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Synthesis-Guided Structure Revision of the Sarcodonin, Sarcoviolin, and Hydnellin Natural Product Family

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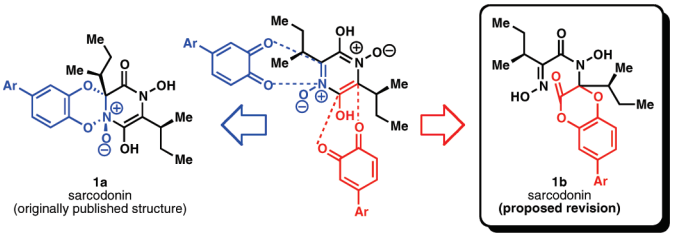

A sweeping structural revision of the sarcodonin natural product family (published structures **1a**−**13a**) is proposed after extensive studies aimed at their chemical synthesis. Key features of revised structure **1b** include replacement of the *N*,*N*-dioxide moiety with an oxime, ring-opening of the central diketopiperazine, and transposition of the terphenyl wing from the 1β−2β position of **1a** to the 2β−3β position of **1b**. This structure revision arose from the serendipitous synthesis of a benzodioxane aminal (**44**) whose structure was unambiguously determined by X-ray crystallography and whose spectral properties bore considerable resemblance to the published data for the sarcodonins. A versatile new method for *O*-arylation of hydroxamic acids is also reported herein, as well as a manganese(III)-mediated α-oxidation of hydroxamic acids to aminals.

Introduction

Modern NMR spectroscopy has facilitated a revolution in natural products chemistry. By making it possible to elucidate structural and stereochemical elements of compounds even when only milligram quantities are available, NMR now permits the determination of complex natural product architectures in remarkably rapid fashion.[1]

NMR spectroscopy, however, is not a definitive technique for structure determination. The chemical literature contains numerous structures initially proposed using NMR studies which have been subsequently corrected.[2] Most such revisions correct stereocenter assignments, olefin geometries, or peripheral heteroatomic substitutions, as in the recent cases of palau'amine,[3] azaspiracid,[4] vannusals A and B,[5] phostriecin,[6] and yatakemycin.[7] However, more radical structural revisions are necessary from time to time, when total synthesis reveals substantial constitutional errors in published structures. The diversonolic esters,[8] brosimum

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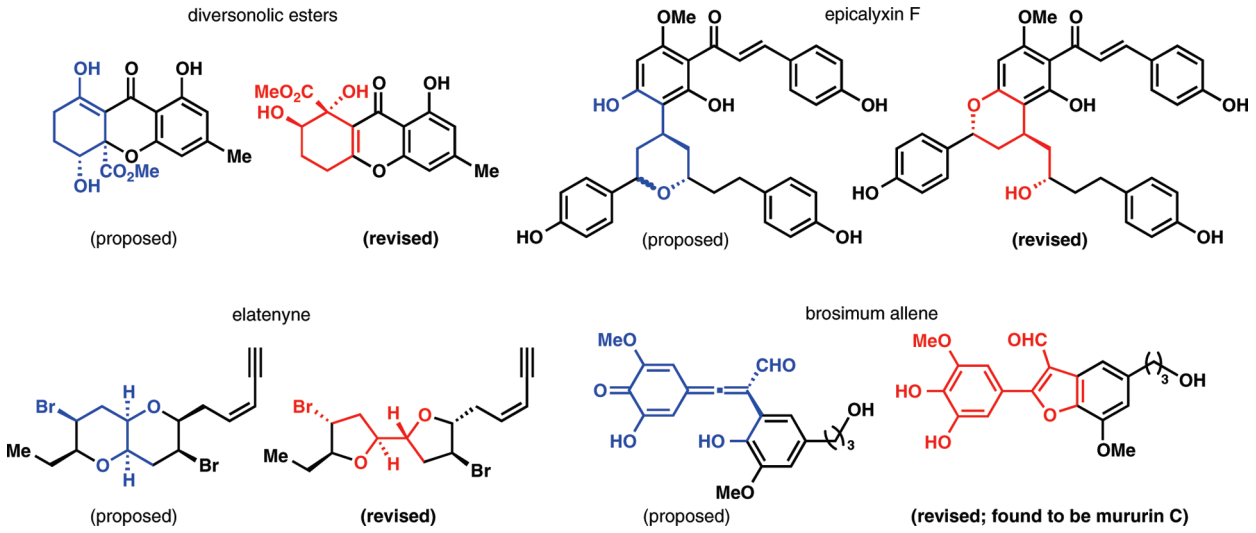

FIGURE 1. Selected natural products which have recently undergone significant structure revisions.

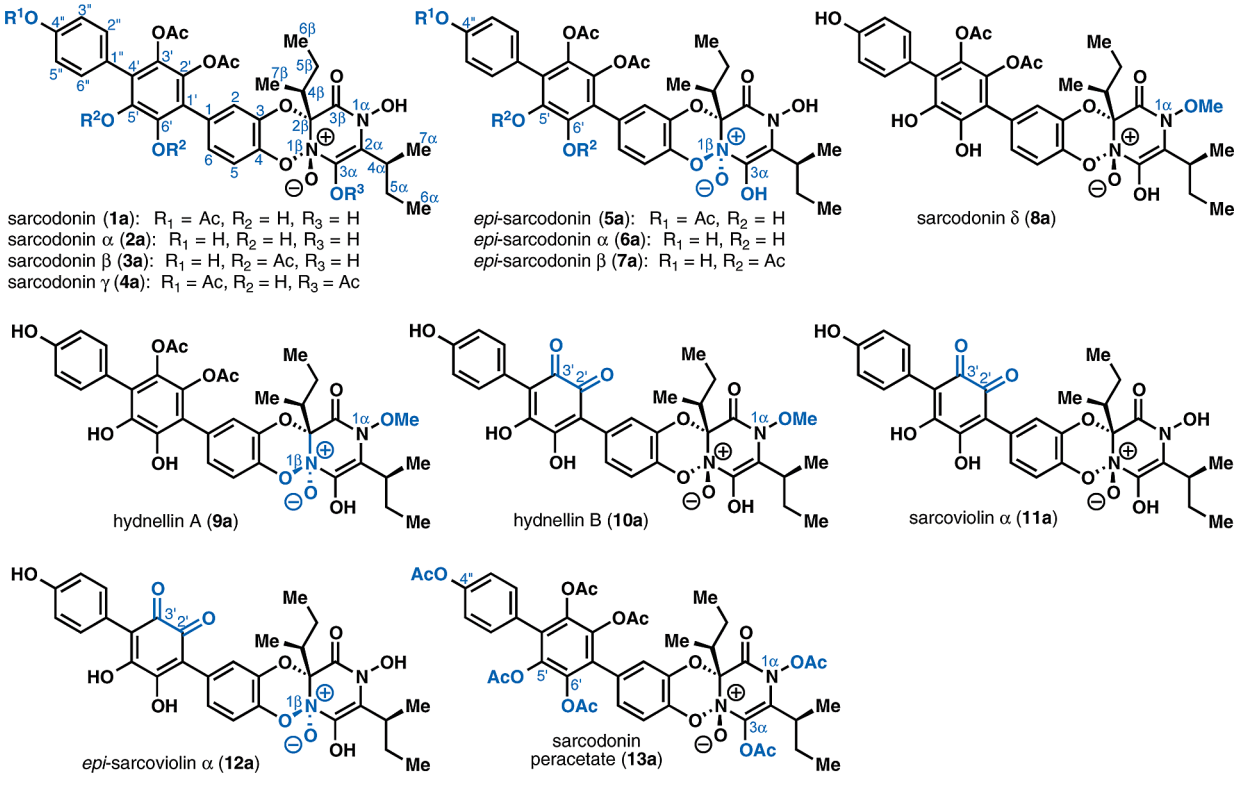

FIGURE 2. Published structures of the sarcodonin, sarcoviolin, and hydnellin natural product family. Highlighted in blue are key differences in acetylation patterns, oxidation states, and stereoconfigurations between family members.

allene,[9] elatenyne,[10] and epicalyxin F[11] (Figure 1), to name a few recent examples, illuminate both the gravity of these errors and the essential role total synthesis plays in their correction.

The recently disclosed family of natural products called the sarcodonins (**1a**−**13a**) falls into this category (Figure 2). Sarcodonin (**1a**) was initially reported[12] in 2000 as an unstable alkaloid which could not be fully characterized by NMR spectroscopy without considerable degradation and of which crystals could not be prepared for X-ray analysis. Spectroscopic studies were therefore performed on the stable peracetate (**13a**) and eventually led to the proposal of an

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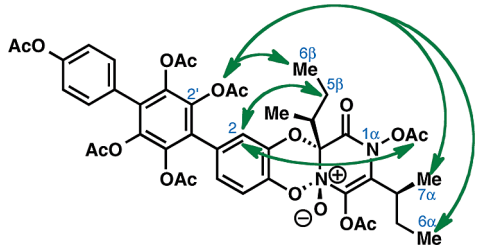

FIGURE 3. ROESY interactions between terphenyl and dipeptide wings of sarcodonin peracetate (**13a**).

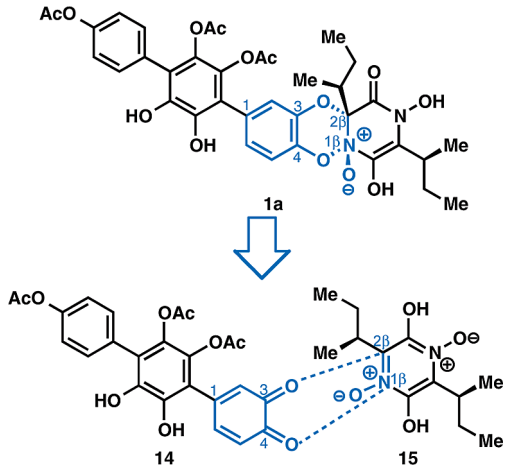

FIGURE 4. Proposed biosynthesis of sarcodonin (**1a**) via cycloaddition.

extraordinary structure featuring a benzodioxazine core and an *N,N*-dioxide ring junction. The position of the biaryl side chain at C-1 of the benzodioxazine as well as the configuration of the 1β(*R*) and 2β(*R*) stereocenters were based on a combination of ROESY experiments and molecular modeling studies (Figure 3). These striking structural motifs, several with minimal literature precedent (especially the *N,N*-dioxide), were proposed by the isolation chemists to be derived via a [4 + 2] cycloaddition between the 3,4-benzoquinone of terphenyl **14** and the 1β−2β double bond of *N*-oxopyrazine **15** (Figure 4). Subsequent studies by several different groups[13] described related family members (Figure 2), which differ in (1) the acetyl substitution patterns at the 3α, 5′, 6′, and 4″ alcohols (**2a**−**4a**); (2) the oxidation state of the central aryl ring at the 2′ and 3′ carbons (**10a**−**12a**); (3) the methylation of the hydroxamic acid at 1α (**8a**−**10a**); and (4) epimerization at the 1β *N,N*-dioxide (**5a**−**7a**, **9a**, **12a**). Thus, three research groups independently came to the same conclusion that the overall structures of these natural products correspond to those depicted in Figure 2.

Our interest in the sarcodonins was twofold. First, the forbidding and unprecedented molecular architecture of the sarcodonins, particularly its many N−O bonds, is an ideal proving ground for the development of new synthetic methods in heterocyclic chemistry, a class of compounds with undisputed importance to bio-organic and medicinal chemistry.

We were also intrigued by the diverse range of anti-HIV, antioxidant, and anticancer activities which this natural product family offers. We thus targeted the stable sarcodonin peracetate **13a** and its benzodioxazine core for total synthesis. In this full account, we trace our extensive studies of this natural product family, which began in 2004, and how they led to the realization that the originally proposed structures of these alkaloids are in need of revision.

Results and Discussion

Studies toward the Published Structure. Our studies toward the published structure of sarcodonin peracetate (**13a**) are globally summarized in Figure 5. We initially sought to mimic the proposed biosynthetic Diels−Alder reaction (Figure 4) by preparing the *N*-oxopyrazine **15** and testing whether it would undergo the desired cycloaddition[14] with a model 1,2-benzoquinone **20a**. However, despite intensive efforts, a viable synthetic route to **15** could not be devised (path A), nor could a route to a potential surrogate for **15**, the dichloropyrazine[15] **16** (path B). In the midst of these efforts, the monohydroxypyrazines[16] **17a** and **17b** were generated, but these substrates did not undergo the desired coupling with **20a** (path C).

The use of monomeric imines, which have a rich history as heterodienophiles,[17] also seemed promising. To this end, a number of *N*-substituted imines[18] (**18a**−**f**) were prepared and subjected to cycloaddition studies (path D). Of these substrates, only the nitronate ether[19] **18f** (path E) was observed to form any cycloadduct (**19**), as determined by extensive two-dimensional NMR analysis. Unfortunately, **19** proved resistant to further chemical modification−methyl ester saponification took place in very low yield, and TBS removal appeared to result in benzodioxazine ring-opening. Moreover, a screen of different 1,2-benzoquinones found that only the *tert*-butyl substrate **20a** successfully underwent cycloaddition with **18f**, suggesting that further study would prove fruitless.

We were also briefly attracted to more exotic strategies employing the α-bromonitroso[20] **21** and the oxaziridine[21] **22**

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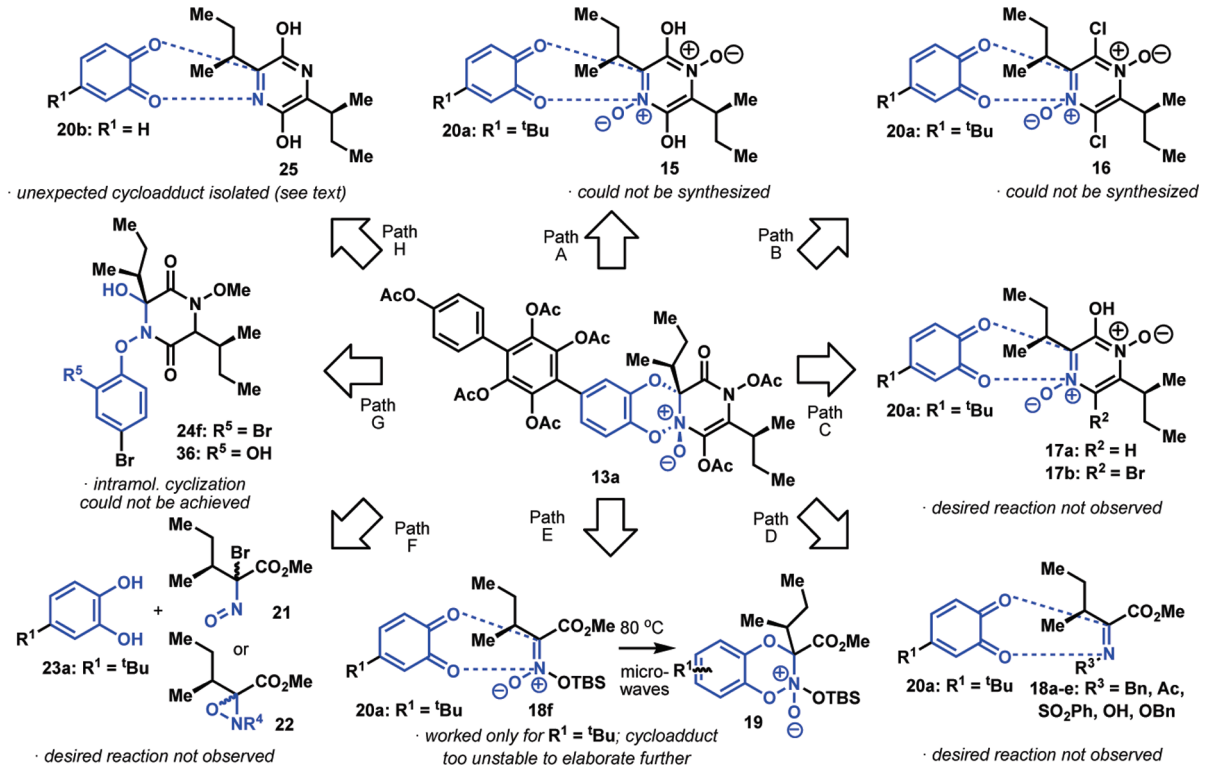

FIGURE 5. Graphical summary of approaches toward the published structure of sarcodonin.

