A General Entry to *Ganoderma* Meroterpenoids: Synthesis of Lingzhiol via Photoredox Catalysis

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**Abstract:** *Ganoderma* meroterpenoids are a fungal-derived hybrid natural product class containing a 1,2,4-trisubstituted benzene ring and a polycyclic terpenoid part. The representatives *applanatumol* E, H and I, *lingzhilactone* B and *meroapplanin* B share the same bicyclic lactone moiety connected to the arene via a flexible C2-linker. This flexibility is lost for lingzhiol as the β-position of the lactone is fused to the arene to form a tetralone subunit. Employing a diastereoselective iodocarbocyclization and a photo-Fries rearrangement as the key-steps enabled a general entry to these natural products. For the synthesis of the tetracyclic framework of lingzhiol, we made use of a powerful photoredox oxidative decarboxylation/Friedel–Crafts sequence.

*Ganoderma* is a wood decay fungus that has been used in traditional Chinese medicine to treat a variety of medical conditions such as hypertension, chronic bronchitis and diabetes.[1] The secondary metabolites from these fungi cover the classes of polysaccharides, (mero)terpenoids, steroids and fatty acids of which polysaccharides were found to be the main bioactive component. To date, more than 100 meroterpenoids belonging to this natural product class were isolated including the *applanatumols* (1, 2, 3),[2] *lingzhilactone* B (4),[3] the recently isolated *meroapplanin* B (5)[4] and *lingzhiol* (6, Figure 1).[5] These natural products have a bicyclic lactone moiety in common which is connected at C2 via a two-carbon linker to a 1,2,4-trisubstituted benzene ring. In the case of lingzhiol, the aromatic core is further linked to the bicycle at C6 to give a unique tetralone subunit. Bioactivity assays revealed *lingzhilactone* B (4) and *lingzhiol* (6) to protect against renal injuries by increasing the activity of antioxidants and hence might be beneficial for anti-kidney disease drug design.[6] Owing to their structural complexity and medicinal relevance, meroterpenoids from the *Ganoderma* genus constitute an attractive target for total synthesis. While syntheses for *lingzhilactone* B (4)[7] and *lingzhiol* (6)[8] were reported in the past, synthetic strategies to access the *applanatumol* natural product family and *meroapplanin* B are still unknown. Here, we report a general entry to this natural product class involving an efficient iodocarbocyclization and two photochemical reactions as key-steps.

**Figure 1.** Selected polycyclic *Ganoderma* meroterpenoids sharing the same lactone unit and a polysubstituted benzene ring.

We began our endeavor with the retrosynthetic analysis of *applanatumol* E (1) for which a photo-Fries retron was found (Scheme 1). Disconnecting the ketone from the arene revealed ester 7 as the required precursor. Further dissection gave commercially available hydroquinone (not shown) and the corresponding acid 8. The
The functional group pattern of 8 was derived from bicyclic lactone 9 via Krapcho decarboxylation of the methyl ester at C2 followed by alkylation and sequential oxidation. For the installation of the crucial bicyclic lactone component 9, we identified a highly diastereoselective iodonion cyclization of employing malonate 10.

Scheme 1. Retrosynthetic analysis of applanatumol E (1) based on a photo-Fries rearrangement and a diastereoselective iodonion cyclization.

