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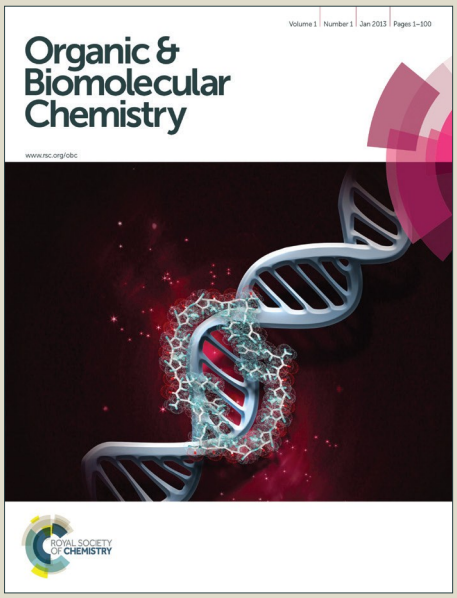

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COMMUNICATION

Total Synthesis of (±)-Ganocins B and C

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The first total synthesis of structurally unique polycyclic phenolic meroterpenolids, ganocins B and C is reported. The synthesis features gold-catalyzed intramolecular cascade cyclization to construct the C/D ring bearing an angular methyl group, diastereoselective Michael addition, and acid-mediated one-pot Robinson cyclization/deprotection/isomerization.

Ganoderma, which has long been used to treat and prevent various diseases, is one of the most well-known traditional medicines.[1] Its unusual biological activity has fuelled an intensive investigation into the identification of the actual chemical constituent. In this context, a series of novel phenolic meroterpenolids have been isolated[2] and found to exhibit interesting biological activities including antitumor, renoprotective, antioxidant, liver-protective, and anti-acetylcholinesterase (anti-AChE) activity.[2,3] In 2014, a new family of ganocins, possessing four unprecedented polycyclic phenolic meroterpenoids (Figure 1), were isolated from the fruiting bodies of *Ganoderma cochlear* by Qiu and coworkers.[4] Initial biological evaluation revealed that they exhibit anti-AChE activity. Structurally, ganocins feature four fused and highly strained ring system (A/B/C/D), within two to four consecutive stereocenters containing a compact quaternary carbon (C6'). Because of this unusual structure and the potential for novel biological properties, we sought to explore their total synthesis. To our knowledge, total synthesis of these molecules has not been reported thus far. In this study, we report the first total synthesis of ganocins B and C involving gold-catalyzed cascade cyclization and Robinson cyclization as the key steps.

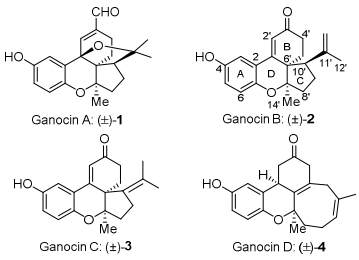
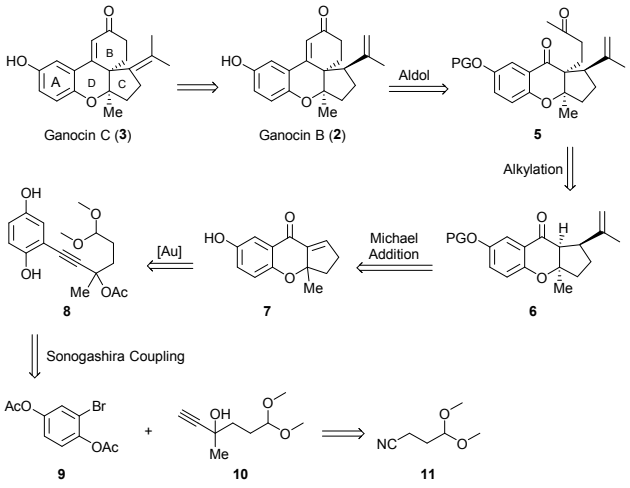


Figure 1. The structure of ganocins.

Our retrosynthetic analysis of ganocins B (Fig.1-**2**) and C (Fig.1-**3**) is illustrated in Scheme 1. Ganocin C was expected to be formed from ganocin B upon olefin isomerization. The ring B of ganocin B would be constructed via a Robinson cyclization of structure **5**, which could be assembled from the diastereoselective alkylation of structure **6**. Alkene **6** might be obtained by a directed Micheal addition to the key intermediate 2,3-fused chromone **7**, which was envisioned to be accessible from a gold-catalyzed[5,6] intramolecular cascade cyclization of phenolic propargyl acetate **8** by using Wong's



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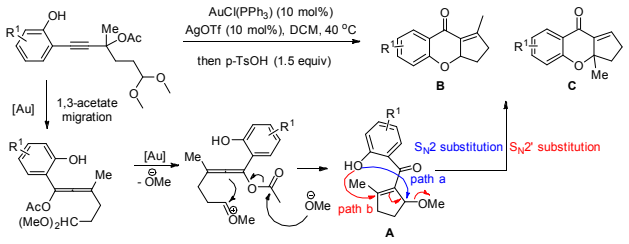
Scheme 1. Retrosynthetic analysis of Ganocins B and C. PG = protecting group.

