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Synthesis of Amino-1,4-benzoquinones and Their Use in Diels−Alder Approaches to the Aminonaphthoquinone Antibiotics

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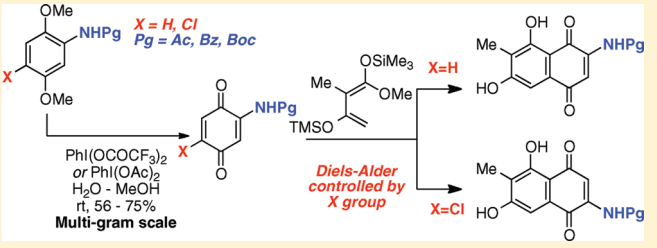
Supporting Information

ABSTRACT: A new protocol for the synthesis of protected amino-1,4-benzoquinones by oxidation of the corresponding 2,5-dimethoxyaniline derivatives using $PhI(OAc)_2$ or $PhI(OCOCF_3)_2$ in water containing 2.5% methanol is reported. The process represents an improvement over previously reported methods, both in terms of yield and number of steps, and in the range of nitrogen protecting groups that it tolerates. A number of novel aminobenzoquinones were prepared and subsequently used as dienophiles in Diels−Alder reactions to form building blocks for the synthesis of the aminonaphthoquinone antibiotics such as salinisporamycin.



INTRODUCTION

Aminonaphthoquinones are found at the core of a number of commercially and biologically important natural products and their derivatives (Figure 1).[1] Rifabutin, a semisynthetic derivative of rifamycin S (**1**), is a current frontline treatment for tuberculosis,[2,3] and other members of this family show various biological activities. The recently isolated natural product salinisporamycin (**2**) also shows promising antibacterial and anticancer properties.[4]

Our ongoing interest in the synthesis of naturally occurring quinones,[5−9] and in particular the Cdc25A inhibitor **3**,[10] prompted consideration of a range of routes to such aminonaphthoquinones. One particularly attractive approach is the Diels−Alder reaction of electron rich dienes with protected aminobenzoquinones (Scheme 1A) because it reduces the need for excessive classical manipulation of the aromatic naphthalene ring system, as found in many older syntheses of natural products of this type. However, this is a surprisingly underused tactic, possibly because preparation of the quinone dienophile is not straightforward due to the fact that oxidation of electron rich anilines and anilides is often plagued by side reactions and only tolerates a very narrow range of protecting groups, which can complicate synthetic operations after the Diels−Alder reaction. Also, as far as we aware, the regiochemical outcome of Diels−Alder reactions involving aminobenzoquinones has never been systematically studied despite the fact that control of regiochemistry would be essential if the reaction were to be used in synthesis. Hence, there is but one example of this reaction being applied in natural product synthesis, in Kelly and co-workers' approach to the tricyclic core of the rifamycins.[11] In this synthesis of the rifamycin core **7**, the Diels−Alder reaction between the electron rich diene **4** and 6-halo-2-acetamidobenzoquinones **5** and **6** gave a single naphthoquinone regioisomer (Scheme 1B). Acidic workup assisted the loss of methanol and HX to give the fully aromatic product in good yield. The role of the halogen atom was thought to be crucial in directing the regiochemical course of the cycloaddition in addition to facilitating aromatization.

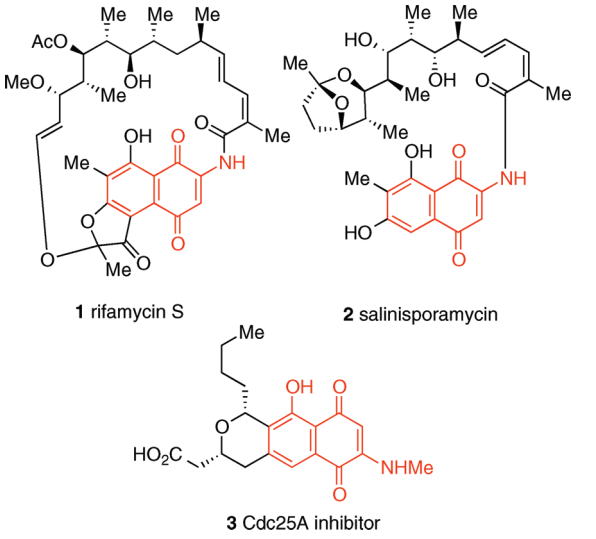


Figure 1. Some naturally occurring aminonaphthoquinones.

