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Iodine(V) Reagents in Organic Synthesis. Part 2. Access to Complex Molecular Architectures via Dess−Martin Periodinane-Generated *o*-Imidoquinones

K. C. Nicolaou,* K. Sugita, P. S. Baran, and Y.-L. Zhong

Contribution from the Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, and Department of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, California 92093

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Abstract: *o*-Imidoquinones, a rather rare class of compounds, are prepared from anilides by the action of Dess−Martin periodinane (DMP) and water. Their chemistry has been extensively investigated and found to lead to *p*-quinones and polycyclic systems of diverse molecular architectures. Applications of this methodology to the total synthesis of the naturally occurring compounds, epoxyquinomycin B and BE-10988, are described. Finally, another rare chemical entity, the ketohydroxyamide moiety, has been accessed through this DMP-based synthetic technology, and its reactivity has been studied. Among its most useful reactions is a set of cascade heterocyclic annulations leading to a variety of polycyclic systems of possible biological relevance.

Introduction

In the preceding paper we described our investigations into the scope and generality of a novel tandem reaction, initiated by DMP (Dess−Martin periodinane) and traversing through *o*-imidoquinones, for the construction of a plethora of polycycles based on the phenoxazine scaffold.[1] The isolation of *p*-quinones as byproducts in these reactions prompted us to extend our investigations into the chemistry of the hitherto unexplored potential of *o*-imidoquinones which we conjectured to be fleeting precursors to *p*-quinones (see Figure 1). The benefits of developing a mild, chemoselective, and direct route to *p*-quinones from anilides are obvious since such structures are powerful intermediates in organic synthesis and they also frequently occur within the molecular frameworks of natural products. In a preliminary communication, we recently reported such a method using DMP which permits the construction of an array of *p*-quinones from a variety of anilide systems.[2] During that study, we also encountered the formation of stable *o*-imidoquinones and explored their intermolecular hetero Diels−Alder reactions. Because the reactivity of *o*-imidoquinones still represented uncharted terrain, we then proceeded to explore further their potential for the construction of complex polycyclic architectures resembling known natural products.[3] Herein, we present a full account of these explorations and inquiries which led to the design and discovery of novel cascade reactions, new chemical entities, and useful synthetic technologies.

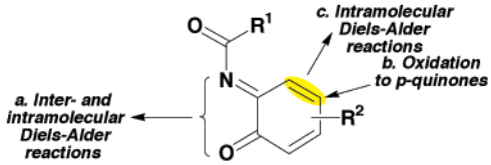


Figure 1. Reactivity analysis of *o*-azaquinones as versatile chemical entities for the construction of molecular diversity. (a) Participation in inter- and intramolecular Diels−Alder reactions, (b) oxidation to *p*-quinones, and (c) proposed intramolecular Diels−Alder reactions.

Results and Discussion

1. Mechanistic and Optimization Studies of *p*-Quinone Formation. The synthetic explorations described herein were designed on the basis of insights gained during a mechanistic study of the DMP-induced conversion of anilides to *p*-quinones. Because isotope labeling studies with $H_2{}^{18}O$ had revealed that two molecules of Ac-*o*-iodoxybenzoic acid (IBX) were involved in *p*-quinone formation,[1] we postulated the mechanism shown in Scheme 1 for this reaction. Thus, DMP and Ac-IBX interact with an anilide (**I**) to furnish the intermediate *o*-imidoquinone (**II**) as described in the previous paper.[1] If a proximate olefin is appended to this quinone, an intramolecular hetero Diels−Alder reaction may take place to afford a phenoxazine-based polycycle.[1] A competitive reaction pathway involves another molecule of Ac-IBX which attacks **II** to furnish intermediate **III**. As an easily oxidized species, the latter leads to the observed *p*-quinone **V** upon expulsion of byproduct **IV** (Scheme 1).

As predicted from our mechanistic rationale, 1 equiv of DMP and 2 equiv of Ac-IBX were sufficient to convert anilide **1a** to the *p*-quinone **2a** in 40% yield (entry 3, Table 1). As further shown in Table 1, we found that the optimum conditions required 2 equiv each of DMP and Ac-IBX (entry 4, Table 1),

(1) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Sugita, K. *J. Am. Chem. Soc.* **2002**, *124*, 2212−2220 and references therein.
(2) Nicolaou, K. C.; Sugita, K.; Baran, P. S.; Zhong, Y.-L. *Angew. Chem., Int. Ed.* **2001**, *40*, 207.
(3) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S.; Sugita, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 2145.

10.1021/ja012125p CCC: $22.00

Scheme 1. Mechanistic Rationale for the Generation of *p*-Quinones (V) from Anilides (I)

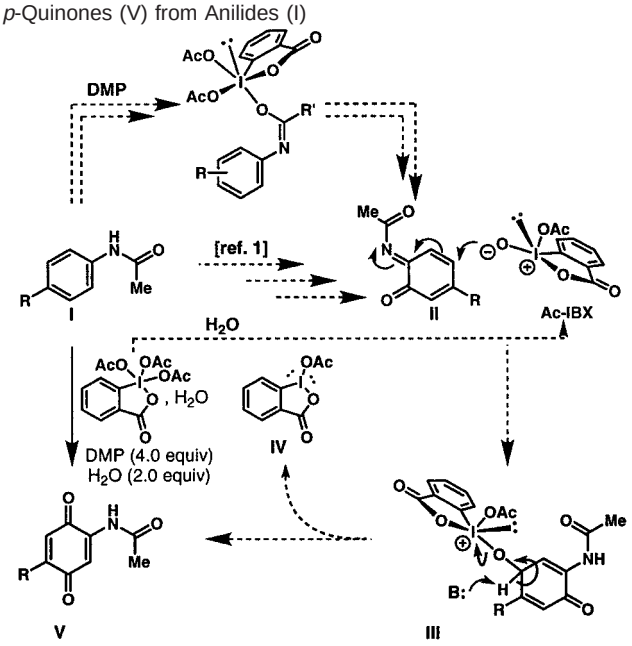
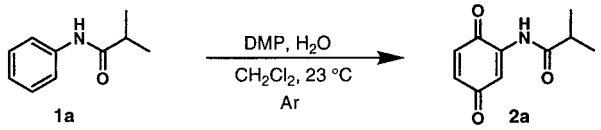


Table 1. Optimization of the Stoichiometry of DMP and Water Employed in the Conversion of Anilide **1a** to Quinone **2a**[a]



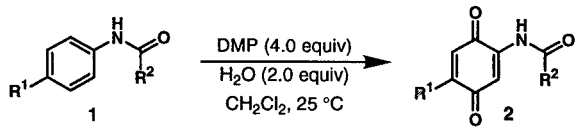
entry	DMP (equiv)		H_2O [Ac-IBX] (equiv)	yield (%)[b]
1	0		1.0	0
2	2.0		1.0	trace
3	3.0		2.0	40
4	*4.0*	*optimum cond.*	*2.0*	*43*
5	0		4.0	0
6	8.0		4.0	45
7	8.0		0	0

[a] Reactions were carried out on a 0.1 mmol scale in CH_2Cl_2 solution at ambient temperature under argon for 1−5 h. [b] Yields refer to chromatographically pure isolated materials.

although slightly higher yields could be realized with larger amounts of reagents (entry 6, Table 1). As a further support of our mechanistic postulate, no reaction was observed in the presence of only DMP (entry 7, Table 1) or only Ac-IBX (entries 1 and 5, Table 1). It is known that Ac-IBX is stoichiometrically formed from DMP and H_2O under the employed conditions.[1]

Under these optimal conditions, a variety of *p*-substituted anilides (**1**) were converted into *p*-quinones (**2**, Table 2). An array of substituents (with the exception of the nitro group, entry 11, Table 2) on the aromatic nucleus and the amide side chain were found to be well tolerated. The failure of the nitro-substituted anilides is surprising since they enter the DMP-initiated polycyclization reaction.[1] Significantly, the reaction was not limited to simple anilides, as even the naphthalene amide **3** led smoothly to the corresponding benzoquinone **4** in 30% yield (Scheme 2). The workup and isolation procedures are crucial to the success of these reactions. Thus, to isolate these unstable *p*-quinones in optimum yields, a neutral workup procedure was employed. Often, the reaction mixture could be directly loaded onto a pad of silica for purification after removal of the bulk of the solvent under vacuo. Therefore, the isolated yields reported in Table 1 and Scheme 2 represent minimum values.

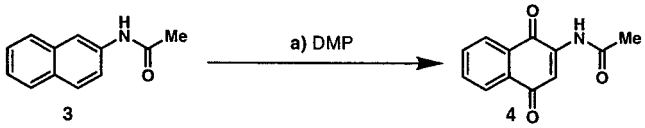
Table 2. Synthesis of *p*-Quinones from Anilides Using DMP[a]



entry	substrate	time (h)	product	yield (%)[b]
1	**1a**: R^1 = H, R^2 = *i*-Pr	4	**2a**	43
2	**1b**: R^1 = H, R^2 = Me	2	**2b**	42
3	**1c**: R^1 = Et, R^2 = Me	4	**2c**	53
4	**1d**: R^1 = *t*-Bu, R^2 = Me	4	**2d**	36
5	**1e**: R^1 = Ph, R^2 = Me	1.5	**2e**	44
6	**1f**: R^1 = OMe, R^2 = Me	24	**2f**	46
7	**1g**: R^1 = F, R^2 = Me	24	**2g**	27
8	**1h**: R^1 = Cl, R^2 = Me	24	**2h**	30
9	**1i**: R^1 = Br, R^2 = Me	24	**2i**	25
10	**1j**: R^1 = I, R^2 = Me	72	**2j**	22
11	**1k**: R^1 = NO_2, R^2 = Me	12	**2k**	<1
12	**1l**: R^1 = H, R^2 = Ph	280	**2l**	40
13	**1m**: R^1 = H, R^2 = *t*-Bu	12	**2m**	41

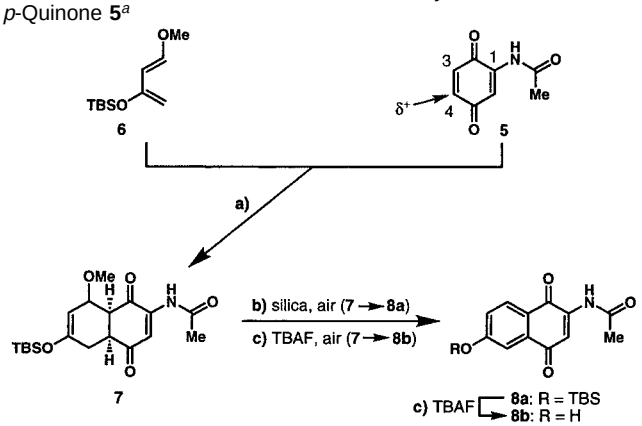
[a] Reactions were carried out on a 0.1 mmol scale in CH_2Cl_2 solution at ambient temperature under argon for the time indicated. [b] Yields refer to chromatographically pure isolated materials.

