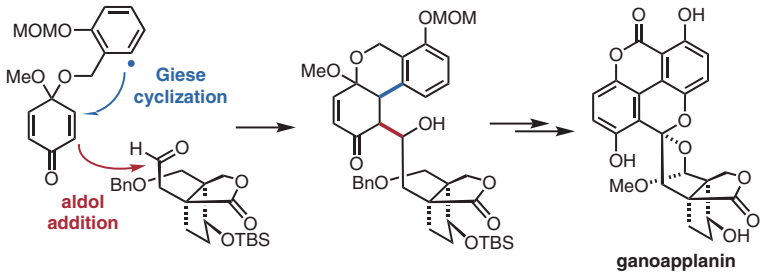
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Development of a Triethylborane-Mediated Giese Cyclization/ Aldol Reaction Cascade for the Total Synthesis of Ganoapplanin

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Abstract We present our synthetic endeavors towards the *Ganoderma* meroterpenoid ganoapplanin. This natural product was isolated from a *Ganoderma* fungus in 2016 and was found to be an inhibitor for T-type voltage-gated calcium channels. Our synthetic approach is based on a powerful intramolecular Giese cyclization/intermolecular aldol cascade to link the northern aromatic to the southern terpenoid fragment. This article highlights the synthetic studies that ultimately led to the successful development of the key cascade reaction, culminating in the first total synthesis of ganoapplanin.

1 Introduction
2 Synthesis of the Southern Terpenoid Fragment
3 Synthesis of the Northern Terpenoid Fragment
4 Triethylborane-Mediated Giese Cyclization/Aldol Reaction Cascades
5 Completion of the Total Synthesis of Ganoapplanin
6 Conclusion

Keywords *Ganoderma*, meroterpenoids, total synthesis, cascade reactions, radicals

1 Introduction

Ganoderma fungi are well-known in traditional medicine for their wide range of pharmacological activities such as cytotoxic, antibacterial, or antioxidant.[1] Among their bioactive compounds, meroterpenoids have attracted considerable interest from synthetic chemists due to their structural complexity and diverse biological properties.[2] One such meroterpenoid is ganoapplanin (**6**), a natural product isolated in 2016 by Qiu from *Ganoderma applanatum*, a medicinal mushroom long valued in traditional remedies.[3] From a structural point of view, **6** consists of a tetra-*ortho*-substituted biaryl motif and a dioxatricyclo[4.3.3.0]dodecane scaffold forming a unique spiro bis-acetal motif. Ganoapplanin (**6**) also features five contiguous stereocenters, two of which are quaternary. Beyond its structural complexity, racemic ganoapplanin (**6**) was reported to inhibit T-type voltage-gated calcium channels (IC_{50} = 36.6 μM),[3] highlighting its potential as a drug against neurodegenerative diseases, such as epilepsy and Parkinson's disease.[4,5]

In recent years, our group developed synthetic approaches to access polysubstituted (hetero)arenes[6–9] and total syntheses of related *Ganoderma* meroterpenoids.[10] However, we found that these methods were incompatible with the unique framework of ganoapplanin (**6**), specifically the spiro bis-acetal skeleton connecting the tetra-*ortho*-substituted biaryl motif with the terpenoid moiety.

To access ganoapplanin (**6**), we designed a synthetic route based on a triethylborane-mediated Giese cyclization/aldol reaction cascade. This approach was inspired by the seminal work of Utimoto,[11] who reported radical formation from *tert*-butyl iodide (**1**) by treatment with BEt_3 (triethylborane) and triphenyltin hydride. The *tert*-butyl radical **I** was added in a 1,4-fashion to methyl vinyl ketone followed by in situ formation of boron enolate **II**, which participated in an aldol reaction with benzaldehyde (Scheme 1A). In 2015, Inoue demonstrated an expansion of this three-component cascade to the decarbonylation of α-alkoxyacyl tellurides.[12] The generated radical **III** underwent a Giese addition to enone **4** followed by an aldol reaction with benzaldehyde (Scheme 1B).

