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

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

Keisuke Nishikawa,*[a] Toshiki Niwa,[a] Kento Nishikibe,[a] Momochika Kumagai,[a,b] and Yoshiki Morimoto*[a]

Abstract: Feroniellin analogs isolated from *Feroniella lucida* possess a furanocoumarin skeleton connected with monoterpenic 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 monoterpenic five- to seven-membered ethereal rings through the chemical sythesis 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

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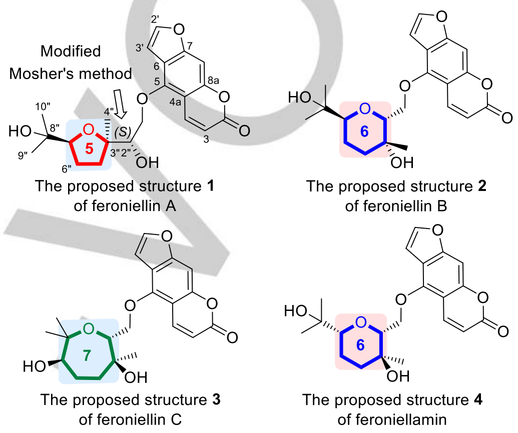
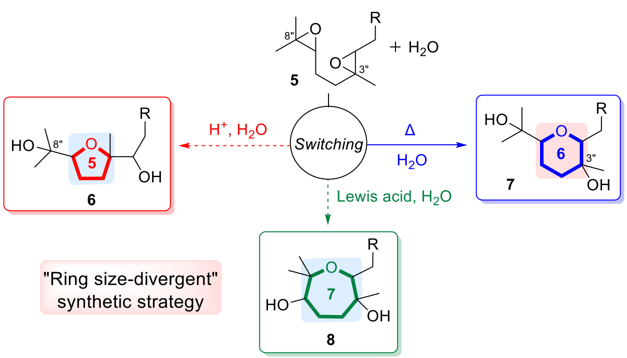


Figure 1. Chemical structures **1**–**4** of feroniellins.

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 H_2O only affords in a stereospecific manner THP products **7** (R = Me) accompanied by a nucleophilic attack of H_2O 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 Brønsted acid-catalyzed hydrolysis at C8".[7] Further according to reports of McDonald et al.,[8] it was envisioned that

