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Enantioselective Total Syntheses of Manginoids A and C and Guignardones A and C

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Abstract: An enantioselective synthetic approach for preparing manginoids and guignardones, two types of biogenetically related meroterpenoids, is reported. This bioinspired and divergent synthesis employs an oxidative 1,3-dicarbonyl radical-initiated cyclization and cyclodehydration of the common precursor to forge the central ring of the manginoids and guignardones, respectively, at a late stage. Key synthetic steps include silica-gel-promoted semipinacol rearrangement to form the 6-oxabicyclo[3.2.1]octane skeleton and the Suzuki-Miyaura reaction of vinyl bromide to achieve fragment coupling. This synthesis protocol enables the asymmetric syntheses of four fungal meroterpenoids from commercially available materials.

Fungal meroterpenoids are secondary metabolites derived from hybrid terpenoid biosynthetic pathways, which possess intriguing architectures and exhibit excellent biological and pharmacological activities.[1] Manginoids (**1-2**, Figure 1) and guignardones (**3-4**) are two types of biogenetically related meroterpenoids discovered from fungus *Guignardia mangiferae* [2a, 2b] Structurally, manginoids and guignardones contain a highly substituted cyclopentane moiety and 6-oxabicyclo[3.2.1]octane fragment, which are forged via C–C and C–O cyclization of the above-mentioned subunits, respectively. The hyperbeanol family (**5-6**) is also likely derived from a similar biosynthetic pathway.[2c, 2d] Notably, these fungal meroterpenoids exhibit diverse biological activities. Manginoid A (**1**) shows potent inhibition of 11β-hydroxysteroid dehydrogenase type 1 (IC_{50} = 0.84 μM) [2a] and guignardone compounds show promising inhibitory activities against *Candida albicans*.

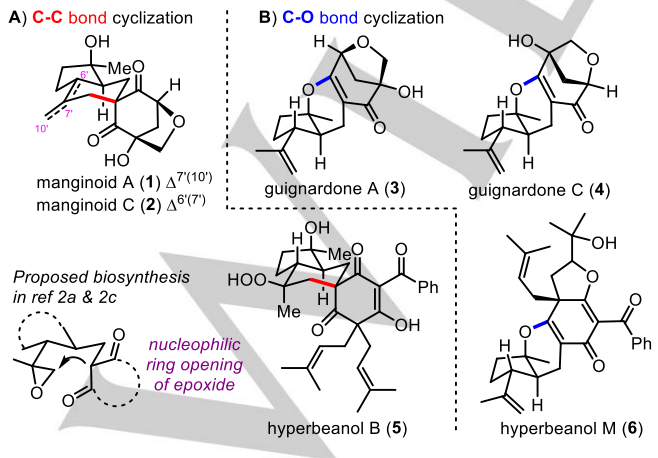
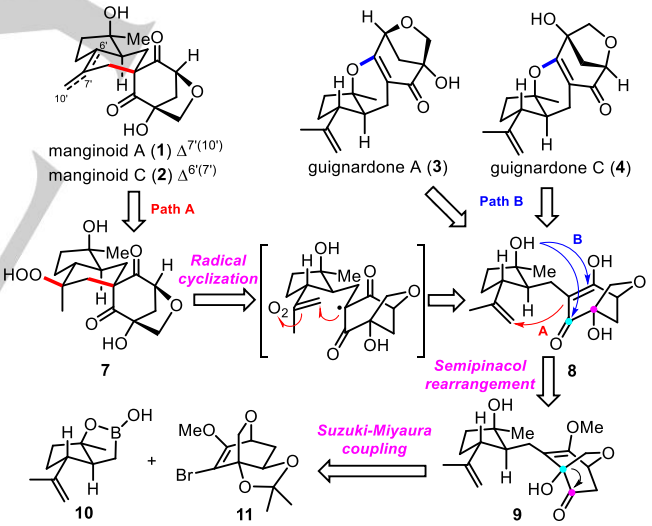


Figure 1. Representative structures of manginoids and guignardones.