Inspired by these compelling seminal studies, we designed a synthetic strategy for ganoapplanin (**6**) that involves an intramolecular version of the radical step.[13] To

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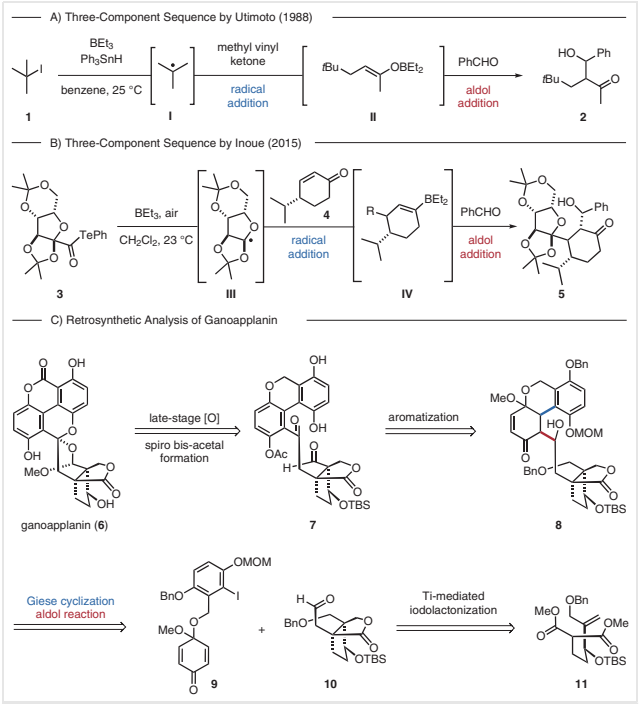


(from left to right) **Thomas Magauer** was born in Linz in 1983 and grew up in Steyr, Upper Austria. In 2002 he moved to Vienna to study chemistry at the University of Vienna and in 2007 he joined the laboratory of Prof. Johann Mulzer for his PhD studies. Two years later, in 2009, he moved to Harvard University (USA) as an FWF Erwin Schrödinger fellow to work with Prof. Andrew G. Myers. In 2012, he started his independent research career as FCI Liebig and DFG Emmy Noether Group Leader at LMU Munich. In 2017, Tommy was honored with the Goering visiting professorship at the University of Wisconsin, Madison and was appointed full professor of Synthesis and Synthetic Methods at the University of Innsbruck (Austria), where he now heads the Institute of Organic Chemistry. His research has been supported by numerous industrial collaborations, the Austrian Science Fund (FWF), and major European grants, including an ERC Starting Grant (2017–2022) and an ERC Consolidator Grant (2022–2027).

Nicolas Müller grew up in Oberkirch, a small city in southern Germany. In 2013, he moved to Munich to study chemistry at Ludwig-Maximilians University. For his Bachelor's thesis, he joined Prof. Trauner's group. In 2018, he conducted research for his Master's thesis in Prof. Sarpong's group at the University of California, Berkeley, focusing on the synthesis of xishacorene natural products. After graduating, he joined the group of Prof. Carreira at the ETH Zurich to work on palladium-catalyzed aminoalkynylations of alkenes. Since 2021, he is a PhD student in Prof. Magauer's group at the University of Innsbruck in Austria, where he is currently working on the synthesis of *Ganoderma* natural products.

Ondřej Kováč received his BSc and MSc at Palacký University in Olomouc. He pursued PhD studies under the supervision of Dr. Jiří Pospíšil, where he worked on a diversity-oriented synthesis and organocatalysis methodology development. In 2020, he received a prestigious postdoctoral fellowship from the Experientia Foundation for an internship in the group of Professor Thomas Magauer at Innsbruck University in Austria, where he was engaged in natural product synthesis. In 2024, he began his independent research supported by an Experientia Foundation start-up grant as Head of the Laboratory of Synthesis of Natural Products (Palacký University Olomouc, Czech Republic).

this end, we chose to form the lactone in the northern aromatic fragment and the central spiro bis-acetal at a later stage, starting from hydroquinone **7**. Further simplification through dearomatization led to hydroxy ketone **8**, which could be accessed via an intramolecular Giese cyclization of aryl iodide **9**, followed by an intermolecular aldol addition with the southern terpenoid fragment **10**. Finally, the key aldehyde **10** was envisioned to be obtained through a titanium(IV)-mediated iodolactonization of alkene **11** (Scheme 1C).



Scheme 1 A) BEt_3-mediated formation of alkyl radicals, followed by Giese addition and aldol reaction; B) BEt_3/O_2-mediated decarbonylation of α-alkoxyacyl tellurides, followed by Giese addition and aldol reaction; C) retrosynthetic analysis of ganoapplanin.

