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Biomimetic Syntheses of (−)-Gochnatiolides A−C and (−)-Ainsliadimer B

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Supporting Information

ABSTRACT: We report the first biomimetic syntheses of (−)-gochnatiolides A−C and (−)-ainsliadimer B based on our proposed biogenetic pathway. Our synthesis features one-pot cascade transformations including Saegusa oxidation, intermolecular Diels−Alder cycloaddition, and radical-mediated allylic oxidation, which allow for the rapid generation of (−)-gochnatiolides A−C in a collective manner. We also disclose an unprecedented "copper effect" on the stereochemical outcome of the radical-mediated allylic oxidation. Our synthetic endeavors led to the structural reassignment of (−)-gochnatiolide B. Ultimately, a biomimetic transformation from gochnatiolide B to ainsliadimer B was achieved through a remarkable direct enone hydration.

The guaianolide-type sesquiterpenoid dimers represent a unique class of sesquiterpenoid natural products that exhibit a wide array of biological activities, including antitumor, anti-inflammation, and anti-HIV activities.[1] Biosynthetically, most of these molecules originate from two monomeric units via either Diels−Alder or hetero-Diels−Alder cycloadditions. Although a number of remarkable syntheses of disesquiterpenoids have been reported,[2] significant challenges still exist in exploring the biomimetic routes. Gochnatiolides A (**1**), B (**2**), and C (**3**) (Figure 1) were initially isolated by Robinson and co-workers from *Gochnatia* species in 1980s.[3] More recently, Zhang and co-workers also isolated **1** and **3**[4] as well as a related natural product, ainsliadimer B (**4**), from *Ainsliaea fulvioides*, together with two unprecedented sesquiterpene trimers, ansliatrimers A (**5**) and B (**6**).[5] Gochnatiolides A−C and ainsliadimer B all possess a complex heptacyclic ring system with an intriguing spiro[4,5]decane moiety. As part of an ongoing program aimed at the development of a general and biomimetic approach toward this unique family of sesquiterpenoids, we now report the first syntheses of **1**−**4**, which are guided by our proposed biosynthetic pathway. The synthetic studies also enabled us possibly to revise the originally proposed structure of gochnatiolide B (**2′**).

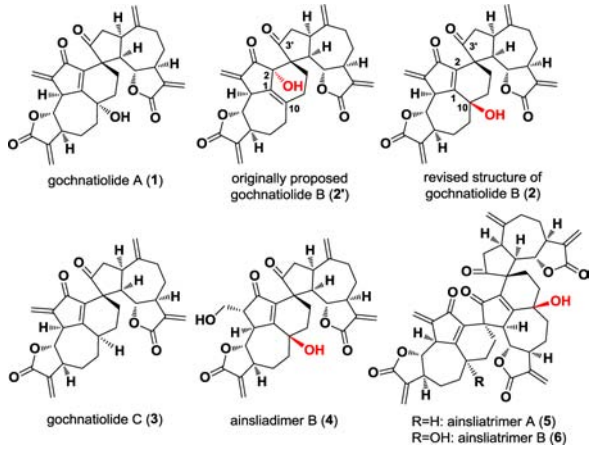

Figure 1. Sesquiterpenoid dimers and trimers.

