results. Interestingly, as depicted in the Table 1, it was found that the polarity of solvents significantly affected the regioselectivity of this reaction. Further investigation unveiled that the presence of a strong base could control the regioselectivity effectively. NaH was among the best reagents which completely controlled the direction of the reaction to yield **7** in 98% yield. As shown in Scheme 3, the Claisen rearrangement process appeared to be a kinetic controlled reaction (pathway A) and compound **15** was a main product of the reaction. However, compound **7** had the linear structure and probably is more stable than **15**. Thus, under the strong alkaline conditions, the C-ring of compound **15** was opened and reclosed to form **7**[7] in a quantitative yield. The above-mentioned assumption was further confirmed by the Claisen rearrangement of **10**[8] which gave **11** in 98% yield (pathway C). Methylation of **7** under standard manipulations with Me_2SO_4 gave **8** in 96% yields. The C-ring of **8** was opened with piperidine in MeOH and subsequently treated with I_2 in the presence of 2 equiv of pyridine to yield **2** in 89% overall yield.[9]

Table 1
The regioselective cyclization of **6**

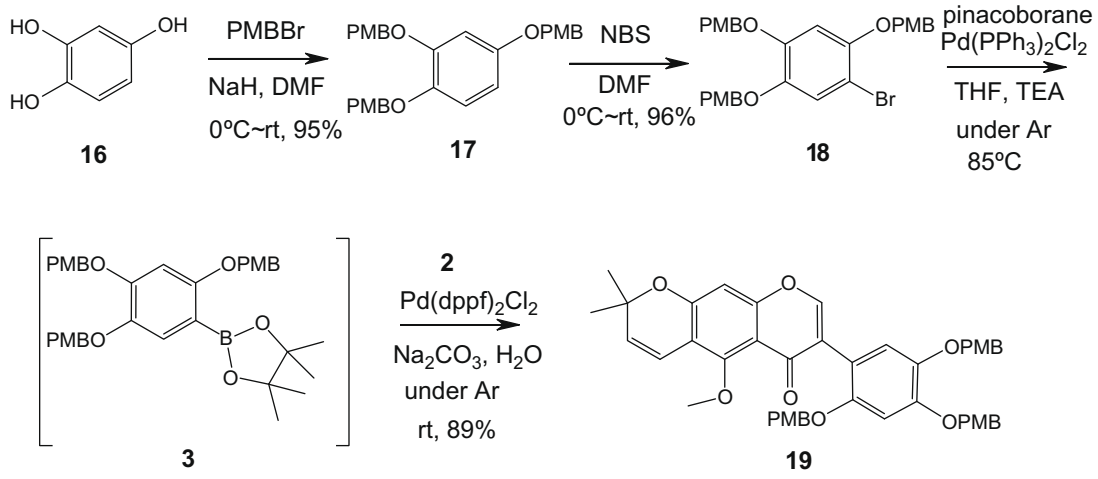
Conditions	Temp (°C)	Times	Yield[a]	7:15	
AcOH	120	20 h	98	22	78
DMF	130	30 h	98	20	80
DMA	130	30 h	83	26	74
Tol.	120	150 h	70[b]	47	53
Xylene	130	30 h	98	60	40
DMF, MW	165	15 min	98	22	78
DMSO, MW	210	18 min	90	24	76
DEA, MW	220	18 min	88	32	68
Diox., $PtCl_4$	70	5 h	98	31	69
Py	120	20 h	98	24	76
Xylene, $Ca(OH)_2$[c]	130	20 h	98	87	13
Xylene, Cs_2CO_3[c]	130	16 h	98	96	4
Xylene, KOH[c]	130	16 h	95[d]	>99	Trace[e]
Xylene, NaH[c]	130	16 h	98	>99	Trace[e]

[a] Calculated based on ^{1}H NMR and HPLC signals.
[b] About 30% of **6** was recovered.
[c] 6 equiv of base was used.
[d] About 5% of **5** was obtained.
[e] Observed by HPLC and TLC. DMA = *N*,*N*′-dimethyl aniline; DEA = *N*,*N*′-diethylaniline.

With the key intermediate **2** in hand, we focused on the synthesis of **19** (Scheme 4). Protection of the phenol groups of 1,3,4-trihydroxybenzene (**16**) with PMBBr afforded **17**,[10] which was subsequently brominated with NBS to form **18**[11] in 96% yield. The boronation of **18** with pinacoborane according to modified Yashima's procedure[12] went smoothly, which gave borate ester **3**. The crude product **3** could be used directly for the coupling with **2** without further purification and afforded **19** in an 89% overall