2 Synthesis of the Southern Terpenoid Fragment

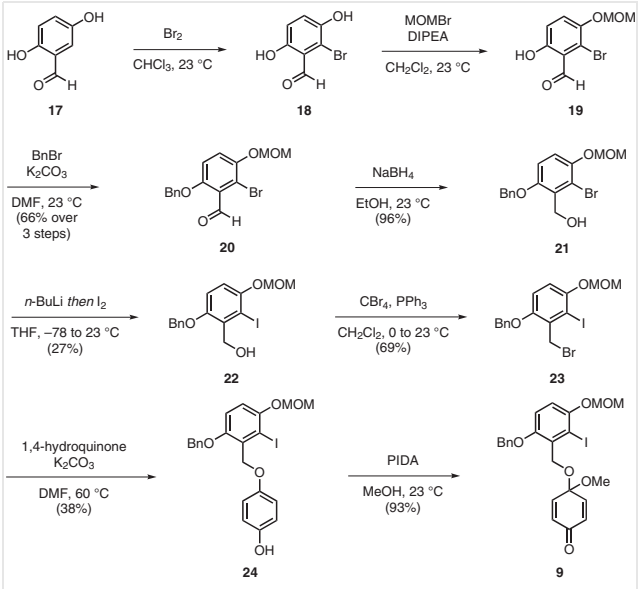
Our synthesis of the southern terpenoid fragment **10** began with a Nozaki–Hiyama–Kishi (NHK) reaction between readily available aldehyde **12**[14,15] and vinyl iodide **13**[16,17], forming the corresponding secondary alcohol (not shown), which was subsequently protected in situ as silyl ether **11** (Scheme 2A). To construct the bicyclic lactone core of the southern fragment, we carried out an iodolactonization exploiting reaction conditions reported by Taguchi ($Ti(O\textit{t}\text{-}Bu)_4$, CuO, and I_2) to form lactone **14**.[18,19] Mechanistically, this reaction is thought to proceed via a 5-*exo*-trig cyclization (Scheme 2B) that stereoselectively forms three consecutive stereocenters, two of which are quaternary. The key aldehyde **10** was prepared upon Krapcho decarboxylation (LiCl; H_2O, DMSO, 150 °C) followed by allylation and oxidative cleavage of the olefin under standard reaction conditions (O_3, PPh_3).

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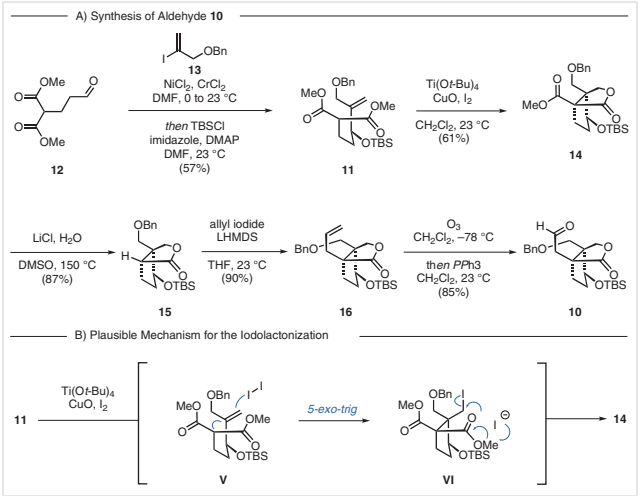
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3 Synthesis of the Northern Aromatic Fragment

Our synthetic endeavor towards aryl iodide **9**, required for our key step, commenced with an attempt of iodination of commercially available 2,5-dihydroxybenzaldehyde (**17**, Scheme 3), which proved to be unfeasible. Therefore, we performed a regioselective bromination to afford bromohydroquinone **18** and aimed for the installation of the iodo substituent at a later stage. Its phenolic groups were subsequently protected as MOM and benzyl ethers to afford arene **20**. Furthermore, the remaining aldehyde moiety was reduced using sodium borohydride to yield benzyl alcohol **21**. To access aryl iodide **22**, the bromo substituent was exchanged for an iodine by lithium–halogen exchange and quenching with iodine. The benzylic alcohol was then converted into benzyl bromide **23** under Appel conditions, which was subsequently substituted with 1,4-hydroquinone under basic conditions. Finally, oxidative dearomatization using (diacetoxyiodo)benzene (PIDA) produced quinone monoacetal **9**.



Scheme 3 Synthesis of aryl iodide **9**.