The structural diversification and potent biological activities render these compounds attractive targets for organic synthesis.[3] Yang group reported the first asymmetric total synthesis of *ent*-guignardone A and B from D-quinic acid in 2020.[3c] Recently, the first total synthesis of (±)-manginoid A (**1**) was described by Snyder et al.[3d] Their elegant synthetic strategy involved challenging Pinacol coupling and bicycle-forming etherification. Despite these innovative strategies, the asymmetric synthesis of manginoids has not been achieved, and efforts directed toward more divergent routes are scarce. Herein, a bioinspired strategy to achieve the asymmetric total syntheses of manginoid A, C, guignardone A, and C is described.



Scheme 1. Synthetic analysis of manginoids and guignardones.

Biosynthetically, manginoids have been proposed to generate from **8** via epoxidation and the nucleophilic ring opening of epoxide (Figure 1).[2a, 2c] From a chemistry perspective, an alternative hypothesis involving an oxidative 1,3-dicarbonyl radical-initiated cyclization is presented (Scheme 1).[4] We envisioned that the synthetic diversity of these meroterpenoids could be realized through late-stage bioinspired cyclizations of the common precursor **8**. The 6-oxabicyclo[3.2.1]octane subunit of **8** could be constructed through a key semipinacol rearrangement of **9**,[5] which could be accessible by the Suzuki-Miyaura coupling of **10** and **11**.[3b, 6]

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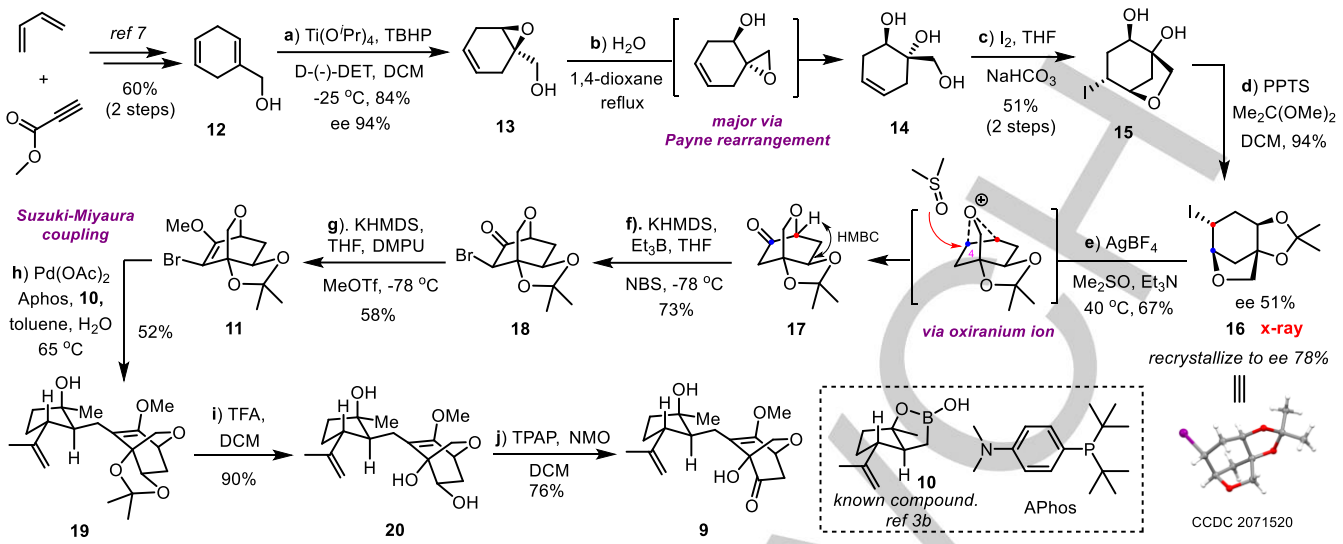
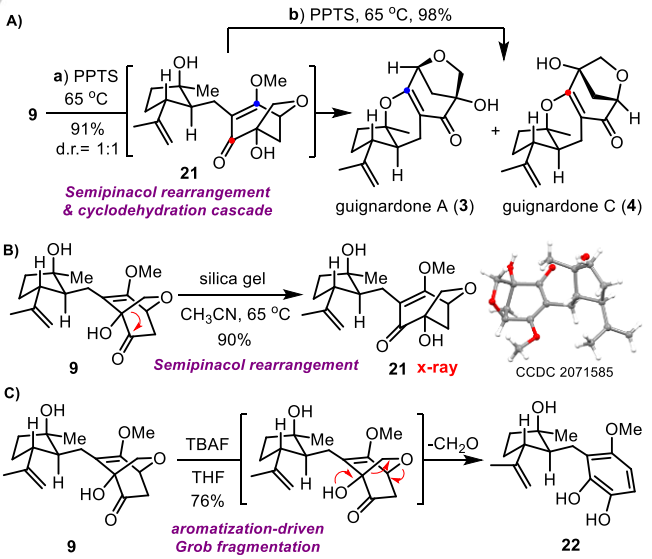


