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Convergent Synthesis and Structural Confirmation of Phellodonin and Sarcodonin ε

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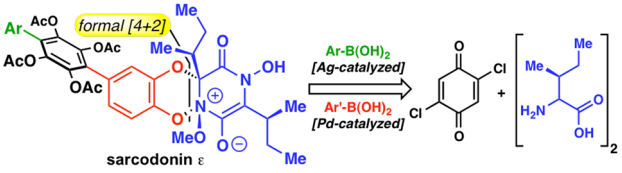
ABSTRACT



The first synthesis of members of the sarcodonin family, phellodonin and sarcodonin ε, is reported herein. This verifies that the unprecedented and seemingly unstable *N,N*-dioxide-containing benzodioxazine framework can be constructed in the laboratory and lends further support to the proposed structures. The key step in the synthesis involves a biomimetic hetero-Diels–Alder reaction between a pyrazine *N*-oxide and an ortho-quinone.

Phellodonin (**1a**) is an alkaloid isolated from the fungus *Phellodon niger* in 2010 (Figure 1A)[1] and is part of a growing family of sarcodonin natural products (Figure 1B).[2] All of the members of this family were reported to have a striking molecular architecture consisting of a tricyclic benzodioxazine core and an unprecedented *N*,*N*-dioxide ring junction (see structure **1**).[3] A series of elegant but inconclusive NMR and molecular modeling studies were used to establish the connectivity and relative stereochemistry of the benzodioxazine ring junction. Following the initial report,[3a,b] two other research groups[3c,d] have published similar structural assignments, although all subsequently disclosed structures were based on the original assignment. From these structures, it was postulated that the sarcodonins are biosynthetically formed via an unusual [4 + 2] cycloaddition between an ortho-quinone (**2**) and the C=N double bond of an appropriately oxidized pyrazine (**3**).

Our laboratory took an interest in the striking molecular architecture of the sarcodonins as well as its intriguing bioactivity, and undertook studies toward the total synthesis of this natural product family.[4] However, when we attempted to mimic the proposed biosynthetic [4 + 2] cycloaddition, we obtained not the proposed tricyclic benzodioxazine (with the core structure shown in **1**) but a bicyclic benzodioxanone (with the core of **1′**) instead, a result confirmed by X-ray crystallography.[4] Because of the unprecedented nature of the structure of **1** and the spectroscopic similarity of the crystalline benzodioxanone to the natural sarcodonins, we proposed a significant structural revision of the sarcodonin family members from the original structure **1** to the structure **1′**, although no ultimate conclusions were drawn.

Even with this reassignment, several key structural issues were left unresolved in **1′**: (1) the *E*/*Z* configuration of the 2α oxime, (2) whether the methyl group found in some members of the natural product family is located on the hydroxamic acid at 1*β* or on the 1α oxime, (3) the location of the biaryl substituent at C1 or C6 of the benzodioxanone, and (4) the relative configuration of the 2*β* aminal stereocenter. To solve these questions as well as to

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(1) Fang, S.-T.; Zhang, L.; Li, Z.-H.; Li, B.; Liu, J.-K. *Chem. Pharm. Bull.* **2010**, *58*, 1176–1179.
(2) See preceding paper: Masubuti, H.; Endo, Y.; Araya, H.; Uekusa, H.; Fujimoto, Y. *Org. Lett.* **2013**, DOI: 10.1021/ol400595k.
(3) (a) Geraci, C.; Neri, P.; Paternò, C.; Rocco, C.; Tringali, C. *J. Nat. Prod.* **2000**, *63*, 347–351. (b) Calì, V.; Spatafora, C.; Tringali, C. *Eur. J. Org. Chem.* **2004**, 592–599. (c) Ma, B. J.; Liu, J. K. *Z. Naturforsch. B* **2005**, *60b*, 565–568. (d) Hashimoto, T.; Quang, D. N.; Kuratsune, M.; Asakawa, Y. *Chem. Pharm. Bull.* **2006**, *54*, 912–914.
(4) (a) Lin, D. W.; Masuda, T.; Biskup, M. B.; Nelson, J. D.; Baran, P. S. *J. Org. Chem.* **2011**, *76*, 1013–1030. (b) Lin, D. W. Ph. D. Thesis, The Scripps Research Institute, La Jolla, CA, 2010.