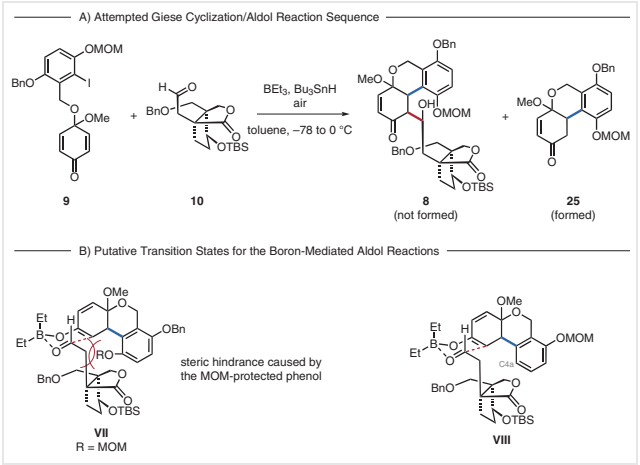
Scheme 2 A) Synthesis of aldehyde **10**; B) plausible mechanism for the iodolactonization.

4 Triethylborane-Mediated Giese Cyclization/Aldol Reaction Cascades

With both fragments in hand, we turned our attention to the key transformation. Unfortunately, when we subjected aldehyde **10** and aryl iodide **9** to triethylborane and tributyltin hydride (Bu_3SnH) in toluene under an air atmosphere, we were unable to detect the desired hydroxy ketone **8** (Scheme 4A). At temperatures between –78 °C and 0 °C, we observed the formation of tricycle **25** as a main product and recovered unreacted aldehyde **10** in quantitative amounts. Unfortunately, isolation of tricycle **25** turned out to be difficult, due to its instability on silica gel. On warming the reaction to 23 °C, decomposition of the aromatic fragment began.

We attribute the unexpected failure of the aldol reaction to steric hindrance. Typical boron-mediated aldol reactions proceed through a six-membered transition state. For substrate **9**, the MOM-protected phenol may introduce steric hindrance, preventing the aldehyde **10** from approaching and forming the required transition state **VII** (Scheme 4B, left structure).

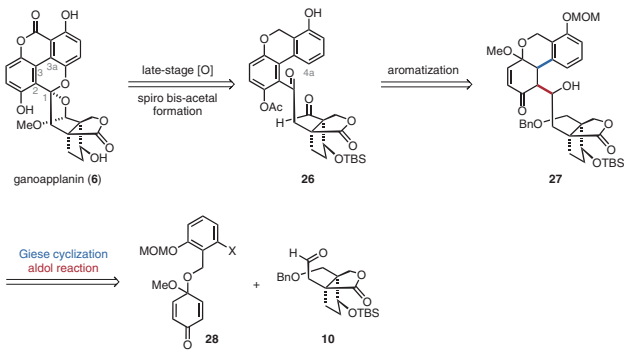
Based on these considerations and the successful formation of the tricyclic **25** via the Giese cyclization, we set out to adapt the retrosynthesis. Thus, in our revised synthetic approach, we chose to introduce the phenolic alcohol at



Scheme 4 A) Attempted Giese cyclization/aldol reaction cascade using aryl iodide **9** and aldehyde **10**; B) putative transition states for the boron-mediated aldol reactions.

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Scheme 5 Revised retrosynthetic analysis.

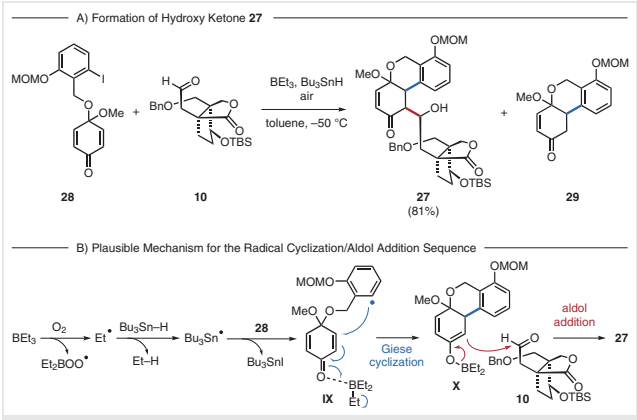
C4a, which is required for the characteristic spiro bis-acetal formation, through late-stage oxidation (Scheme 5). This adjustment allows us to explore the key step using aryl halide **28**, which lacks the additional phenol group and should therefore adapt the six-membered transition state as shown in Scheme 4B (right structure, **VIII**).