Scheme 2. Synthesis of all carbon precursor **9**. TBHP = *tert*-butyl hydroperoxide, DET = diethyl tartrate, DCM = dichloromethane, THF = tetrahydrofuran, PPTS = pyridinium *p*-toluenesulfonate, KHMDS = potassium bis(trimethylsilyl)amide, NBS = *N*-bromosuccinimide, MeOTf = methyl trifluoromethanesulfonate, DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone, APhos = (4-dimethylaminophenyl)di-*tert*-butylphosphine, TPAP = tetra-*n*-propylammonium perruthenate, TFA = trifluoroacetic acid, NMO = *N*-methylmorpholine oxide.

The synthesis commenced with the preparation of allylic alcohol **12**, which was readily obtained by the Diels–Alder reaction of propiolic acid methyl ester and subsequent reduction (see Supporting Information).[7] Allylic alcohol **12** was subjected to Sharpless asymmetric epoxidation to afford epoxide **13** in 84% yield and 94% ee.[5e, 8] (Scheme 2). The hydrolysis of epoxide **13** with boiling water mainly produced triol **14** via Payne rearrangement,[9] and the absolute configuration was determined by comparison of the X-ray diffraction data of **16**.[10] Iodoetherification of triol **14** generated iodoether **15**, and subsequent protection with dimethoxypropane produced 6-oxabicyclo[3.2.1]octane **16** with 51% ee, which was further improved to 78% ee by recrystallization. Some loss of optical purity could be caused by the direct epoxide opening with water. Interestingly, when modified Kornblum oxidation ($AgBF_4$/Me_2SO) was employed to convert alkyl iodide **16** into the corresponding ketone, an unusual skeletal rearrangement of **16** into oxabicyclo[2.2.2]octane **17** was observed. It was speculated that the mechanism of this novel oxidation involved an oxiranium ion intermediate, and **17** was derived from the solvolysis of the oxiranium ion by attack at the C4 center (Scheme 2).[11] While an unexpected rearrangement occurred, it was envisioned that if semipinacol rearrangement was later successfully employed to reconvert it into oxabicyclo[3.2.1]octane skeleton, compound **17** could still be exploit.

Thereafter, ketone **17** was efficiently monobrominated by treatment of the resulting enol triethyl borate with N-bromosuccinimide after extensive screening of the reaction conditions (see Supporting Information for details).[12] Upon treatment with KHMDS/MeOTf, the formed α-monobrominated ketone **18** was converted into the desired vinyl bromide **11**. With **11** in hand, attempts to perform the Suzuki-Miyaura reaction with known boronic monoester **10** (prepared from (*R*)-carvone) were made.[13] Gratifyingly, the anticipated coupling product **19** was isolated in 30% yield using Romo's protocol in the presence of palladium acetate and Aphos.[3b] Next, the ligands and bases were screened to determine the optimal conditions to improve the yield of **19** (see Supporting Information for details), and better results were later obtained using water as an additive.[6] Acetonide was removed using trifluoroacetic acid to afford diol **20**. The oxidation of the secondary alcohol of **20** to provide ketone **9** presented an unexpected challenge, i.e., attempts using PDC, DMP, or IBX failed. Finally, treatment of **20** under Ley condition generated the desired ketone **9**.[14]



Scheme 3. Total syntheses of (+)-guignardones A (**3**) and C (**4**). PPTS = pyridinium *p*-toluenesulfonate, TBAF = tetra-*n*-butylammonium fluoride, THF = tetrahydrofuran.

