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Establishing a “Ring Size-Divergent” Synthetic Strategy: Synthesis, Structural Revision, and Absolute Configuration of Feroniellins

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Abstract: Feroniellin analogs isolated from Feroniella lucida possess a furanocoumarin skeleton connected with monoterpene five- to seven-membered ethereal rings by an ether linkage and exhibit a broad spectrum of biological activities. In this contribution, we intended to establish a “ring size-divergent” synthetic strategy for the monoterpene five- to seven-membered ethereal rings through the chemical synthesis of feroniellins. Herein, we report the short and comprehensive synthesis of feroniellins has been achieved in only 2 steps from easily available bergamottin based on the “ring size-divergent” strategy. In addition, these syntheses resulted in revision of the proposed structures for feroniellins A and B and the determination of all the absolute configurations of feroniellins, and further their preliminary anti-inflammatory activities were investigated as well.

Feroniellin analogs were first isolated by Phuwapraisirisan and co-workers from the roots of Feroniella lucida in 2006, leading to the identification of furanocoumarin monoterpene ethers named feroniellins A, B, and C (shown in Figure 1 as 1, 2, and 3, respectively). 1 Feroniellin A-induced autophagy is reported to cause apoptosis in multidrug-resistant human A549 lung cancer cells, 2 whereas feroniellin B effectively inhibited human platelet aggregation. 3 The chemical structures of feroniellins A, B, and C possess a furanocoumarin skeleton connected with a five-membered ether (tetrahydrofuran, THF) ring, a six-membered ether (tetrahydropyran, THP) ring, and a seven-membered ether (oxepane) ring, respectively. Their relative configurations were assigned through 2D NMR analysis. Applying a modified Mosher’s method to feroniellin A revealed that the absolute configuration at the C2” position was (S). 1 The absolute configurations of feroniellins B and C are still unknown. Feroniellamin (4), a diastereomer of feroniellin B, was also isolated from Feroniella lucida and is known to inhibit lipid peroxidation. 4 Although its relative configuration was determined via 2D NMR, its absolute configuration remains unknown. These feroniellins have never been synthesized.

Biomimetic epoxide-opening cascades of polyepoxides have enabled the efficient and rapid construction of polyether frameworks. 5 Considering the synthesis of feroniellins with five- to seven-membered ethereal rings, if their ethereal rings could ring size-divergently be constructed from a common precursor diepoxide 5, the method would allow their efficient and comprehensive synthesis (Scheme 1). Then, it will be a problem to control the regio- and site-selectivity of cyclizations and incoming water, respectively. In our previous studies, it has been found that heating diepoxides 5 (R = Me) in neutral H2O only affords in a stereospecific manner THF products 7 (R = Me) accompanied by a nucleophilic attack of H2O at C3. 6 On the other hand, it was expected that the reaction of polyepoxides such as 5 in acidic aqueous media would provide THF products such as 6 via Brensted acid-catalyzed hydrolysis at C8. 7 Further according to reports of McDonald et al., 8 it was envisioned that

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**Figure 1.** Chemical structures 1–4 of feroniellins.

**Scheme 1.** “Ring size-divergent” synthetic strategy.
the regioselective construction of oxepane rings 8 could also be realized from diepoxides 5. Thus, we intended to establish a “ring size-divergent” synthetic strategy for monoterpenic five- to seven-membered ethereal rings through the chemical synthesis of feroniellins. In this contribution, we report the short and comprehensive synthesis of feroniellins based on the “ring size-divergent” strategy, resulting in revision of the proposed structures 1 and 2 and the determination of all the absolute configurations of feroniellins, and their preliminary anti-inflammatory activities.