(path F), hypothesizing that a catechol (**23a**) could undergo tandem nucleophilic substitutions to forge the benzodioxazine core. Neither of these approaches succeeded.

Another noncycloaddition based strategy drew inspiration from recent advances in amine and alcohol arylation (path G). Substrate **24f** might cyclize to the desired benzodioxazine using either Buchwald−Hartwig[22] or Chan−Lam[23] alcohol arylation conditions. Alternatively, phenol substrate **36** might cyclize under dehydrating conditions via ketal exchange. Accessing **24f** and **36** could in principle be achieved directly by arylation of hydroxamic acids (**34a**−**d**), again using either the Buchwald−Hartwig or Chan−Lam alcohol arylation.

Preparation of the desired hydroxamic acid coupling partners **34a**−**d** proved surprisingly challenging. Employing previously described routes to diketopiperazines[24] such as **33a**−**c** failed, apparently due to the sterically challenging *sec*-butyl side chains of isoleucine, which hindered the key cyclization step. Ultimately, a six-step sequence[25] starting from L-isoleucine was devised to reach **33a** (Scheme 1). The key intramolecular alkylation[26] of **31** proved difficult to control, as nucleophilic displacement of the bromide preferentially took place with the carbonyl oxygen of the hydroxamate rather than the amide nitrogen to yield oxime ester **32**. Fortunately, careful optimization studies using phase-transfer catalysis[27] led to scalable conditions which yielded gram-scale quantities of hydroxamate **33a**. The structures of both **32** and **33a** were confirmed by X-ray crystallographic studies on their dibenzyl analogues **32′** and **33a′** (prepared in a similar fashion to **32** and **33a**; see the Supporting Information for details). Subsequent deprotection[28] yielded the desired hydroxamic acids **33b**,**c**.

α-Oxidation of **33b** and **33c** was also a problematic task; while oxidation of amines[29] and hydroxylamines[30] to nitrones and of hydroxamic acids[31] to acylnitrosos is well-established,

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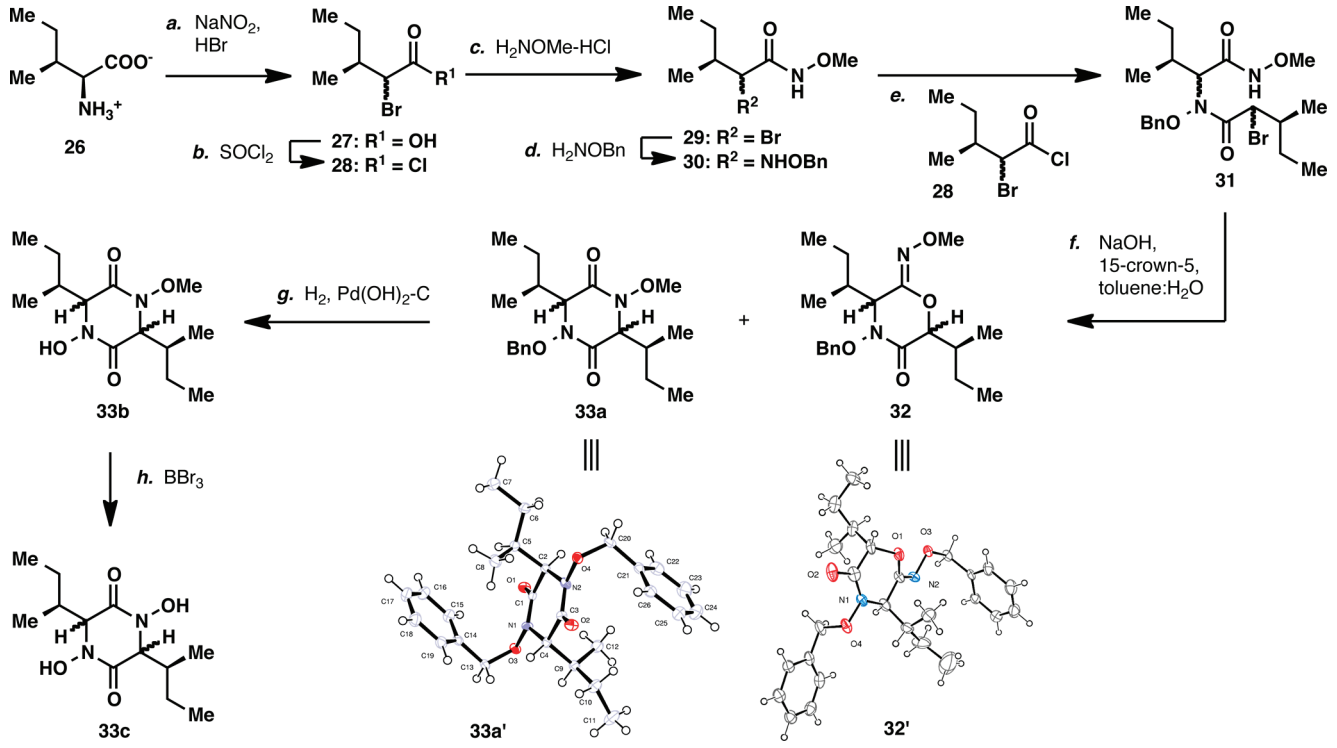
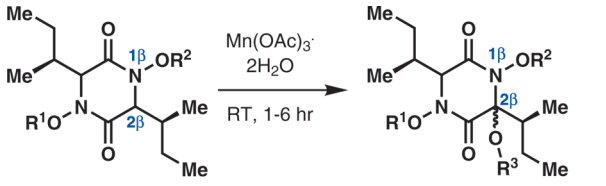
SCHEME 1. Preparation of 33a−c via Intramolecular Alkylation[a]



[a]Reagents and conditions: (a) $NaNO_2$ (1.5 equiv), 6 M aq HBr, 0 °C, 4 h, 76%; (b) $SOC1_2/CHC1_3$ (1:1 v/v), reflux, 83%; (c) H_2NOMe−HCl (2.0 equiv), Et_3N (2.0 equiv), CH_2C1_2, rt, 2 h, 95%; (d) H_2NOBn (1.6 equiv), K_2CO_3 (2.0 equiv), THF, reflux, 1.5 h, 40%; (e) **30** (1.0 equiv), **28** (1.2 equiv), Et_3N (2.0 equiv), CH_2C1_2, rt, 3 h, 65%; (f) 2.0 M aq NaOH (20 equiv), 15-crown-5 (1.0 equiv), toluene, 95 °C, 2 h, 50% (for **32**) + 35% (for **33a**); (g) H_2, $Pd(OH)_2$−C, THF, rt, 1.5 h, 94%; (h) BBr_3 (3.0 equiv), CH_2C1_2, rt, 30 min, 92%.

as well as the α-oxidation of diketopiperazines[32] to hemiaminals, extensive oxidant screens still proved necessary. Eventually it was found that manganese(III) acetate[32c,33] effected the desired oxidation to give products **34a−d** in respectable yields (Scheme 2). To the best of our knowledge, this is the first example of the oxidation of hydroxamic acids to the corresponding α-aminals. The presence of the free hydroxyl is essential, as the *O*-benzylhydroxamate **33a′** fails to undergo oxidation. Formation of the aminals proceeds under mild conditions at room temperature with slight amounts of acid or base. Of all the substrates screened, the oxidation of **33b** to **34c** occurs most readily, presumably since there is only one free hydroxamic acid available for oxidation; the lower yields observed for **34a** and **34b** are likely a consequence of oxidation at both free hydroxamic acid sites. Interestingly, formation of methoxyaminal **34d** is invariably accompanied by isolation of similar amounts of hydroxyaminal **34c**. While the mechanism of this oxidation is uncertain, it appears that

SCHEME 2. Hydroxamate Oxidation to the Hemiaminal



33b: R^1 = Me, R^2 = H
33c: R^1 = H, R^2 = H
33a': R^1 = Bn, R^2 = Bn

34a: R^1 = H, R^2 = H, R^3 = H
34b: R^1 = H, R^2 = H, R^3 = Me
34c: R^1 = Me, R^2 = H, R^3 = H
34d: R^1 = Me, R^2 = H, R^3 = Me

33c: 20:1 MeCN:2 M NaOH, 30% (**34a**)
33c: 12.5:1 MeOH:2 M NaOH, 36% (**34b**)
33b: MeCN, solid K_2CO_3, 45% (**34c**)
33b: 20:1 MeCN:AcOH, 55%[a] (**34c**)
33b: 50:1 MeOH:1 M NaOAc, 38%[a] (**34d**)
33b: MeOH, solid NaOAc, 47% (**34d**)
33a': various conditions & solvents, 0% (**33a'** recovered)
[a]*based on recovered starting material*

water can outcompete methanol in attacking the incipient hydroxyiminium species formed at the 2β carbon.

The hydroxamates **34c** and **34d** were then subjected to a battery of different alcohol arylation conditions. To our surprise, Buchwald−Hartwig conditions[22] with aryl halides failed in our hands, as did Chan−Lam conditions with arylboronic acids which had been previously reported[34] to arylate *N*-hydroxyphthalimides. Hypothesizing that a different aryl donor might yield better results, we prepared a

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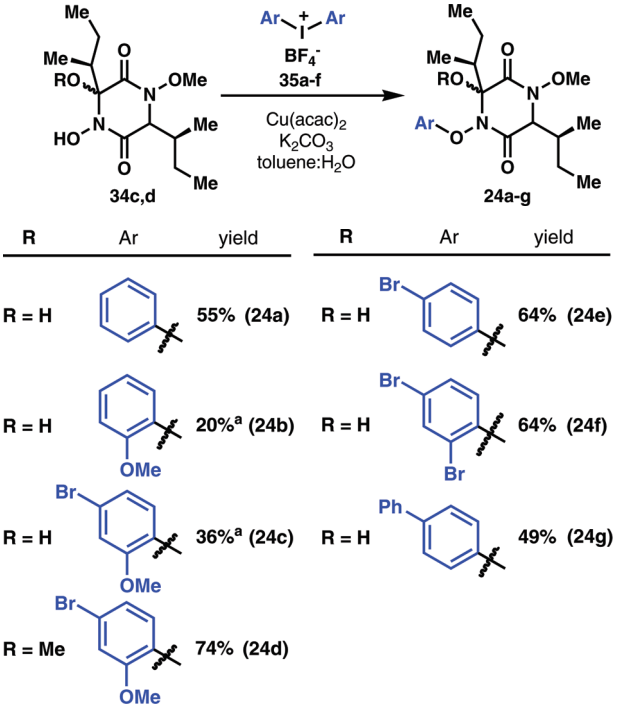
TABLE 1. Modified Chan−Lam Arylation Conditions for Hydroxamic Acids

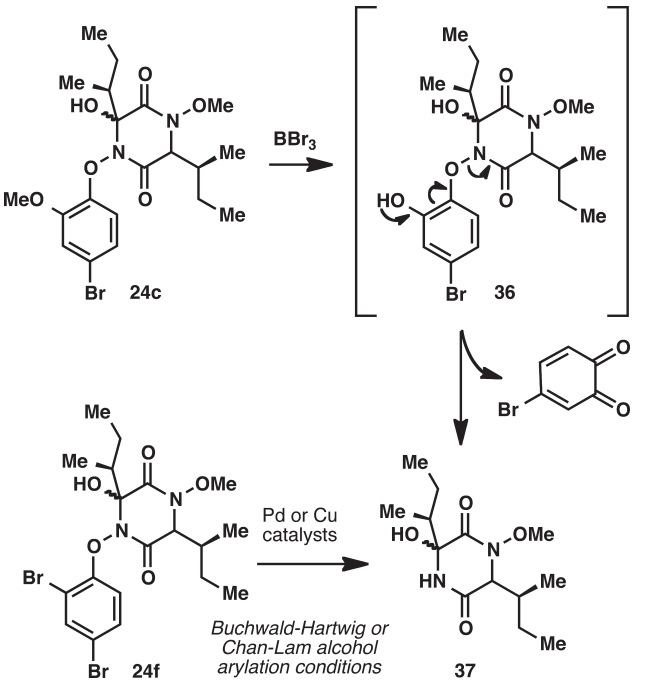


[a]40−60% starting material typically recovered.

number of different aryl substrates known to participate in Chan−Lam couplings and found to our delight that aryliodonium salts[35] (**35a**−**f**) formed the desired arylation products **24a**−**g** in the presence of copper(II) acetylacetonate (Table 1). The coupling conditions are mild and quite versatile, tolerating a number of different substituents about the aryl ring. Moreover, the necessary aryliodonium salts can be rapidly prepared from the corresponding aryl iodides in just three operationally simple steps[36] (see the Supporting Information). This procedure, by expanding the scope of alcohol substrates to include hydroxamic acids,[37] represents a useful addition to the scope of the Chan−Lam method.

With substrates **24a**−**g** in hand, cyclization studies began in earnest. To our dismay, however, despite screening many different oxidative, radical, and transition-metal-mediated conditions, no benzodioxazine products were ever isolated. Two results proved particularly discouraging (Scheme 3). First, efforts to demethylate the phenolic ether of **24c** led only to complex product mixtures. NMR studies indicated that the aryl group had been removed, and LCMS suggested that the remaining diketopiperazine moiety had also been deoxygenated. Together

SCHEME 3. Cyclization Studies Result Only in N−O Bond Cleavage



these implied the formation of dearylated substrates like **37**. The apparent N−O bond cleavage may take place via intermediate **36**. Second, treating **24f** with Buchwald−Hartwig and Chan−Lam arylation conditions also furnished similarly dearylated product mixtures. These results suggested that cleavage of the N−O bond was particularly facile.

These results necessitated reconsideration of the biomimetic [4 + 2] strategy (Figure 4). We hypothesized that the hydroxypyrazine **25** might undergo cycloaddition to yield the benzodioxazine core of sarcodonin (Figure 5, path H). While it was unclear how the subsequent *N*-hydroxylations would be achieved, the need to first establish a route—any route—to the unprecedented benzodioxazine skeleton overrode these concerns. Hydroxypyrazine **25** had the additional advantage of being more electron-rich than the previous pyrazines studied (**15**, **16**, and **17a**,**b**) and therefore better electronically matched[14a,b,17b,38] for a Diels−Alder reaction with the electron-deficient 1,2-benzoquinone (**20a**−**c**).

Thus, **25** was prepared in three steps[39] from the known diketopiperazine[40] **38** (Scheme 4). Subjecting **25** to 1,2-benzoquinone generated in situ from catechol then yielded an unexpected product, the benzodioxane aminal **42**, on the basis of exhaustive NMR analysis. Also isolated from the reaction mixture was a second cycloadduct **43** whose structure was unambiguously determined by X-ray crystallography. Compound **42** appears to form via cycloaddition of 1,2-benzoquinone with the enol double bond of pyrazine **25** to initially form tricycle **41**; subsequent collapse of the imine and expulsion of ammonia yields the isolable benzodioxane **42**.