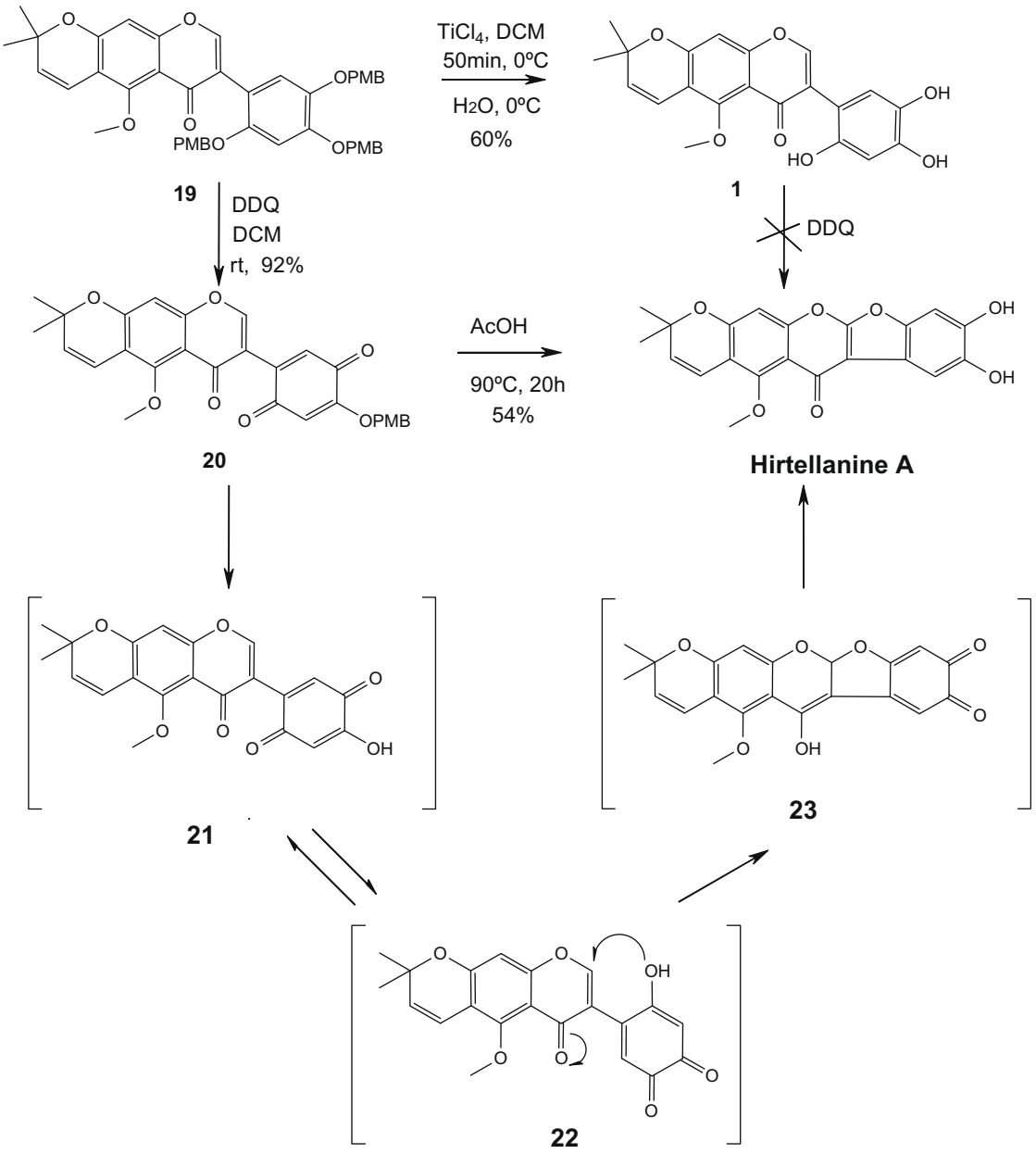
Scheme 3. Proposed mechanism of the regioselectivity.



Scheme 4. One-pot boronation and Suzuki coupling.

yield. In fact, the boronation and subsequent coupling could be performed conveniently in one flask.[13] This one-pot protocol effectively simplified the operation and avoided the stability issue of borate ester **3**.

Removing the PMB protection groups on the 3-substituted 5-methoxy dimethylchromene pyran-4-one **19** in acidic condition gave compound **1** in a reasonable yield.[14] However, the oxidative cyclization of **1** with various oxidative reagents was tried without success and, in all cases, only a decomposed mixture was obtained. It was reported that DDQ itself could be used as a reagent to remove PMB protection group.[15] Thus, we adopted the reaction condition, and hoped that the oxidative cyclization would happen after the deprotection. Interestingly, DDQ only removed two PMB groups at para positions and the quinone **20** was obtained in 92% yield. The cyclization was blocked due to the third PMB-protecting group being kept intact. Fortunately, treatment of **20** with various acids ($MeSO_3H/CHCl_3$, AcOH, and HCl/EtOH) led to the formation of desired hirtellanine A exclusively. This conversion might involve



Scheme 5. Proposed mechanism for the cascade tautomerization.

the following mechanistic steps (Scheme 5): removal of PMB protection group, tautomerization, intra-molecule oxy-Michael addition, and subsequent cascade tautomerizations which led to the formation of hirtellanine A in 54% yield. The spectroscopic data of hirtellanine A synthesized were identical with the authentic sample obtained from plant material.

In summary, we have developed the first synthetic route toward hirtellanine A wherein regioselective pyran ring formation, one-pot tandem boronation and Suzuki coupling as well as a cascade tautomerization are used as key reactions. The overall yield starting from acetylphloroglucinol **4** to hirtellanine A is 31.6% in eight steps.

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Supplementary data

Supplementary data (detailed experiment procedures, compound characterization, and copies of spectra data.) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.03.092.

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