A possible biogenetic precursor of feroniellins, furanocoumarin monoterpenoid ethers, would be the natural product bergamottin (9) that is a component of grapefruit juice and many Citrus species[9] and ubiquitous in nature. Therefore, we started the synthesis of feroniellins from bergamottin (9)[10a] (Scheme 2). The cyclization precursor, which was a mixture of syn- and anti-diepoxides rac-10 and rac-11, respectively, was prepared from bergamottin (9) via the nonstereoselective epoxidation of the two alkenes using m-chloroperbenzoic acid (mCPBA). At first, the cyclization of the diepoxides under the acidic conditions using a Brønsted acid pTsOH provided the proposed structure rac-1 of feroniellin A and its 7′-epimer rac-12 in good yield (36% and 37%, respectively). The relative configuration of the THF products was unambiguously determined via NOESY experiments and X-ray analysis.[10b] As expected, the regioselective and stereospecific formation of THF products could be explained by the reaction mechanism through acid-catalyzed hydrolysis at the more substituted C8* of the more water-accessible terminal epoxide in I, followed by kinetically favored 5-exo cyclization.[6,7,10c] The spectral data of the synthetic rac-1 were not identical to those reported for the natural sample,[11] while those of its 7′-epimer rac-12 were consistent. Therefore, the proposed structure 1 of feroniellin A has to be revised to rac-12.

Next, the diepoxides rac-10 and rac-11 were subjected to the conditions of only heating in neutral water. The cyclization reaction predictably afforded THF product rac-13 and the proposed structure rac-4 of feroniellamin in 23% and 40% yields, respectively.[10d] As we previously reported, the stereospecific THF production occurred via a kinetically favored exo-selective S2 attack of the internal epoxide oxygen to the less substituted C7* of the H2O-activated terminal epoxide in III, followed by ring-opening by H2O at C3* in epoxonium ion intermediate IV.[8] The lower yield of rac-13, when compared with that of rac-4, was reportedly due to 1,3-diaxial interactions of the bulky substituent at C2* in the chair-like THF ring.[8b] Surprisingly, the spectral data of synthetic rac-13 were consistent with those reported for the natural feroniellin B.[11] Therefore, the proposed structure 2 with (2′R,3′R,3′R)-configuration for feroniellin B was revised to rac-13 with (2′R,3′R,3′R)-configuration. The 13C-NMR data of synthetic rac-4 were identical to those reported for the natural feroniellamin.[11] The remaining task is the construction of oxepane rings. After many experiments,[10e] the diepoxides rac-10 and rac-11 were treated with a Lewis acid tris(pentafluorophenyl)borane (B(C6F5)3, 2 equiv) and H2O (8 equiv) in CH2Cl2 at −40 °C for 2 h to furnish the proposed structure rac-3 of feroniellin C and oxepane product rac-14 in 34% and 26% yields, respectively.[10e] Under acidic conditions, the regioselective and stereospecific formation of oxepanes could be achieved via coordination of bulky B(C6F5)3 to the more accessible terminal epoxide in V and subsequent endo-selective attack of the internal epoxide oxygen at the more substituted C8*, followed by ring-opening by H2O at C3* in epoxonium ion intermediate VI.[8,10e] The spectral data of synthetic rac-3 were identical to those reported for the natural feroniellin C.[11] Thus, the ring size-divergent synthetic method for monoterpenic five- to seven-membered ethereal rings has been established through the synthesis of all feroniellins in only 2 simple steps from 9.

Scheme 2. “Ring size-divergent” synthesis of feroniellins A (rac-12), B (rac-13), and C (rac-3), and feroniellamin (rac-4).

The asymmetric total synthesis of feroniellins B (13) and C (3)
Asymmetric synthesis of feroniellin A and feroniellamin was carried out (Scheme 4). The diepoxide 11,\(^{10a}\) which possessed an anti configuration and was diastereomeric to 10, was prepared via the asymmetric epoxidation of (+)-15 using the L-ketone. The cyclization of 11 using pTsOH afforded 12 in 65% yield. However, the optical rotation of 12 ([α]\(^D\)\(_{15}^c\) = -4.4 (c 0.16, MeOH)) was not identical to that of the natural sample ([α]\(^D\)\(_{25}^c\) = +18.8 (c 0.85, MeOH)).\(^{11a}\) Next, we synthesized the enantiomer ent-12\(^{10b}\) from ent-15 via ent-11\(^{10a}\) using the same cyclization reaction. The sign of the optical rotation of ent-12 ([α]\(^D\)\(_{10}^c\) = +4.1 (c