Scheme 2. Oxidation of Naphthalene Amide **3** to the Benzoquinone **4**[a]



[a] Reagents and conditions: (a) DMP (4.0 equiv), H_2O (2.0 equiv), CH_2Cl_2, 25 °C, 4 h, 30%.

Scheme 3. Diels−Alder Union of Danishefsky's Diene **6** with *p*-Quinone **5**[a]



[a] Reagents and conditions: (a) **6** (1.5 equiv), toluene, 95 °C, 3 h, 100%; (b) silica gel, air, CH_2Cl_2, 25 °C, 12 h, 86%; (c) TBAF (1.5 equiv, 1.0 M solution in THF), THF, 25 °C, air, 3 h, **7** → **8b**, 68%; **8a** → **8b**, 95%.

2. Synthetic Applications of DMP-Generated *p*-Quinones. The reactivity of the DMP-generated N-containing quinones was demonstrated by employing both inter- and intramolecular Diels−Alder reactions which proceeded regio- and stereoselectively to furnish products of considerable molecular complexity and synthetic utility. An example of the former scenario is depicted in Scheme 3 and involves the union of *p*-quinone **5** with Danishefsky's diene **6**[4] in toluene at 95 °C to

(4) Danishefsky, S. J.; Kitahara, T.; Yan, C. F.; Morris, J. *J. Am. Chem. Soc.* **1979**, *101*, 6996. Danishefsky, S. J.; Yan, C. F.; Singh, R. K.; Gammill, R. B.; McCurry, P.; Fritsch, N.; Clardy, J. C. *J. Am. Chem. Soc.* **1979**, *101*, 7001.

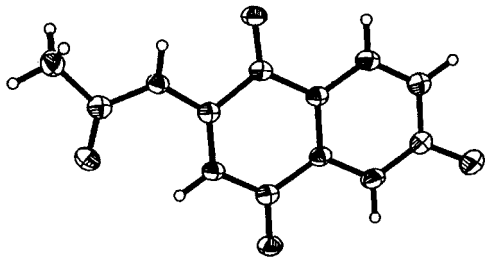


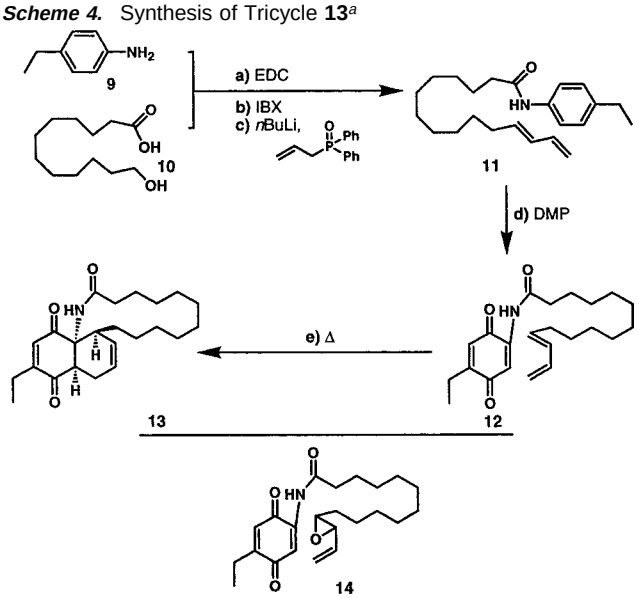
Figure 2. ORTEP representation of quinone **8a** (silyl group removed for clarity).

afford **7** in quantitative yield. Compound **8a** was formed in 86% yield upon exposure of **7** to silica gel in air. Phenol **8b** could be accessed either from **8a** or from **7** upon treatment with TBAF in THF. In our initial disclosure we reported the opposite regiochemical outcome for this Diels−Alder reaction, on the basis of spectroscopic evidence alone.[2] We were soon alerted to the elegant studies of T. Ross Kelly and co-workers which suggested that our regiochemical assignment may require revision.[5] To resolve this discrepancy, we carefully sought a crystalline derivative suitable for crystallographic analysis and found the TBS-protected phenol **8a**. Indeed, the correct regiochemical outcome was reverse to the one originally thought and is correctly depicted as shown in Figure 2 (ORTEP drawing).[6] This outcome can be rationalized by invoking the electron-donating effect of the amide group which polarizes the adjacent carbonyl groups such that C-4 is a better electron acceptor than C-3 (see Scheme 3, structure **5**).

An intramolecular variant of this Diels−Alder reaction was then designed and pursued as depicted in Scheme 4. This sequence, which leads to the complex macrocyclic system **13**, commences with the simple building blocks **9** and **10**. Thus, EDC-mediated coupling of aniline **9** with carboxylic acid **10** (97%) followed by oxidation of the resulting hydroxy amide to the corresponding aldehyde (IBX, DMSO, 100%) and a Wittig-type olefination with the anion of allyldiphenylphosphine oxide led to the diene construct **11** (72% yield). The DMP-tandem oxidation protocol was then employed to generate the *p*-quinone **12** in 29% yield along with 19% of the accompanying epoxide byproduct **14** (vide infra for further discussion on this observation). Finally, heating a solution of **12** in xylenes (145 °C) led exclusively to the tricycle **13** (63% yield) as confirmed by X-ray crystallographic analysis (see Figure 3 for ORTEP structure).[6] Not surprisingly, diene **12** reacted this time at the less reactive N-substituted site of the quinone due to conformational restraints within the overall structure of the molecule. This mode of capture leaves the other side of the quinone open for further elaboration, and, therefore, it may prove useful in future studies along such lines.

3. Applications of the DMP-Induced Conversion of Anilides to *p*-Quinones to the Total Synthesis of Natural Products. To test the applicability of the newly discovered chemistry to the construction of complex and sensitive natural

Scheme 4. Synthesis of Tricycle **13**[a]



[a] Reagents and conditions: (a) EDC (1.5 equiv), 4-DMAP (0.5 equiv), aniline (5.0 equiv), CH_2Cl_2, 0 → 25 °C, 12 h, 97%; (b) IBX (2.0 equiv), DMSO, 25 °C, 12 h, 100%; (c) $Ph_2P(O)CH_2CH{=}CH_2$ (3.0 equiv), *n*-BuLi (2.5 equiv), HMPA (6.0 equiv), THF, −78 °C, 20 min; then add aldehyde, −78 → 25 °C, 12 h, 72%; (d) DMP (3.5 equiv), H_2O (2.3 equiv), CH_2Cl_2, 0 °C, 22 h, 29% **12** plus 19% **14**; (e) xylene, 145 °C, 24 h, 63%.

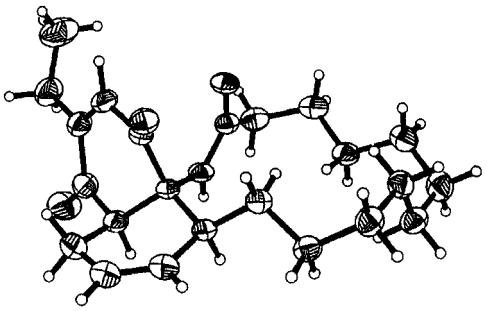


Figure 3. ORTEP representation of tricycle **13**.

products, we initiated a program directed toward the total synthesis of such target molecules. As a first example, an expeditious entry into the epoxyquinomycin class of natural products was demonstrated by a concise total synthesis of epoxyquinomycin B (**20**, Scheme 5). The epoxyquinomycins, isolated from *Amycolatopsis sp.* MK299-95F4, are a class of structurally related weak antibiotics.[7] Furthermore, these compounds have been shown to inhibit type II-collagen-induced arthritis in vivo with low associated toxicity.[7] More recently, they have been demonstrated to be potent inhibitors of rat embryo histidine decarboxylase, an enzyme implicated in inflammation.[8] Because of their potential therapeutic applications as antiinflammatory agents and for the treatment of rheumatoid arthritis, the epoxyquinomycins and related compounds have received considerable attention from the synthetic community.[9] Our total synthesis of epoxyquinomycin B (**20**), the most potent member of this class, represents the shortest route to these compounds, featuring only four synthetic operations from simple

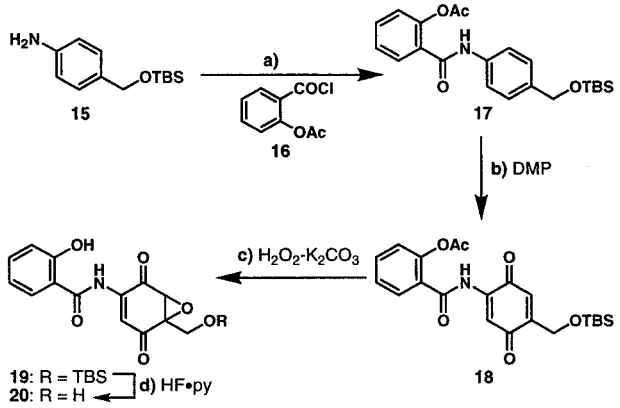
(5) We thank Professors T. Ross Kelly and Antonio M. Echavarren for inducing us to reexamine this issue, see: Kelly, T. R.; Behforouz, M.; Echavarren, A.; Vaya, J. *Tetrahedron Lett.* **1983**, *24*, 2331.