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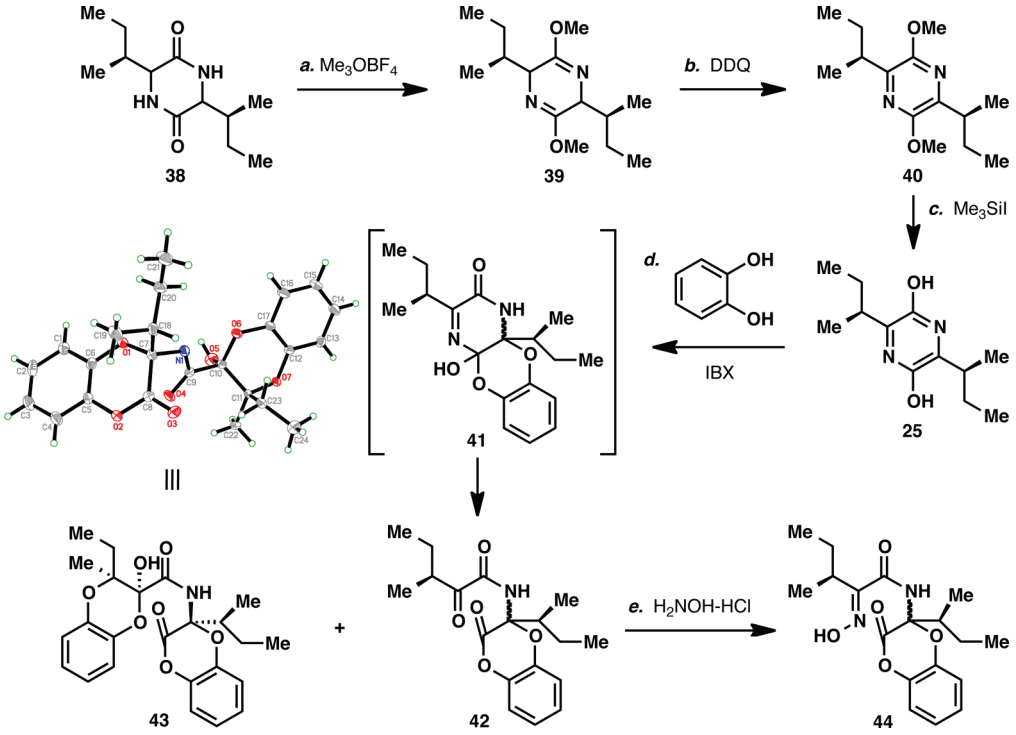
(40) Cook, B.; Hill, R. R.; Jeffs, G. E. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1199.

SCHEME 4. Hydroxypyrazine 25 Produces a Cycloadduct with Unexpected Regioselectivity[a]



[a]Reagents and conditions: (a) Me_3OBF_4 (3.1 equiv), CH_2Cl_2, rt, 4 days, 88%; (b) DDQ (3.0 equiv), toluene, 100 °C, 5 h, 64%; (c) Me_3SiI (5.0 equiv), neat, 100 °C, 18 h, 96%; (d) catechol (10 equiv), IBX (10 equiv), THF, rt, 4 h, 16% (for **42**) and 9% (for **43**); (e) $H_2NOH{-}HCl$ (4.7 equiv), 20:1 $THF{-}H_2O$, 70 °C, 1 h, 96%.

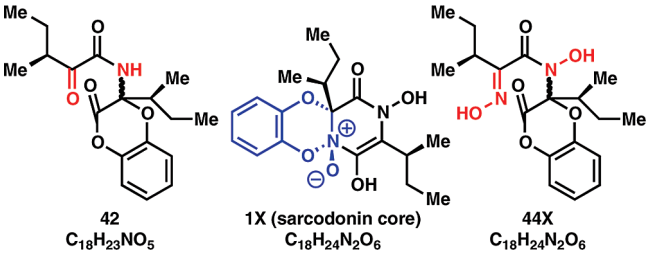


FIGURE 6. Comparison of **42**, benzodioxazine **1X**, and a postulated **44X** derived from **42** to account for the differences in molecular formulae.

Structural Revision of the Sarcodonins. Interestingly, the ^1H and ^{13}C NMR spectra of **42** exhibit noticeable similarity to those of sarcodonin peracetate. In fact, if one excludes the biaryl side chain of sarcodonin, the molecular formula of **42** ($C_{18}H_{23}NO_5$) only differs from that of the benzodioxazine core of sarcodonin **1X** ($C_{18}H_{24}N_2O_6$) by one hydrogen, nitrogen, and oxygen (Figure 6). Since the ^{13}C NMR spectrum of sarcodonin (**1a**) does not allow for a ketone, we surmised that replacing the ketone of **42** with an oxime might account for the missing nitrogen and hydrogen and produce a quaternary carbon center more in tune with the spectral properties of sarcodonin. Replacing the amide bond in **42** with a hydroxamic acid accounts for the missing oxygen and gives the postulated structure **44X**, which now has a molecular formula identical to that of **1X**.

To test whether **44X** might match the spectral data for sarcodonin, **42** was converted to the oxime[24] **44** (Scheme 4) and its NMR spectra compared with those of sarcodonin α (Figure 7). The spectra of **44** bear surprising parallels with those of sarcodonin α, particularly in the ^{13}C NMR spectrum where the signals assigned to the two carbonyl carbons (3α, 3β), the oxime carbon (2α), and the aminal carbon (2β) of **44** bear a striking resemblance to the similarly assigned signals for sarcodonin α.

These observations led us to consider a radical structural revision for the sarcodonin natural product family (Figure 8). Instead of a benzodioxazine core (**1a**) as originally proposed, we hypothesized that a benzodioxane aminal core (**1b**) was in fact the correct structure. The key structural differences are (1) replacement of the *N,N*-dioxide with an oxime, (2) opening of the diketopiperazine core to form an acyclic pseudodipeptide, and (3) transposition of the terphenyl side chain from the 1β−2β positions adjacent to the *N,N*-dioxide to the 2β−3β positions adjacent to the nitrogen of the hydroxamic acid.

There are several considerations which favor our postulated structure **1b**. Foremost is that **1b** is a much more plausible chemical structure than **1a**. An exhaustive search of the literature for stable benzodioxazine structures similar to **1a** yields only a handful of publications, none of which characterize the described structures in any detail. A similar search for stable organic compounds exhibiting the *N,N*-dioxide motif yields similarly meager results. By contrast, a literature search for benzodioxanone aminals like the core of **1b** yields multiple well-documented compounds.[41] Moreover, by invoking an oxime and altering the position of the terphenyl side chain, **1b** eliminates the need to invoke the speculative and unprecedented *N,N*-dioxide of **1a** as well as the unlikely enol tautomer proposed at the 2α−3α position of **1a**. Finally, the stereoisomers observed in the sarcodonin family can now be logically attributed to epimerization of the

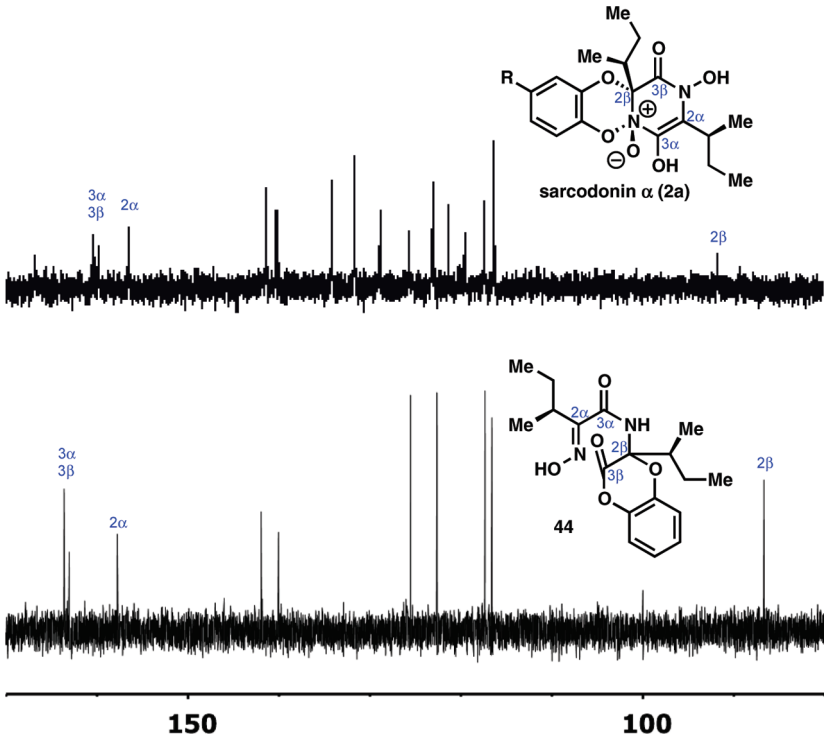


FIGURE 7. Comparison of ^{13}C NMR spectra for sarcodonin α and **44** reveals striking similarities (scale in ppm).

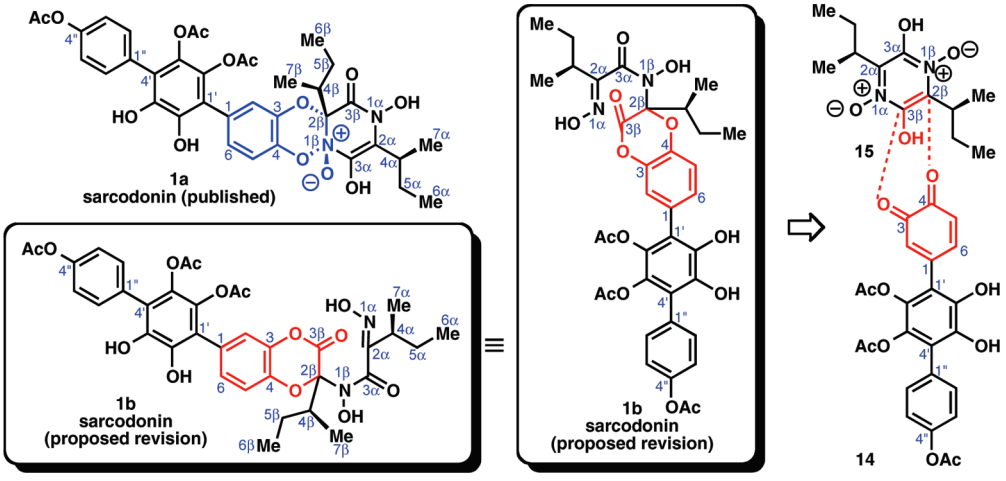


FIGURE 8. Proposed structure revision for the sarcodonins, comparison with published structure, and revised biosynthetic hypothesis.

2β aminal stereocenter of **1b**, rather than that of the 1β *N,N*-dioxide stereocenter in **1a**.

Second, **1b** better fits the observed spectral data for the sarcodonins than **1a**. Both **1b** and **1a** fit many of the key features of the sarcodonin NMR data, particularly the structure of the terphenyl wing, the two isoleucine side chains, and the 2β aminal. There are, however, some odd inconsistencies in the original NMR signal assignments for **1a**. On the basis of two-dimensional NMR studies, the sarcodonin ^{13}C NMR signals at 168.5, 159.6, and 157.7 ppm were assigned to the hydroxamate carbonyl at 3β and the enol carbons at 2α and 3α of **1a**. It seems unlikely that both enol carbon signals would be found this far downfield,[42] even in the presence of the adjacent *N,N*-dioxide. By contrast, these ^{13}C NMR signals are reasonably assigned to the 3β and 3α carbonyls and the 2α oxime of **1b**. Additionally, the ^{15}N NMR signal at 367.0 ppm (assigned to the *N,N*-dioxide nitrogen of **1a**) can be assigned to the oxime nitrogen of **1b**, consistent with ^{15}N NMR literature precedent for oxime nitrogens.[43]

(41) (a) Riordan, J. M.; Stammer, C. H. *Tetrahedron Lett.* **1976**, *17*, 1247. (b) Riordan, J. M.; Sato, M.; Stammer, C. H. *J. Org. Chem.* **1977**, *42*, 236. (c) Friedrichsen, W.; Schwarz, I. *Tetrahedron Lett.* **1977**, *18*, 3581. (d) Friedrichsen, W.; Schroer, W.-D.; Debaerdemaeker, T. *Liebigs Ann. Chem.* **1980**, 1836. (e) Friedrichsen, W.; Schwarz, I.; Epe, B.; Hesse, K.-F. *Z. Naturforsch. B* **1981**, *36b*, 622. (f) Friedrichsen, W.; Schwarz, I.; Debaerdemaeker, T. *Z. Naturforsch. B* **1982**, *37b*, 663.

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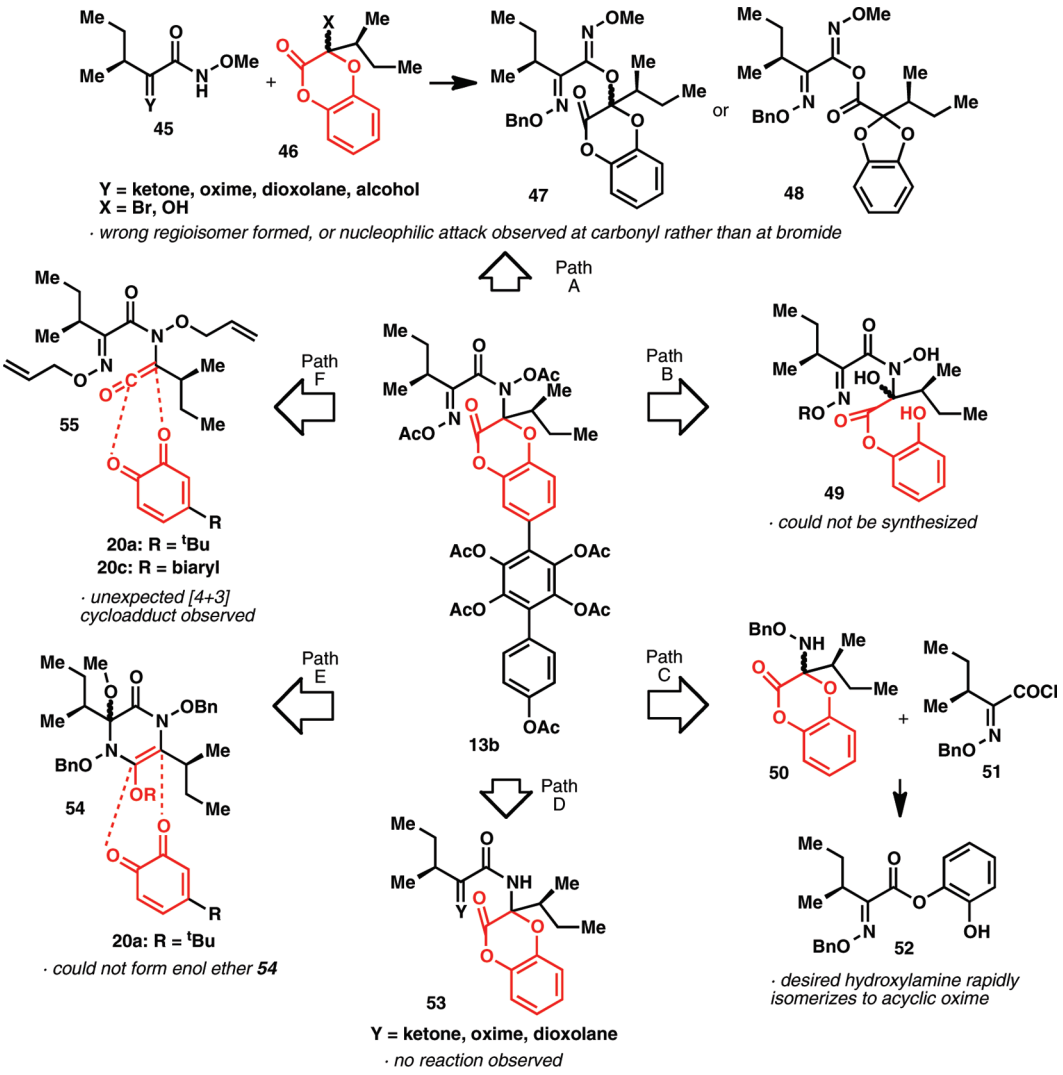

FIGURE 9. Graphical summary of failed approaches toward the proposed structure for sarcodonin.

Third, the biosynthetic hypothesis ventured for **1a** is actually more plausible for **1b**. While 1,2-benzoquinones have a rich history as heterodienes in Diels–Alder chemistry, their electron-deficient nature mandates electron-rich dienophiles as coupling partners.[14] The nitrone-like 1β–2β double bond of dienophile **15** (Figure 4) does not seem to have the requisite electronic density to meet this basic requirement. Alternatively, the enol-like 2β–3β double bond of **15** is considerably more electron-rich, and in fact, enols have been employed as coupling partners with 1,2-benzoquinones[14d,44] in [4 + 2] cycloadditions. The cycloadduct (Figure 8) resulting from a union of **14** with the 2β–3β double bond of **15** could undergo the same imine collapse and ring fission observed previously (Scheme 4) to become our revised structure **1b**.