This step would allow for the installation of both vicinal quaternary stereocenters and the correct relative stereochemistry of the alcohol at C5. Further carbon–carbon disconnections revealed inexpensive cyclopentene (11) as the starting point of the synthesis. As depicted in Scheme 2, our synthesis commenced with the ozonolysis of cyclopentene to give known aldehyde 12 (67%). A subsequent 1,2-addition employing vinyl iodide 13 gave the allylic alcohol 14 and silylation (TBSCl, imidazole, DMAP) provided ester 15 in 53% over two steps. Sequential treatment of ester 15 with LDA and methyl chloroformate at −78 °C gave the prerequisite malonate 10 in 56% yield. For the following iodonion cyclization reaction we were inspired by the seminal work of Taguchi. According to their protocol, treatment of 10 with Ti(O-t-Bu)$_4$, I$_2$ and CuO initiated an orchestrated 5-exo-dig cyclization/lactonization to afford the bicyclic lactone 9 as a single diastereomer with the desired relative configuration at C5. A Krapcho decarboxylation using LiCl in DMSO/water at elevated temperature (140 °C) allowed for clean removal of the ester group of 9 to furnish 16 in 87% yield. The use of NaCl instead of LiCl under otherwise similar reaction conditions gave 16 in slightly lower yields (68%). For the subsequent debenzylation of 16, Pearlman’s catalyst and a hydrogen pressure of 40 bar proved to be the conditions of choice. At lower pressure or when employing Pd/C, only slow conversion of 16 to alcohol 17 was observed. Oxidation of 17 was accomplished under Swern conditions to provide aldehyde 18 in 64% yield over two steps. Surprisingly, for the subsequent conversion of 18 to dimethyl acetal 19 most standard conditions failed (see Supporting Information for details). After extensive experimentation, we found that the use of acidic Dowex resin in combination with trimethyl orthoformate was highly effective to give 19 in 81% yield. Subsequent treatment with KHMDS and allyl iodide at 23 °C completed the installation of the vicinal quaternary stereocenters in 64% yield. Noteworthy, at standard cryogenic temperatures either no reaction took place or an intermolecular Dieckmann-type addition was observed. Finally, aldehyde 20 was obtained in 95% yield by oxidative cleavage (O$_3$, then PPh$_3$) of the remote alkene.
Scheme 2. Synthesis of the bicyclic lactone 20. Reagents and conditions: a) O$_3$, NaHCO$_3$, CH$_2$Cl$_2$, MeOH, –78 °C, 30 min, then NEt$_3$, Ac$_2$O, CH$_2$Cl$_2$, 0 °C to 23 °C, 4 h, 67%; b) 13, t-BuLi, Et$_2$O, –78 °C, 1 h, then 12, Et$_2$O, –78 °C, 1 h; c) TBSCI, imH, DMAP, DMF, 23 °C, 6 h, 53% over two steps; d) LDA, methyl chloroformate, THF, –78 °C, 1 h, 56%; e) Ti(t-BuO)$_4$, CuO, I$_2$, CH$_2$Cl$_2$, 23 °C, 8 h, 61%; f) LiCl, DMSO, H$_2$O, 140 °C, 4 h, 87%; g) H$_2$ (40 bar), Pd(OH)$_2$/C, THF, 23 °C, 6 h; h) (COCl)$_2$, DMSO, NEt$_3$, CH$_2$Cl$_2$, –78 °C, 4 h, 64% over two steps; i) Dowex 50WX4, HC(O)Me$_3$, 23 °C, 14 h, 81%; j) KHMDS, allyl iodide, THF, 23 °C, 2 h, 64%; k) O$_3$, then PPh$_3$, CH$_2$Cl$_2$, –78 °C, 2 h. TBSCl = tert-butyldimethylsilyl chloride, imH = imidazole, DMAP = 4-dimethylaminopyridine, DMF = N,N-dimethylformamide, LDA = lithium diisopropylamide, THF = tetrahydrofuran, DMSO = dimethyl sulfoxide, KHMDS = potassium bis(trimethylsilyl)amide.

With robust access to aldehyde 20, we continued our synthesis by first performing a Pinnick–Lindgren–Kraus oxidation[18] to access acid 8 in 78% yield (Scheme 3A). Subsequent treatment of 8 with Yamaguchi’s reagent,[19] NEt$_3$ and TBS-hydroquinone 21 afforded ester 7 in 78% yield. The use of this protocol was crucial since attempted formation of an acid chloride employing oxalyl chloride and DMF only furnished propellane 22 (53%, d.r. = 2:1 at C8). To access the 1,2,4-trisubstituted phenyl group inherent to the Ganoderma meroterpenoids we resorted to a Fries rearrangement.[20] Since the use of standard conditions involving Lewis acids (e.g. AlCl$_3$, BF$_3$·OEt, TiCl$_4$) was considered to be too harsh for both the silyl and the acetal protecting groups we opted for the rare photochemical variant.[21],[22] To our delight, irradiation of 7 at 254 nm in n-hexane (see Supporting Information for more details) afforded the photo-Fries product 23 in 50% yield despite competing substrate decomposition. To complete the synthesis of applanatumol E (1), 23 was treated with 3 HF·NEt$_3$ (95%). The analytical data for 1 ($^1$H NMR, $^{13}$C NMR, HRMS) fully matched those reported for the natural compound. We were also able to convert applanatumol E (1) to lingzhilactone B (4) in 55% yield by means of acetal removal employing p-TsOH in the presence of aqueous acetone. Lingzhilactone B (4) was further oxidized under Pinnick–Lindgren-Kraus conditions to deliver applanatumol I (3) in 78% yield.
Scheme 3. Total synthesis of lingzhilactone B, applanatumol E and I and meroapplanin B. Reagents and conditions: a) KH$_2$PO$_4$, NaClO$_2$, 2-methyl-2-buten, t-BuOH, H$_2$O, 0°C to 23°C, 4 h, 78%; b) (COCl)$_2$, DMF, 23°C, 20 min, 53%, d.r. = 2:1 at C8; c) 21, 2,4,6-trichlorobenzoyl chloride, NEt$_3$, DMAP, THF, 23°C, 2 h, 78%; d) 254 nm, n-hexane, 23°C, 4 h, 50%; e) 3 HF•NEt$_3$, THF, 23°C, 3 d, 95%; f) p-TsOH, acetone, H$_2$O, 23°C, 18 h, 55%; g) KH$_2$PO$_4$, NaClO$_2$, 2-methyl-2-buten, t-BuOH, H$_2$O, 0°C to 23°C, 2 h, 78%; h) NH$_4$OAc, MeOH, 50°C, 12 h, 85%.