We envisioned that biosynthetically the monomeric sesquiterpene lactone dehydrozaluzanin C (**7**), which was readily prepared in 11 steps from α-santonin, could serve as a common precursor for both gochnatiolides and ainsliadimers through three pathways (Scheme 1).[2c] In a previous study, we demonstrated that the BINOL-promoted hetero-Diels−Alder dimerization of **7** smoothly realizes a biomimetic approach to afford the key homodimer **8**, which was further elaborated to generate (+)-ainsliadimer A (**9**) in two steps (Scheme 1, pathway A).[2c] Concurrent with these efforts, we also became interested in exploring the feasibility of constructing the gochnatiolide skeleton from **7** through Diels−Alder cycloaddition. We hypothesized two biosynthetically inspired pathways for gochnatiolides: In pathway B, α-hydroxy ketone **10** could be derived from Rubottom oxidation of **7**.[6] Further oxidation of **10** may afford α-hydroxy enone **11**, which may undergo subsequent Diels−Alder cycloaddition with **7** to generate the originally proposed gochnatiolide B structure (**2′**). Finally, 1,3-isomerization of allylic alcohol **2′** should furnish gochnatiolide A (**1**). Alternatively, in pathway C, dienone precursor **12** could be derived from ketone **7** via Saegusa oxidation. Subsequent Diels−Alder cycloaddition between **7** and **12** should afford the key intermediate dimer **13**, which may serve as a common biosynthetic intermediate for gochnatiolides A−C through either direct allylic oxidation or double-bond isomerization followed by allylic oxidation. Notably, two crucial questions remained to be addressed for these biogenetic pathways: (1) how to achieve the desired cross-Diels−Alder cycloaddition instead of homo-Diels−Alder dimerization and

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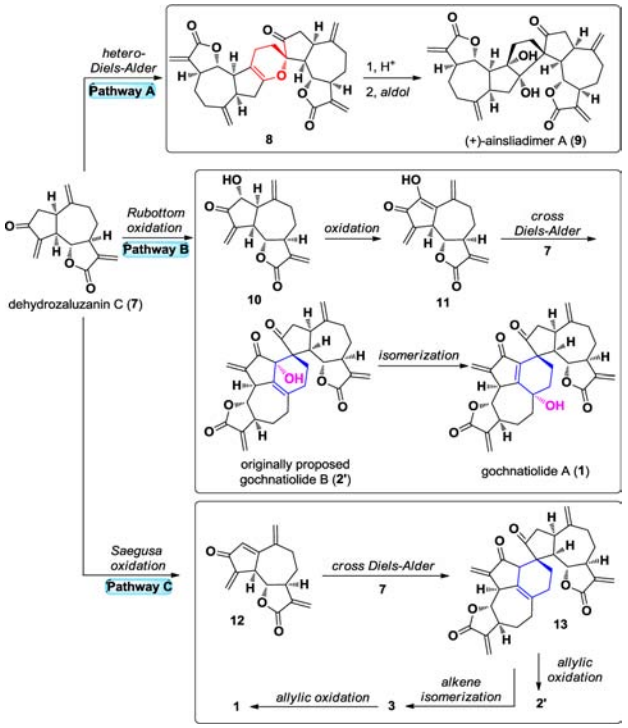
Scheme 1. Proposed Biogenetic Pathways for Gochnatiolides and Ainsliadimers



(2) how to install the tertiary hydroxy functionality regioselectively at C2 or C10 with correct stereochemistry.

Initial attempts at achieving pathway B failed, as evidenced by the rapid decomposition of intermediate **11** without production of any trace amount of the desired dimers.[6] Therefore, we examined the feasibility of pathway C. Diene **12** was prepared via Saegusa oxidation[7] of silyl enol ether **14**, which was generated by treating **7** with hexamethyldisilazane (HMDS) and trimethylsilyl iodide (TMSI).[8] Surprisingly, over the course of many attempts to isolate diene **12**, we obtained only the unexpected dimer **15**. The structure of **15** was unambiguously confirmed by X-ray crystal structure analysis to be a homodimer of diene **12** (Figure 2). Conceivably, diene **12** is prone to homo-Diels–Alder dimerization, which would be followed by alkene isomerization and allylic oxidation to generate the undesired homodimer **15**. Nevertheless, this result supported our proposed pathway C for achieving a biomimetic approach targeting the gochnatiolides.