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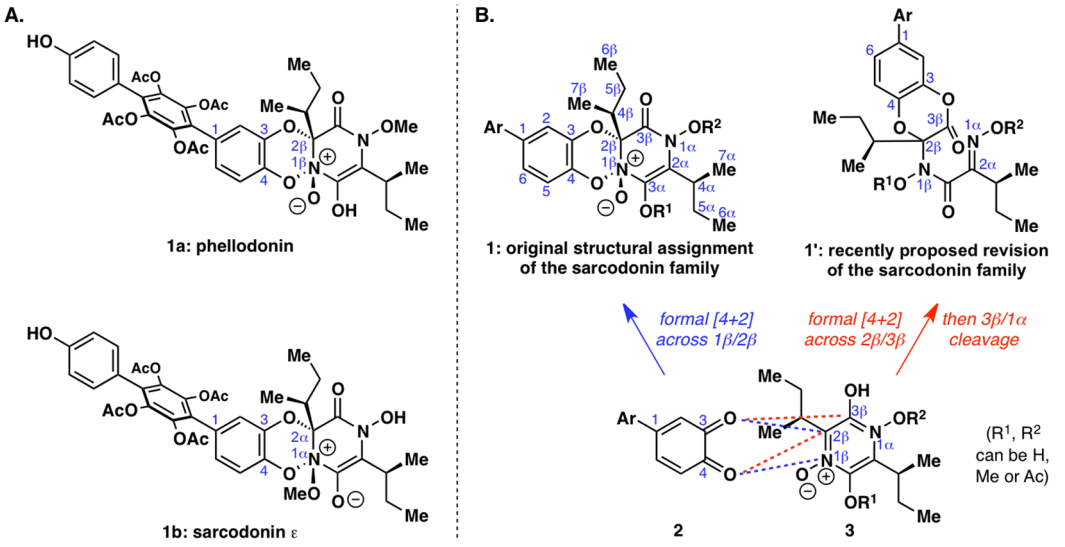
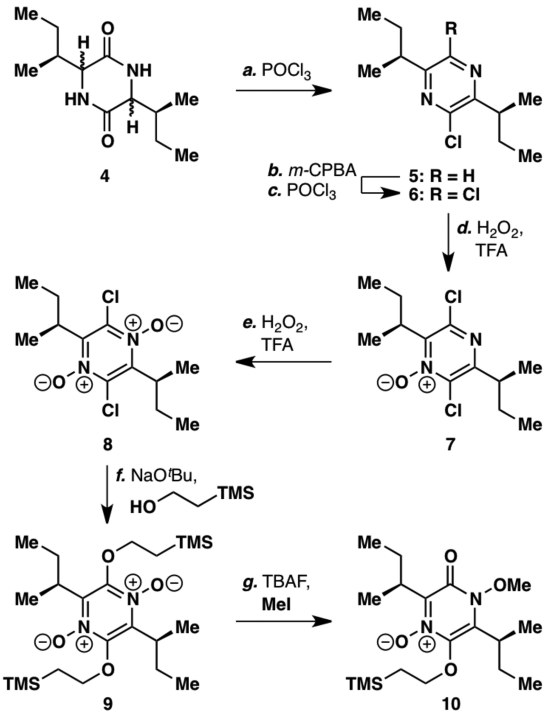


Figure 1. (A) Structures of recently isolated natural products, phellodonin (**1a**) and sarcodonin ε (**1b**). (B) Originally published structure for the sarcodonin family (**1**) and our recently proposed structure revision (**1′**), both arising from a hypothetical biosynthesis via a formal [4 + 2] cycloaddition of ortho-quinone **2** and pyrazine derivative **3**.

unambiguously identify the core structure of the sarcodonin family, it was realized that only determination by X-ray crystallography would be effective. Recent X-ray analysis conducted by Fujimoto and co-workers have now indicated that a benzodioxazine similar to **1** forms the core structure of the sarcodonins, and that the unprecedented *N*,*N*-dioxide moiety is a stable chemical entity.[2] Furthermore, they have isolated a new sarcodonin natural product, sarcodonin ε (**1b**). Herein, we report the first synthesis of phellodonin (**1a**) and sarcodonin ε (**1b**) and acknowledge Fujimoto's confirmation of the originally proposed structure[3] for this unusual heterocyclic natural product family.