(6) Crystallographic data for compounds **8a**, **13**, **42**, **45**, **54a**, and **60a** have been deposited at the Cambridge Crystallographic Data Center as Supplementary publications nos. CCDC-169249, -148280, -159145, -168714, -1591466, and -159147, respectively. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (fax, (+44) 1223-336-033; e-mail, deposit@ccc.cam.ac.uk).

(7) Matsumoto, N.; Tsuchida, T.; Umekita, M.; Kinoshita, N.; Iinuma, H.; Sawa, T.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1997**, *50*, 900. Matsumoto, N.; Iinuma, H.; Sawa, T.; Takeuchi, T.; Hirano, S.; Yoshioka, T.; Ishizuka, M. *J. Antibiot.* **1997**, *50*, 906.

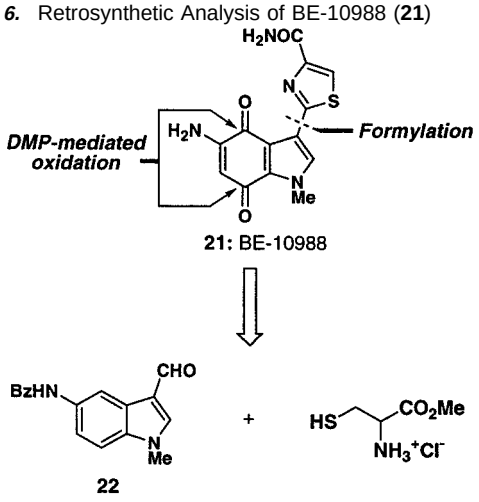
(8) Matsumoto, N.; Agata, N.; Kuboki, H.; Iinuma, H.; Sawa, T.; Takeuchi, T.; Umezawa, K. *J. Antibiot.* **2000**, *53*, 637.

Scheme 5. Total Synthesis of Epoxyquinomycin B (**20**)[a]



[a] Reagents and conditions: (a) **15** (1.0 equiv), **16** (1.0 equiv), Et_3N (1.1 equiv), CH_2Cl_2, 25 °C, 20 min, 100%; (b) DMP (3.0 equiv), H_2O (2.0 equiv), CH_2Cl_2, 25 °C, 3 h, 43%; (c) H_2O_2 (30% solution in H_2O, 3.0 equiv), K_2CO_3 (1.0 equiv), THF, 25 °C, 30 min, 95%; (d) HF•py (5.0 equiv), THF, 10 min, 95%.

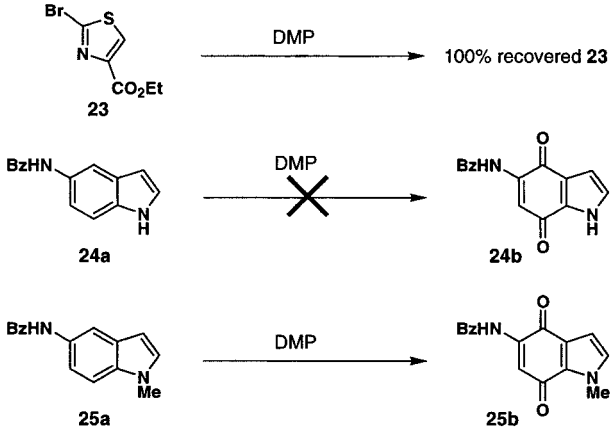
Scheme 6. Retrosynthetic Analysis of BE-10988 (**21**)



and readily available starting materials and proceeding in 38% overall yield (see Scheme 5). Thus, the aniline **15** was combined with the carboxylic acid chloride **16** in the presence of triethylamine to furnish the amide **17** in quantitative yield. Treatment of **17** with DMP in CH_2Cl_2 then gave the quinone **18** in 43% yield after directly loading the reaction mixture onto a pad of silica gel for high-speed purification. Regioselective epoxidation of **18** with hydrogen peroxide in the presence of K_2CO_3 in aqueous THF was accompanied by concomitant acetate cleavage to give, after desilylation with HF•py, epoxyquinomycin B (**20**) (via **19**), whose spectral data were found to be identical to those reported for the natural product.

As a second target for total synthesis in this program, we identified the interesting metabolite BE-10988 (**21**, Scheme 6). Isolated from the culture broth of a strain of Actinomycetes, BE-10988 represents a promising topoisomerase-II inhibitor.[10] Type-II topoisomerases are essential enzymes implicated in DNA replication, recombination, transcription, and repair by virtue of their ability to modulate the 3-dimensional structure

Scheme 7. Model Studies en Route to BE-10988 (**21**)[a]



[a] Reagents and conditions: (a) DMP (4.0 equiv), H_2O (2.0 equiv), CH_2Cl_2, 25 °C, 12 h, 36% for **25b**.

of DNA.[10] Because proliferating tumor cells exhibit much higher levels of topoisomerase-II, selective inhibition of this critical enzyme represents a unique opportunity for the design and discovery of new antitumor agents.[11] To date, two elegant total syntheses of **21** have been reported, one from Moody and Swann[12] and the other from the Shizuri camp.[13]

The molecular structure of BE-10988 (**21**) contains a novel thiazole-substituted indole-quinone and as such provides a unique forum to test the utility of the tandem DMP oxidation. Retrosynthetically, and as depicted in Scheme 6, we disconnected the molecule using an indole formylation. Condensation with cysteine to implement the thiazole ring and a late-stage DMP oxidation would then provide the natural product after removal of protecting groups. Model studies were first performed as shown in Scheme 7 to probe the viability of the aforementioned strategy. Although the unprotected indole **24a** did not lead to the desired indolequinone **24b**, N-protected indole **25a** led smoothly to indolequinone **25b** in 36% yield. Encouragingly, the bromothiazole **23** was inert to the conditions used for DMP-mediated *p*-quinone construction.

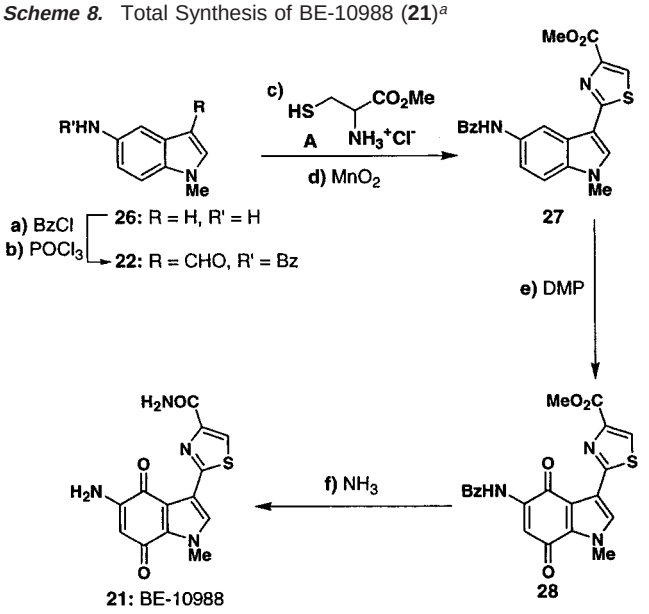
Armed with the confidence provided by these experiments, we set forth toward the total synthesis, as summarized in Scheme 8. Thus, the known indole **26**[14] was converted to its *N*-benzoyl derivative (**25a**) followed by formylation with $POCl_3$/DMF (**22**, 100% overall). Condensation with cysteine methyl ester followed by oxidation of the resulting thiazoline led to the thiazole **27** (37% overall, 85% conversion). DMP-mediated oxidation of **27** led to the indole-quinone **28** (67% yield) which, after treatment with ammonia in MeOH, led to synthetic BE-10988 (**21**). Synthetic **21** exhibited identical spectroscopic properties to those reported for natural **21**.[10] Our total synthesis of BE-10988 (**21**) represents the shortest and most efficient (24% isolated yield overall, 54% yield based on recovered starting material) route to this important antitumor compound.

The total syntheses of epoxyquinomycin B (**20**) and BE-10988 (**21**) serve to illustrate the advantage of the DMP-

(9) Matsumoto, N.; Ariga, A.; To-E, S.; Nakamura, H.; Agata, N.; Hirano, S.-I.; Inoue, J.-I.; Umezawa, K. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 865. Block, O.; Klein, G.; Altenbach, H.-J.; Brauer, D. J. *J. Org. Chem.* **2000**, *65*, 716. Wipf, P.; Coish, P. D. G. *J. Org. Chem.* **1999**, *64*, 5053. Alcaraz, L.; Macdonald, G.; Ragot, J.; Lewis, N. J.; Taylor, R. J. K. *Tetrahedron* **1999**, *55*, 3707. For the first total synthesis, see: Matsumoto, N.; Iinuma, H.; Sawa, T.; Takeuchi, T. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2945.

(10) Oka, H.; Yoshinari, T.; Murai, T.; Kuwamura, K.; Satoh, F.; Funaishi, K.; Okura, A.; Suda, H.; Okanishi, M.; Shizuri, Y. *J. Antibiot.* **1991**, *44*, 486.
(11) Ross, W. E. *Biochem. Pharmacol.* **1985**, *34*, 4191.
(12) Moody, C. J.; Swann, E. *Tetrahedron Lett.* **1993**, *34*, 1987.
(13) Suda, H.; Ohkubo, M.; Matsunaga, K.; Yamamura, S.; Shimomoto, W.; Kimura, N.; Shizuri, Y. *Tetrahedron Lett.* **1993**, *34*, 3797.
(14) Prepared from 4-nitroindole by N-methylation followed by reduction of the nitro group. See: Forbes, I. T.; Jones, G. E.; Murphy, O. E.; Holland, V.; Baxter, G. S. *J. Med. Chem.* **1995**, *38*, 855.