\[\text{Scheme 3. Asymmetric synthesis of feroniellins B (13) and C (3).}\]

was performed to determine their absolute configuration (Scheme 3). Here, the asymmetric epoxidation of 9 using Shi’s α-ketone\(^{11a}\) afforded the desired diepoxide 10\(^{10a}\) (26%) with a syn configuration and (+)-epoxybergamottin (15) (54%), which was first isolated from grapefruit juice.\(^{10a,12}\) The diastereomeric ratio and optical purity of 10 were determined via chiral HPLC analysis (dr 82:18, 98% ee).\(^{10b}\) The exo-selective epoxide-opening cascade of 10 in H\(_2\)O afforded 13, which had an optical rotation of ([α]\(^D\)\(_{5}^c\) = +57.7 (c 0.51, MeOH) that was identical in sign to that of the natural product ([α]\(^D\)\(_{5}^c\) = +21.7 (c 0.92, MeOH)).\(^{11}\) Since the optical rotation did not exactly match that of the natural sample, we also synthesized its enantiomer, ent-13, from 9 via ent-10\(^{10a}\) using the same 2 steps procedure mentioned above, including the epoxidation step using Shi’s L-ketone. The optical rotation of ent-13 ([α]\(^D\)\(_{5}^c\) = -56.8 (c 0.52, MeOH)) was opposite in sign to that of the natural sample. Thus, the authors propose that the absolute configuration of natural feroniellin B should be determined to be (2'R,3'S,7'R). We also accomplished the asymmetric total synthesis of feroniellin C. Compound 3 was synthesized from 10 via an endo-selective epoxide-opening cascade utilizing B(C\(_6\)F\(_4\))\(_3\).

The optical rotation of 3 ([α]\(^D\)\(_{5}^c\) = +9.4 (c 0.29, MeOH)) was similar to that of the natural feroniellin C ([α]\(^D\)\(_{5}^c\) = +10.6 (c 0.24, MeOH)). The authors synthesized ent-3 from ent-10 and confirmed the opposite optical rotation ([α]\(^D\)\(_{5}^c\) = -10.5 (c 0.19, MeOH)). Although the modified Mosher’s method of synthetic 3 was conducted for determining the absolute configuration of 3, the absolute configuration could not be determined from the ΔΔH\(_{ex}^t\) values.\(^{10a}\) After trial and error, the absolute configuration of 3 was determined via single-crystal X-ray diffraction using Cu radiation\(^{10b}\) thus, the absolute configuration of feroniellin C was unambiguously established as (2'R,3'S,7'R).

Next, the asymmetric total synthesis of feroniellin A and feroniellamin was carried out (Scheme 4). The diepoxide 11,\(^{10a}\) which possessed an anti configuration and was diastereomeric to 10, was prepared via the asymmetric epoxidation of (+)-15 using the L-ketone. The cyclization of 11 using pTsOH afforded 12 in 65% yield. However, the optical rotation of 12 ([α]\(^D\)\(_{15}^c\) = -4.4 (c 0.16, MeOH)) was not identical to that of the natural sample ([α]\(^D\)\(_{25}^c\) = +18.8 (c 0.85, MeOH)).\(^{11a}\) Next, we synthesized the enantiomer ent-12\(^{10b}\) from ent-15 via ent-11\(^{10a}\) using the same cyclization reaction. The sign of the optical rotation of ent-12 ([α]\(^D\)\(_{10}^c\) = +4.1 (c