Aiming for the synthesis of phellodonin (**1a**), our retrosynthesis mimics the proposed biosynthesis of the sarcodonins, with ortho-quinone **2** undergoing a [4 + 2] cycloaddition with a suitably oxidized pyrazine **3** to give the desired benzodioxanone core (see Figure 1). To pursue this approach, however, a pyrazine *bis*-*N*-oxide had to be prepared as the dienophile, which we had previously been unable to achieve.[4] After further investigation, a synthetic route was devised, and therefore a diketopiperazine of L-isoleucine (**4**) was converted into *bis*-chloropyrazine **6** in three steps using known conditions (Scheme 1).[5] The first *N*-oxidation of **6** was quite facile; however, the resulting *mono*-*N*-oxide **7** was highly deactivated, and vigorous oxidizing conditions were necessary to achieve the second *N*-oxidation to give **8** in sufficient quantities.[6] After this difficult second oxidation, preparation of the dienophile **10** was completed without serious incident: nucleophilic aromatic substitution of the heteroaryl chlorides

Scheme 1. Preparation of Pyrazine Dienophile **10**[a]

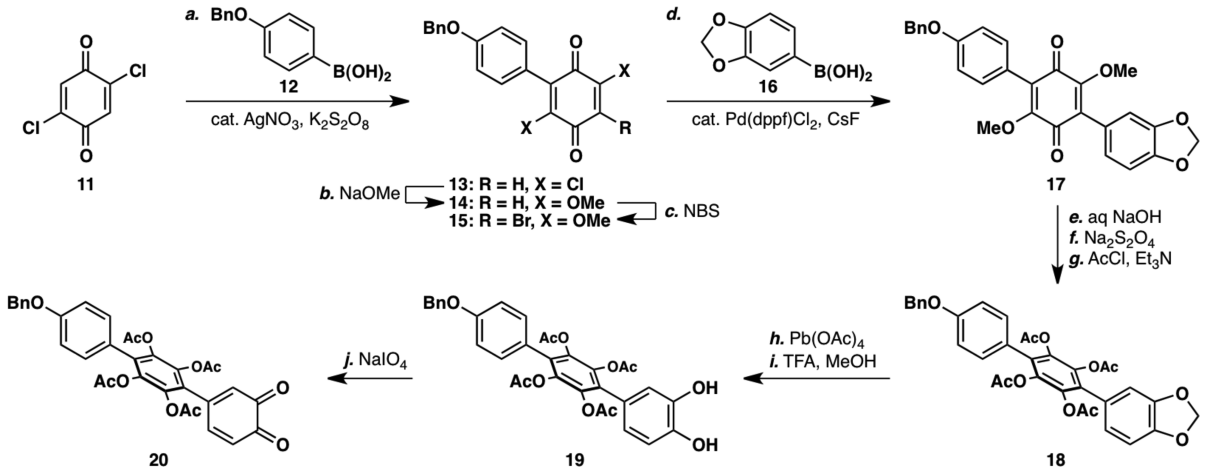


[a] Reagents and conditions: (a) $POCl_3$, neat, 100 °C, 10 h, 70% **5** + 4% **6**; (b) *m*-CPBA (3.0 equiv), CH_2Cl_2, 40 °C, 4 h; (c) $POCl_3$, neat, 100 °C, 2 h, 61% from **5**; (d) H_2O_2 (6.0 equiv), TFA, 50 °C, 3 h, 70% **7** + 1% **8**; (e) H_2O_2 (6.0 equiv), TFA, 50 °C, 3 h, 25% (52% brsm) from **7**; (f) 2-TMS-ethanol (3.3 equiv), NaO′Bu (3.5 equiv), THF, 23 °C, 12 h, 63%; (g) TBAF (1.0 equiv), then MeI (5.0 equiv), THF, 23 °C, 2 h, 99%.