Scheme 8. Total Synthesis of BE-10988 (**21**)[a]



[a] Reagents and conditions: (a) BzCl (1.3 equiv), Et_3N (1.8 equiv), CH_2Cl_2, 0 → 25 °C, 1 h, 100%; (b) $POCl_3$ (10 equiv), DMF, −20 → 0 °C, 1 h; then add **22**, 0 → 25 °C, 3 h, 100%; (c) **A** (2.0 equiv), py, 25 °C, 12 h; (d) MnO_2 (20 equiv), py:benzene (10:1), 2 h, 37% overall, 85% conversion; (e) DMP (4.0 equiv), H_2O (2.0 equiv), CH_2Cl_2, 25 °C, 12 h, 67%; (f) NH_3 (10 equiv), THF, −78 → 25 °C, 48 h, 95%.

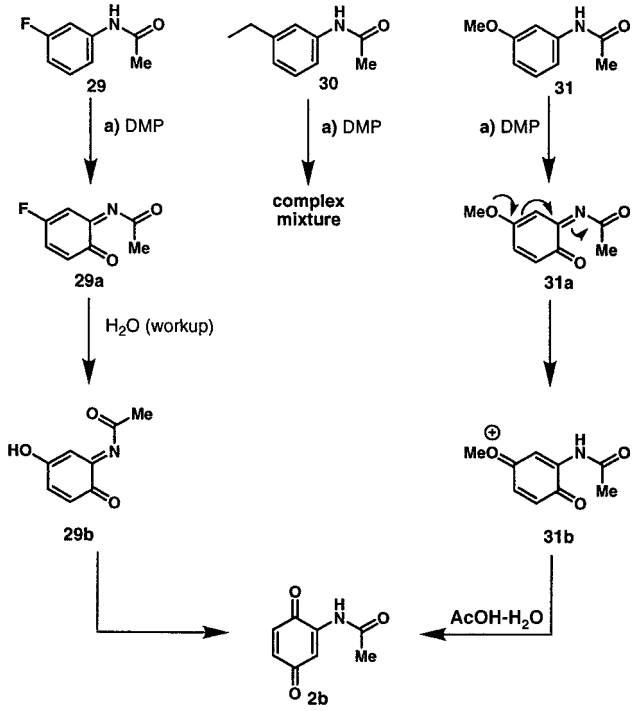
mediated construction of *p*-quinones over conventional methods.[15] Specifically, in planning the synthesis of a *p*-quinone-containing molecule, the necessity to include in the aromatic nucleus the normally obligatory one or two protected oxygen atoms is no longer a requirement. In essence, an anilide moiety may be considered to be a latent *p*-quinone system, since both oxygen atoms may be installed at once using DMP.

4. Generation of Stable *o*-Imidoquinones from Anilides and DMP. Having established that *p*-substituted anilides reliably lead to *p*-quinones under the oxidative influences of DMP, we set out to investigate the reactivity of substrates with other substitution patterns on the aromatic residue. Unfortunately, the DMP oxidation of *m*-substituted anilides proved to be rather complex and unpredictable. For example, while the *m*-substituted ethyl anilide **30** upon treatment with DMP under the usual conditions led to a complex mixture of unidentified products, the same reaction with the *m*-fluoro- and *m*-methoxy-substituted anilides **29** and **31** led to the *p*-quinone **2b** in 21 and 34% yield, respectively (Scheme 9). To explain this unexpected, but interesting, observation, we propose the mechanism shown Scheme 9.

However, to our delight, when the same oxidation was attempted with *o*-substituted anilides (**32**), only *o*-imidoquinones (**33**) were obtained (Table 3). We hypothesize that the 2-substituent of the anilide blocks another molecule of Ac-IBX from attacking the initially formed product and, thus, prevents formation of the corresponding *p*-quinone. Alternatively, the *o*-substituent might force the amide group into a twist, thus preventing conjugation of the amide lone-pair of electrons and disfavoring attack by another molecule of Ac-IBX (see Scheme 1). As shown in Table 3, the reaction is efficient for the construction of a variety of *o*-imidoquinones harboring a critical

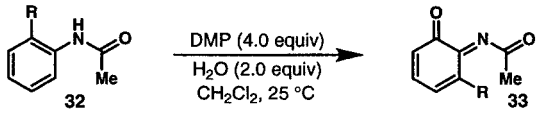
(15) For a recent review on the synthesis of quinones, see: Owton, W. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2409 and references therein.

Scheme 9. Mechanistic Rationale for the Generation of *p*-Quinone **2b** from *m*-Substituted Anilides **29** and **31**[a]



[a] Reagents and conditions: (a) DMP (4.0 equiv), H_2O (2.0 equiv), 25 °C, 3 h, 21% **2b** from **29**, 34% **2b** from **31**.

Table 3. Synthesis of *o*-Azaquinones from 2-Substituted Anilides[a]



entry	R	time (h)	product	yield (%)[b]
1	**32a**: Br	6	**33a**	32
2	**32b**: *t*-Bu	4	**33b**	88
3	**32c**: Ph	6	**33c**	41
4	**32d**: I	6	**33d**	44
5	**32e**: Et	4	**33e**	64
6	**32f**: Cl	6	**33f**	71

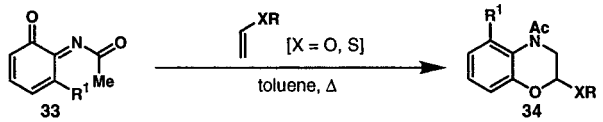
[a] Reactions were carried out on a 0.1 mmol scale in CH_2Cl_2 solution at ambient temperature under argon for the time indicated. [b] Yields refer to chromatographically pure isolated materials.

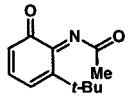
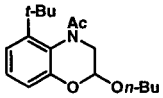
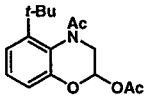
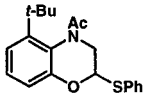
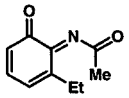
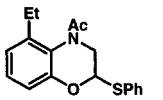
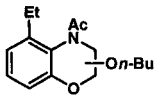
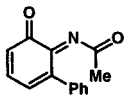
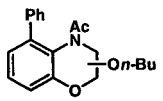
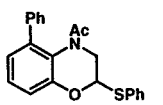
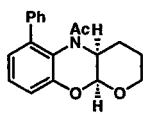
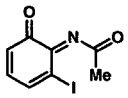
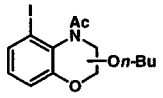
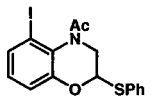
2-substituent. Reaction times are much shorter, and the yield is generally higher as compared to that of the corresponding process leading to *p*-quinones (see Table 2).

If the red-wine-colored *o*-imidoquinones are shielded from light and stored under argon at low temperatures, they are stable for several months. Given our studies of intramolecular inverse electron demand Diels−Alder reactions with *o*-imidoquinones generated in situ,[1] it was not surprising that these remarkably stable entities proved to be willing partners in the intermolecular variant of this process. Table 4 demonstrates the molecular diversity accessible through this chemistry, including compounds equipped with sites for further elaboration (e.g., iodide, anomeric, *N*-acetyl). It is interesting to note that these *o*-imidoquinones did not react with simple alkenes, such as cycloheptene, even under forcing conditions, in contrast to the intramolecular variant where unactivated olefins reacted efficiently even at room temperature.[1]

5. Cascade Reactions of *o*-Imidoquinones Leading to Novel and Complex Molecular Diversity. The facile generation of

Table 4. Intermolecular Diels–Alder Reactions of *o*-Imidoquinones[a]

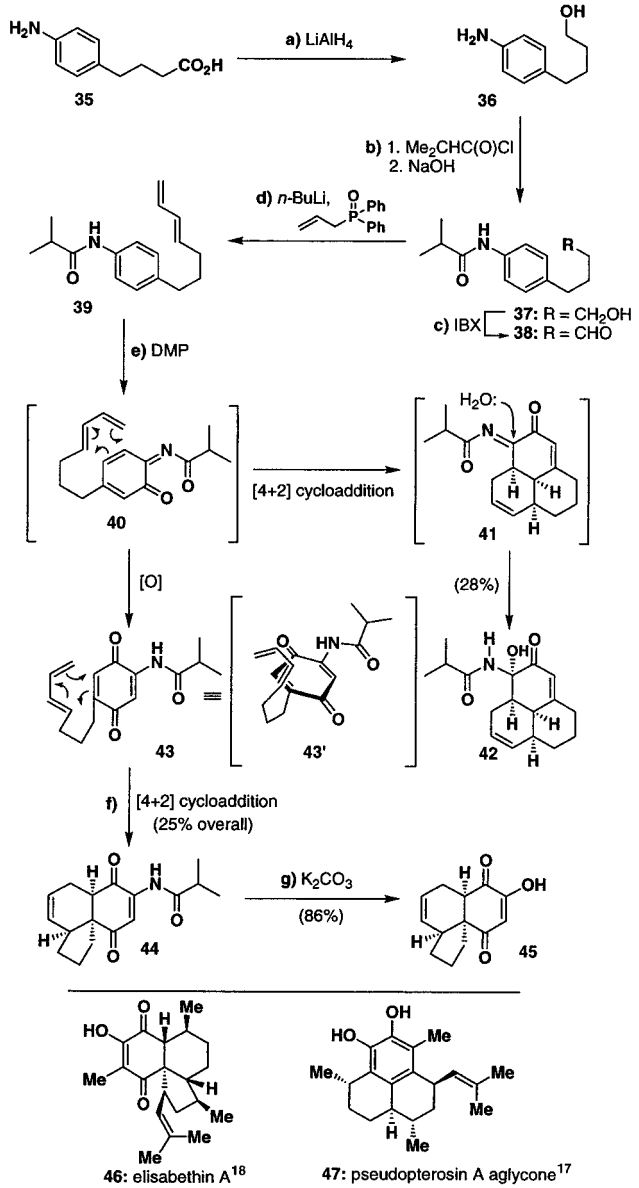


Entry	Substrate	Dienophile	Product	Yield (%)[b]
1	 33b		 34b-1	95
2	33b		 34b-2	83
3	33b		 34b-3	95
4	 33e		 34e-1	95[c]
5	33e		 34e-2	90[c]
6	 33c		 34c-1	95[d]
7	33c		 34c-2	95[c]
8	33c		 34c-3	71
9	 33d		 34d-1	95[d]
10	33d		 34d-2	95[c]