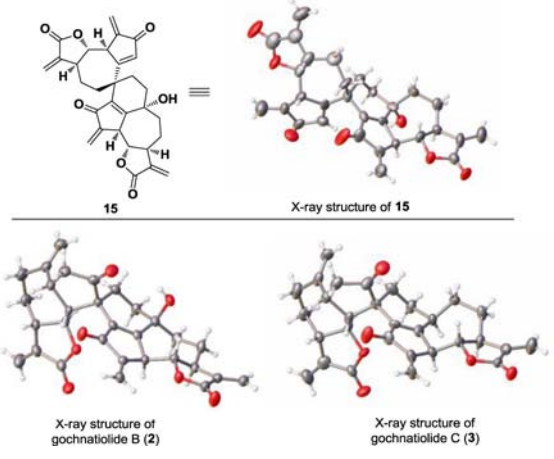
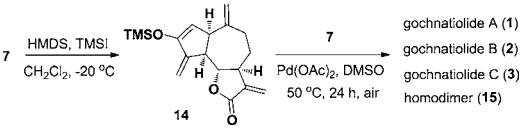


Figure 2. X-ray structures of **2**, **3**, and **15**.

To prevent homodimerization of the diene during its isolation process, a dimethyl sulfoxide (DMSO) solution of silyl enol ether **14** and monomer **7** was treated with $Pd(OAc)_2$ under air. To our delight, the desired gochnatiolides **1**–**3** were isolated in 16, 2, and 6% yield, respectively, along with homodimer **15** in 20% yield (Table 1, entry 1). Because the undesired homodimerization was still favored, we decided to optimize the cascade transformations further through extensive reaction screening. Although attempts to use a number of different Lewis and Brønsted acids, solvents, and reaction temperatures unfortunately failed, a direct and effective solution was identified. Increasing the amount of dienophile **7** to disfavor the homodimerization of diene **12** gratifyingly improved the total yields of gochnatiolides A–C (Table 1, entries 2–4). However, when the reaction was performed in an anaerobic glovebox, only **3** was isolated in 14% yield (Table 1, entry 5), suggesting that oxygen is a prerequisite for the allylic oxidation.

Table 1. Biomimetic Synthesis of Gochnatiolides



		isolated yields (%)			
entry	equiv of 7[a]	**1**	**2**	**3**	**15**
1	2	16	2	6	20
2	4	31	4	7	14
3	**6**	**40**	**6**	**9**	**11**
4	8	35	4	6	6
5[b]	6	0	0	14	0

[a]70–77% of **7** was recovered after the reaction. [b]The reaction was performed in an anaerobic glovebox.

Synthetic **1** and **3** exhibited ^1H and ^{13}C NMR spectra indistinguishable from those reported for the natural isolates,[3,4] and the structure of **3** was further unambiguously confirmed by X-ray crystallographic analysis (Figure 2). The ^1H NMR spectrum of synthetic gochnatiolide B matched the one for the natural compound reported by Robinson and co-workers,[3a] but unfortunately, the ^{13}C NMR spectrum was not available for comparison.[9] To determine further the structure of the synthetic molecule, we did extensive 2D NMR studies. However, the results suggested a revised structure **2** instead of the originally proposed structure **2′**.[6] This reassigned structure was further unambiguously confirmed by X-ray crystallographic analysis (Figure 2). Although the originally proposed structure **2′** for natural gochnatiolide B still cannot be completely ruled out because of the unavailability of the ^{13}C NMR spectrum for comparison, it is highly likely that gochnatiolide B has the revised structure **2**, which also possesses the same relative stereochemistry at C10 as ainsliadimer B (**4**). In addition, the optical rotations of synthetic **1** and **3** were consistent with the natural ones, which also established the absolute configurations of **1** and **3**.

The remarkable one-pot cascade transformations provoked our interest in investigating this process further (Scheme 2). Initially, a small quantity of hydroperoxide intermediate **18a** was isolated and fully characterized from a large-scale reaction.[6]

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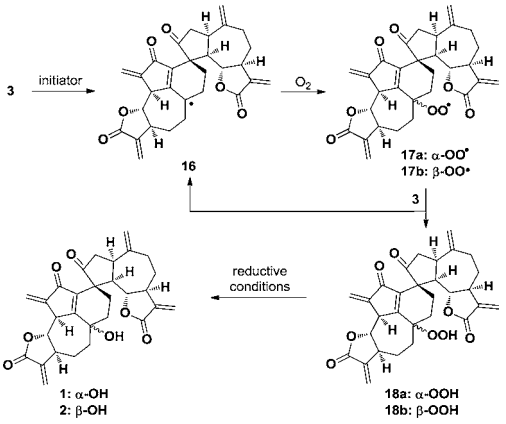
Scheme 2. Proposed Reaction Mechanism of the Facile Allylic Oxidation