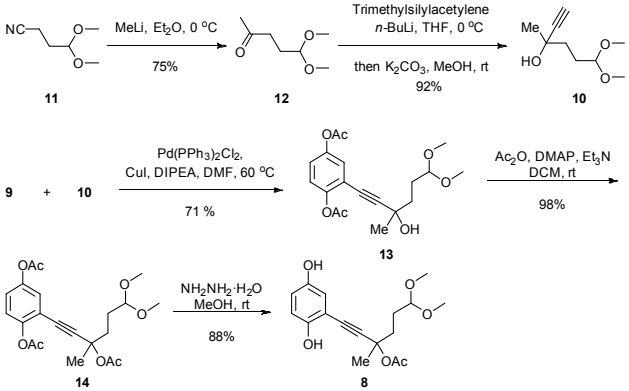


Scheme 2. Proposed mechanism for Wong's Au-catalyzed cascade cyclization.

protocol.[7] The precursor, structure **8** could be synthesized by Sonogashira coupling from commercially available bromide **9** and propargyl alcohol **10**. Commercially available molecule 4,4-dimethoxybutanenitrile **11** was suggested to be the precursor of structure **10**.

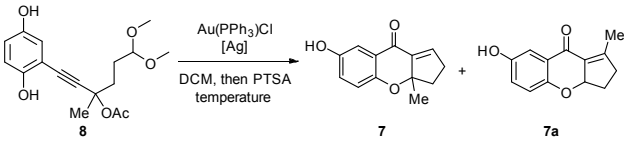
It should be mentioned that in Wong's cyclization reaction, the S_N2 substitution (last step, Scheme 2) product tricyclic chromones **B** were predominately formed. However, based on their mechanistic hypothesis and literature precedent,[8] we reasoned that the S_N2' substitution, forming the corresponding tricyclic product **C** bearing an angular methyl group, might be also possible by a judicious tuning of the electronic properties of the phenol nucleophile and finding the right reaction conditions, thus providing an extraordinary simple access to the core structure (ADC ring) of ganocins A-C.

Our total synthesis was begun by construction of the phenolic Au-catalyzed precursor, propargyl acetate **8** (Scheme 3). Exposure of nitrile **11** to an ethereal solution of methyllithium at 0 °C afforded ketone **12** in 75% yield. Upon treatment with



Scheme 3. Synthesis of key Au-catalyzed cyclization precursor **8**. DIPEA = *N,N*-diisopropylethylamine, DMAP = 4-dimethylaminopyridine, THF = tetrahydrofuran, DMF = *N,N*-dimethylformamide.

Table 1. Au-catalyzed cascade cyclization of the propargyl acetate **8**.[a]



entry	[Ag]	temperature	**7**	**7a**
1	AgOTf	40 °C	0	38%
2	AgOTf	25 °C	42%	29%
3[b]	AgOTf	25 °C	34%	0
4	$AgBF_4$	25 °C	55%	0

[a] $Au(PPh_3)Cl$ (10 mol %), [Ag] (10 mol %), PTSA (1.0 equiv), 3 h, isolated yield. [b] Without addition of PTSA. PTSA = *p*-toluenesulfonic acid.

an *in situ* generated lithium trimethylsilylacetylide and follow-up removal of the silyl group, ketone **12** was converted to propargyl alcohol **10** in 92% overall yield. The bonding of acetylene **10** and commercially available bromide **9**[9] (Scheme 1) was accomplished by Sonogashira coupling[10] to produce 71% yield of tertiary alcohol **13**, which was then protected with an acetyl group by treating with Ac_2O/DMAP. The selective deprotection of both phenolic acetyl groups with hydrazine[11] in methanol, furnished the key cyclization substrate **8** in high yield.

With the intermediate **8** in hand, the stage was set for the key Au-catalyzed cascade cyclization reaction (Table 1). Unfortunately, when substrate **8** was subjected to previously reported reaction conditions,[7] S_N2 substitution (Scheme 2) product **7a** was formed with a 38% yield without the detection of the desired product **7** (entry 1), in accordance with a previous observation. Interestingly, by lowering the temperature to 25°C, the desired S_N2' substitution product **7** was obtained in 42% yield accompanied by 29% yield of **7a** (entry 2). We speculate that the tertiary ether **7** might be unstable under acidic conditions and high temperatures due to its propensity for formation of a stable tertiary carbocation, and thereby being converted to the undesired product, **7a**.[12] Indeed, the omission of *p*-toluenesulfonic acid (PTSA) led to the exclusive formation of substrate **7**, although in a decreased yield of 34% (entry 3). Fortunately, the highest yield was obtained by the use of $AgBF_4$ in place of AgOTf as an additive (55%, entry 4).