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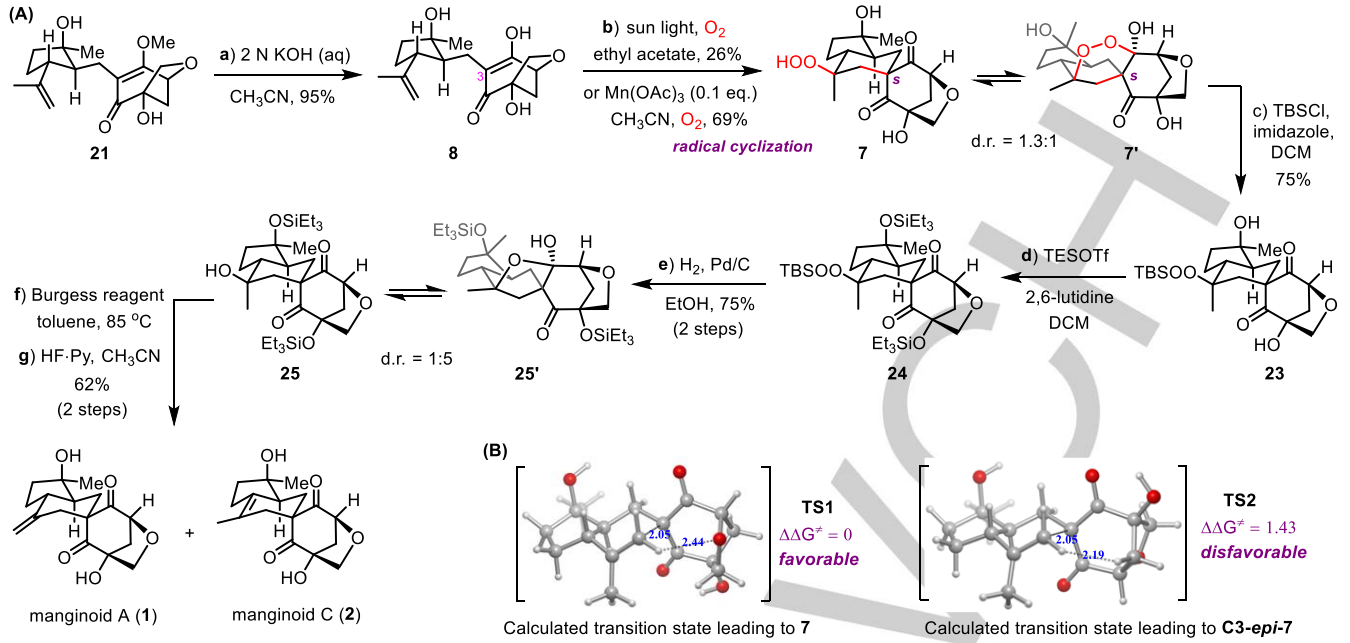

Scheme 4. Total syntheses of (+)-manginoid A (**1**) and (-)-manginoid C (**2**) and the transition states of the radical cyclizations calculated at the PCM-UB3LYP-D3/6-311+g(2d, p)//UB3LYP-D3/6-31g(d) level in ethyl acetate solution. TBSCl = *tert*-butyldimethylsilyl chloride, TESOTf = triethylsilyl trifluoromethanesulfonate.

Next, pivotal semipinacol rearrangement was investigated.[5] Various acids or bases to induce this transformation were evaluated, and we were pleased to find that natural guignardones A (**3**) and C (**4**) could be obtained by adding pyridinium *p*-toluenesulfonate (Scheme 3A). This process involved 1,2-allyl migration and C–O bond formation through semipinacol rearrangement and cyclodehydration cascade reaction. Spectroscopy data collected for these two synthetic meroterpenoids were consistent with those reported in the literature. [2b] Compound **21** could not be obtained under various conditions because of competitive cyclodehydration. Upon careful examination, it was observed that the desired compound **21** was formed in small amounts during purification by silica gel chromatography. Hence, this challenging semipinacol rearrangement was ultimately accomplished using silica gel (Scheme 3B). The structure of **21** was unambiguously confirmed by X-ray diffraction analysis. It is worth noting that a novel aromatization-driven Grob fragmentation of **9** proceeded smoothly by employing *n*-Bu_4NF to generate phenol **22** (Scheme 3C).[15]