\[\text{Scheme 4. Asymmetric synthesis of feroniellin A (ent-12) and feroniellamin (ent-4).}\]
0.20, MeOH) was identical to that of the natural sample, confirming that feroniellin A is ent-12. We conducted a modified Mosher's analysis of our synthetic 12 and ent-12. Here, we determined that the C2" position in 12 was (S)-configuration and the configuration in ent-12 was (R) in contradiction to that proposed for 1. We examined the reported data on the use of a modified Mosher's method for the natural feroniellin A. The selected ΔδHser values of our synthetic 12 bearing the (S)-configuration were opposite in sign to those of the natural sample. As a result, we propose that the (S)-configuration at C2" reported for the natural feroniellin A is incorrect and the actual configuration is (R). Therefore, the absolute configuration of feroniellin A is presumed to be (2'R,3'S,7'S). Finally, we also accomplished the asymmetric total synthesis of feroniellin by subjecting 11 and ent-11 to the exo-selective epoxide-opening cascade in H2O. The comparison of the optical rotations of 4 ([α]D28 = −44.8 (c 0.21, MeOH)) and ent-4 ([α]D28 = +41.0 (c 0.25, MeOH)) with that of the natural sample ([α]D28 = +30.2 (c 0.20, MeOH)) revealed that the structure of ent-4 represents the absolute configuration of the natural feroniellin. Therefore, the absolute configuration of natural feroniellin A was determined to be (2'R,3'S,7'S).

It is reported that many furanocoumarins exhibit strong anti-inflammatory activities. With synthetic 3, ent-3, 4, ent-4, 12, ent-12, 13, ent-13, rac-13 in hand, we evaluated their nitric oxide (NO) production inhibitory activities using RAW 264 cells. The cells were treated with samples and exposed to lipopolysaccharide (LPS) for 24 h, and NO production was measured using the Griess reagent and calculated from control (LPS+). The cell viability was assessed by a water-soluble tetrazolium salt (WST) cytotoxicity assay using the Cell Counting Kit-8. No significant cytotoxicity of synthetic coumarins was observed (up to 100 μM). All synthetic furanocoumarins exhibited NO production inhibitory activities in LPS-stimulated RAW264 cells (approximately 20–60% at 100 μM). Further investigation of the biological activity is ongoing.

In conclusion, we have developed a “ring size-divergent” strategy that enabled us to synthesize the five-, six-, and seven-membered ether rings of feroniellin analogs from the diepoxide precursors under simple acidic or neutral conditions. Herein, the divergent synthesis of all feroniellins was accomplished using bergamottin as the starting material in only 2 steps. Additionally, the structures of feroniellins A and B were revised and the absolute configuration of all feroniellins was determined via their asymmetric synthesis. Further application of this synthetic strategy to other natural products is currently under investigation.

**Experimental Section**

Experimental procedures, spectroscopic data, copies of 1H, 13C-, and 19F-NMR spectra, and crystallographic data are available in the Supporting Information.

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**Keywords:** cyclization • divergent synthesis • diastereoselectivity • natural products • furanocoumarin

10. a) For the preparation of bergamottin (9), see the Supporting Information; b) For X-ray crystallographic analyses of rac-1, rac-13, rac-4, rac-3, rac-4, 3, and ent-12, see the Supporting Information; Deposition numbers CCDC 2034972 (for rac-1), CCDC 2035472 (for rac-13), CCDC 2034980 (for rac-4), CCDC 2036494 (for rac-3), CCDC 2046290 (for rac-14), CCDC 2060138 (for 3), and CCDC 2034966 (for ent-12) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures; c) Theses reaction mechanisms have finally been confirmed by the asymmetric synthesis of feroniellins (Schemes 3 and 4); d) For examination of the endo-selective epoxide-opening of a mixture of diepoxides rac-10 and rac-11, see the Supporting Information; e) For HPLC analyses of diepoxides 10, ent-10, 11, and ent-11, see the Supporting Information; f) For synthesis of diepoxide 10 from epoxybergamottin (15), see the Supporting Information; g) For modified Mosher’s analyses of 3, 12, and ent-12, see the Supporting Information; h) Although the p-bromobenzoyletylated and ferrocene derivatives of 3 were synthesized for determination of its absolute configuration using X-ray diffraction, they were unfortunately oils, see the Supporting Information.
"Ring size-divergent" strategy enabled us to divergently synthesize the five-, six-, and seven-membered ether rings of feroniellin analogs from the diepoxides under simple acidic or neutral conditions in only 2 steps from bergamottin. Additionally, the proposed structures of feroniellins A and B were revised and the absolute configurations of all feroniellins were determined via their asymmetric synthesis.