Three critical issues remain unresolved by this structure reassignment. First is the regiochemistry of the presumed biosynthetic [4 + 2] cycloaddition, which determines whether the biaryl side chain is attached at the C1 or C6 position of **1b**. This issue was left largely unresolved in the original isolation paper; while ROESY experiments on peracetate **13a** suggested interactions of H-2 with H-5β and 1α-OAc and of 2′-OAc with H-6β, H-6α, and H-7α (Figure 3), these experiments do not seem to definitively establish the position of the biaryl side chain. A second issue is the absolute configuration of the 2β aminal stereocenter, which cannot be determined on the basis of the published data. Since there is no obvious source of substrate-based stereocontrol in the biosynthetic [4 + 2], it is likely that both 2β epimers are produced (explaining the existence of the *epi*-sarcodonins). The third issue is the *E*/*Z* configuration of the oxime which is also not established. If the revised biosynthetic hypothesis is correct, the *E* configuration (as drawn in Figure 8) is more likely, since the oxime would originate from the fragmentation of a cyclic *N*-oxide in which it would have the *E* configuration.

Studies toward the Revised Structure. A number of different approaches were initially explored in our efforts to construct the revised structure of sarcodonin peracetate (**13b**), as summarized in Figure 9. One of the most promising

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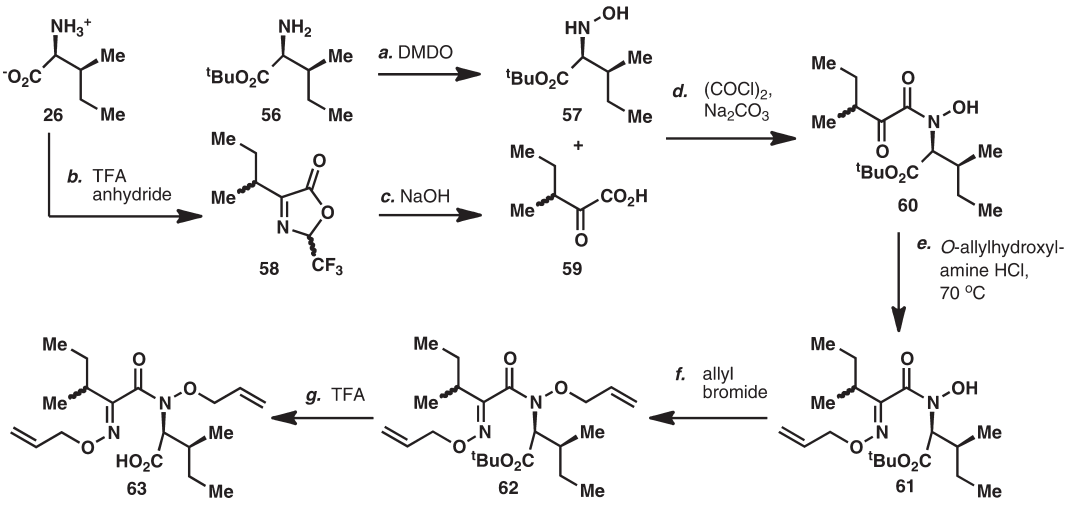
(44) (a) Nair, V.; Kumar, S. *J. Chem. Soc., Chem. Commun.* **1994**, 1341. (b) Omote, Y.; Tomotake, A.; Kashima, C. *J. Chem. Soc., Perkin Trans. 1* **1988**, 151.

SCHEME 5. Preparation of Ketene Precursor 63[a]



[a]Reagents and conditions: (a) DMDO (0.4 equiv) in acetone, CH_2Cl_2, 0 °C, 1 h, 18%; (b) TFA anhydride (3.0 equiv), reflux, 8 h, 67%; (c) NaOH (1.1 equiv), rt, 12 h, 99%; (d) **59** (1.0 equiv), $(COCl)_2$ (1.0 equiv), 200:1 CH_2Cl_2/DMF, rt, 30 min, then **57** (1.25 equiv), aq Na_2CO_3 (5.0 equiv), rt, 1 h, 67% based on **59**; (e) $H_2C{=}CHCH_2ONH_2{-}HCl$ (5.0 equiv), 20:1 THF/H_2O, 70 °C, 4 h, 68%; (f) allyl bromide (4.0 equiv), THF, 1.0 M K_2CO_3 (10 equiv), *n*-Bu_4NBr (2.0 equiv), rt, 7 h, 99%; (g) 5:1 CH_2Cl_2/CF_3COOH, 55 °C, 1 h, 99%.

involved alkylation of a bromoacetal or hemiacetal **46** with hydroxamic acid **45** (path A);[26] unfortunately, despite screening a variety of different alkylation promoters, only the wrong alkylation regioisomers **47** and **48** were isolated. This is consistent with observations made previously during our studies of the alkylative cyclization of **31** (Scheme 1), where the carbonyl oxygen of the hydroxamate proved more nucleophilic than the amide nitrogen. Attempting an intramolecular cyclization instead on **49** (path B) was also explored, but this precursor could not be prepared. Peptide coupling of aminal **50** with acid chloride **51** was considered (path C), but **50** was unexpectedly found to rapidly isomerize to the open chain oxime **52**; free amine hemiaminals such as **50** do not appear to be stable. The somewhat speculative approach of direct amide *N*-hydroxylation was tested on amide **53** (path D); no conditions were found to induce the desired hydroxylation.

In the wake of these results, the biomimetic [4 + 2] strategy was revived. Since the biomimetic pyrazine substrate **15** could not be prepared (Figure 5; Figure 9, path E) the enol ether **54** was instead targeted as a reasonable substitute. Unfortunately, this could not be achieved; the basic conditions typically employed for forming enol ethers resulted only in N−O bond cleavage. However, drawing inspiration from the considerable precedent in the literature for ketene−quinone cycloadditions,[45] we directed our attention to the acyclic ketene **55**, which could conceivably serve as a useful dienophile (path F).

Preparation of **63**, the carboxylic acid precursor to ketene **55**, was eventually achieved in seven steps from isoleucine (Scheme 5). One notable feature of this synthetic sequence is use of Danishefsky's method[46] with dimethyldioxirane (DMDO) to prepare the hydroxylamine **57** directly from L-isoleucine *tert*-butyl ester **56**. While the isolated yield of this first step is low, it can be carried out on multigram scale (limited only by the amount of DMDO which can be prepared[47] in a single batch), and the unreacted **56** is easily recovered and recycled. Another notable feature is the highly selective *N*-acylation of **57** with racemic **59** to make dipeptide **60** as a mixture of diastereomers; no *O*-acyl product is isolated. Remarkably, *O*-protected hydroxylamine analogues (such as *O*-benzyl, *O*-CBZ, and *O*-BOC) of **57** fail to undergo any *N*-acylation, possibly the result of steric congestion about the amine. Third, performing the oxime installation and hydroxamate alkylation in the order shown is critical; if the hydroxamate is alkylated first, the oxime cannot be subsequently installed.

Preparation of quinone coupling partner **20c** was based primarily on the Suzuki coupling strategy charted recently in syntheses of the terphenyl natural products terprenin[48] and vialinin A[49] (Scheme 6). The tetrabenzyl ether **64** was brominated,[50] then coupled[48] with boronic acid **66** to form the biaryl **67**. A second sequence of bromination and Suzuki coupling with the boronic acid **69** completed construction of the terphenyl carbon skeleton. Deprotection to the catechol[51] **71** and oxidation[52] completed synthesis of the 1,2-benzoquinone **20c**. This compound proved surprisingly stable and could even be purified by silica gel flash chromatography.

With both coupling partners in hand, studies of the proposed [4 + 2] cycloaddition commenced. Employing a simplified variant of the Lectka conditions[45b] yielded a

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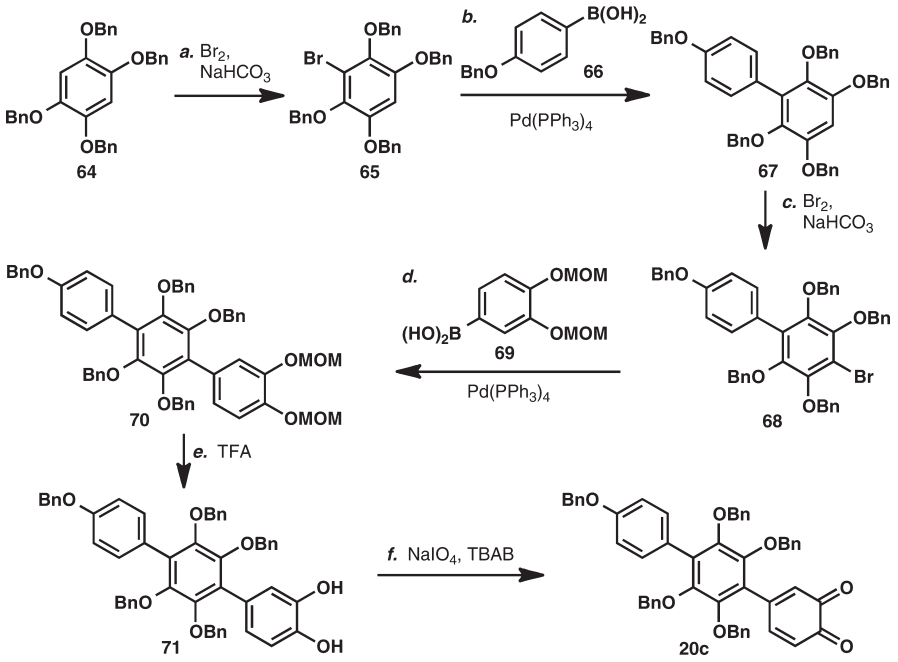
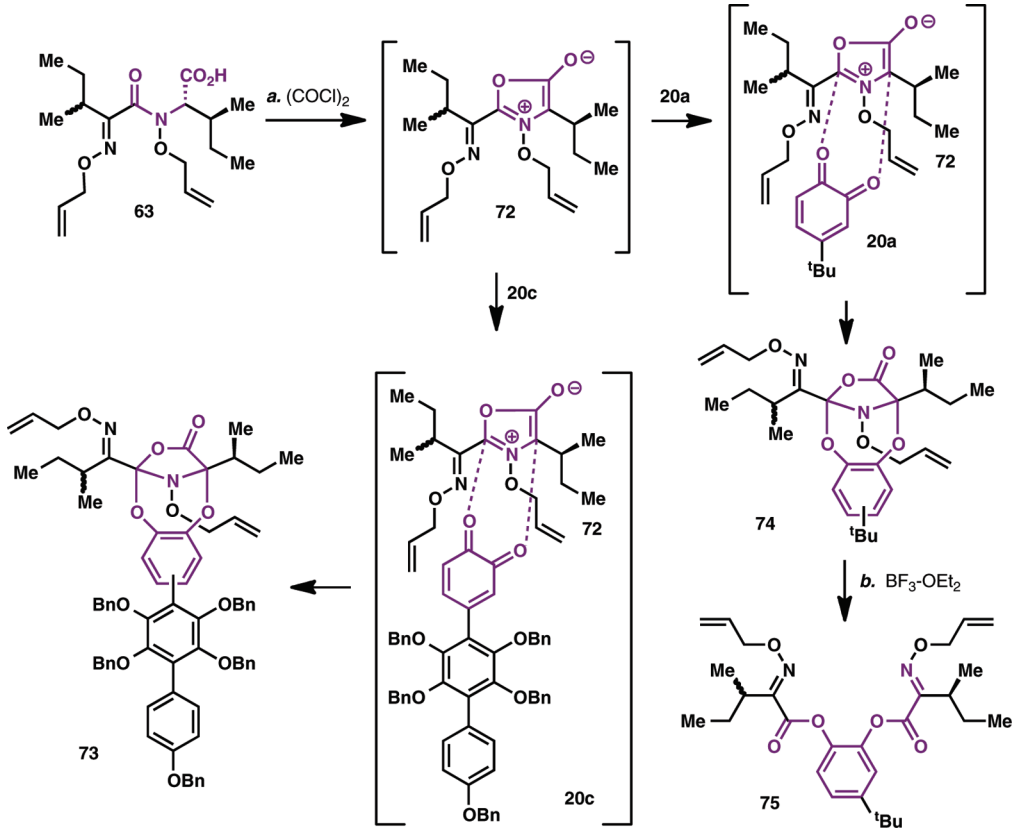
SCHEME 6. Preparation of Quinone 20c[a]



[a]Reagents and conditions: (a) Br_2 (1.5−2.0 equiv), $NaHCO_3$ (10 equiv), CH_2Cl_2, rt, 10−15 h, 50%; (b) **65** (1.0 equiv), **66** (1.6 equiv), $Pd(PPh_3)_4$ (0.05 equiv), 12:1 DME/EtOH, aq. Na_2CO_3 (20 equiv), 90 °C, 12 h, 68%; (c) Br_2 (1.8 equiv), $NaHCO_3$ (10 equiv), CH_2Cl_2, rt, 17 h, 46%; (d) **68** (1.0 equiv), **69** (1.5 equiv), $Pd(PPh_3)_4$ (0.2 equiv), 4:1 DME/EtOH, aq. Na_2CO_3 (10 equiv), 90 °C, 19 h, 75%; (e) 10:1 CH_2Cl_2/TFA, rt, 2 h, 56%; (f) $NaIO_4$ (1.05 equiv), 10:1 CH_2Cl_2/H_2O, *n*-Bu_4NBr (1.0 equiv), rt, 60 min, 84%.

SCHEME 7. Attempted Ketene−Quinone Coupling Yields a Formal [4 + 3] Product[a]



[a]Reagents and conditions: (a) **20a** (3.0 equiv) or **20c** (1.0 equiv), DMF (0.25 equiv), $(COCl)_2$ (1.0 equiv), $^iPr_2NEt$ (2.5 equiv), THF:CH_2Cl_2, rt, 60 min, 16% (for **73**) or 47% (for **74**); (b) BF_3−OEt_2 (2.0 equiv), CH_2Cl_2, 0 °C, 75 min, 60%.

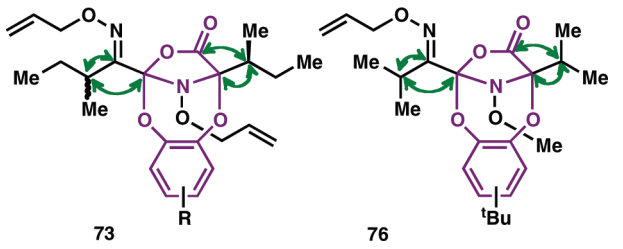


FIGURE 10. Key HMBC interactions for **73** and valine analogue **76**.

coupling product which exhibited great spectroscopic similarity to the desired sarcodonin core. However, careful examination of the spectroscopic data revealed the loss of one of the carbonyl signals and the appearance of a new set of signals at 105−110 ppm in the ^{13}C NMR spectrum. Two-dimensional NMR analysis of this compound suggested that it is the extraordinary [4.2.1] heterobicycle **73** (Scheme 7), based on the observation of several key HMBC interactions (Figure 10). A simplified analogue of this product (**76**; see the Supporting Information for its preparation) also demonstrated these HMBC interactions. This structure is consistent with a series of studies by Friedrichsen and co-workers[41d−f,53] which showed that this [4.2.1] bicycle is formed from 1,2-benzoquinones and 2-amidocarboxylic acids under similar reaction conditions.[54] Degradation studies on the *tert*-butyl analogue **74** bolstered this structure assignment, as the rearrangement product **75** isolated (Scheme 7) is similar to degradation products observed by Friedrichsen.[41d,f]

As depicted in Scheme 7, the nascent ketene is likely intercepted by the adjacent hydroxamate to form the *N*-alkoxy münchnone **72**, which then couples with the quinone substrate. Surprisingly, **73** is the dominant product observed, and none of the desired [4 + 2] adduct was isolated under any circumstances, even when different terphenyl, oxime, and hydroxamate protecting groups were employed. By contrast, the Friedrichsen studies frequently encountered a mixture of [4 + 2] and [4 + 3] adducts.[41d]

Conclusions

This venture into the uncharted territory of the sarcodonin, sarcoviolin, and hydnellin natural product family has yielded persuasive evidence that their chemical structure, *as published by three independent research groups*,[12,13] is incorrect. The serendipitous discovery of cycloadducts **42**−**44**, their unambiguous structure determination, and their spectral properties strongly suggest that the originally proposed tricyclic benzodioxazine **1a** should instead be replaced by the benzodioxanone **1b**, a structure which offers the advantages of greater precedent in the chemical literature and more plausible biosynthetic origins.