proceeded smoothly, after which careful control of deprotection conditions permitted the selective removal of one

(5) Ohta, A.; Akita, Y.; Hara, M. *Chem. Pharm. Bull.* **1979**, *27*, 2027–2041.
(6) Blake, K. W.; Sammes, P. G. *J. Chem. Soc. C* **1970**, 1070–1073.

Scheme 2. Preparation of ortho-Quinone Heterodiene **20**[a]



[a] Reagents and conditions: (a) Boronic acid **12**, $AgNO_3$ (20 mol %), $K_2S_2O_8$ (3 equiv), α,α,α-trifluorotoluene, H_2O, 23 °C, 10 h, 73%; (b) NaOMe, MeOH, 23 °C, 1 h, 47%; (c) *N*-bromosuccinimide (3.0 equiv), MeCN, 70 °C, 3 h, 40−60%; (d) boronic acid **16** (1.5 equiv), $Pd(dppf)Cl_2$ (2 mol %), CsF (2 equiv), toluene, 70 °C, 2 h, 88%; (e) aq NaOH, MeOH, 80 °C, 2 h; (f) $Na_2S_2O_4$ (7.0 equiv), MeOH:H_2O (6:1), 23 °C, 1 h; (g) AcCl (30 equiv), Et_3N (27 equiv), DMAP (0.6 equiv), dioxane, 23 °C, 1 h, 69% over three steps; (h) $Pb(OAc)_4$ (2.0 equiv), benzene, 80 °C, 12 h; (i) TFA:MeOH:H_2O (1:1:1), 23 °C, 1 h, 51% over two steps; (j) $NaIO_4$ (1.1 equiv), $^nBu_4NBr$ (1.5 mol %), CH_2Cl_2, 23 °C, 1 h, 81%.

2-(trimethylsilyl)ethyl (TMSE) group and generation of methoxy compound **10**.

Preparation of the other Diels−Alder partner, the ortho-quinone moiety, was achieved via a combination of our previous studies,[3] literature precedent[7] and our recently reported conditions[8] for quinone arylation with boronic acids (Scheme 2). To this end, 2,5-dichloro-1,4-benzoquinone (**11**) was first arylated using the reported conditions for silver-mediated arylation of quinones,[8] giving arylquinone **13**. Chloride displacement, then selective bromination followed by a Suzuki cross-coupling furnished **17**. The complete terphenyl skeleton now in place, the methoxy groups were replaced with hydroxyl groups, the central quinone was reduced,[7a] and the resulting tetraol was fully acetylated to give terphenyl **18**. Finally, oxidative deprotection of the catechol[7b] and oxidation using previously reported conditions[7c] gave the desired ortho-quinone **20**.

With the two coupling partners in hand, the convergent assembly of phellodonin began with an acidic deprotection of the remaining TMSE group on pyrazine **10** (Scheme 3). The *in situ*-generated enol **21** was then immediately treated with ortho-quinone **20**; gratifyingly, desired cycloaddition[9] adducts **22a** and **22b** were obtained in 69% yield as a 1:1 mixture that could be chromatographically separated. However, **22a** was actually present as a 2:1 mixture of inseparable epimers, most likely containing an epimer at the 1*β* nitrogen atom (**1*β*-*epi*-22a**); likewise, **22b** was generated as a 1:3 mixture of inseparable epimers, most likely containing an epimer at the 1α nitrogen atom (**1α-*epi*-22b**). The mixtures **22a:1*β*-*epi*-22a** and **22b:1α-*epi*-22b** were then deprotected separately: **22a:1*β*-*epi*-22a** was found to give a deprotection product whose NMR spectroscopic properties matched those reported for phellodonin (**1a**),[1] and **22b:1α-*epi*-22b** gave sarcodonin *ε* (**1b**).[2] This marks the completion of the first synthesis of members of the sarcodonin natural product family.[10] Two epimeric sarcodonins **1*β*-*epi*-1a** and **1α-*epi*-1b** were synthesized as well, which are quite possibly natural products themselves.[11] To the best of our knowledge, these compounds represent the most highly oxidized diketopiperazine-derived molecules synthesized to date, and this was achieved by a series of oxidative events on diketopiperazine **4**.