Thereafter, a copper-mediated conjugated addition to α,β-unsaturated ketone **7** resulted in the formation of *cis*-fused **15** as a single stereoisomer in 87% yield (Scheme 4).[13] The desired stereochemistry was presumed to arise from the steric hindrance from the angular methyl group at C7'. Protection of

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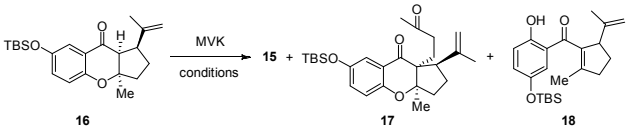
Table 2. Studies of Michael addition of **16**.[a]



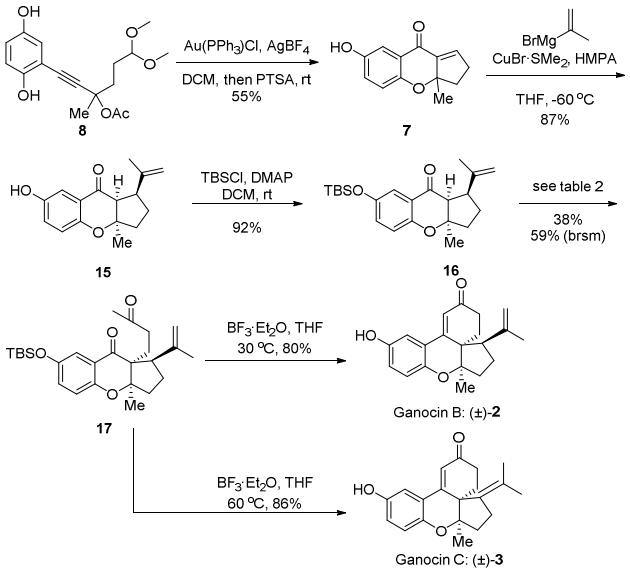
entry	conditions	15	16	17	18
1	NaOMe in MeOH, rt	81%	0	0	0
2	LHMDS in THF, -60 °C	0	84%	trace	0
3	DBU in THF, rt	0	0	16%	53%
4	NaOH in THF, rt	0	23%	17%	22%
5	NaOH in THF, 0 °C to rt	0	36%	38% (59% brsm)	0
6[b]	$Sc(OTf)_3$ in DCM, rt	75%	0	0	0

[a]Reaction conditions: **16** (0.1 mmol, 1.0 equiv), MVK (0.15 mmol, 1.5 equiv), base (0.05 mmol, 0.5 equiv), solvent (1 mL), 2 h, isolated yields. [b] $Sc(OTf)_3$ (20 mol %) was employed. MVK: methyl vinyl ketone; DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene; brsm: based on the recovered starting material.

phenol **15** with TBSCl/DMAP produced substrate **16** in 92% yield.

We then focussed on construction of ring B. Alkylation at this position proved to be difficult due to the profound steric hindrance and a retro-oxa-Michael addition side reaction. After several attempts, we found that Michael addition to methyl vinyl ketone (MVK) could give the desired diketone product **17** as a single diastereomer (Scheme 4). Thus, a variety of reaction parameters (mainly the base/Lewis acid, solvent and temperature) were examined, and some of the representative results are summarized in Table 2. Only the silyl-deprotected product **15** was obtained with 81% yield under NaOMe/MeOH conditions (entry 1). The use of the classical lithium bis(trimethylsilyl)amide (LHMDS) as a base resulted in the recovery of the starting material (entry 2). Unexpectedly, DBU gave a 16% yield of the desired product **17**, along with a considerable amount of retro-oxa-Michael addition side product **18** (entry 3). The use of NaOH instead of DBU provided a comparable yield but with much fewer side reactions (entry 4). The best result was obtained when the reaction was run at lower temperature (0-25 °C), with a 59% yield based on the recovered starting material (entry 5). The step where Lewis acid promoted Michael addition is known from the literature.[14] However, from our experience, the use of $Sc(OTf)_3$ as a catalyst only led to the deprotection of the silyl group (entry 6).

To finish the total synthesis, it was observed that $BF_3{\cdot}Et_2O$ was a good primer for the aldol condensation. Thus, treatment of



Scheme 4. Completion of the synthesis of ganocins B and C. HMPA = hexamethylphosphoric triamide, TBS = *t*-butyldimethylsilyl.

the diketone **17** with $BF_3{\cdot}Et_2O$ in THF at 30 °C, the acid mediated Robinson cyclization/deprotection took place in one-pot, producing ganocin B (**2**) in a good yield of 80%. To our surprise, the simple elevation of the temperature to 60 °C rendered an *in-situ* olefin isomerization to give ganocin C (Fig 1-**3**) in 86% yield. The spectroscopic data of our synthetic samples (^1H and ^{13}C NMR) matched well in all respects to those reported in the literature.[4]

Conclusions

In summary, we have accomplished the first total synthesis of ganocins B and C, two phenolic meroterpenolid natural products possessing a spiro[4,5]decane ring system. The approach is highly convergent and the linear sequence is 10 steps starting from commercially available 4,4-dimethoxybutanenitrile substrate **11**. The synthesis features gold-catalyzed intramolecular cascade cyclization to assemble the 6-6-5 tricyclic core of ganocins B and C and acid-mediated successive Robinson cyclization/deprotection/isomerization to construct ring B. The synthesis of ganocin analogs using our protocol and their related biological evaluation are ongoing in our laboratory.

Acknowledgements

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