During the course of these studies, a mild oxidation of hydroxamic acids to the corresponding α-aminals was invented, the first example of such a transformation. An interesting variant of the Chan−Lam alcohol arylation was also developed for the *O*-arylation of hydroxamic acids. These mild and practical conditions exhibit greater substrate scope than those previously employed and should be of great utility within the chemical and pharmaceutical community. Studies with the aim of conclusively establishing the revised structure of sarcodonin are ongoing. The results of these studies will be disclosed in due course.

Experimental Section

(3*S*)-2-Bromo-*N*-methoxy-3-methylpentanamide (29). To a suspension of *O*-methylhydroxylamine hydrochloride (3.50 g, 42.2 mmol) in dichloromethane (100 mL) under nitrogen atmosphere at room temperature was added triethylamine (5.8 mL, 42.2 mmol) and then a solution of (3*S*)-2-bromo-3-methylpentanoyl chloride **28** (prepared in a two-step sequence from L-isoleucine via published literature procedures,[25a,55] 4.50 g, 21.1 mmol) in dichloromethane (10 mL). The reaction was stirred at room temperature for 2 h and then diluted with ethyl acetate. The organic phase was washed with 2 N HCl and the aqueous phase back-extracted once with ethyl acetate. The combined organic extracts were washed with saturated aqueous sodium bicarbonate and then brine, dried with magnesium sulfate, filtered, and concentrated in vacuo to give **29** (4.99 g, 95%) as a mixture of two isomers (∼4:1 as determined by NMR) which could not be separated chromatographically: white crystalline solid; mp 58−63 °C; ^{1}H NMR, major isomer (500 MHz, $CDCl_3$) δ (ppm) 0.89 (t, 3 H), 1.01 (d, 3 H), 1.25−1.30 (m, 1 H), 1.62−1.70 (m, 1 H), 2.11−2.16 (m, 1 H), 3.78 (s, 3 H), 4.13 (d, 1 H), 9.81 (br s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 10.9, 11.5, 14.2, 16.4, 26.2, 26.7, 38.4, 54.4, 63.8, 64.3, 64.6, 166.5; IR (thin film) ν_{max} 1667, 2968, 3155 (broad) cm^{-1}; HRMS calcd for $C_7H_{14}Br^{79}NO_2$ 224.0286 $[M + H]^+$, found (ESI) *m*/*z* 224.0281; calcd for $C_7H_{14}Br^{81}NO_2$ 226.0266 $[M + H]^+$, found (ESI) *m*/*z* 226.0262.

(3*S*)-2-((Benzyloxy)amino)-*N*-methoxy-3-methylpentanamide (30).[25b] To a solution of **29** (5.9 g, 26.3 mmol) in THF (53 mL) under nitrogen atmosphere was added *O*-benzylhydroxylamine (4.9 mL, 42.1 mmol) and then solid potassium carbonate (7.3 g, 52.7 mmol). The reaction was heated to reflux at 85 °C for 1.5 h. After being cooled to room temperature, the reaction was poured into water and extracted with diethyl ether. The organic extract was dried with magnesium sulfate, filtered, and concentrated in vacuo. The crude was purified by silica gel flash chromatography (hexanes/acetone, 90:10 to 60:40 v/v) to give **30** (2.8 g, 40%) as a ∼3:2 mixture of diastereomers as determined by NMR: colorless oil; ^{1}H NMR, major isomer (500 MHz, $CDCl_3$) δ (ppm) 0.83−0.91 (m, 6 H), 1.18−1.25 (m, 1 H), 1.39−1.48 (m, 1 H), 1.67−1.73 (m, 1 H), 3.28 (d, 1 H), 3.73 (s, 3 H), 4.68 (s, 2 H), 5.74 (br s, 1 H), 7.33−7.36 (m, 5 H), 8.78 (br s, 1 H); ^{1}H NMR, minor isomer (500 MHz, $CDCl_3$) δ (ppm) 0.83−0.91 (m, 6 H), 1.11−1.17 (m, 1 H), 1.52−1.58 (m, 1 H), 1.78−1.83 (m, 1 H), 3.19 (d, 1 H), 3.74 (s, 3 H), 4.68 (s, 2 H), 5.74 (br s, 1 H), 7.33−7.36 (m, 5 H), 8.70 (br s, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 11.3, 11.7, 15.2, 15.8, 25.8, 26.5, 35.4, 35.7, 64.5, 64.6, 67.6, 68.0, 76.2, 128.2, 128.3, 128.6, 128.6, 128.7, 128.7, 137.3, 137.4, 170.6, 170.7; IR (thin film) ν_{max} 1655, 2964, 3174 (broad) cm^{-1}; HRMS calcd for $C_{14}H_{22}N_2O_3$ 267.1709 $[M + H]^+$, found (ESI) *m*/*z* 267.1709.

(3*S*)-*N*-(Benzyloxy)-2-bromo-*N*-((3*S*)-1-(methoxyamino)-3-methyl-1-oxopentan-2-yl)-3-methylpentanamide (31). To a solution of **30** (5.0 g, 18.8 mmol, dried azeotropically by dissolving in benzene and concentrating in vacuo) in dichloromethane (120 mL) under nitrogen atmosphere was added triethylamine (5.2 mL, 37.5 mmol) and then a solution of **28** (prepared in a two-step sequence from L-isoleucine via published literature

(53) Friedrichsen, W.; Schroer, W.-D.; Debaerdemaeker, T. *Liebigs Ann. Chem.* **1980**, 1850.

(54) A similar [4 + 3] between orthoquinones and oxazoles under photochemical conditions has recently been reported: Wang, L.; Huang, Y.-C.; Liu, Y.; Fun, H.-K.; Zhang, Y.; Xu, J.-H. *J. Org. Chem.* **2010**, *75*, 7757.

(55) Tanasova, M.; Yang, Q.; Olmsted, C. C.; Vasileiou, C.; Li, X.; Anyika, M.; Borhan, B. *Eur. J. Org. Chem.* **2009**, 4242.

procedures,[25a,55] 4.80 g, 22.5 mmol) in dichloromethane (70 mL) over 7 min by cannula under positive nitrogen pressure. The reaction was stirred at room temperature for 3 h and then diluted with ethyl acetate. The organic phase was washed with 2 N HCl and the aqueous phase back-extracted once with ethyl acetate. The combined organic extracts were washed with saturated aqueous sodium bicarbonate and then brine, dried with magnesium sulfate, filtered, and concentrated in vacuo. The crude was purified by silica gel flash chromatography (hexanes/ethyl acetate, 90:10 to 65:35 v/v) to give **31** (5.43 g, 65%) as a mixture of diastereomers: yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 0.77−0.89 (m, 6 H), 0.94−1.08 (m, 6 H), 1.14−1.19 (m, 1 H), 1.23−1.36 (m, 1 H), 1.54−1.64 (m, 1 H), 1.78−2.11 (m, 2 H), 2.43−2.51 (m, 1 H), 3.79 (s, 3 H), 4.19−4.31 (m, 1 H), 4.45−4.70 (m, 1 H), 4.91−5.00 (m, 1 H), 5.25−5.31 (m, 1 H), 7.39−7.41 (m, 5 H), 9.33−9.71 (m, broad, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 10.2, 10.3, 10.4, 11.0, 11.1, 11.4, 11.7, 11.8, 15.5, 15.8, 16.0, 16.1, 16.8, 16.8, 25.4, 25.7, 25.9, 26.4, 26.4, 26.8, 27.0, 27.2, 31.7, 32.0, 32.5, 32.9, 33.0, 36.9, 37.5, 37.6, 37.9, 48.7, 48.7, 50.1, 50.3, 64.5, 64.6, 78.6, 78.7, 78.8, 78.9, 129.0, 129.0, 129.4, 129.4, 129.5, 129.5, 129.6, 129.7, 133.7, 167.5, 167.5, 171.3, 171.4, 171.5, 171.6; IR (thin film) ν_{max} 1643, 1666, 2965, 3222 (broad) cm^{-1}; HRMS calcd for $C_{20}H_{31}Br^{79}N_2O_4$ 443.1546 $[M + H]^+$, found (ESI) m/z 443.1549; calcd for $C_{20}H_{31}Br^{81}N_2O_4$ 445.1525 $[M + H]^+$, found (ESI) m/z 445.1523.

Cyclization to 32 and 33a.[26] To a solution of **31** (4.40 g, 9.92 mmol) in toluene (220 mL) were added 2 M aqueous NaOH (100 mL, 200 mmol) and 15-crown-5 (2.2 mL, 9.92 mmol) under ambient atmosphere. The reaction was heated to 95 °C for 2 h and then diluted with ethyl acetate. The organic phase was washed with water and then brine, dried with magnesium sulfate, filtered, and concentrated. The crude was purified by silica gel flash chromatography (benzene/acetone, 98:2 to 95:5 v/v) to give both **32** (1.72 g, 50%) and **33a** (1.25 g, 35%), each as inseparable mixtures of diastereomers.

4-(Benzyloxy)-2,5-di((*S*)-*sec*-butyl)-6-(methoxyimino)morpholin-3-one (32): colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 0.85−1.11 (m, 12 H), 1.20−1.56 (m, 3 H), 1.58−1.64 (m, 1 H), 1.93−2.08 (m, 1 H), 2.17−2.32 (m, 1 H), 3.79−3.81 (m, 3 H), 3.93−4.01 (m, 1 H), 4.40−4.66 (m, 1 H), 4.87−5.03 (m, 2 H), 7.35−7.43 (m, 5 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 11.6, 11.7, 11.8, 12.0, 12.1, 12.8, 14.1, 14.7, 15.5, 15.5, 15.5, 23.0, 24.6, 24.9, 25.9, 26.0, 26.1, 37.1, 37.7, 38.3, 38.8, 38.8, 39.0, 62.6, 62.6, 62.8, 63.5, 64.2, 64.7, 76.5, 76.9, 77.1, 81.2, 81.6, 82.8, 83.1, 128.5, 128.8, 128.8, 129.2, 129.6, 134.5, 147.8, 148.2, 148.3, 164.5, 164.6, 165.0; IR (thin film) ν_{max} 1645, 1680, 2963 cm^{-1}; HRMS calcd for $C_{20}H_{30}N_2O_4$ 363.2284 $[M + H]^+$, found (ESI) m/z 363.2282. The structure of the dibenzyl analogue **32′** was determined by X-ray crystallography; see the Supporting Information for the corresponding CIF and for the preparation of **32′**.

1-(Benzyloxy)-3,6-di((*S*)-*sec*-butyl)-4-methoxypiperazine-2,5-dione (33a): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.88−1.01 (m, 9 H), 1.07−1.13 (m, 3 H), 1.21−1.82 (m, 4 H), 2.11−2.40 (m, 2 H), 3.72−3.79 (m, 3 H), 4.02−4.06 (m, 1 H), 4.17−4.29 (m, 1 H), 4.83−4.90 (m, 1 H), 4.98−5.07 (m, 1 H), 7.36−7.43 (m, 5 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 12.1, 12.2, 12.2, 12.3, 12.3, 12.4, 12.4, 12.5, 14.4, 14.8, 14.8, 14.9, 15.0, 15.1, 15.7, 15.8, 25.6, 25.8, 25.9, 26.0, 26.0, 26.2, 26.6, 26.6, 37.3, 37.5, 37.6, 37.6, 38.3, 38.4, 38.8, 38.9, 61.4, 61.5, 62.1, 64.4, 64.9, 65.4, 65.4, 65.6, 65.9, 66.1, 66.3, 66.8, 76.0, 76.4, 76.5, 127.1, 127.7, 128.6, 128.7, 128.8, 129.2, 129.2, 129.3, 129.5, 129.6, 129.7, 134.2, 134.3, 134.7, 134.7, 161.9, 162.6, 162.8, 163.0, 163.3, 163.4, 163.4; IR (thin film) ν_{max} 1671, 2964 cm^{-1}; HRMS calcd for $C_{20}H_{30}N_2O_4$ 363.2284 $[M + H]^+$, found (ESI) m/z 363.2280. The structure of the dibenzyl analogue **33a′** was determined by X-ray crystallography; see the Supporting Information for the corresponding CIF and for the preparation of **33a′**.

3,6,-Di((*S*)-*sec*-butyl)-1-hydroxy-4-methoxypiperazine-2,5-dione (33b).[28a] A suspension of **33a** (2.0 g, 5.52 mmol) and $Pd(OH)_2$−C (20% Pd, 250 mg) in THF (56 mL, degassed immediately prior to use by bubbling through nitrogen gas for 15 min) was stirred while hydrogen gas was bubbled through the suspension for 90 min. The solution was purged of hydrogen gas by bubbling nitrogen gas through the suspension for 10 min and then the solution opened to ambient atmosphere. The $Pd(OH)_2$−C was removed by filtration through a pad of Celite 545, washing with ethyl acetate, and the resulting clear solution concentrated in vacuo. The crude was purified by silica gel flash chromatography (dichloromethane/acetone, 98:2 to 80:20 v/v) to give **33b** (1.42 g, 94%); all four possible diastereomers were isolated, which could be partially separated into two sets of diastereomers. **33b**, upper diastereomers: orange amorphous solid; mp = 145−155 °C dec; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 0.87−1.03 (m, 12 H), 1.24−1.65 (m, 4 H), 2.27−2.34 (m, 1 H), 2.41−2.49 (m, 1 H), 3.76−3.77 (m, 3 H), 4.33−4.34 (m, 1 H), 4.39−4.40 (m, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 12.3, 12.3, 12.4, 12.5, 14.3, 14.7, 14.7, 25.5, 25.7, 25.8, 26.4, 37.2, 37.6, 38.7, 38.8, 61.7, 61.8, 63.8, 64.2, 65.0, 65.3, 159.9, 160.7, 161.9, 162.8; IR (thin film) ν_{max} 1625, 1670, 2964, 3121 (broad) cm^{-1}; HRMS calcd for $C_{13}H_{24}N_2O_4$ 273.1814 $[M + H]^+$, found (ESI) m/z 273.1819. **33b**, lower diastereomers: orange gum; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 0.96−1.12 (m, 12 H), 1.29−1.76 (m, 4 H), 2.15−2.38 (m, 2 H), 3.80−3.82 (m, 3 H), 4.23−4.31 (m, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 12.2, 12.3, 12.4, 12.4, 14.8, 14.9, 15.4, 15.5, 25.8, 25.9, 26.5, 27.1, 37.2, 37.4, 38.0, 38.4, 61.7, 62.2, 64.9, 65.1, 65.5, 65.9, 160.5, 161.2, 162.4, 162.9; IR (thin film) ν_{max} 1652, 2964, 3148 (broad) cm^{-1}; HRMS calcd for $C_{13}H_{24}N_2O_4$ 273.1814 $[M + H]^+$, found (ESI) m/z 273.1818.

3,6,-Di((*S*)-*sec*-butyl)-1,4-dihydroxypiperazine-2,5-dione (33c).[28b] To a solution of **33b** (30 mg, 0.110 mmol, dried azeotropically by dissolving in benzene and concentrating in vacuo) in dichloromethane (1.1 mL) under nitrogen atmosphere at room temperature was added boron tribromide (1.0 M in dichloromethane, 0.33 mL, 0.330 mmol). The reaction was stirred at room temperature for 30 min, and then the reaction was quenched by the addition of saturated aqueous sodium bicarbonate until the pH of the aqueous phase was 8−9 as measured by pH paper. The mixture was extracted with ethyl acetate and the organic extract dried with magnesium sulfate, filtered, and concentrated in vacuo to give **33c** (26 mg, 92%) as an inseparable mixture of diastereomers: yellow-white solid; mp = 145−155 °C dec; ^{1}H NMR (600 MHz, CD_3OD) δ (ppm) 0.92−1.08 (m, 12 H), 1.39−1.73 (m, 4 H), 2.27−2.40 (m, 2 H), 4.22−4.28 (m, 2 H); ^{13}C NMR (150 MHz, CD_3OD) δ (ppm) 12.5, 12.6, 14.6, 15.0, 15.5, 15.6, 26.9, 26.9, 27.5, 27.7, 28.0, 38.4, 38.5, 39.4, 39.9, 67.3, 67.7, 67.8, 67.9, 68.0, 163.4, 164.2, 164.4, 165.0; IR (thin film) ν_{max} 1622, 2963, 3140 (broad) cm^{-1}; HRMS calcd for $C_{12}H_{22}N_2O_4$ 259.1658 $[M + H]^+$, found (ESI) m/z 259.1645.