To test this hypothesis, we carried out the key step with aryl iodide **28**.[13] Gratifyingly, treating a mixture of aryl iodide **28** and aldehyde **10** with BEt_3, Bu_3SnH, and air in toluene at –50 °C produced an inconsequential diastereomeric mixture of hydroxy ketone **27** in 81% yield, along with varying amounts of tricycle **29** (Scheme 6A). The diastereomeric mixture primarily consists of two main products in 1:0.45 ratio, along with trace amounts of additional diastereomers. Unfortunately, the use of the corresponding aryl bromide instead of aryl iodide **28** did not lead to the desired hydroxyketone **27** or tricycle **29**; instead, only decomposition of the aromatic fragment was observed.

Importantly, this cascade reaction enabled the efficient convergent fusion of both fragments, forming the critical C3–C3a and C1–C2 bonds of ganoapplanin (**6**) in a single step. Overall, BEt_3 revealed itself as a crucial component for this key transformation and played a dual role in the whole process: (1) radical initiation, generating ethyl radicals[20] that drive the 6-*exo*-trig cyclization of aryl radical **28**, and (2) formation of boron enolate **X**, which promotes the aldol reaction (Scheme 6B). Notably, a stepwise approach involving isolation of the tricyclic ketone intermediates, followed by generation of the boron enolate (via deprotonation and subsequent addition of either dibutylboron triflate (*n*-Bu_2BOTf) or dicyclohexylboron triflate (*c*-Hex_2BOTf)), proved to be ineffective in achieving the aldol addition with aldehyde **10**.

5 Completion of the Total Synthesis of Ganoapplanin

Having ample amounts of hydroxyketone **27**, we turned our attention towards the remaining challenges to complete the synthesis of ganoapplanin (**6**) that involved: (1) aromatization of enone **27**, (2) oxidation at C4a to convert the phenolic moiety into a hydroquinone and concomitant formation of the spiro bis-acetal structure, and (3) C–H oxidation of the cyclic ether to the corresponding lactone.



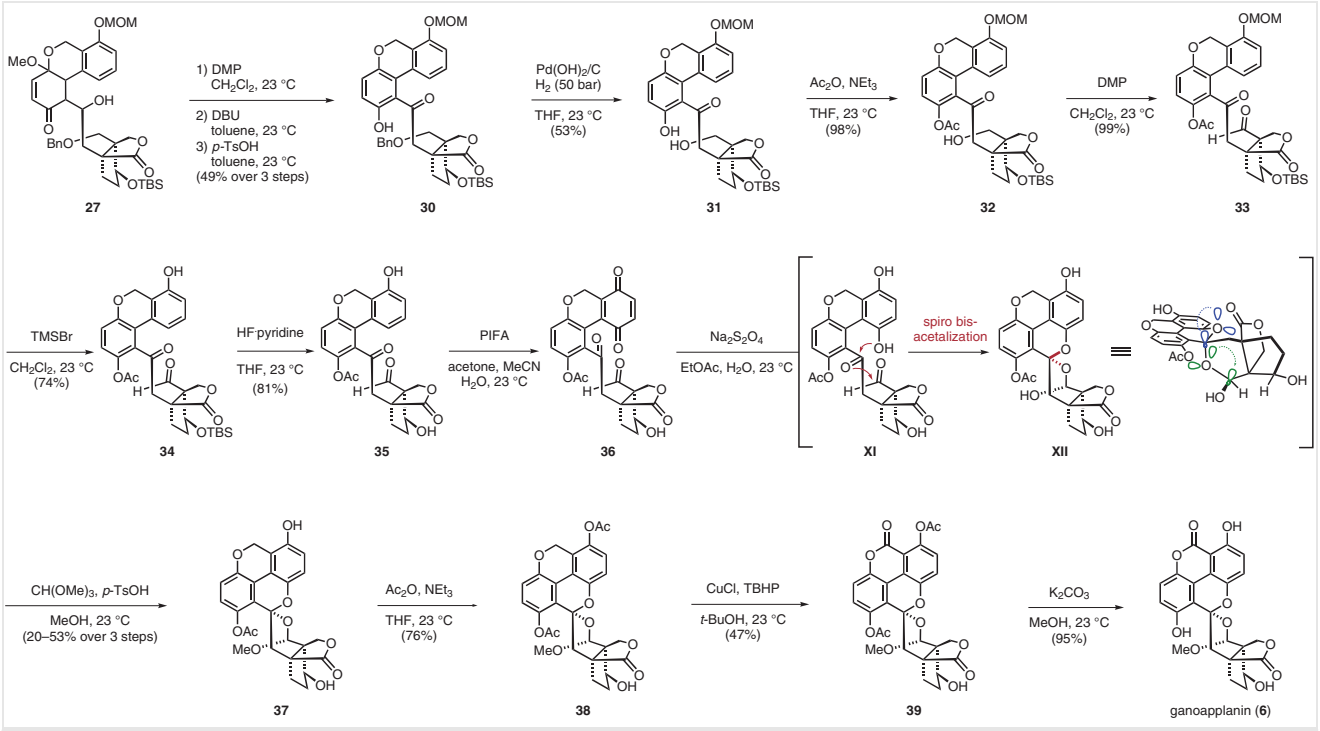
Scheme 6 A) Formation hydroxy ketone **27**; B) plausible mechanism for the Giese cyclization/aldol reaction sequence.