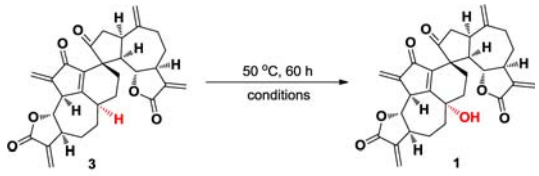
18a ⟶ 1

Entry	Conditions	Yield(%)[a]
1	Me_2S/EtOAc	quant.
2	palladium black/AcOH, DMSO	67%

[a]Isolated yields.

In addition, **18a** could be smoothly reduced to generate **1** in the presence of Me_2S or palladium black. Control experiments also showed that the allylic oxidation was inhibited when the reaction was performed in an anaerobic glovebox (Table 1, entry 5) and that the allylic oxidation did proceed in the presence of the radical inhibitor butylated hydroxytoluene (BHT), albeit with reduced yield.[6] We also observed that **3** could be directly transformed to **1** in the presence of either $Mn(OAc)_3$ or KF under O_2 gas in 19 and 23% yield, respectively (Scheme 3). However, the allylic oxidation of **3**

Scheme 3. Direct Oxidation of Gochnatiolide C



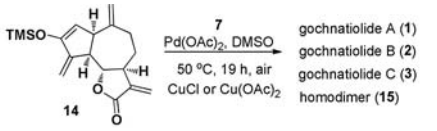
Entry	Conditions	Yield(%)[a]
1	$Mn(OAc)_3$•$2H_2O$, DMSO, O_2	19%, 40% (brsm)
2	KF, O_2, DMSO	23%
3	O_2, DMSO	0%

[a]Isolated yields.

did not occur only under oxygen gas. These studies strongly suggested a radical process,[10] as shown in Scheme 2. Initially, the tertiary radical **16** was generated from **3** and stabilized by the newly formed enone moiety. Subsequent reaction with oxygen afforded peroxyl radical **17**, which abstracted a hydrogen atom from **3** to furnish hydroperoxide **18** and regenerate radical **16**. Finally, **18** was reduced in situ to afford **1** and **2**.

The high diastereoselectivity of α-peroxide formation in **17a**, which ultimately led to the selective synthesis of **1** (Table 1, entry 3), is presumably due to steric effects. To improve the synthesis of **2**, we needed to consider an alternative approach to reverse the diastereoselectivity. Serendipitously, we found that the β-peroxide formation was more favored when the reaction was performed in the presence of a catalytic amount of $Cu(OAc)_2$ (Scheme 4, entry 1).[11] Further screening of different copper additives (CuCl, CuBr, CuI) revealed that using CuCl

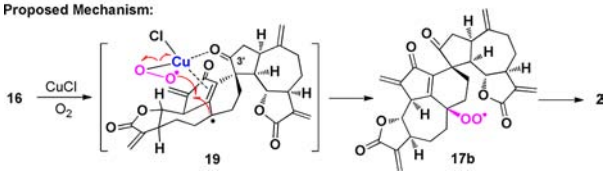
Scheme 4. Synthesis of Gochnatiolide B



Entry	Equivalent of 7	Isolated Yield (%) (1)	(2)	(3)	(15)
1[a]	2	6	16	2	12
2[b]	2	3	18	3	11
3[b]	4	6	27	5	6

[a] 0.1 equiv of $Cu(OAc)_2$ was used; [b] 0.1 equiv of CuCl was used.