Manganese(III) Acetate Oxidations. Representative Method A. To a solution of **33b** (50 mg, 0.184 mmol) in acetonitrile (HPLC grade, "wet", ~5% water, 5.0 mL) under ambient atmosphere was added solid potassium carbonate (63 mg, 0.459 mmol) and then manganese(III) acetate dihydrate (98 mg, 0.367 mmol). The reaction was sonicated to ensure a fine suspension and then stirred rapidly for 2.5 h at room temperature. The reaction was quenched by adding first 2 N HCl and then 30% aqueous ethylenediaminetetraacetic acid (EDTA), tetrasodium salt, in a ratio of 5:3 HCl/EDTA (v/v) and then extracting with ethyl acetate. The organic extract was dried with magnesium sulfate, filtered, and concentrated in vacuo. The crude was purified by silica gel flash chromatography (dichloromethane/acetone, 98:2 to 90:10 v/v, then dichloromethane/acetone/methanol, 90:10:1 to 75:25:1 v/v/v) to give **34c** (24 mg, 45%) as two major diastereomeric products as an inseparable mixture.

Manganese(III) Acetate Oxidations. Representative Method B. To a solution of **33b** (20 mg, 0.0734 mmol) in acetonitrile (HPLC grade, "wet", ~5% water, 2.0 mL) under ambient atmosphere was added glacial acetic acid (100 μL) and then manganese(III) acetate dihydrate (48 mg, 0.180 mmol). The reaction was stirred rapidly for 6 h at room temperature. The reaction was quenched by adding first 2 N HCl and then 30% aqueous ethylenediaminetetraacetic acid (EDTA), tetrasodium salt, in a ratio of 5:3 HCl/EDTA (v/v) and then extracting with ethyl acetate. The organic extract was dried with magnesium sulfate, filtered, and concentrated in vacuo. The crude was purified by silica gel flash chromatography (dichloromethane/acetone, 98:2 to 90:10 v/v, then dichloromethane:acetone/methanol, 90:10:1 to 75:25:1 v/v/v) to give **34c** (7.8 mg, 37% isolated, 55% based on recovered starting material) as two major diastereomeric products in an inseparable mixture. Unreacted **33b** was also recovered (6.5 mg). Physical and spectroscopic data for **34c** are given below; physical and spectroscopic data for **34a**,**b**,**d** are included in the Supporting Information.

3,6-Di((*S*)-*sec*-butyl)-3,4-dihydroxy-1-methoxypiperazine-2,5-dione (34c): orange gum; ^{1}H NMR (600 MHz, CD_3OD) δ (ppm) 0.91−1.10 (m, 12 H), 1.21−1.91 (m, 4 H), 2.19−2.33 (m, 1 H), 2.36−2.42 (m, 1 H), 3.75−3.78 (m, 3 H), 4.36−4.53 (m, 1 H); ^{13}C NMR (150 MHz, CD_3OD) δ (ppm) 12.6, 12.7, 12.7, 12.7, 13.0, 13.2, 13.3, 13.7, 14.2, 14.2, 14.5, 15.0, 15.1, 15.1, 15.5, 24.8, 25.1, 25.3, 25.4, 26.9, 27.0, 27.2, 27.4, 38.2, 38.5, 39.5, 40.1, 42.6, 42.6, 43.7, 43.9, 61.4, 61.9, 62.0, 65.5, 65.5, 65.8, 66.0, 91.5, 91.7, 91.8, 92.0, 163.2, 164.0, 164.5, 164.9; IR (thin film) ν_{max} 1655, 2967, 3382 (broad) cm^{-1}; HRMS calcd for $C_{13}H_{24}N_2O_5$ 289.1764 $[M + H]^+$, found (ESI) *m*/*z* 289.1758.

Typical Procedure for *O*-Arylation of Hydroxamic Acids. To a mixture of diphenyliodonium tetrafluoroborate **35a** (19 mg, 0.0520 mmol, see the Supporting Information for preparation of **35a**−**f**) and copper(II) acetylacetonate (18 mg, 0.0694 mmol) in toluene (1.5 mL) was added aqueous potassium carbonate (1.0 M, 104 μL, 0.104 mmol) and then **34c** (10 mg, 0.0347 mmol) as a solution in toluene (0.5 mL). The reaction was sonicated to ensure a fine suspension of the only somewhat soluble iodonium and copper salts and then stirred vigorously at room temperature for 2.5 h. The reaction was quenched by adding first 30% aqueous ethylenediaminetetraacetic acid (EDTA), tetrasodium salt, and then 2 N HCl, in a 3:5 ratio of EDTA/HCl. The aqueous layer was extracted with ethyl acetate and the resulting extract washed one more time with the 3:5 EDTA/HCl aqueous mixture. The organic extract was dried with magnesium sulfate, filtered, and concentrated in vacuo. The crude was purified by silica gel preparative thin-layer chromatography (plates were pretreated with triethylamine vapors to neutralize trace acid, which was necessary to avoid decomposition of the highly acid-sensitive products; plates were run in 95:5 v/v dichloromethane/acetone or 1:1 v/v hexanes/ethyl acetate) to give the desired arylation product **24a** in the yield given below. The reaction is generally tolerant of reaction time (up to 8 h before significant decomposition was observed) and workup conditions (less HCl may be used, though the EDTA workup is necessary to avoid the isolation of copper chelates with unreacted starting **34c**). Physical and spectroscopic data for **24a** are reported below; physical and spectroscopic data for **24b**−**g** are included in the Supporting Information.

3,6-Di((*S*)-*sec*-butyl)-3-hydroxy-1-methoxy-4-phenoxypiperazine-2,5-dione (24a): isolated as an inseparable mixture of four diastereomers: yield = 7.0 mg, 55%; white needles; mp 115−119 °C; ^{1}H NMR (600 MHz, C_6D_6) δ (ppm) 0.76−0.81 (m, 6 H), 0.92−1.08 (m, 6 H), 1.16−1.28 (m, 1 H), 1.33−1.38 (m, 1 H), 1.51−1.64 (m, 1 H), 1.75−1.84 (m, 1 H), 2.19−2.28 (m, 1 H), 2.49−2.59 (m, 1 H), 3.21−3.42 (m, 3 H), 3.57−3.59 and 4.17−4.22 (m, broad, 1 H), 4.12−4.19 (m, 1 H), 6.78−6.83 (m, 1 H), 7.04−7.09 (m, 2 H), 7.37−7.39 (m, 2 H); ^{13}C NMR (150 MHz, C_6D_6) δ (ppm) 12.3, 12.4, 12.7, 12.8, 13.4, 13.6, 14.8, 15.0, 24.2, 24.2, 26.0, 26.4, 37.3, 39.0, 44.1, 44.1, 61.0, 61.1, 65.8, 66.5, 91.6, 91.6, 113.6, 115.7, 115.8, 123.6, 123.6, 129.4, 129.4, 160.2, 160.3, 163.3, 163.8; IR (thin film) ν_{max} 1668, 2968, 3366 (broad) cm^{-1}; HRMS calcd for $C_{19}H_{28}N_2O_5$ 365.2076 $[M + H]^+$, found (ESI) *m*/*z* 365.2064.

2,5-Di((*S*)-*sec*-butyl)-3,6-dimethoxy-2,5-dihydropyrazine (39).[39c] To a flask charged with a magnetic stir bar and solid diketopiperazine[40] **38** (dried overnight in vacuo prior to use, 3.07 g, 13.6 mmol) was added under nitrogen in a glovebag trimethyloxonium tetrafluoroborate (6.18 g, 41.8 mmol). The flask was sealed with a rubber septum and pressurized with nitrogen, and then dichloromethane was added (100 mL). The suspension was stirred under nitrogen atmosphere at room temperature for 4 days and then quenched by pouring carefully into a mixture of saturated aqueous sodium bicarbonate and solid sodium bicarbonate. The resulting slurry was partitioned between water and dichloromethane, and the aqueous layer was extracted several times more with dichloromethane. The organic extract was dried with magnesium sulfate, filtered, and concentrated in vacuo. The crude was purified by silica gel flash chromatography (hexanes/diethyl ether, 100:0 to 90:10 v/v) to give **39** (3.03 g, 88%): colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 0.62 (d, 3 H), 0.86 (t, 3 H), 0.96 (t, 3 H), 0.99 (d, 3 H), 1.01−1.06 (m, 1 H), 1.19−1.25 (m, 1 H), 1.34−1.40 (m, 1 H), 1.57−1.63 (m, 1 H), 1.93−2.01 (m, 2 H), 3.66 (s, 3 H), 3.68 (s, 3 H), 3.95 (d, 1 H), 4.01 (d, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 12.1, 12.2, 13.9, 15.7, 24.4, 26.1, 38.1, 38.9, 52.1, 52.2, 58.6, 60.5, 163.3, 163.5; IR (thin film) ν_{max} 1232, 1694, 2961 cm^{-1}; HRMS calcd for $C_{14}H_{26}N_2O_2$ 255.2072 $[M + H]^+$, found (ESI) *m*/*z* 255.2078.

2,5-Di(*sec*-butyl)-3,6-dimethoxypyrazine (40).[39a] To a solution of **39** (3.03 g, 11.9 mmol) in toluene (150 mL) under ambient atmosphere was added 2,3-dichloro-5,6-dicyanobenzoquinone (8.18 g, 36.0 mmol). The solution was heated to 100 °C for 5 h. After being cooled to room temperature, the reaction was diluted with ethyl acetate, washed with saturated aqueous sodium bicarbonate, dried with magnesium sulfate, filtered, and concentrated in vacuo. The resulting brown residue was suspended in hexanes, filtered through a pad of Celite 545 to remove insolubles, concentrated in vacuo, and then purified by silica gel flash chromatography (hexanes) to give **40** (1.93 g, 64%): colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 0.84 (t, 6 H), 1.19 (d, 6 H), 1.53−1.58 (m, 2 H), 1.74−1.83 (m, 2 H), 3.00−3.04 (m, 2 H), 3.89 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 12.4, 19.0, 28.7, 35.8, 53.8, 142.0, 152.9; IR (thin film) ν_{max} 1026, 1346, 1456, 2962 cm^{-1}; HRMS calcd for $C_{14}H_{24}N_2O_2$ 253.1916 $[M + H]^+$, found (ESI) *m*/*z* 253.1909.

3,6-Di(*sec*-butyl)pyrazine-2,5-diol (25).[39b] Iodotrimethylsilane (2.0 mL, 14.1 mmol) was added to **40** (dried in vacuo prior to use, 710 mg, 2.81 mmol) and the reaction warmed to 100 °C under nitrogen atmosphere for 18 h. The reaction was cooled to 0 °C, methanol was added to quench the remaining iodotrimethylsilane, and the resulting clear solution was concentrated in vacuo. The crude was purified by silica gel flash chromatography (hexanes/ethyl acetate, 85:15 to 50:50 v/v) to give **25** (605 mg, 96%): yellow powder; mp 175−185 °C dec; ^{1}H NMR (400 MHz, CD_3OD) δ (ppm) 0.85 (t, 6 H), 1.19 (d, 6 H), 1.50−1.60 (m, 2 H), 1.72−1.83 (m, 2 H), 2.94−3.03 (m, 2 H); ^{13}C NMR (150 MHz, CD_3OD) δ (ppm) 12.5, 18.8, 29.0, 36.7, 141.3 (br), 152.0; IR (thin film) ν_{max} 1135, 1440, 1610, 2604 (broad), 2960 cm^{-1}; HRMS calcd for $C_{12}H_{20}N_2O_2$ 225.1603 $[M + H]^+$, found (ESI) *m*/*z* 225.1591.

Pyrazine−Quinone Cycloaddition. To a mixture of solid **25** (210 mg, 0.936 mmol), 2-iodoxybenzoic acid (2.6 g, 9.36 mmol), and catechol (1.0 g, 9.36 mmol) was added THF (21 mL) under nitrogen atmosphere. The resulting suspension was stirred vigorously at room temperature for 4 h. The insolubles were

removed by filtration through a pad of Celite 545, and the filtrate was concentrated in vacuo. The crude was resuspended in ethyl acetate, washed with saturated aqueous sodium bicarbonate, dried with magnesium sulfate, filtered once more through a pad of Celite 545, and concentrated in vacuo. The crude was purified by silica gel flash chromatography (hexanes/ethyl acetate, 95:5 to 80:20 v/v) to give **42** (50 mg, 16%) as an inseparable mixture of two diastereomers (3:1 ratio by NMR) and **43** (38 mg, 9%) as an inseparable mixture of diastereomers (2:1 ratio by NMR). Reducing the stoichiometries to 2.0 equiv of IBX and 0.95 equiv of catechol led to an increase in the yield of **42** to 23% and virtually no **43**.

***N*-(2-(*sec*-Butyl)-3-oxo-2,3-dihydrobenzo[*b*][1,4]dioxin-2-yl)-3-methyl-2-oxopentanamide (42):** off-white crystals; mp 43−45 °C; ^{1}H NMR (500 MHz, $CDCl_3$), major diastereomer δ (ppm) 0.83 (t, 3 H), 1.03 (t, 3 H), 1.07 (d, 3 H), 1.10 (d, 3 H), 1.32−1.41 (m, 2 H), 1.64−1.69 (m, 1 H), 1.74−1.79 (m, 1 H), 2.16−2.22 (m, 1 H), 3.31−3.37 (m, 1 H), 6.91 (dd, J = 1.6, 8.0 Hz, 1 H), 6.97 (dt, J = 1.6, 7.8 Hz, 1 H), 7.03 (dt, J = 1.7, 7.7 Hz, 1 H), 7.08 (dd, J = 1.7, 7.9 Hz, 1 H), 7.84 (br s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 11.4, 11.7, 12.8, 15.0, 22.4, 25.2, 40.4, 42.0, 86.3, 116.3, 116.9, 122.6, 125.3, 139.7, 141.1, 159.6, 161.9, 200.7; IR (thin film) ν_{max} 1289, 1495, 1689, 1766, 2971, 3345 (broad) cm^{-1}; HRMS calcd for $C_{18}H_{23}NO_5$ 334.1654 $[M + H]^+$, found (ESI) m/z 334.1655.

***N*-(2-(*sec*-Butyl)-3-oxo-2,3-dihydrobenzo[*b*][1,4]dioxin-2-yl)-3-ethyl-2-hydroxy-3-methyl-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxamide (43).** Isolated as an mixture of diastereomers (approximately 2:1 ratio): dirty white needles; mp 165−175 °C dec; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.72−0.77 (m, 3 H), 0.84−1.02 (m, 3 H), 1.06−1.23 (m, 3 H), 1.25−1.37 (m, 1 H), 1.34−1.56 (m, 3 H), 1.57−1.63 (m, 1 H), 1.70−1.80 (m, 1 H), 1.91−2.13 (m, 1 H), 2.40−2.52 (m, 1 H), 6.75−7.08 (m, 10 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 6.9, 7.0, 11.2, 11.8, 12.1, 13.6, 13.6, 17.8, 17.9, 21.6, 23.9, 25.0, 43.5, 43.6, 43.7, 43.7, 78.7, 82.8, 82.8, 82.9, 83.0, 92.4, 92.8, 117.6, 117.7, 118.2, 118.3, 118.5, 118.5, 120.4, 120.4, 123.1, 123.1, 123.4, 123.5, 125.1, 125.3, 127.2, 127.2, 139.8, 140.2, 140.4, 140.5, 140.6, 140.6, 140.6, 150.0, 150.0, 162.2, 162.3, 162.3, 162.4, 168.2, 168.3, 168.3, 168.4; IR (thin film) ν_{max} 1258, 1490, 1675, 2969, 3091 (broad) cm^{-1}. This structure was confirmed by X-ray crystallography (see the corresponding CIF in the Supporting Information).