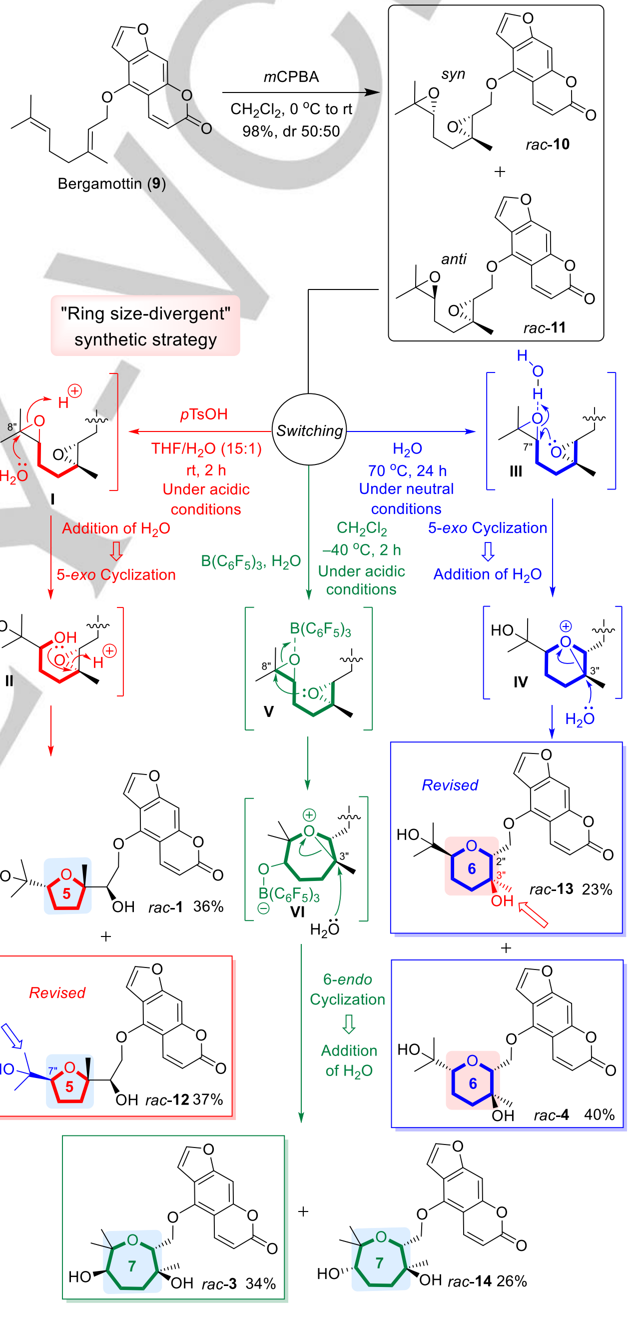


Scheme 1. "Ring size-divergent" synthetic strategy (this work).

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.

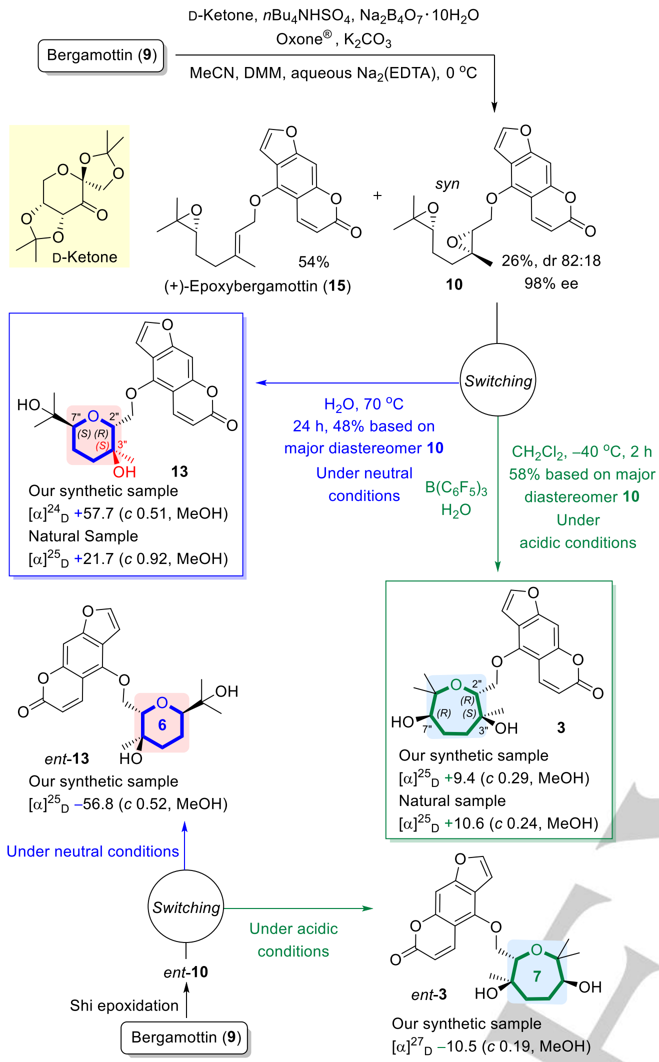
A possible biogenetic precursor of feroniellins, furanocoumarin monoterpene ethers, would be the natural product bergamottin (**9**) that is a component of grapefruit juice and many *Citrus* species[9] and ubiquitous in nature. Therefore, we started the synthesis of feroniellins from bergamottin (**9**)[10a] (Scheme 2). The cyclization precursor, which was a mixture of *syn*- and *anti*-diepoxides *rac*-**10** and *rac*-**11**, respectively, was prepared from bergemottin (**9**) via the nonstereoselective epoxidation of the two alkenes using *m*-chloroperoxybenzoic acid (*m*CPBA). At first, the cyclization of the diepoxides under the acidic conditions using a Brønsted acid *p*TsOH 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,[1] 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 THP product *rac*-**13** and the proposed structure *rac*-**4** of feroniellamin in 23% and 40% yields, respectively.[10b] As we previously reported, the stereospecific THP production occurred via a kinetically favored *exo*-selective S_N2 attack of the internal epoxide oxygen to the less substituted C7" of the H_2O-activated terminal epoxide in **III**, followed by ring-opening by H_2O at C3" in epoxonium ion intermediate **IV**.[6] 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 THP ring.[10b] Surprisingly, the spectral data of synthetic *rac*-**13** were consistent with those reported for the natural feroniellin B.[1] Therefore, the proposed structure **2** with (2"*RS*,3"*RS*)-configuration for feroniellin B was revised to *rac*-**13** with (2"*RS*,3"*SR*)-configuration. The ^{13}C-NMR data of synthetic *rac*-**4** were identical to those reported for the natural feroniellamin.[4] The remaining task is the construction of oxepane rings. After many experiments,[10d] the diepoxides *rac*-**10** and *rac*-**11** were treated with a Lewis acid tris(pentafluorophenyl)borane ($B(C_6F_5)_3$, 2 equiv) and H_2O (8 equiv) in CH_2Cl_2 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.[10b] Under acidic conditions, the regioselective and stereospecific formation of oxepanes could be achieved via coordination of bulky $B(C_6F_5)_3$ 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 H_2O at C3" in epoxonium ion intermediate **VI**.[8,10c] The spectral data of synthetic *rac*-**3** were identical to those reported for the natural feroniellin C.[1] 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**).