Interestingly, more than two decades later, a report from the Nicolaou laboratory showed that the simple unhalogenated 2-acetamidobenzoquinone **9** reacted with the Danishefsky diene **8** to give, after aerial oxidation, a single product, the naphthoquinone **10** (Scheme 1C).[12] This outcome was rationalized by the observation that the product **10** simply resulted from attack of the most nucleophilic end of the diene with the more

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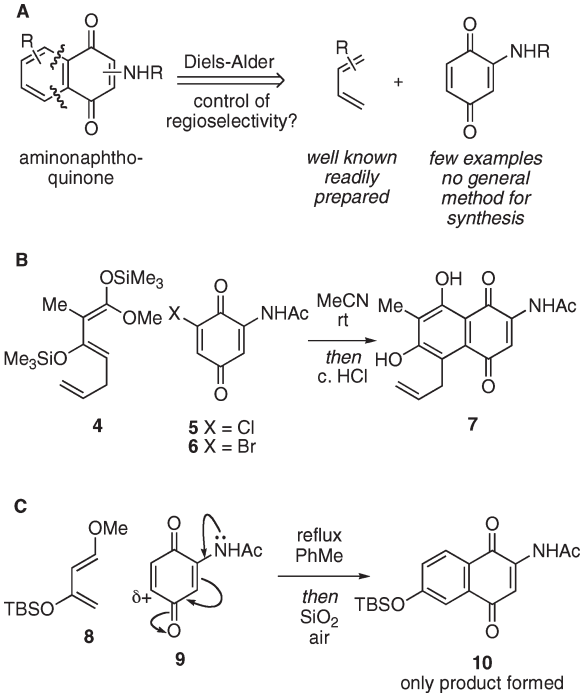
Scheme 1. (A) The Diels–Alder Disconnection of Aminonaphthoquinones, (B) Use of 6-Halo-2-acetamidobenzoquinones, (C) Use of 2-Acetamidobenzoquinone



electrophilic position on the dienophile (i.e., the position 1,4 to the carbonyl not deactivated by the amide-type resonance shown in Scheme 1C). This result was significant as it meant that the "directing" halogen thought to be essential by Kelly and coworkers could be dispensed with, as it was not required to control the regiochemical outcome of the Diels–Alder reaction, nor to facilitate the aromatization step. We therefore set out to explore the use of simple aminobenzoquinones such as **9** in approaches to naturally occurring aminonaphthoquinones and also to compare the reactivity of 5-halo-2-aminobenzoquinones in Diels–Alder reactions with their 6-halo isomers (cf. Scheme 1B). However, at the outset, there was no general method suitable for the preparation of the range of benzoquinones required for our studies, and therefore this became our initial priority.

RESULTS AND DISCUSSION

Few aminobenzoquinones are reported in the literature, the most common being 2-acetamido-1,4-benzoquinone (**9**). There is a single report of the direct oxidation of 2,5-dimethoxyacetanilide into the corresponding quinone **9**,[13] but the method uses 8 equiv of cerium(IV) ammonium nitrate (CAN) under dilute conditions and therefore would not be suitable for preparing larger amounts of material. Syntheses that start from such compounds have therefore relied on variations of a two-step protocol whereby dimethoxyacetanilide is first demethylated using boron tribromide and the resulting hydroquinone is then oxidized.[14] Although yields over two steps are often reasonable, the choice of aniline protecting group is limited to the fairly narrow subset that is stable to strong Lewis acids, and this very property may complicate deprotection later in the synthesis. Oxidation to the quinone monoketal under anhydrous conditions, followed by a separate acid hydrolysis step, has also been