***N*-(2-(*sec*-Butyl)-3-oxo-2,3-dihydrobenzo[*b*][1,4]dioxin-2-yl)-2-(hydroximino)-3-methylpentanamide (44).**[24] To a solution of **42** (10 mg, 0.0300 mmol) in 20:1 v/v THF/H_2O (0.63 mL) under ambient atmosphere was added hydroxylamine hydrochloride (10 mg, 0.143 mmol). The suspension was heated to 70 °C in a sealed reaction vessel for 60 min. After being cooled to room temperature, the reaction was diluted with ethyl acetate, washed with water and then with brine, dried with magnesium sulfate, filtered, and concentrated in vacuo. The crude was purified by silica gel preparative thin-layer chromatography (hexanes/ethyl acetate, 3:1 v/v) to give **44** (10 mg, 96%) as a mixture of two isomers, presumed to be *E*/*Z* isomers (stereoconfiguration of major product not assigned): colorless oil; ^{1}H NMR, major isomer (500 MHz, $CDCl_3$) δ (ppm) 0.78 (t, 3 H), 0.99 (t, 3 H), 1.09 (d, 3 H), 1.14 (d, 3 H), 1.34−1.40 (m, 1 H), 1.52−1.60 (m, 1 H), 1.70−1.80 (m, 2 H), 2.13−2.19 (m, 1 H), 3.15−3.22 (m, 1 H), 6.91 (dd, J = 1.6, 8.0 Hz, 1H), 6.95 (td, J = 1.6, 7.7 Hz, 1H), 7.02 (td, J = 1.5, 7.6 Hz, 1H), 7.08 (dd, J = 1.6, 7.9 Hz, 1 H), 7.54 (br s, 1H), 7.64 (br s, 1H); ^{13}C NMR, major isomer (125 MHz, $CDCl_3$) δ (ppm) 12.0, 12.4, 13.2, 16.2, 22.7, 25.9, 32.5, 42.5, 86.4, 116.3, 117.1, 122.4, 125.3, 139.8, 141.7, 157.5, 162.8, 163.4; IR (thin film) ν_{max} 1494, 1674, 1775, 2967, 3363 (broad) cm^{-1}; HRMS calcd for $C_{18}H_{24}N_2O_5$ 349.1764 $[M + H]^+$, found (ESI) m/z 349.1770.

(2*S*,3*S*)-*tert*-Butyl 2-(Hydroxyamino)-3-methylpentanoate (57).[46] Into a solution of L-isoleucine *tert*-butyl ester (free base, 2.9 g, 18.5 mmol) in dichloromethane (15 mL) at 0 °C and under ambient atmosphere was added a solution of dimethyldioxirane in acetone (~0.1 M, prepared by literature procedure,[47] 75 mL, 7.5 mmol). The reaction was stirred at 0 °C for 60 min, removed from the cooling bath, and concentrated in vacuo. The crude was purified by silica gel flash chromatography (hexanes/ethyl acetate, 95:5 to 50:50 v/v) to give **57** (680 mg, 18% isolated, 52% based on recovered starting material) and recovered L-isoleucine *tert*-butyl ester (1.70 g): pale yellow needles; mp = 30−34 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 0.89 (t, 3 H), 0.90 (d, 3 H), 1.15−1.23 (m, 1 H), 1.48 (s, 9 H), 1.45−1.53 (m, 1 H), 1.61−1.68 (m, 1 H), 3.42 (d, 1 H), 5.61 (br s, 1 H), 6.57 (br s, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 11.5, 15.7, 26.3, 28.3, 35.7, 70.3, 81.7, 172.7; IR (thin film) ν_{max} 1732, 2972, 3231 (broad), 3271 (broad) cm^{-1}; HRMS calcd for $C_{10}H_{21}NO_3$ 204.1600 $[M + H]^+$, found (ESI) m/z 204.1602.

3-Methyl-2-oxopentanoic Acid (59).[56] Compound **58** (prepared as per literature procedure,[57] with ^{1}H NMR matching that reported[57a] in the literature included in the Supporting Information as documentation of purity; 13.06 g, 62.4 mmol) was cooled to 0 °C. NaOH (2.0 M, 35 mL, 70 mmol) was added slowly portionwise. Five minutes after the last batch of NaOH was added, the reaction was allowed to warm to room temperature and stirred overnight under ambient atmosphere. The solution was acidified to pH = 1 by the addition of 2 N HCl and the aqueous solution extracted with diethyl ether. The organic extract was dried with magnesium sulfate, filtered, and concentrated in vacuo (no less than 80 Torr). The crude material was purified by silica gel flash chromatography (hexanes/diethyl ether, 90:10 to 50:50 v/v) to give racemic **59** (8.1 g, 99%): white moist needles; mp = 19−22 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.93 (t, 3 H), 1.18 (d, 3 H), 1.44−1.55 (m, 1 H), 1.76−1.86 (m, 1 H), 3.33−3.42 (m, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 11.5, 15.0, 25.4, 41.9, 159.8, 199.3; IR (thin film) ν_{max} 1719, 2972, 3229 (broad) cm^{-1}; HRMS calcd for $C_6H_{10}O_3$ 153.0528 $[M + Na]^+$, found (ESI) m/z 153.0521.

***tert*-Butyl 2-(*N*-Hydroxy-3-methyl-2-oxopentanamido)-3-methylpentanoate (60).** To a solution of **59** (350 mg, 2.70 mmol, dried azeotropically by dissolving in benzene and concentrating in vacuo) in dichloromethane (14 mL) was added DMF (70 μL) and then oxalyl chloride (0.23 mL, 2.70 mmol). The reaction was stirred at room temperature for 30 min, and then the solution was added to a biphasic solution of **57** (685 g, 3.37 mmol) in dichloromethane (16 mL) and 1.0 M aqueous sodium carbonate (13.5 mL, 13.5 mmol). The biphasic solution was stirred under ambient atmosphere at room temperature for 60 min and diluted with dichloromethane, and the phases were separated. The organic phase was washed with water and then brine, dried with magnesium sulfate, filtered, and concentrated in vacuo. The crude was purified by silica gel flash chromatography (hexanes/ethyl acetate, 95:5 to 70:30 v/v) to give **60** (570 mg, 67% based on **59**) as an inseparable mixture of diastereomers as well as unreacted **57** (205 mg): orange glassy solid; ^{1}H NMR, major isomer (600 MHz, $CDCl_3$) δ (ppm) 0.92 (t, 3 H), 0.96 (t, 3 H), 1.05 (d, 3 H), 1.18 (d, 3 H), 1.32−1.40 (m, 1 H), 1.44−1.51 (m, 1 H), 1.50 (s, 9 H), 1.51−1.57 (m, 1 H), 1.80−1.87 (m, 1 H), 2.16−2.20 (m, 1 H), 2.80−2.87 (m, 1 H), 4.85 (dd, 1 H), 7.38 (br s, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 11.4, 11.5, 11.5, 11.6, 11.6, 11.7, 11.8, 12.5, 14.0, 14.1, 14.5, 15.0, 16.0, 16.0, 16.1, 16.6, 24.5, 24.5, 24.9, 25.0, 25.9, 25.9, 26.3, 26.3, 28.1, 28.2, 34.5, 34.6, 35.7, 35.7, 43.9, 44.0, 44.9, 45.0, 62.0, 62.0, 67.1, 67.2, 83.0, 83.0, 84.1, 84.1, 166.9, 167.0, 171.3, 171.3, 203.7; IR (thin film)

(56) Endo, Y.; Shudo, K.; Itai, A.; Hasegawa, M.; Sakai, S.-i. *Tetrahedron* **1986**, *42*, 5905.

(57) (a) Weygand, F.; Steglich, W.; Mayer, D.; Philipsborn, W. v. *Chem. Ber.* **1964**, *97*, 2023. (b) Leyendecker, J.; Niewohner, U.; Steglich, W. *Tetrahedron Lett.* **1983**, *24*, 2375.

ν_{max} 1636, 1717, 2969, 3299 (broad) cm^{-1}; HRMS calcd for $C_{16}H_{29}NO_5$ 338.1943 $[M + Na]^+$, found (ESI) *m*/*z* 338.1949.

***tert*-Butyl 2-(2-(Allyloxyimino)-*N*-hydroxy-3-methylpentanamido)-3-methylpentanoate (61).**[24] To a solution of **60** (250 mg, 0.792 mmol) in THF/H_2O, 20:1 v/v (8.4 mL) was added *O*-allylhydroxylamine hydrochloride (prepared as per literature procedure,[58] 430 mg, 3.96 mmol). The reaction was heated in a sealed vessel to 70 °C for 4 h and then diluted with ethyl acetate. The organic extract was washed with water and then brine, dried with magnesium sulfate, filtered, and concentrated. The crude was purified by silica gel flash chromatography (hexanes/ethyl acetate, 97.5:2.5 to 85:15 v/v) to give **61** (200 mg, 68%) as an inseparable mixture of isomers: orange gum; ^{1}H NMR, major isomer (400 MHz, $CDCl_3$) δ (ppm) 0.89 (t, 3 H), 0.95 (t, 3 H), 1.01 (d, 3 H), 1.17 (t, 3 H), 1.25−1.33 (m, 1 H), 1.39−1.52 (m, 2 H), 1.48 (s, 9 H), 1.67−1.78 (m, 1 H), 2.14 −2.22 (m, 1 H), 2.53−2.62 (m, 1 H), 4.57 (d, 2 H), 4.85 (br s, 1 H), 5.19 (dd, 1 H), 5.29 (dd, 1 H), 5.91−6.01 (m, 1 H), 7.37 (br s, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 11.2, 11.5, 11.8, 15.8, 16.3, 17.9, 26.0, 26.2, 27.3, 28.1, 34.8, 35.2, 38.2, 38.4, 61.8, 62.1, 75.3, 83.0, 118.2, 133.9, 158.0, 165.1, 170.7; IR (thin film) ν_{max} 1620, 1645, 1739, 2967, 3232 (broad) cm^{-1}; HRMS calcd for $C_{19}H_{34}N_2O_5$ 371.2546 $[M + H]^+$, found (ESI) *m*/*z* 371.2550.

***tert*-Butyl 2-(*N*-(Allyloxy)-2-(allyloxyimino)-3-methylpentanamido)-3-methylpentanoate (62).** To a solution of **61** (200 mg, 0.540 mmol) in THF (5.4 mL) under ambient atmosphere was added 1.0 M aqueous potassium carbonate (2.7 mL, 2.70 mmol), allyl bromide (93 μL, 1.08 mmol), and then tetra-*n*-butylammonium bromide (170 mg, 0.540 mmol). The biphasic solution was mixed rapidly for 3 h, and then more 1.0 M potassium carbonate (2.7 mL, 2.70 mmol), allyl bromide (93 μL, 1.08 mmol), and tetra-*n*-butylammonium bromide (170 mg, 0.540 mmol) were added. The reaction was stirred for another 4 h, with monitoring by TLC until no starting material remained. The reaction was diluted with ethyl acetate, and the phases were separated. The organic extract was washed with water and then brine, dried with magnesium sulfate, filtered, and concentrated in vacuo to give **62** (220 mg, 99%), isolated as an inseparable mixture of isomers and in sufficient purity for further elaboration: colorless gummy solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.88−0.95 (m, 6 H), 0.96−1.00 (m, 3 H), 1.15−1.17 (m, 3 H), 1.16−1.24 (m, 1 H), 1.45−1.55 (m, 10 H), 1.70−1.81 (m, 2 H), 2.07−2.25 (m, 1 H), 2.42−2.56 (m, 1 H), 4.40−4.68 (m, 5 H), 5.16−5.31 (m, 4 H), 5.82−5.96 (m, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 11.8, 12.7, 12.7, 13.0, 16.4, 16.5, 16.6, 17.0, 17.2, 18.3, 18.7, 26.0, 26.1, 26.6, 26.7, 27.4, 27.5, 27.7, 27.8, 28.8, 30.6, 34.5, 34.5, 34.6, 35.7, 35.8, 38.4, 38.6, 39.2, 39.4, 65.3, 65.5, 66.6, 66.7, 69.0, 75.8, 75.8, 79.0, 79.1, 79.1, 79.3, 82.7, 82.7, 118.6, 118.6, 118.7, 118.8, 120.5, 120.7, 120.8, 120.9, 132.1, 132.5, 134.4, 134.5, 134.6, 134.7, 159.9, 160.0, 166.4, 166.8, 167.2, 167.6, 167.9, 168.0, 170.4; IR (thin film) ν_{max} 1668, 1738, 2968 cm^{-1}; HRMS calcd for $C_{22}H_{38}N_2O_5$ 411.2859 $[M + H]^+$, found (ESI) *m*/*z* 411.2866.

2-(*N*-(Allyloxy)-2-(allyloxyimino)-3-methylpentanamido)-3-methylpentanoic Acid (63). To a flask charged with **62** (220 mg, 0.536 mmol) was added a solution of dichloromethane/trifluoroacetic acid, 5:1 v/v (7.2 mL). The reaction was stirred in a sealed reaction vessel warmed to 55 °C under ambient atmosphere for 60 min. After being cooled to room temperature, the reaction vessel was carefully vented, diluted with benzene, and concentrated in vacuo. The crude was twice more diluted with benzene and concentrated in vacuo to azeotropically remove residual trifluoroacetic acid, then purified by silica gel flash chromatography (hexanes/ethyl acetate, 90:10 to 75:25 v/v, then hexanes/ethyl acetate:acetic acid, 50:50:1 v/v/v) to give **63** (187 mg, 99%) as an inseparable mixture of isomers: yellow gum; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 0.90−0.93 (m, 6 H), 1.03−1.05 (m, 3 H), 1.13−1.15 (m, 3 H), 1.21−1.28 (m, 1 H), 1.40−1.47 (m, 1 H), 1.63−1.73 (m, 2 H), 2.24−2.30 (m, 1 H), 2.43−3.10 (m, 1 H), 4.42−4.60 (m, 5 H), 5.16−5.31 (m, 4 H), 5.79−5.86 (m, 1 H), 5.91−5.99 (m, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 10.9, 11.0, 11.1, 11.9, 12.3, 15.9, 16.0, 16.0, 16.4, 17.7, 17.9, 25.7, 25.8, 26.1, 26.7, 26.9, 33.9, 34.7, 37.6, 37.8, 38.5, 65.1, 65.4, 67.4, 67.6, 75.1, 75.4, 78.1, 78.3, 78.4, 118.1, 118.2, 120.2, 120.6, 120.9, 121.1, 130.9, 131.3, 133.6, 134.0, 158.4, 158.9, 166.8, 167.2, 167.7, 168.3, 172.4, 173.4, 173.7, 174.7; IR (thin film) ν_{max} 1647, 1746, 2967, 3083 (broad) cm^{-1}; HRMS calcd for $C_{18}H_{30}N_2O_5$ 355.2233 $[M + H]^+$, found (ESI) *m*/*z* 355.2240.

1,2,4,5-Tetrakis(benzyloxy)benzene (64). A solution of 1,2,4,5-tetrakis(hydroxy)benzene (prepared[59] according to literature procedure from 2,5-dihydroxy-1,4-benzoquinone; this compound was found to be readily oxidized in air and thus was immediately carried forward crude, 3.00 g, 21.1 mmol) in DMF (20 mL) was degassed with argon and then cooled to 0 °C under argon atmosphere. Sodium hydride was added (60% dispersion in mineral oil, 4.22 g, 176 mmol) and then the cooling bath removed and the reaction allowed to warm to room temperature for 30 min. Benzyl bromide (15.1 mL, 127 mmol) was added and the reaction stirred at room temperature under argon atmosphere for 2.5 h. The reaction was diluted with ethyl acetate, and the organic phase washed once with 2 N HCl, three times with generous amounts of water, and once with brine, and then dried with magnesium sulfate, filtered, and concentrated in vacuo. Recrystallization (hexanes/ethyl acetate) of the crude gave pure **64** (4.05 g, 38%): white powdery solid; mp = 152−156 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 5.02 (s, 8 H), 6.65 (s, 2 H), 7.31−7.39 (m, 20 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 72.8, 107.4, 127.7, 128.0, 128.6, 137.5, 143.8; IR (thin film) ν_{max} 692, 722, 1009, 1188, 1212, 1517, 2854, 2921, 3033, 3062 cm^{-1}; HRMS calcd for $C_{34}H_{30}O_4$ 503.2222 $[M + H]^+$, found (ESI) *m*/*z* 503.2217.