The regioselectivity of the pyrazine-quinone formal [4 + 2]-cycloaddition merits additional discussion. As originally observed in our model studies with simple pyrazines,[4] the ortho-quinone underwent reaction exclusively with the enol double bond, giving rise to a benzodioxanone structure

(7) (a) Ye, Y. Q.; Koshino, H.; Onose, J.-i.; Negishi, C.; Yoshikawa, K.; Abe, N.; Takahashi, S. *J. Org. Chem.* **2009**, *74*, 4642–4645. (b) Nicolaou, K. C.Tang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3449–3453. (c) Pieken, W. A.; Kozarich, J. W. *J. Org. Chem.* **1989**, *54*, 510–512.

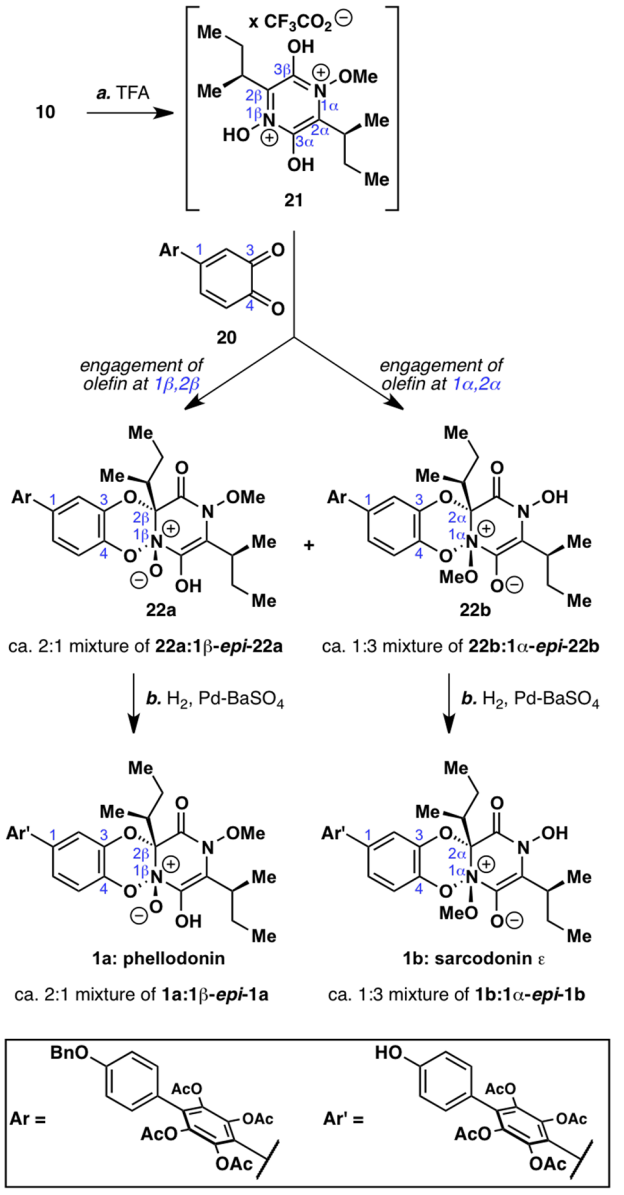
(8) Fujiwara, Y.; Domingo, V.; Seiple, I. B.; Gianatassio, R.; Del Bel, M.; Baran, P. S. *J. Am. Chem. Soc.* **2011**, *133*, 3292–3295.