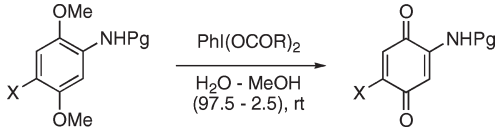
Table 1. Oxidation of 2,5-Dimethoxyaniline Derivatives to 2-Aminobenzoquinones[a]

entry	X	Pg	R	quinone	yield/%
1	H	Ac	Me	**9**	73[b]
2	H	Boc	Me	**11**	56
3	H	Bz	Me	**12**	75
4	Cl	Ac	CF_3	**13**	68
5	Br	Ac	CF_3	**14**	53
6	Cl	Boc	CF_3	**15**	66
7	Cl	Bz	CF_3	**16**	73

[a] All reactions performed on protected aniline (1 mmol) using PhI(OAc)$_2$ (2.0–2.5 equiv), H_2O–MeOH, rt, 2 h, or PhI(OCOCF$_3$)$_2$ (1.2–1.5 equiv), H_2O–MeOH, rt, 0.5–2 h. [b] Essentially identical yield obtained on 10 g (50 mmol) scale.

reported, although again only for acetamides.[15] The shortest, if not the most practical, route to this class of compounds was published in 2002 when the Nicolaou group reported the remarkable oxidation of acetanilide into acetamidobenzoquinone in a single step, using the Dess–Martin peridiodinane in dichloromethane–water.[16–18] A yield of 43% was reported for this step, which is impressive for the transformation accomplished. However, 4 equiv of the oxidant were required and commercial Dess–Martin periodinane is expensive. Furthermore, when we attempted to apply these conditions to a larger range of substrates, we found the reaction to be very sensitive to the nature of the nitrogen protecting group, often resulting in much lower yields. We therefore sought to develop a more general and practical procedure for the preparation of these compounds.

In 2001, Kita and co-workers reported an efficient method for conversion of 1,2,4-trimethoxybenzene into 2-methoxy-1,4-benzoquinone using 1.2 equiv of inexpensive PhI(OAc)$_2$ as oxidant in water containing a small amount of methanol.[19] It is worth noting that this transformation is difficult using conventional methods; CAN gave only a very low yield of dimerized products and AgO–HNO_3 only caused degradation. Given the success of this method in oxidizing such an electron rich system, we applied these conditions to 2,5-dimethoxacetanilide. After optimization of stoichiometry and concentration, we were able to obtain the corresponding quinone **9** in a good yield simply by stirring 2,5-dimethoxacetanilide with 2 equiv of PhI(OAc)$_2$ in water–methanol (97.5–2.5) in an open flask for two hours. With this result in hand, we applied the same conditions to a range of protected anilines to test the scope of this transformation (Table 1). Thus the Boc- and benzoyl-protected aminobenzoquinones **11** and **12** were similarly prepared in good yield (Table 1).



In addition to the protected aminoquinones **9**, **11**, and **12**, a number of halogenated quinones were also prepared by oxidation of the corresponding 2,5-dimethoxyaniline derivatives. These substrates were easily prepared by protection of commercially availably 4-chloro-2,5-dimethoxyaniline or by bromination of 2,5-dimethoxyacetanilide. It should be noted that preparation of haloaminobenzoquinones is generally somewhat easier than the preparation of the corresponding unhalogenated quinones because the halogen atom serves to block the main site of

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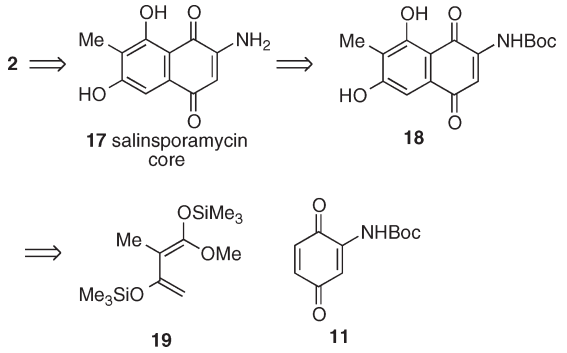
Scheme 2. A Diels–Alder Approach to the Aminonaphthoquinone Core of Salinisporamycin