In addition, meroapplanin B (5) was accessible in 85% yield when a solution of 4 in methanol was treated with NH$_4$OAc at 50°C. Applanatumol H (2) was synthesized from benzyl ether 16 in seven steps following the established conditions (see Supporting Information for details). With access to applanatumol I (3), we wondered if transformation to lingzhio (6) would be feasible by means of an oxidative decarboxylation/Friedel–Crafts sequence (Scheme 4). While the biosynthesis of *Ganoderma* meroterpenoids is largely unexplored, we hypothesized that the decarboxylation of 3 might also be part of the biosynthesis of 6 and the related applanatumol J (R = Cl, compare Figure 1).[2]

Scheme 4. Strategy for the conversion of applanatumol I (3) to lingzhio (6).

For the investigation of this transformation in the chemical laboratory, we first prepared phenol 24 from acid 8 (49% yield over two steps) through the well-established esterification/photo-Fries sequence (Scheme 5). To reduce the risk of overoxidation of the delicate phenol during the key-step, we protected the remaining phenolic hydroxy group as a methyl ether (K$_2$CO$_3$, MeI, 96%). Acetal removal with p-TsOH gave aldehyde 25 which was further oxidized to the acid (81%). Based on recent work by Doyle on the photocatalytic fluorination of redox-active esters,[23] the intermediate acid was converted to the N-hydroxypthalimide ester 26 (92%). Fortunately, by employing the Ir(dFppy)$_3$ catalyst (10 mol%) in combination with a catalytic amount of 3 HF•NEt$_3$ at 419 nm (blue light), 26 was cleanly converted to tetralone 27 in 71% yield. According to the mechanistic proposal, an initial single electron reduction forms an intermediate carboxyl radical. After extrusion of carbon dioxide, a single
electron oxidation gives a stabilized tertiary carbocation. This is then attacked by the arene in a Friedel–Crafts reaction to give tetralone 27. Global deprotection of the silyl protecting group (TBAF, 73%) and the methyl ethers (BBr₃, 68%) afforded the natural product lingzhiol (6). The spectroscopic data (¹H and ¹³C NMR, HRMS) for 6 were in full agreement with those reported for the naturally occurring substance.

**Scheme 5.** Total synthesis of lingzhiol. Reagents and conditions: a) 4-methoxyphenol, 2,4,6-trichlorobenzoyl chloride, NEt₃, DMAP, THF, 23 °C, 2 h, quantitative; b) 254 nm, n-hexane, 23 °C, 3 h, 43%; c) K₂CO₃, MeI, acetone, 23 °C, 12 h, 96%; d) p-TsOH, acetone, H₂O, 23 °C, 12 h, 72%; e) KH₂PO₄, NaClO₂, 2-methyl-2-butene, t-BuOH, H₂O, 0 °C to 23 °C, 3 h, 81%; f) N-hydroxyphthalimide, DCC, DMAP, CH₂Cl₂, 23 °C, 3 d, 68%. DCC = N,N'-dicyclohexylcarbodiimide, Ir(dfppy)₃ = tris[2-(2,4-difluorophenyl)pyridine]iridium(III), TBAF = tetrabutylammonium fluoride.

In conclusion, we accomplished the total synthesis of six *Ganoderma* meroterpenoids. The robust route features a highly orchestrated and diastereoselective iodocarbocyclization to rapidly access the bicyclic lactone motif inherent to these natural products. Formation of the 1,2,4-trisubstituted benzene ring was achieved by employing a powerful, yet rare photo-Fries rearrangement. The natural product lingzhiol (6) was synthesized by photoredox catalysis that enabled an efficient oxidative decarboxylation/Friedel–Crafts sequence. The realization of this sequence highlights the synthetic potential of oxidative decarboxylation processes and constitutes a valuable starting point to access related *Ganoderma* natural products. Studies in this direction are currently underway in our laboratories and will be reported in due course.

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**Keywords:** natural products • meroterpenoids • total synthesis • photo-Fries rearrangement • photoredox catalysis


The choice of benzyl and TBS protecting groups for the allylic alcohols was crucial for the realization of the subsequent reactions (see Supporting Information).

Attempts to render the 1,2-addition enantioselective were met with failure. For selected methods for enantioselective addition of vinyl species to aldehydes, see: a) W. Oppolzer, R. N. Radinov, 

The relative stereochemistry was determined by NOESY correlations and validated by X-Ray crystallography on a related derivative, see Supporting Information for further details.


Further details can be found in the Supporting Information.