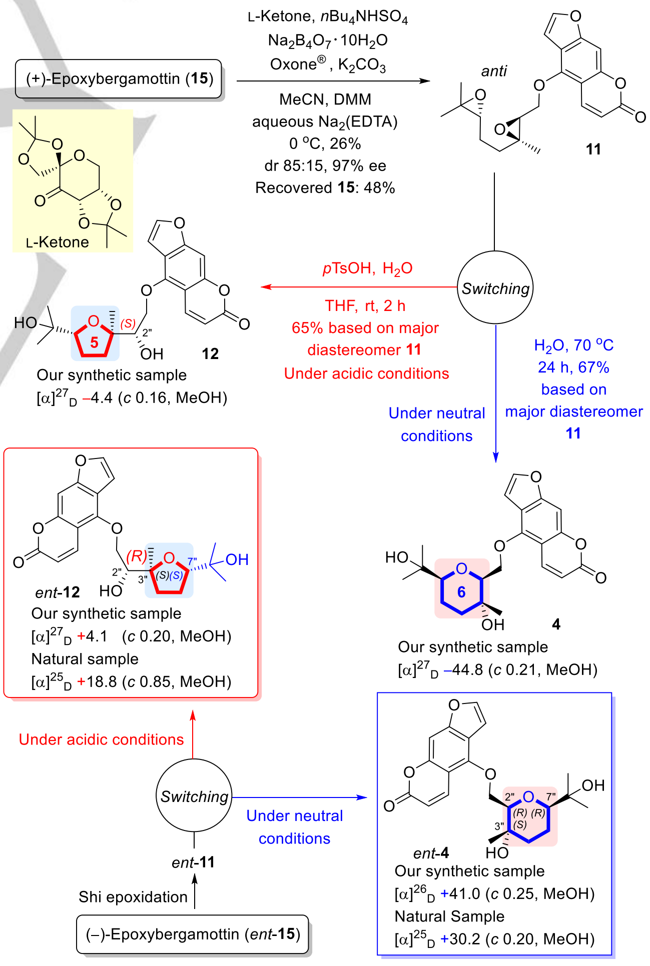
The asymmetric total synthesis of feroniellins B (**13**) and C (**3**)