1,2,5,6-Tetrakis(benzyloxy)-3-bromobenzene (65).[50] To a solution of **64** (5.5 g, 10.9 mmol) in dichloromethane (110 mL) under argon atmosphere was added solid sodium bicarbonate (9.24 g, 110 mmol) and then bromine (1.75 g, 10.9 mmol) as a solution in dichloromethane (20 mL). The reaction was stirred rapidly at room temperature, with more bromine (0.88 g, 5.50 mmol) in dichloromethane (20 mL) added periodically every 3−5 h until starting material was consumed. The reaction was then diluted with dichloromethane, and the organic phase was washed with 15% aqueous sodium thiosulfate, then saturated aqueous sodium bicarbonate, and then brine, dried with magnesium sulfate, filtered, and concentrated in vacuo. The crude was purified by recrystallization (hexanes/dichloromethane) to give **65** (3.20 g, 50%): off-white powdery solid; mp = 146−150 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 5.00 (s, 4 H), 5.04 (s, 4 H), 6.65 (s, 1 H), 7.32−7.38 (m, 16 H), 7.48−7.50 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 72.3, 75.2, 103.7, 127.7, 128.2, 128.3, 128.4, 128.7, 128.8, 136.8, 137.3, 141.2, 149.1; IR (thin film) ν_{max} 690, 741, 962, 1015, 1202, 1366, 3028 cm^{-1}; HRMS calcd for $C_{34}H_{29}Br^{79}O_4$ 581.1328 $[M + H]^+$, found (ESI) *m*/*z* 581.1318, with the expected isotopic distribution.

2,3,4′,5,6-Pentakis(benzyloxy)-1,1′-biphenyl (67).[48] To a solution of **65** (653 mg, 1.12 mmol) and **66** (see the Supporting Information for preparation; 400 mg, 1.75 mmol) in DME (70 mL) under argon atmosphere was added absolute ethanol (6 mL) and then 1.0 M aqueous sodium carbonate (25 mL, 25 mmol). The biphasic solution was degassed by sonication while a stream of argon gas was bubbled through it, and then

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tetrakis(triphenylphosphine)palladium(0) (65 mg, 0.056 mmol) was added. The reaction was warmed to reflux at 90 °C overnight. After being cooled to room temperature, the reaction was poured into a biphasic solution of ethyl acetate and sufficient 2 N HCl to neutralize the remaining aqueous base. The phases were separated, and the aqueous phase was extracted with more ethyl acetate. The combined organic extracts were washed with saturated aqueous sodium bicarbonate, then water, and then brine, dried with sodium sulfate, filtered, and concentrated in vacuo. The crude was purified by silica gel flash chromatography (hexanes/dichloromethane, 60:40 to 10:90 v/v) to give **67** (525 mg, 68%): white powdery solid; mp = 64−66 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 4.65 (s, 4 H), 5.12 (s, 4 H), 5.18 (s, 2 H), 6.72 (s, 1 H), 7.01−7.05 (m, 6 H), 7.17−7.23 (m, 6 H), 7.36−7.47 (m, 15 H), 7.53 (d, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 70.2, 72.1, 75.2, 103.1, 114.3, 126.6, 127.6, 127.7, 127.8, 128.1, 128.2, 128.6, 128.7, 128.7, 131.9, 132.2, 137.3, 137.4, 137.5, 140.8, 148.7, 158.1; IR (thin film) ν_{max} 693, 731, 1021, 1151, 1218, 1452, 2867, 3030 cm^{-1}; HRMS calcd for $C_{47}H_{40}O_5$ 685.2954 $[M + H]^+$, found (ESI) m/z 685.2931.

2,3,4′,5,6-Pentakis(benzyloxy)-4-bromo-1,1′-biphenyl (68).[50] To a solution of **67** (1.86 g, 2.71 mmol) in dichloromethane (54 mL) under argon atmosphere was added solid sodium bicarbonate (2.28 g, 27.1 mmol) and then a solution of bromine (520 mg, 3.25 mmol) in dichloromethane (16 mL). The solution was stirred rapidly for 15 h, and then more bromine (260 mg, 1.63 mmol) in dichloromethane (8 mL) was added. The reaction was stirred rapidly for another 2 h, with monitoring by TLC until all starting material was consumed. The reaction was diluted with dichloromethane and washed with 15% aqueous sodium thiosulfate. The thiosulfate phase was back-extracted with dichloromethane. The combined organic extracts were again washed with 15% aqueous sodium thiosulfate, then saturated aqueous sodium bicarbonate, and then brine, dried with magnesium sulfate, filtered, and concentrated in vacuo. Recrystallization of the crude (hexanes/dichloromethane) gave pure **68** (961 mg, 46%): off-white powdery solid; mp = 133−135 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 4.68 (s, 4 H), 5.11 (s, 4 H), 5.19 (s, 2 H), 6.96 (d, 4 H), 7.05 (d, 2 H), 7.19−7.27 (m, 6 H), 7.34−7.40 (m, 9 H), 7.44 (t, 2 H), 7.52−7.55 (m, 6 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 70.2, 75.6, 75.7, 113.2, 114.5, 125.8, 127.6, 128.1, 128.2, 128.3, 128.4, 128.5, 128.8, 128.8, 129.0, 131.3, 132.1, 136.8, 137.0, 137.2, 147.1, 147.4, 158.4; IR (thin film) ν_{max} 696, 738, 1026, 1359, 1432, 2872, 3031 cm^{-1}; HRMS calcd for $C_{47}H_{39}Br^{79}O_5$ 763.2059 $[M + H]^+$, found (ESI) m/z 763.2058, with expected isotopic distribution.

2′,3′,4″,5′,6′-Pentakis(benzyloxy)-3,4-bis(methoxymethoxy)-1,1′:4′,1″-terphenyl (70).[48] To a mixture of **68** (145 mg, 0.190 mmol) and **69** (see the Supporting Information for preparation, 70 mg, 0.285 mmol) in a solution of DME/95% ethanol (4:1 v/v, 1.9 mL) under argon atmosphere was added 2.0 M aqueous sodium carbonate (0.95 mL, 1.90 mmol). The biphasic solution was degassed by sonication while bubbling through a stream of argon gas. Tetrakis(triphenylphosphine)palladium(0) (22 mg, 0.019 mmol) was then added, and the reaction vessel was sealed under argon atmosphere and warmed to 90 °C for 6 h. The reaction vessel was briefly unsealed, and more tetrakis(triphenylphosphine)palladium(0) (22 mg, 0.019 mmol) was added. The reaction was purged with argon before being resealed and warmed to 90 °C for another 13 h. After being cooled to room temperature, the reaction vessel was unsealed and diluted with ethyl acetate and water. The phases were separated, and then the organic extract was washed with 2 N HCl, then water, and then brine, dried with magnesium sulfate, filtered, and concentrated in vacuo. The crude was purified by silica gel flash chromatography (hexanes/dichloromethane, 50:50 to 100:0 v/v, then hexanes/ethyl acetate, 98:2 to 95:5 v/v) to give pure **70** (125 mg, 75%): off-white amorphous solid; mp = 92−94 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.43 (s, 3 H), 3.62 (s, 3 H), 4.72 (s, 4 H), 4.78 (s, 4 H), 5.15 (s, 2 H), 5.20 (s, 2 H), 5.34 (s, 2 H), 6.96−7.02 (m, 8 H), 7.06−7.23 (m, 15 H), 7.32−7.54 (m, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 56.3, 56.3, 70.2, 75.5, 75.6, 95.7, 95.8, 114.5, 116.6, 119.6, 125.4, 126.5, 127.6, 127.9, 128.0, 128.1, 128.2, 128.3, 128.5, 128.6, 128.8, 128.8, 130.5, 130.9, 132.3, 137.3, 137.5, 146.6, 146.8, 146.9, 146.9, 158.2; IR (thin film) ν_{max} 696, 734, 987, 1247, 1358, 2867, 3033 cm^{-1}; HRMS calcd for $C_{57}H_{52}O_9$ 881.3690 $[M + H]^+$, found (ESI) m/z 881.3686.

2′,3′,4″,5′,6′-Pentakis(benzyloxy)[1,1′:4′,1″-terphenyl]-3,4-diol (71).[51] To a solution of **70** (100 mg, 0.114 mmol) in dichloromethane (distilled, 2.2 mL) under ambient atmosphere was added trifluoroacetic acid (100 μL). The reaction was stirred at room temperature for 60 min, and then more trifluoroacetic acid (100 μL) was added. After another 75 min, the reaction was diluted with toluene and concentrated in vacuo. The crude was redissolved in toluene and again concentrated in vacuo to azeotropically remove residual trifluoroacetic acid. The crude was purified by silica gel flash chromatography (hexanes/ethyl acetate, 80:20 to 75:25 v/v) to give pure **71** (50 mg, 56%), along with a mixture of partially deprotected mono-MOM compounds (27 mg, 28%) which could be resubjected to the deprotection conditions to give **71**: yellow gum; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 4.71 (s, 4 H), 4.75 (s, 4 H), 4.97 (br s, 1 H), 5.19 (s, 2 H), 5.34 (br s, 1 H), 6.91 (d, 1 H), 6.96−7.00 (m, 6 H), 7.02 (dd, 4 H), 7.07 (d, 2 H), 7.18−7.25 (m, 12 H), 7.37 (t, 1 H), 7.43−7.46 (m, 4 H), 7.52−7.54 (d, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 70.2, 75.5, 75.6, 114.4, 114.9, 118.3, 124.4, 126.4, 126.5, 127.6, 128.0, 128.0, 128.1, 128.3, 128.3, 128.8, 128.8, 128.9, 130.4, 130.8, 132.3, 137.3, 137.3, 142.5, 143.4, 146.8, 146.8, 158.2; IR (thin film) ν_{max} 694, 732, 1023, 1266, 1358, 2928, 3031, 3357 (broad) cm^{-1}; HRMS calcd for $C_{53}H_{44}O_7$ 793.3165 $[M + H]^+$, found (ESI) m/z 793.3155.

2′,3′,4″,5′,6′-Pentakis(benzyloxy)[1,1′:4′,1″-terphenyl]-3,4-dione (20c).[52] To a solution of **71** (155 mg, 0.195 mmol) in dichloromethane (20 mL) under ambient atmosphere was added a solution of sodium periodate (44 mg, 0.205 mmol) in water (2.1 mL) and then tetra-*n*-butylammonium bromide (63 mg, 0.195 mmol). The biphasic solution was stirred rapidly at room temperature for 60 min, with monitoring by TLC until no starting material remained and the reaction had gone from colorless to deep brown. The reaction was diluted with dichloromethane. The phases were separated, and the organic phase was washed with water, dried with magnesium sulfate, filtered, and concentrated in vacuo. The crude was purified by silica gel flash chromatography (hexanes/ethyl acetate, 90:10 to 75:25 v/v) to give **20c** (130 mg, 84%): brown foam; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 4.68 (s, 4 H), 5.00 (s, 4 H), 5.21 (s, 2 H), 6.05 (dd, J = 0.8, 10.9 Hz, 1 H), 6.16 (dd, J = 0.8, 2.1 Hz, 1 H), 6.73 (dd, J = 2.1, 10.1 Hz, 1 H), 6.99 (d, 4 H), 7.09 (d, 2 H), 7.14 (dd, 4 H), 7.20−7.28 (m, 12 H), 7.39 (t, 1 H), 7.42 (d, 2 H), 7.45 (t, 2 H), 7.54 (d, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 70.2, 75.4, 76.5, 114.5, 125.5, 126.8, 127.3, 127.6, 128.2, 128.3, 128.4, 128.6, 128.8, 128.9, 128.9, 129.4, 131.5, 132.3, 133.9, 136.3, 136.6, 137.1, 144.5, 145.7, 146.0, 146.8, 158.5, 179.8, 180.4; IR (thin film) ν_{max} 694, 731, 1023, 1241, 1276, 1658, 2955, 3035 cm^{-1}; HRMS calcd for $C_{53}H_{42}O_7$ 791.3009 $[M + H]^+$, found (ESI) m/z 791.3008.

11-(Allyloxy)-2-(1-((allyloxy)imino)-2-methylbutyl)-5-(*sec*-butyl)-8*-(2,3,4′,5,6-pentakis(benzoyloxy)[1,1′-biphenyl]-4-yl)-2,5-epiminobenzo[*d*][1,3,6]trioxocin-4(5*H*)-one (73). **Substitution of the biphenyl side chain has not been conclusively established; this side chain may be found at either the C8 or C9 position.* To a solution of **63** (12.5 mg, 0.0353 mmol, dried azeotropically by dissolving in benzene and concentrating in vacuo) in dichloromethane (0.35 mL) was added DMF (0.7 μL, 0.0088 mmol) and then

oxalyl chloride (3.0 μL, 0.0353 mmol). The solution was stirred at room temperature for 30 min and then transferred by cannula under positive nitrogen pressure into a solution of **20c** (28 mg, 0.0353 mmol, dried azeotropically by dissolving in benzene and concentrating in vacuo), anhydrous ethyldiisopropylamine (freshly distilled under nitrogen atmosphere over potassium hydroxide, 16 μL, 0.0882 mmol), and THF (0.70 mL). The combined reaction solution was stirred at room temperature for 30 min. The reaction solution was then loaded on a plug of silica gel (prepacked in hexanes), eluted with hexanes/ethyl acetate (3:1 v/v), and concentrated in vacuo. The crude was purified by silica gel preparative thin-layer chromatography (hexanes/dichloromethane, 1:1 v/v) to give **73** (6.3 mg, 16%) as an inseparable mixture of multiple isomers. Also recovered was unreacted **20c**, which could be recycled in subsequent cycloaddition reactions: yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 0.90−1.07 (m, 6 H), 1.22−1.38 (m, 6 H), 1.44−1.51 (m, 1 H), 1.66−1.82 (m, 1 H), 1.89−2.01 (m, 1 H), 2.04−2.23 (m, 1 H), 2.28 − 2.36 (m, 1 H), 2.88−3.12 (m, 1 H), 4.41−4.47 (m, 2 H), 4.58−4.63 (m, 2 H), 4.70−4.76 (m, 8 H), 5.20 (s, 2 H), 5.21−5.35 (m, 4 H), 5.89−6.02 (m, 2 H), 6.96−7.24 (m, 25 H), 7.37 (t, 1 H), 7.41−7.45 (m, 4 H), 7.53 (d, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 11.6, 11.8, 12.5, 12.6, 12.6, 12.7, 13.4, 13.4, 18.1, 19.5, 23.2, 23.9, 23.9, 27.4, 27.5, 28.6, 29.0, 29.9, 37.1, 38.4, 39.0, 39.1, 39.1, 70.2, 75.5, 75.6, 75.7, 75.7, 76.4, 76.5, 76.9, 90.4, 90.5, 90.6, 90.6, 90.8, 105.0, 105.0, 105.1, 114.5, 118.2, 118.2, 119.7, 119.7, 121.0, 121.0, 121.0, 124.8, 124.9, 126.4, 127.6, 128.0, 128.3, 128.4, 128.8, 128.9, 128.9, 129.4, 130.2, 130.3, 131.2, 131.2, 132.2, 132.3, 134.1, 134.2, 134.2, 136.9, 137.0, 137.2, 137.2, 137.3, 138.6, 138.9, 138.9, 138.9, 139.0, 143.2, 143.3, 143.3, 143.3, 146.5, 146.5, 146.6, 146.7, 146.8, 153.7, 153.7, 153.8, 153.8, 158.2, 158.2, 166.6, 166.7; IR (thin film) ν_{max} 695, 733, 988, 1022, 1237, 1820, 2965, 3031 cm^{-1}; HRMS calcd for $C_{71}H_{70}N_2O_{11}$ 1127.5058 $[M + H]^+$, found (ESI) m/z 1127.5070. Additional NMR spectra for **73**, including HMBC spectral data which show a long-range coupling interaction between the ^{1}H NMR signals at 2.88−3.12 ppm and the ^{13}C NMR signals at 105.0−105.1 ppm, are also provided in the Supporting Information.

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Supporting Information Available: General methods, NMR spectra for all compounds described in Schemes 1−7, and preparative methods for **32′**, **33a′**, **34a−d**, **35a−f**, **58**, **66**, **69**, and **74−76**. This material is available free of charge via the Internet at http://pubs.acs.org.