(9) For examples of thermal ortho-quinone Diels−Alder reactions before 1996, see the following review: (a) Nair, V.; Kumar, S. *Synlett* **1996**, 1143–1147. For selected examples after 1996, see ref 7b as well as the following: (b) Kaizer, J.; Speier, G.; Osz, E.; Giorgi, M.; Réglier, M. *Tetrahedron Lett.* **2004**, *45*, 8011–8013. (c) Aoyagi, Y.; Takahashi, Y.; Satake, Y.; Fukaya, H.; Takeya, K.; Aiyama, R.; Matsuzaki, T.; Hashimoto, S.; Shiina, T.; Kurihara, T. *Tetrahedron Lett.* **2005**, *46*, 7885–7887. (d) Kuboki, A.; Yamamoto, T.; Taira, M.; Arishige, T.; Ohira, S. *Tetrahedron Lett.* **2007**, *48*, 771–774. (e) Majetich, G.; Zou, G. *Org. Lett.* **2008**, *10*, 81–83. (f) Nicolaou, K. C.; Wang, J.; Tang, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 1432–1435. (g) Kuboki, A.; Maeda, C.; Arishige, T.; Kuyama, K.; Hamabata, M.; Ohira, S. *Tetrahedron Lett.* **2008**, *49*, 4516–4518.

(10) Natural phellodonin (**1a**) displays a negative optical rotation and natural sarcodonin *ε* (**1b**) shows a positive optical rotation. It is of note that the synthesized mixtures of **1a:1*β*-*epi*-1a** and **1b:1α-*epi*-1b** display negative and positive optical rotations, respectively, thus matching those of the natural samples. It is thus suggested that the correct absolute configuration of these natural products has been generated from L-isoleucine, however, this evidence is not conclusive because the obtained products of the synthesis were mixtures.

(11) Sarcodonin natural products that are epimeric at the nitrogen ring junction are known, see refs 3b and 3d.

Scheme 3. Formal Hetero-Diels–Alder Reaction for the Synthesis of Phellodonin (**1a**) and Sarcodonin ε (**1b**)[a]



[a] Reagents and conditions: (a) TFA, CH_2Cl_2, 23 °C, 30 min, then **20**, $CDCl_3$, 23 °C, 1 h, 69% (of which half consists of a mixture of inseparable epimers **22a:1*β*-*epi*-22a** and the other half is a mixture of **22b:1α-*epi*-22b**); (b) H_2 (1 atm), Pd-$BaSO_4$ (10 mol %), MeOH, 23 °C, 30 min, 82% for **1a:1*β*-*epi*-1a**, 84% for **1b:1α-*epi*-1b**.

whose identity was confirmed by X-ray crystallography. In the case of pyrazine *N*-oxide **21**, however, the ortho-quinone instead undergoes reaction with the nitrone C=N double bond. It is unclear whether the reaction proceeds as a concerted [4 + 2] or whether alternative reaction pathways (such as an initial [3 + 2] dipolar cycloaddition, followed by subsequent rearrangement to the [4 + 2] product) are taking place. However, since epimeric side products are obtained, it is likely that the [4 + 2] union occurs in stepwise fashion.

The unusual and seemingly unstable *N*,*N*-dioxide-containing benzodioxazine framework has prompted a detailed analysis in structural revision,[4] which has subsequently been revisited and reanalyzed by X-ray crystallography.[2] A successful chemical synthesis now supports the conclusions from the X-ray analysis,[2] simultaneously confirming the elusive structure[12] of the sarcodonin family, as well as demonstrating the synthetic feasibility and chemical stability of this family of natural products. In summary, a convergent, biologically inspired synthesis of phellodonin (**1a**) and sarcodonin ε (**1b**) has been accomplished, involving a key formal hetero-Diels–Alder reaction. Combining the strengths of X-ray crystallography and chemical synthesis allows the unambiguous determination of even highly heterosubstituted compounds and verifies that this unprecedented framework can be constructed in a laboratory setting.

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Supporting Information Available. Experimental procedures, copies of all spectral data, and full characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

(12) Nicolaou, K. C.; Snyder, S. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1012–1044.

The authors declare no competing financial interest.