[a] Reactions were carried out on a 0.1 mmol scale in toluene solution at reflux under argon for 5–50 min. [b] Yields refer to chromatographically pure isolated materials. [c] This product was obtained as a mixture of unassigned regioisomers (ca. 2:1 ratio). [d] This product was obtained as a mixture of unassigned regioisomers (ca. 1:1 ratio).

o-imidoquinone-type structures from anilides and DMP and their demonstrated ability to undergo inter- and intramolecular Diels–Alder reactions as heterodienes (reactivity mode a, Figure 1) or to suffer further oxidation to *p*-quinones (reactivity mode b, Figure 1) set the stage for the development of another reaction pathway for these rather rare chemical species. Close inspection

Scheme 10. Rapid Entry into Complex Pseudopterosin A and Elisabethin-Type Structures from Anilides and DMP[a]



[a] Reagents and conditions: (a) $LiAlH_4$ (5.0 equiv), THF, 0 → 25 °C, 2 h, 96%; (b) (1) $Me_2CHC(O)Cl$ (3.0 equiv), Et_3N (4.0 equiv), CH_2Cl_2, 0 → 25 °C, 1 h, (2) 1 N NaOH (3.0 equiv) MeOH, 50 °C, 2 h, 95% for two steps; (c) IBX (2.0 equiv), DMSO, 25 °C, 6 h, 95%; (d) $Ph_2P(O)CH_2CH{=}CH_2$ (3.0 equiv), *n*-BuLi (2.5 equiv), HMPA (6.0 equiv), THF, −78 °C, 20 min; then add aldehyde, −78 → 25 °C, 14 h, 80%; (e) DMP (4.0 equiv), H_2O (2.0 equiv), CH_2Cl_2, 25 °C, 3 h, 28% **42**, 25% **43**; (f) **43**, toluene, 110 °C, 12 h, 100%; (g) K_2CO_3 (10 equiv), MeOH, 25 °C, 1 h, 86%; IBX = *o*-iodoxybenzoic acid; DMP = Dess–Martin periodinane.

of known structures of natural products revealed the potential of utilizing these quinones to rapidly construct complex mimics of such molecules and related compounds with potential for protein binding. Specifically, we reasoned that the electron-deficient olefin adjacent to the imide functionality of the *o*-imidoquinone moiety might also be capable of acting as a dienophile in an intramolecular Diels–Alder fusion (reactivity mode c, Figure 1).

To explore this novel prospect, we designed and synthesized diene **39** as shown in Scheme 10. Thus, treatment of the commercially available amino acid **35** with $LiAlH_4$ led to alcohol **36** in 96% yield. Condensation with isobutyryl chloride

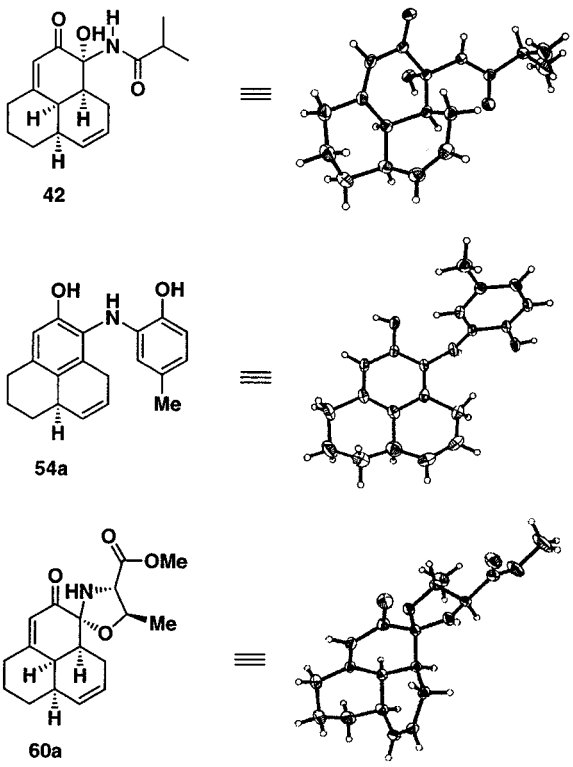


Figure 4. ORTEP structures of complex, natural product-like compounds (**42**, **54a**, and **60a**) synthesized by DMP-initiated cascade reactions.

followed by selective hydrolysis of the resulting crude ester amide with NaOH led to hydroxy amide **37** in 95% yield. Oxidation of **37** using IBX at room temperature led to the aldehyde amide **38** in 95% yield. A Wittig-type reaction on **38** with the anion generated from allyl diphenylphosphine oxide gave diene system **39** in 80% yield. The overall yield of this four-step sequence was 72%. To our delight, exposure of **39** to DMP (4.0 equiv)/H_2O (2.0 equiv) in CH_2Cl_2 at ambient temperature led to ketohydroxyamide **42** (see ORTEP structure, Figure 4)[6] and quinone **44** in 28 and 25% yields, respectively. The novel ketohydroxyamide **42** was presumably formed via hydration of the initially formed Diels−Alder adduct **41**. To the best of our knowledge, the intramolecular Diels−Alder reaction of *o*-imidoquinones (acting as dienophiles) is unprecedented.[16] Notably, the ketohydroxyamide **42** and its derivatives (vide infra) closely resemble the pseudopterosin family of natural products (e.g., pseudopterosin A aglycone, **47**, Scheme 10).[17]

The quinone **44** was presumably formed via an intramolecular Diels−Alder reaction of the diene system and the closest quinone face of the intermediate *p*-quinone **43**, which was, in turn, generated from *o*-imidoquinone **40** by the oxidative action of DMP. Quinone **44** embodies the full carbocyclic skeleton of the naturally occurring substance elisabethin A (**46**).[18] It has not escaped our attention that the structures of these two seemingly unrelated natural product classes (pseudopterosins and elisabethins) are produced by the same organism in nature,[18] just as the present DMP-initiated cascade furnishes both complex pseudopterosin- and elisabethin-type structural analogues in the same pot. It is also noteworthy that facile hydrolysis of quinone **44** could be simultaneously accomplished upon exposure to K_2CO_3 (10 equiv) in MeOH at 25 °C (86% yield) to furnish the crystalline quinone **45**. X-ray crystallographic analysis of this compound (see ORTEP structure, Figure 5)[6] revealed its relative stereochemistry leading us to revise our original assignment[3] for compound **44**. Therefore, the Diels−Alder reaction of **43** must proceed through the endo transition state (**43′**) as shown in Scheme 10.

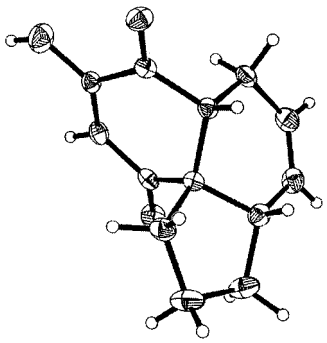


Figure 5. ORTEP structure of quinone **45**.

The availability of gram quantities of ketohydroxyamide **42**, coupled with the scarcely investigated chemistry of this moiety,[19] enticed us into exploring its reactivity and synthetic potential. It was soon found, as shown in Scheme 11, that ketohydroxyamide **42** undergoes a diverse range of novel transformations. Despite its misleading appearance, **42** does not react as a simple protected α-diketone. Thus, under reductive conditions using an excess of $NaBH_4$ (5.0 equiv) and $CeCl_3$ (10 equiv)[20] in MeOH at room temperature, compound **42** was transformed into diol **48** in essentially quantitative yield (ca. 1:1 mixture of diastereomers). By conducting the reaction at 0 °C and employing the same excess of reducing agent but only 1.1 equiv of $CeCl_3$, we were able to isolate the amido alcohol **49** in essentially quantitative yield and as a single isomer. A mechanistic rationale to account for this remarkable result is shown in Scheme 12. Thus, we postulate that at room temperature and with excess $CeCl_3$ the diketone **50** is formed, which is subsequently reduced to give a mixture of two diastereomeric diols. At 0 °C, however, and with only 1.1 equiv of $CeCl_3$, dehydration occurs to furnish the *o*-imidoquinone **51**. A subsequent stereo- and chemoselective 1,2-reduction of the latter compound takes place from the convex face of the molecule. The excess $NaBH_4$ then reduces the resulting α-amido ketone **52** selectively (again from the convex face) to afford, exclusively, the observed amido alcohol **49**.

In further exploring the chemistry of ketohydroxyamide **42**, we found that under aqueous acidic conditions (PPTS, H_2O) this compound was converted cleanly to diphenol **53** in 75% yield (see Scheme 11). We reasoned that the diketone, which is apparently an intermediate en route to diphenol **53**, might be intercepted with an array of nucleophiles as an opportunity to

(16) For a recent report of an intramolecular Diels−Alder reaction onto a *p*-imidoquinone, generated from the corresponding *p*-hydroxyanilide using $Pb(OAc)_4$, see: Johnson, T. W.; Corey, E. J. *J. Am. Chem. Soc.* **2001**, *123*, 4475.