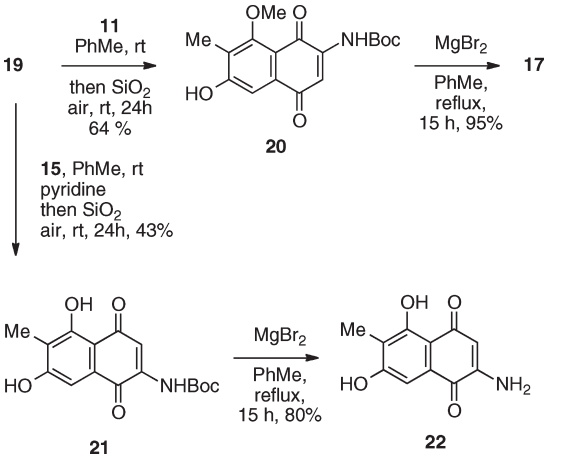


dimerization in these molecules and reduce side reactions. Interestingly, it was found that that $PhI(OCOCF_3)_2$ was a much better oxidant for the preparation of haloquinones, giving higher yields and shorter reaction times than $PhI(OAc)_2$ in all cases. In contrast, $PhI(OAc)_2$ remains a superior oxidant for unhalogenated compounds. It is also noted that there is a requirement for both an electron withdrawing *N*-protecting group and an NH bond. 2,5-Dimethoxyanilines bearing NMeBoc or NMeBz groups are inert to the above oxidizing conditions, even after several days. Similarly, a number of di-Boc-protected 2,5-dimethoxyanilines were prepared and also failed to undergo the desired oxidation. This observation is consistent with a mechanism in which the first step is formation of a covalent bond to the oxidant, through the amide oxygen, followed by generation of an *ortho*-azaquinone, as has been proposed for similar systems.[12,20]

With a range of protected aminobenzoquinones in hand, we investigated their utility in the synthesis of building blocks of naphthoquinone natural products, starting with consideration of the recently isolated antibiotic salinosporamycin (Scheme 2).[4] We envisaged that the aminonaphthoquinone core **17** of this natural product could arise from the Diels–Alder reaction between known diene **19**[21] and a suitably protected aminobenzoquinone. On the basis of the precedent discussed above it, was assumed that in the absence of a halogen, the regioselectivity observed in Scheme 1C would prevail.

Thus, diene **19** was reacted with Boc-protected aminobenzoquinone **11** in toluene in room temperature to give, after aromatization and aerial oxidation, naphthoquinone **20** (Scheme 3). Disappointingly, elimination of methanol had not occurred during the aromatization, and thus a methoxy group was present in place of the expected hydroxyl at the 8-position. Addition of bases (pyridine, NEt_3, *i*-Pr_2NEt) did not promote the desired elimination nor did the strongly acidic workup described by Kelly and co-workers in their studies toward the rifamycin core.[11] Interestingly, use of 6-chloro-2-*tert*-butoxycarbonylamino-1,4-benzoquinone (prepared in low yield from *tert*-butyl 3,5-dichloro-2-hydroxyphenyl carbamate) did give predominantly the corresponding 6,8-dihydroxynaphthoquinone **18** along with small amounts of **20**, but we wished to avoid the extra steps and poor yields associated with the preparation of this dienophile. Importantly, although the presence of the methoxy group in naphthoquinone **20** was unplanned, it proved inconsequential because it was readily cleaved along with the Boc group in a single step. Thus heating compound **20** with excess $MgBr_2$ under reflux in toluene gave the desired core naphthoquinone **17**, the core chromophore of salinisporamycin, in excellent yield (Scheme 3).