Further efforts were then directed toward the bioinspired oxidative 1,3-dicarbonyl radical-initiated cyclization to afford manginoids A (**1**) and C (**2**) (Scheme 4A). Demethylation of **21** using HCl or acetic acid directly afforded the cyclodehydration products, guignardones A (**3**) and C (**4**). Other reagents for demethylation, such as LiCl, did not react. Finally, the treatment of **21** with 2 N KOH (aq) afforded desired **8** (see Supporting Information for details). Interestingly, after the preparation of **8**, spontaneous decomposition was observed by NMR and visual analysis after storage. Further experiments involving the dissolution of enol **21** in ethyl acetate and exposure to sunlight and air directly yielded a mixture of keto/hemiketal tautomers **7** and **7'** in 26% yield. As $Mn(OAc)_3$ is an effective oxidant for enolizable carbonyl compounds,[4] excellent yield of 69% was obtained using a catalytic amount of $Mn(OAc)_3$ in this auto-oxidation process.[16] Notably, diastereomer **C3-*epi*-7** could not be isolated using the above reaction conditions. The structures of **7** and **7'** were initially determined using NMR spectroscopy and later confirmed by 2D NMR spectroscopy of derivative **23**. Density functional theory (DFT) calculations were performed to understand the excellent diastereoselectivity observed with substrate **8**.[17] DFT calculations showed that the energy barrier of transition state **TS2** leading to **C3-*epi*-7** is a little higher than that of **TS1**, indicating that **TS2** is not favorable for this radical cyclization in the ethyl acetate solution.

This auto-oxidation and subsequent radical cyclization of the enolizable carbonyl compounds show a general reactivity trend in this type natural product family (*e.g.*, hyperbeanol B, Figure 1),[18] and it is highly likely that peroxide natural products such as **7** can be discovered from *Guignardia mangiferae*. The silylation of the hydroxyl groups in **23** with triethylsilyl trifluoromethanesulfonate delivered **24**. Hydrogenation of **24** catalyzed by Pd/C generated a mixture of keto/hemiketal tautomers **25** and **25'** in 75% yield via reductive O–O bond cleavage.[19] Burgess dehydration of the mixture of **25** and **25'** and subsequent desilylation with pyridine hydrofluoride completed the syntheses of manginoids A (**1**) and C (**2**) in 62% yields. The spectroscopic data for these compounds were consistent with those reported in the literature for the natural products. [2a]

In summary, we have developed an enantioselective synthetic approach for two types of biogenetically related meroterpenoids, manginoids and guignardones, and comprised an additional case of "step-efficient syntheses".[20] An oxidative 1,3-dicarbonyl radical-initiated cyclization and cyclodehydration are employed to generate the central ring of the manginoids and guignardones, respectively. The key features of this bioinspired route include a silica-gel-promoted semipinacol rearrangement to forge the common 6-oxabicyclo[3.2.1]octane subunit and C_{sp3}-C_{sp2} Suzuki-Miyaura coupling of vinyl bromide. The methodologies described for forging complex molecular architectures can be applied for the

syntheses of other structurally related fungal meroterpenoids. Furthermore, owing to the bioinspired characteristics, this work can provide insights into the biosynthetic pathways of these types of meroterpenoids.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: total synthesis • cyclization • natural products • meroterpenoid • asymmetric synthesis

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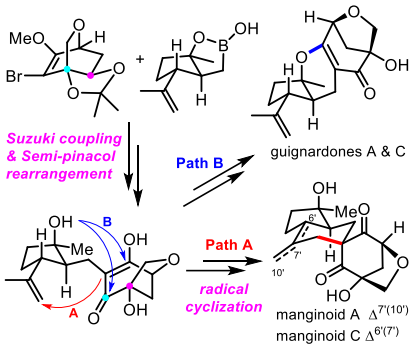

Enantioselective total syntheses of fungal meroterpenoids, manginoids A and C, as well as guignardones A and C, are accomplished. This divergent and bioinspired synthetic strategy involves a C_{sp3}-C_{sp2} Suzuki-Miyaura coupling of vinyl bromide, silica-gel-promoted semipinacol rearrangement, and oxidative 1,3-dicarbonyl radical-initiated cyclization.