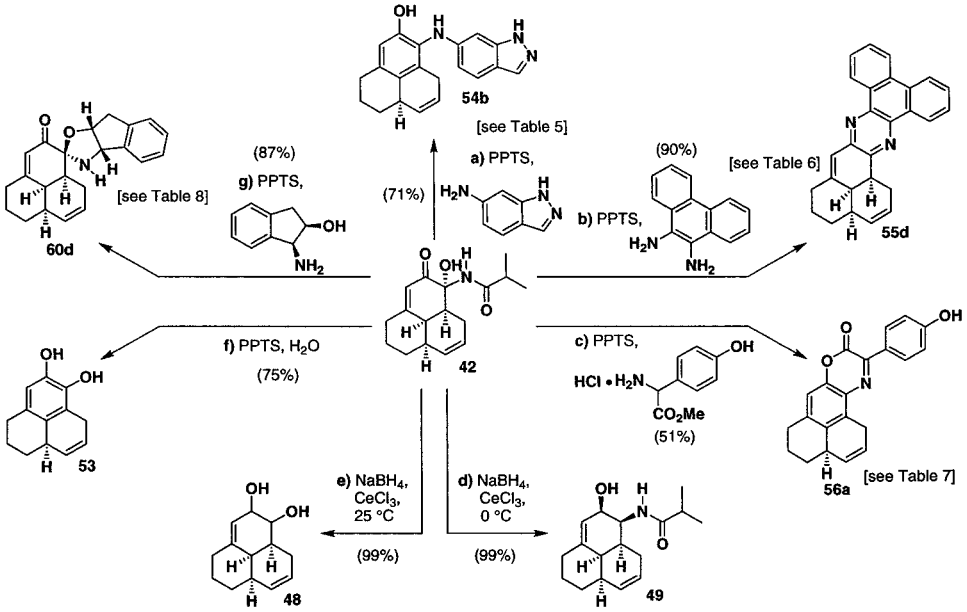
(17) The pseudopterosins are potent antiinflammatory agents: Look, S. A.; Fenical, W.; Matsumoto, G.; Clardy, J. *J. Org. Chem.* **1986**, *51*, 5140. Fenical, W. *J. Nat. Prod.* **1987**, *50*, 1001. Look, S. A.; Fenical, W. *Tetrahedron* **1987**, *43*, 3363. For synthetic studies, see: Corey, E. J.; Lazerwith, S. E. *J. Am. Chem. Soc.* **1998**, *120*, 12777 and references therein.

(18) Rodriguez, A. D.; Gonzalez, E.; Huang, S. D. *J. Org. Chem.* **1998**, *63*, 7083.

(19) To the best of our knowledge, there have been no reported synthetic studies of α,β-unsaturated ketohydroxyamides such as **42**, except for a brief study of the related 3-bromo-2-hydroxy-2-acetamidocyclohexanone, see: Ermolaev, K. M.; Maimind, V. I. *Biol. Akt. Soedin.* **1968**, 142.

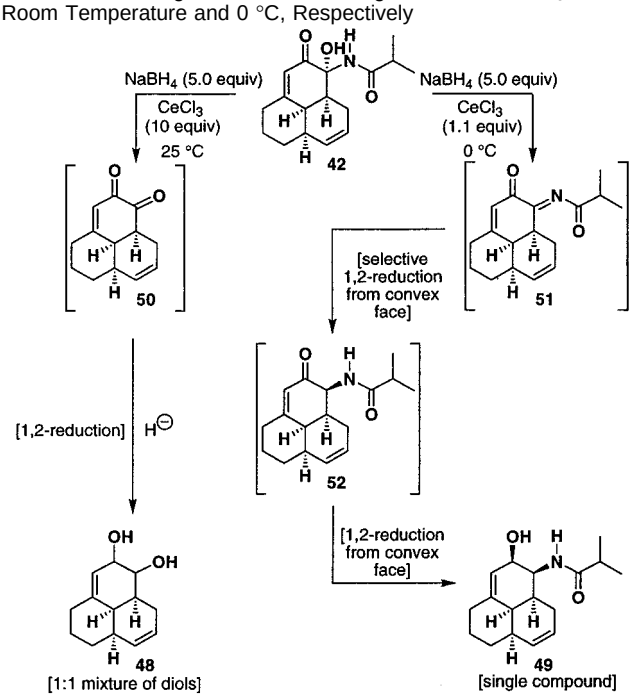
(20) Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

Scheme 11. Remarkable Reactivity of the Unique Ketohydroxyamide **42**[a]



[a] Reagents and conditions: (a) $ArNH_2$ (5.0 equiv), PPTS (0.2 equiv), toluene, 90 °C, 5 h, 71%; (b) diamine (5.0 equiv), PPTS (0.2 equiv), toluene, 90 °C, 4 h, 90%; (c) tyrosine methyl ester (3.0 equiv), PPTS (0.2 equiv), $NaHCO_3$ (3.0 equiv), DMF, 90 °C, 12 h, 51%; (d) $NaBH_4$ (5.0 equiv), $CeCl_3$ (1.1 equiv), THF, 0 °C, 99%; (e) $NaBH_4$ (5.0 equiv), $CeCl_3$ (10.0 equiv), THF, 25 °C, 99%; (f) PPTS (0.2 equiv), H_2O, 50 °C, 30 min, 75%; (g) amino alcohol (3.0 equiv), PPTS (0.2 equiv), toluene, 90 °C, 10 h, 87%; IBX = *o*-iodoxybenzoic acid; DMP = Dess−Martin periodinane; PPTS = pyridinium 4-toluenesulfonate.

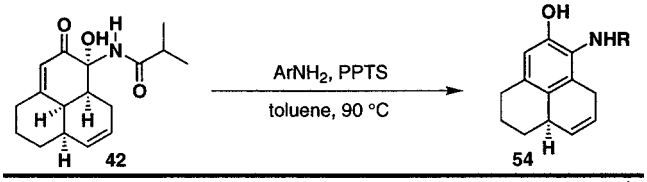
Scheme 12. Postulated Mechanistic Pathways for the Synthesis of **48** and **49** Using $NaBH_4$ and Differing Amounts of $CeCl_3$ at Room Temperature and 0 °C, Respectively

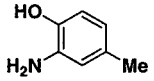
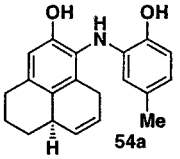
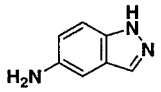
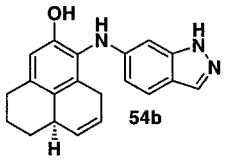
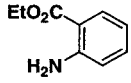
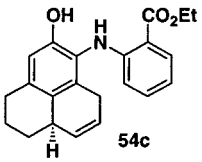
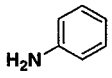
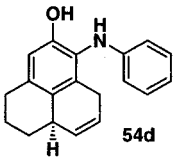


discover new chemistry and as a means to expand on the accessible molecular complexity and diversity by this avenue. Thus, in the presence of PPTS, anilines reacted with **42** in toluene at 90 °C to afford polycyclic amines (**54a**−**d**) as shown in Scheme 11 and Table 5. X-ray crystallographic analysis of **54a** confirmed its structural assignment (see ORTEP structure, Figure 4).[6]

Given their importance in medicinal chemistry, we then turned our attention to the synthesis of pyrazines as seen in Scheme 11 (**42** → **55d**). In an expanded venture and as shown in Table

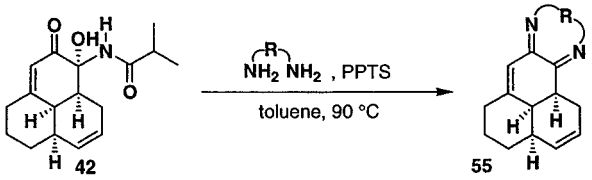
Table 5. Synthesis of Polycyclic Anilines from Ketohydroxyamide **42**[a]

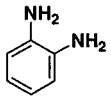
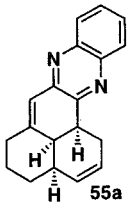
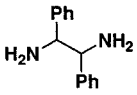
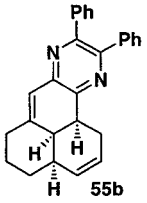
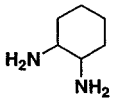
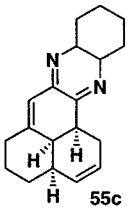
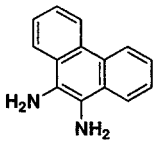
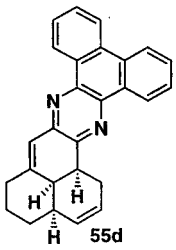


Entry	RNH_2	Product	Yield (%)[b]
1		 54a	84
2		 54b	71
3		 54c	45[c]
4		 54d	89

[a] Reagents and conditions: $ArNH_2$ (5.0 equiv), PPTS (0.2 equiv), toluene, 90 °C, 3−24 h. [b] Yields refer to chromatographically pure isolated materials. [c] Accompanied with 20% **53** (Scheme 11).

Table 6. Synthesis of Polycyclic Pyrazines from Ketohydroxyamide **42**[a]



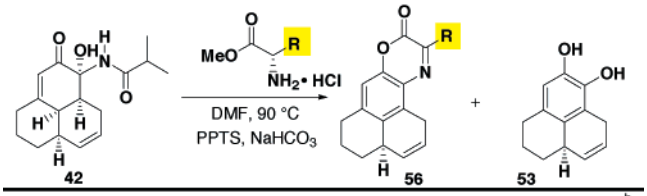
Entry	Diamine	Product	Yield (%)[b]
1		 **55a**	94
2		 **55b**	73
3		 **55c**	88
4		 **55d**	90

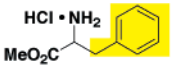
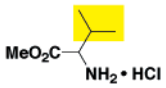
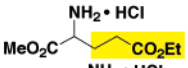
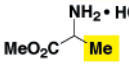
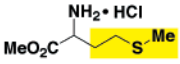
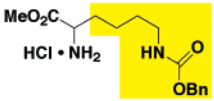
[a] Reagents and conditions: diamine (5−10 equiv), PPTS (0.2 equiv), toluene, 90 °C, 3−8 h. [b] Yields refer to chromatographically pure isolated materials.

6, the combination of ketohydroxyamide **42** with a variety of 1,2-diamines led smoothly to complex polycyclic pyrazines, presumably via a straightforward condensation with the intermediately formed diketone (e.g., **50**, Scheme 12).[21] Because of the high efficiency of these reactions, we proceeded to employ C-protected amino acids as coupling partners and discovered an interesting cascade sequence leading to heterocyclic annulation as shown in Scheme 11 (**42** → **56a**). Under similar conditions as used for amines, ketohydroxyamide **42** was cleanly converted to the complex polycyclic scaffolds **56a**−**g** as shown in Table 7, which demonstrates the versatility and scope of this reaction. A proposed mechanism for this impressive cascade is shown in Scheme 13. Thus, conversion of **42** to the corresponding diketone **50** after expulsion of isobutyramide is followed by either diphenol formation (**53**, after aromatization) or attack by the amino group of the amino acid derivative to form

(21) Flament, I.; Stoll, M. *Helv. Chim. Acta* **1967**, *50*, 1754.