The synthesis was advanced towards the formation of the biaryl motif, initiated via oxidation of secondary alcohol **27** to the corresponding ketone using Dess–Martin periodinane (DMP). Subsequently, treatment with *p*-toluenesulfonic acid (*p*-TsOH) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) provided biaryl **30** with a high overall yield over 3 steps (49%) (Scheme 7).

To realize the challenging C4a oxidation/spiro bis-cyclization, an adjustment of oxidation states was required. Initially, the debenzylation was accomplished using Pearlman's catalyst under 50 bar of hydrogen pressure, providing primary alcohol **31**. The remaining phenolic alcohol was then protected as its acetyl ester by reacting with acetic anhydride and triethylamine, followed by DMP oxidation to aldehyde **33**. For the desired oxidation at C4a, we planned to oxidatively dearomatize the unprotected phenol **35** to the corresponding quinone **36** with subsequent reduction to the hydroquinone. This required global deprotection of the MOM and TBS groups at this stage. Firstly, the methoxymethyl ether was cleaved upon treatment of **33** with trimethylsilyl bromide (TMSBr), liberating the corresponding phenol **34**, and secondly the TBS ether was cleaved with hydrogen fluoride to yield phenol **35**. Finally, the stage was set for a nontrivial oxidation/spiro bis-cyclization sequence. Interestingly, the telescoped protocol without the need for purification of the intermediates proved to be superior, and after optimization, the desired polycycle **37** was obtained in 53% yield over 3 steps. The overall sequence includes: 1) oxidation to quinone **36** using phenyliodine bis(trifluoroacetate) (PIFA) in an aqueous mixture of acetone and acetonitrile, 2) reduction to hydroquinone **XI** using sodium dithionite and 3) mixed acetal formation realized by treatment with *p*-TsOH and trimethyl orthoformate in methanol. A

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Scheme 7 Completion of the total synthesis of ganoapplanin (**6**).

possible explanation for the observed diastereoselectivity in the acetalization step is the anomeric stabilization of the resulting spiro bis-acetal. The reaction likely proceeds under thermodynamic control, favoring the diastereomer that can benefit from this stabilization. The formation of the second acetal offers additional anomeric stabilization, as the axial–axial alignment of spiro-acetal **XII** allows for two anomeric interactions.

With the core structure **37** in place, the remaining challenge was to oxidize the cyclic ether to its lactone. Initially, we attempted direct C–H oxidation with the presence of the unprotected phenol, which ultimately led to failure and forced us to introduce an extra protection–deprotection operation. Thus, after protecting the phenol as acetyl ester **38**, we screened several oxidation conditions, but many resulted in decomposition. Eventually, we discovered that copper(I) chloride and *tert*-butyl hydroperoxide successfully oxidized the ether to lactone **39** in 47% yield.[21] A final deacetylation, using potassium carbonate in methanol, completed the first synthesis of ganoapplanin (**6**). The spectroscopic data for the synthetic compound were fully consistent with those reported in the literature.[3]

6 Conclusion

In summary, we developed a highly efficient two-component intramolecular Giese cyclization/intermolecular aldol sequence to construct the meroterpenoid scaffold of ganoapplanin and enable its first total synthesis. Further highlights are (1) a diastereoselective, titanium(IV)-mediated iodolactonization and (2) a reductive bisacetalization to form the distinctive spirocyclic structure of ganoapplanin. This work highlights the synthetic utility of radical-polar crossover cascade reactions in the synthesis of complex natural products, and we anticipate that the efficiency of our key reaction sequence will pave the way for synthetic approaches to other meroterpenoids using a similar strategy.

Conflict of Interest

The authors declare no conflict of interest.

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