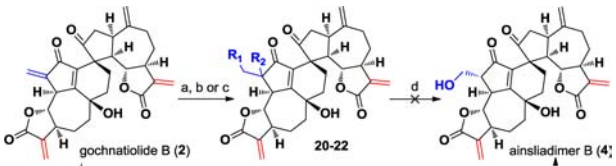
Proposed Mechanism:



improved the yield of **2** to 27% and reversed the **1**:**2** ratio from 6.6:1 (Table 1, entry 3) to 1:4.5 (Scheme 4, entry 3). A proposed mechanism for this unprecedented "copper effect" on the stereochemical outcome observed herein is shown in Scheme 4. In the presence of CuCl, the radical intermediate **16** might react with a monomeric Cu(II)−peroxo species generated by the reaction of CuCl with oxygen.[12] Conceivably as a result of the chelate effect between Cu and the carbonyl at C3′ as well as the alkene moiety in the transition state **19**, the peroxide radical could be delivered from the β-face to generate **17b**, which would be reduced to afford **2**.

Having established a more efficient route for preparing **2**, we began to examine the feasibility of its biomimetic conversion to **4**. Clearly, a direct chemo- and regioselective water addition to the exomethylene−cyclopentenone moiety of **2** in the presence of two α-methylene-γ-butyrolactones would be ideal. However, the direct enone hydration for the synthesis of a β-hydroxy ketone has rarely been reported[13] and proved to be challenging. As shown in Scheme 5, we initially screened both basic and phosphine-catalyzed conditions[13a] for direct hydration as well as the literature-reported stepwise procedures[14] for the installation of a β-hydroxy ketone, but unfortunately, all of

Scheme 5. Synthesis of Ainsliadimer B



Conditions	Desired Product	Result
a) MeOH, aq.$NaHCO_3$	**20** (R_1= OMe, R_2= H)	12 %
b) $PhSiMe_2Li$, CuCN, THF, -78 °C	**21** (R_1= $SiMe_2Ph$, R_2= H)	decomposed
c) Ph_3COOH, NaHMDS, THF, -78 °C	**22** (R_1, R_2= ⟩O⟨)	decomposed
d) **20**, BCl_3 or BBr_3, CH_2Cl_2, -78 °C to rt	**4**	NR at -78 °C decomposed at rt
e) PMe_3, H_2O/CH_3CN, rt.	**4**	decomposed
f) 1N HCl, 50 °C, acetone/CH_2Cl_2/H_2O (6/1/1)	**4**	**27% (82% brsm)**

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these attempts failed. Gratifyingly, after extensive exploration of reaction conditions, we observed that **4** was generated upon treatment of **2** with 1 N HCl in a 6:1:1 acetone/CH_2Cl_2/H_2O solvent mixture. To the best of our knowledge, this work represents the first example of direct hydration of an enone in complex natural product synthesis. Synthetic **4** was confirmed to be identical with natural ainsliadimer B by on the basis of ^{1}H NMR, ^{13}C NMR, and high-resolution mass spectrometry (HRMS) data.[6] The optical rotation of synthetic **4** was $[\alpha]_D$ −90 (*c* 0.24, MeOH), while that of natural **4** was $[\alpha]_D$ −94 (*c* 0.11, MeOH), establishing the absolute configuration of **4**.

In summary, the first biomimetic syntheses of (−)-gochnatiolides A−C (**1**−**3**) and (−)-ainsliadimer B (**4**) have been accomplished. On the basis of the proposed biogenesis of gochnatiolides, we have developed a novel strategy involving a cascade reaction including Saegusa oxidation, intermolecular Diels−Alder cycloaddition, and radical-mediated allylic oxidation to furnish **1**−**3** efficiently in a single operation. Further experiments also provided insights for the facile allylic oxidation. Furthermore, we discovered an unprecedented "copper effect" on the stereochemical outcome of the radical-mediated allylic oxidation, which might find further synthetic application. Of particular note is the structural reassignment of gochnatiolide B (**2**), which established the crucial stereochemistry for the synthesis of ainsliadimer B. Ultimately, a biomimetic transformation from gochnatiolide B to ainsliadimer B was achieved by a remarkable direct chemo- and regioselective enone hydration. Further studies directed toward the syntheses of other related natural products, including ainsliatrimers, are in progress and will be reported in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Complete experimental and characterization details for all new compounds reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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