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 D-ketone[11] afforded the desired diepoxide **10**[10e] (26%) with a *syn* configuration and (+)-epoxybergamottin (**15**) (54%), which was first isolated from grapefruit juice.[10f,12] The diastereomeric ratio and optical purity of **10** were determined via chiral HPLC analysis (dr 82:18, 98% ee).[10e] The *exo*-selective epoxide-opening cascade of **10** in H_2O afforded **13**, which had an optical rotation of $[\alpha]^{24}_D$ +57.7 (*c* 0.51, MeOH) that was identical in sign to that of the natural product ($[\alpha]^{25}_D$ +21.7 (*c* 0.92, MeOH)).[1] 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**[10e] using the same 2 steps procedure mentioned above, including the epoxidation step using Shi's L-ketone. The optical rotation of *ent*-**13** ($[\alpha]^{24}_D$ –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"*S*). We also accomplished the asymmetric total synthesis of feroniellin C. Compound **3** was synthesized from **10** via an *endo*-selective epoxide-opening cascade utilizing $B(C_6F_5)_3$. The optical rotation of **3** ($[\alpha]^{25}_D$ +9.4 (*c* 0.29, MeOH)) was similar to that of the natural feroniellin C ($[\alpha]^{25}_D$ +10.6 (*c* 0.24, MeOH)). The authors synthesized *ent*-**3** from *ent*-**10** and confirmed the opposite optical rotation ($[\alpha]^{27}_D$ –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 $\Delta\delta H_{SR}$ values.[10g] After trial and error,[10h] 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**,[10e] 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 *p*TsOH afforded **12** in 65% yield. However, the optical rotation of **12** ($[\alpha]^{27}_D$ –4.4 (*c* 0.16, MeOH)) was not identical to that of the natural sample ($[\alpha]^{25}_D$ +18.8 (*c* 0.85, MeOH)).[1] Next, we synthesized the enantiomer *ent*-**12**[10b] from *ent*-**15** via *ent*-**11**[10e] using the same cyclization reaction. The sign of the optical rotation of *ent*-**12** ($[\alpha]^{27}_D$ +4.1 (*c*



Scheme 4. Asymmetric synthesis of feroniellin A (*ent*-**12**) and feroniellamin (*ent*-**4**).

0.20, MeOH)) was identical to that of the natural sample,[1] confirming that feroniellin A is *ent*-**12**. We conducted a modified Mosher's analysis of our synthetic **12** and *ent*-**12**.[10g] 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.[1] The selected $\Delta\delta H_{SR}$ 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[1] 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 feroniellamin by subjecting **11** and *ent*-**11** to the *exo*-selective epoxide-opening cascade in H_2O. The comparison of the optical rotations of **4** ($[\alpha]^{27}_D$ −44.8 (*c* 0.21, MeOH)) and *ent*-**4** ($[\alpha]^{26}_D$ +41.0 (*c* 0.25, MeOH)) with that of the natural sample ($[\alpha]^{25}_D$ +30.2 (*c* 0.20, MeOH))[4] revealed that the structure of *ent*-**4** represents the absolute configuration of the natural feroniellamin. Therefore, the absolute configuration of natural feroniellamin was determined to be (2"*R*,3"*S*,7"*R*).

It is reported that many furanocoumarins exhibit strong anti-inflammatory activities.[13] 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 ^{1}H-, ^{13}C-, and ^{19}F-NMR spectra, and crystallographic data are available in the Supporting Information.

Acknowledgements

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

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[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*-**14**, **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 2034984 (for *rac*-**3**), CCDC 2064290 (for *rac*-**14**), CCDC 2060138 (for **3**), and CCDC 2034986 (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*-bromobenzoylated and ferrocene derivatives of **3** were synthesized for determination of its absolute configuration using X-ray analysis, they were unfortunately oils, see the Supporting Information.

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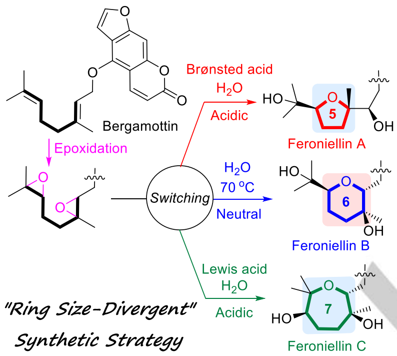
COMMUNICATION

"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.



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