Table 7. Synthesis of Complex Polycyclic Systems from Ketohydroxyamide **42** and C-Protected Amino Acid Derivatives[a]



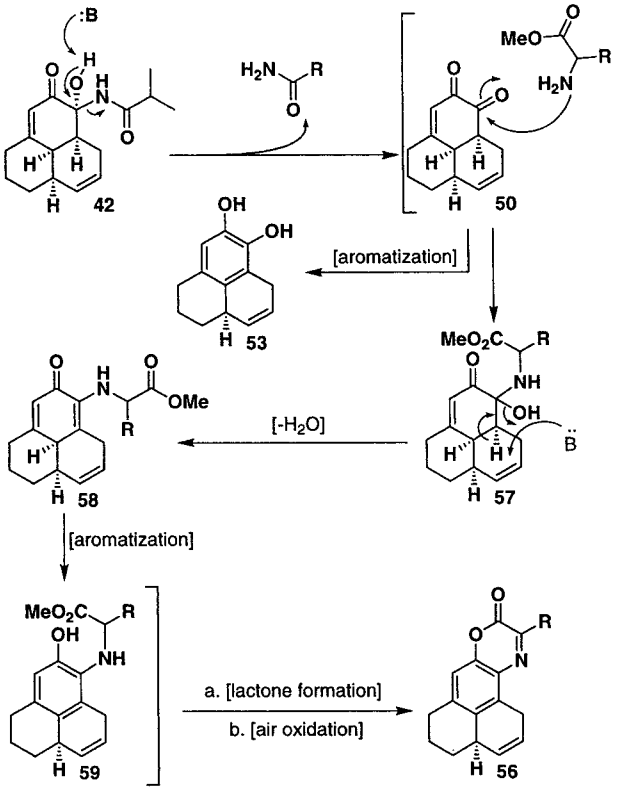
Entry	Protected amino acid	Product (Yield %)	Bis-phenol (Yield %)[b]
1		**56a** (51)	23
2		**56b** (49)	20
3		**56c** (80)	5
4		**56d** (53)	15
5		**56e** (72)	10
6		**56f** (66)	10
7		**56g** (39)	31

[a] Reagents and conditions: C-protected amino acid (3.0 equiv), PPTS (0.2 equiv), $NaHCO_3$ (3.0 equiv) DMF, 90 °C, 6−24 h. [b] Yields refer to chromatographically pure isolated materials.

intermediate **57**. Dehydration followed by aromatization may then furnish, via species **58**, intermediate **59** which may then rapidly cyclize and succumb to air oxidation to furnish the observed product **56**.

When we recruited amino alcohols as partners in this reaction, we uncovered a novel heterocyclic spiroannulation reaction. Thus, under similar conditions used for our other heterocyclic annulations, a series of amino alcohols was employed giving rise to the highly complex spiro compounds **60a**−**d** as shown in Scheme 14 and Table 8. X-ray crystallographic analysis of the crystalline **60a** (see ORTEP structure, Figure 4)[6] facilitated the characterization of these compounds. Utilizing the amino alcohol in entry 1 of Table 8, two pairs of diastereomeric spirocycles were formed, the major pair arising upon closure of the oxygen atom onto the least hindered, convex face of the all-cis fused tricycle (see structure **61**, Scheme 14). In general, the stereochemistry at the spirocenter could be easily predicted using molecular models and postulating that attack of the alcohol onto the putative imine intermediate (**61**) should occur so as to minimize steric interactions with the hindered concave side of the molecule (see Scheme 14). Regardless of whether the alcohol attacks the neighboring ketone (path b, Scheme 14) to furnish the spirocycle **60b** after rearrangement of **62** involving a 1,2-oxygen migration, or of whether it directly engages the imine in **61** leading to **60b**, the stereochemical result should be the same. In the case of the indane-spirocycle **60d**, the steric bulk of the indane ring apparently forces attack by the hydroxy group within **63** toward the hindered, concave side of the molecule. The stereochemistry of all spirocycles was verified via key nOe interactions.

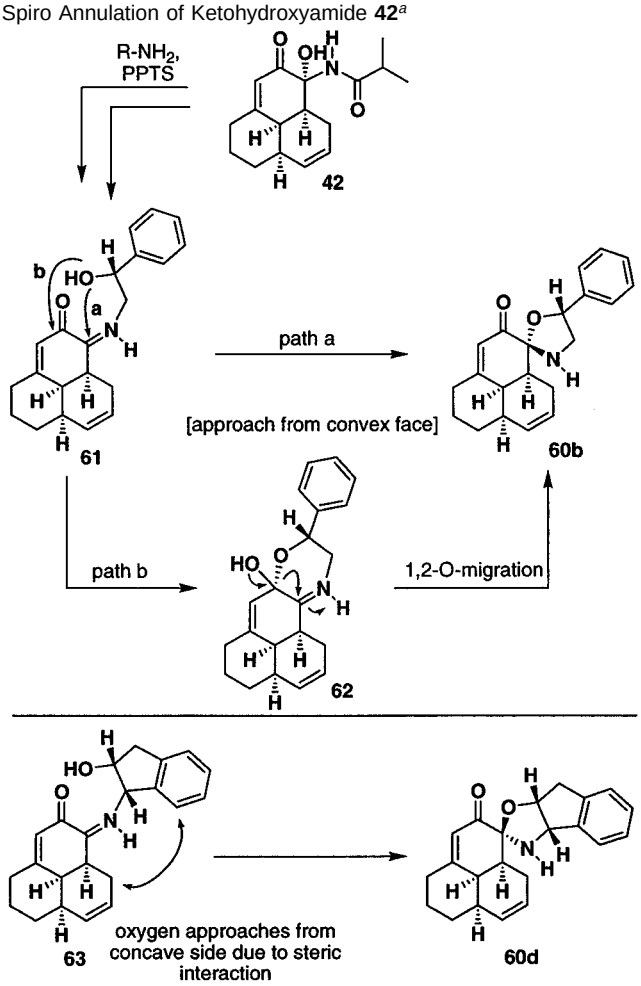
Scheme 13. Postulated Mechanism for the Cascade Leading to Polycyclic Systems **56** from Ketohydroxyamide **42** and Amino Acid Derivatives



We also found that the diamine- and amino acid-derived polycycles (Tables 6 and 7, respectively) could be easily dehydrogenated by heating in air at 100 °C in DMF or toluene (48 h), furnishing unusual polyaromatic systems such as **53d′** and **55c′** (Scheme 15).

6. Explorations of the Regioselective Epoxidation of Alkenes with DMP. Throughout our studies employing diene-anilides, we occasionally observed (see e.g., **14**, Scheme 4) the formation of varying amounts of epoxides as byproducts with the epoxide always residing at the internal olefin position.[22] Following this observation and to explore this interesting reaction further, we prepared the simple diene system **64** (Scheme 16). Interestingly, we found that only Ac-IBX rather than DMP was necessary to convert diene **64** to vinyl epoxide **65**. Thus, treatment of the diene **64** with 2 equiv of Ac-IBX (2.0 equiv of DMP/2.0 equiv of H_2O) for 48 h at room temperature led to an 82% yield of epoxide **65**. Verification that the new oxygen atom arose from Ac-IBX was obtained through labeling studies with Ac-IBX-(^{18}O). On the basis of this information, we proposed the tentative mechanism shown in Scheme 17 to account for oxygen transfer from Ac-IBX to dienes leading to vinyl epoxides. Thus, Ac-IBX might engage diene **A** leading to an intermediate of type **B**. Rearrangement and hydrolysis of intermediate **B** may then furnish epoxide **C**. Despite a number of successful epoxidations with this protocol,

Scheme 14. Mechanistic Considerations for the Stereocontrolled Spiro Annulation of Ketohydroxyamide **42**[a]



[a] Whereas the alcohol approaches from the convex side in **61**, steric interactions between the indane and tricycle force attack from the concave side in **63**.

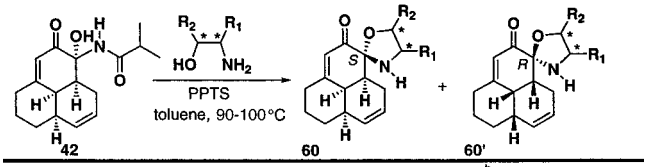
attempts to establish the generality of this transformation were disappointing and plagued with long reaction times and often unpredictable results, partly due to instability of the resulting epoxides. Further explorations along these lines are certainly warranted and may lead to improvements in this potentially highly chemoselective process.

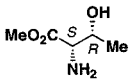
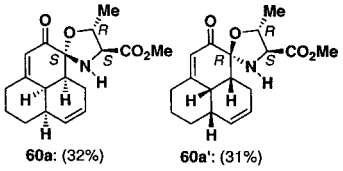
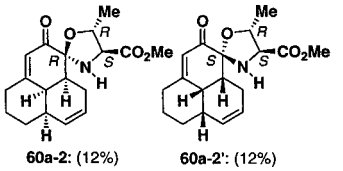
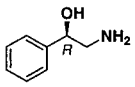
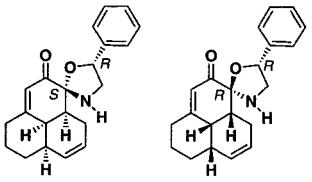
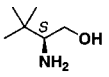
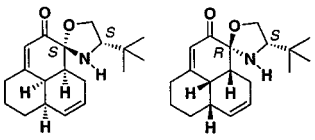
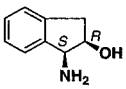
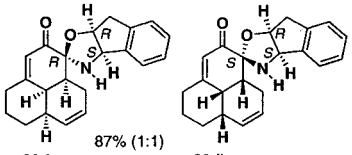
Conclusion

A new cascade oxidation process of anilide-type compounds to amide containing *p*-quinones initiated by DMP and traversing through *o*-imidoquinones is described within this paper. In addition to the detailed examination of the reaction, applications to the total synthesis of epoxyquinomycin B and BE-10988 have been performed demonstrating the power of the method in the synthesis of complex molecules. In related studies, an array of stable *o*-imidoquinones have been synthesized, and their reactivity in inter- and intramolecular Diels−Alder reactions has been investigated leading to new entries into novel heterocyclic compounds. These reactions have been extended to cascade sequences involving the unexplored ketohydroxyamide functionality and furnishing a variety of complex polycyclic systems whose structures resemble those of certain natural products and are believed to possess considerable potential in chemistry and biology of key building blocks, scaffolds, and protein ligands.

(22) Boesing, M.; Noeh, A.; Loose, I.; Krebs, B. *J. Am. Chem. Soc.* **1998**, *120*, 7252 and references therein.
(23) Wunderer, H. *Chem. Ber.* **1972**, *105*, 3479.
(24) Baudry, A.; Junino, A.; Richard, H. Eur. Pat. Appl. 1991, p 16 (CAN: 116:262282).
(25) Kelly, T. R.; Echavarren, A.; Behforouz, M. *J. Org. Chem.* **1983**, *48*, 3849.
(26) Heberer, H.; Schubert, H.; Matschiner, H.; Lukowczyk, B. *J. Prakt. Chem.* **1976**, *318*, 635.

Table 8. Synthesis of Complex Spiroheterocycles from Ketohydroxyamide **42** and 1,2-Hydroxyamines[a]



Entry	Amino-alcohol	Products (Yield)[b]
1		 **60a**: (32%) **60a'**: (31%)  **60a-2**: (12%) **60a-2'**: (12%)
2		 **60b**: (34%) **60b'**: (32%)
3		 **60c** **60c'** 85% (1:1)
4		 87% (1:1) **60d** **60d'**

[a] Reagents and conditions: amino alcohol (3.0 equiv), PPTS (0.2 equiv), toluene, 90−100 °C, 6−24 h. [b] Yields refer to chromatographically pure isolated materials.

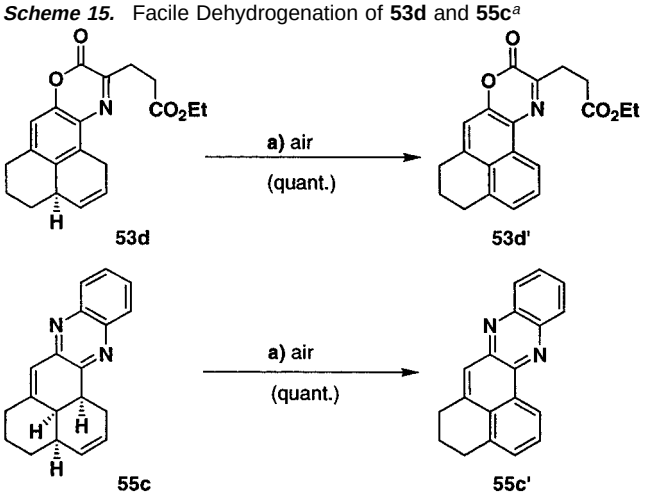
Finally, preliminary studies with DMP suggest its potential as a chemoselective reagent for the epoxidation of dienes and related systems.

Experimental Section

General Procedure for the Synthesis of *p*-Quinones Using DMP. A solution of DMP (85 mg, 0.2 mmol) and water (3.6 mg, 0.2 mmol) in CH_2Cl_2 (1 mL) was added to a solution of anilide (0.1 mmol) and DMP (85 mg, 0.2 mmol) in CH_2Cl_2 (1 mL). The reaction mixture was stirred at 25 °C for a period of time until TLC indicated the disappearance of the starting anilide (see Table 2 for reaction times). The solvent was then removed, and the residue was dissolved with Et_2O:EtOAc (10 mL), concentrated in vacuo, and purified by flash column chromatography (silica gel, hexanes:EtOAc, 10:1, 5:1) to afford the desired *p*-quinone.

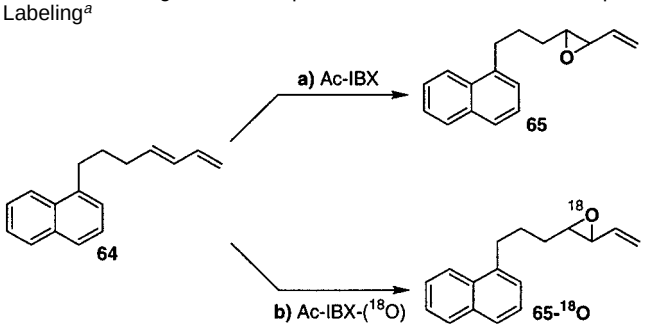
General Procedure for the Synthesis of *o*-Imidoquinones Using DMP. A solution of DMP (85 mg, 0.2 mmol) and water (3.6 mg, 0.2 mmol) in CH_2Cl_2 (1 mL) was added to a solution of anilide (0.1 mmol) and DMP (85 mg, 0.2 mmol) in CH_2Cl_2 (1 mL). The reaction mixture was stirred at 25 °C until TLC indicated the disappearance of the starting anilide (see Table 3 for reaction times). The solvent was then removed, and the residue was dissolved with Et_2O:EtOAc (10 mL), concentrated in vacuo, and purified by flash column chromatography (silica gel, hexanes:EtOAc, 10:1, 5:1) to afford the desired *o*-imidoquinone.

Scheme 15. Facile Dehydrogenation of **53d** and **55c**[a]



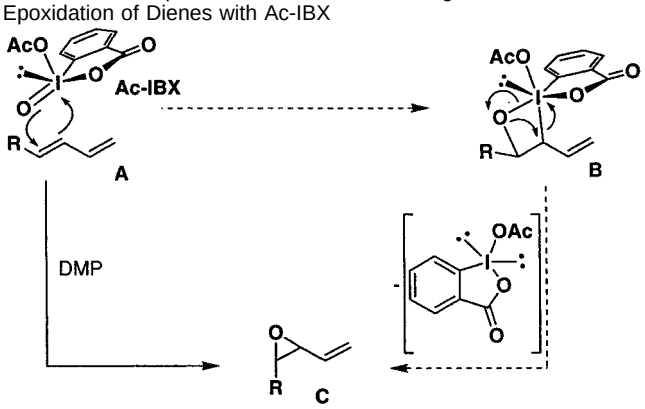
[a] Reagents and conditions: (a) toluene, air, 90 °C, 48 h, 100%.

Scheme 16. Regioselective Epoxidation with Ac-IBX and Isotope Labeling[a]



[a] Reagents and conditions: (a) DMP (2.0 equiv), H_2O (2.0 equiv), CH_2Cl_2, 25 °C, 48 h, 82%; (b) DMP (2.0 equiv), $H_2{}^{18}O$ (2.0 equiv), CH_2Cl_2, 25 °C, 72 h, 87%.

Scheme 17. Proposed Mechanism for the Regioselective Epoxidation of Dienes with Ac-IBX



General Procedure for the Synthesis of Phenoxazine-Type Compounds from *o*-Imidoquinones. To a solution of *o*-imidoquinone (0.1 mmol) in toluene (0.3 mL) was added the appropriate dienophile (see Table 4, 1.0 mmol), and the mixture was heated to reflux until TLC indicated complete consumption of the starting *o*-imidoquinone (usually 5−50 min). The reaction mixture was directly purified by flash column chromatography to afford the corresponding phenoxazine derivatives in high yield.

General Procedure for the Synthesis of Polycyclic Anilines 54a−d. A solution of ketohydroxyamide **42** (10.0 mg, 0.034 mmol), aniline (0.17 mmol), and PPTS (1.7 mg, 0.0068 mmol) in toluene under argon was heated at 90 °C for 3−24 h. After cooling to ambient temperature, the reaction mixture was directly purified by flash column chromatography (silica gel, hexanes:EtOAc, 4:1, 2:1) to give products **54a−d** (45−89%).

General Procedure for the Synthesis of Pyrazines 55a−d. A solution of ketohydroxyamide **42** (10.0 mg, 0.034 mmol), diamine (0.17 mmol), and PPTS (1.7 mg, 0.0068 mmol) in toluene (1.5 mL) was heated at 90 °C for 12 h. After cooling to room temperature, the reaction mixture was directly purified by flash column chromatography (silica gel, hexanes:EtOAc, 6:1, 4:1) to give the desired pyrazine **55a−d**.

General Method for the Synthesis of Compounds 56a−g. A solution of ketohydroxyamide **42** (10.0 mg, 0.034 mmol), amino acid methyl ester hydrogen chloride salt (0.10 mmol), $NaHCO_3$ (8.1 mg, 0.10 mmol), and PPTS (1.7 mg, 0.0068 mmol) in DMF (1.5 mL) under argon was heated at 90 °C for 6−24 h. After cooling to room temperature, the reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were washed with water (2 × 5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography (silica gel, hexanes:EtOAc) to afford the desired products **56a−g** (39−80%) and side-product **53** (5−31%).

General Procedure for the Synthesis of Spirocycles 60a−d. A solution of ketohydroxyamide **42** (10.0 mg, 0.034 mmol), amino alcohol (0.17 mmol), and PPTS (1.7 mg, 0.0068 mmol) in toluene (1.5 mL) was heated at 90−100 °C for 6−24 h. After cooling to ambient temperature, the reaction mixture was directly purified by flash column chromatography (silica gel, hexanes:EtOAc) to give the products (66−87%).

Acknowledgment. We thank Drs. D. H. Huang, G. Siuzdak, and R. Chadha for NMR spectroscopic, mass spectrometric, and X-ray crystallographic assistance, respectively. This work was financially supported by the National Institutes of Health (U.S.), The Skaggs Institute for Chemical Biology, a predoctoral fellowship from the National Science Foundation (to P.S.B.), and grants from Abbott, Amgen, ArrayBiopharma, Boehringer Ingelheim, DuPont, Glaxo, Hoffmann-La Roche, Merck, Pfizer, and Schering Plough.

Supporting Information Available: Experimental procedures and compound characterization (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA012125P