Scheme 3. Synthesis of the Aminonaphthoquinone Core 17 of Salinisporamycin and its Regioisomer 22



The regiochemical outcome of the Diels–Alder reaction could not be unambiguously determined by NMR spectroscopy, and unfortunately neither of the naphthoquinones **17** or **20** gave crystals suitable for X-ray analysis. Therefore, to assist in confirming the structure of **17**, we sought to prepare the 3-amino regioisomer **22** for comparison. In the 1980s, Brassard and coworkers showed that regioselectivity in the Diels–Alder reaction of benzoquinone derivatives could be controlled by the position of a halogen on the quinone dienophile,[22] the more nucleophilic end of the diene reacting with the unhalogenated position on the benzoquinone. However, none of the quinones used in this study displayed the strong regiochemical preference exhibited by our 2-amino-1,4-benzoquinones in the absence of a halogen. We were therefore curious to see if blocking the position *para* to the nitrogen using a halogen atom could overturn the observed regioselectivity of the Diels–Alder reaction that gave exclusively naphthoquinone **20** and hence allow access to the regioisomeric product. Thus, when the reaction was repeated using the 5-chloro-2-aminobenzoquinone derivative **15** as the dienophile, a single regioisomeric product **21** was again obtained which, after deprotection gave the aminonaphthoquinone **22**. The ^{13}C NMR spectra of the two regioisomers **17** and **22** were clearly different, although their ^1H NMR spectra were very similar, except the *peri* hydroxyl protons. In the undesired 3-amino isomer **22**, the peak corresponding to this proton is observed at 13.71 ppm, due to the strong hydrogen bond with the *peri* carbonyl, the Lewis basicity of which is increased by donation from the nitrogen lone pair (this carbonyl can be regarded as a vinylogous amide). In the desired 2-amino regioisomer **17**, where this mesomeric donation is absent, this proton is observed at 12.22 ppm. Thus, by having access to both regioisomers, the regiochemistry can be inferred from the dramatic difference in the chemical shift of this proton in the ^1H NMR spectra.

Thus we have confirmed that the natural regiochemical preference of 2-aminobenzoquinones in Diels–Alder reactions with appropriate electron rich dienes results in formation of a 2-aminonaphthoquinone derivative (cf. Scheme 1C) and that the presence of a 6-halogen substituent in the dienophile (cf. Scheme 1B) is *not* required to achieve this regiospecificity. On the other hand, this Diels–Alder regiochemistry can be completely overridden by the introduction of a 5-halogen substituent into the dienophile.

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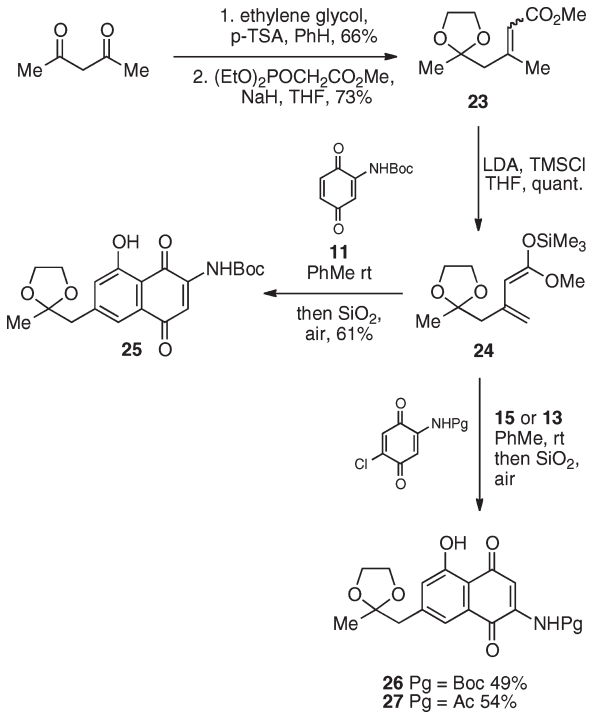
Scheme 4. Diels–Alder Adducts for the Synthesis of the Aminonaphthoquinone Core of the Cdc25A Inhibitor 3



To further demonstrate the ability of a halogen atom to control the regiochemical outcome of quinone Diels–Alder reactions, we investigated application of this methodology to the synthesis of a 3-aminonaphthoquinone precursor to the Cdc25A inhibitor **3**, previously inaccessible by known Diels–Alder chemistry. The diene required for such an approach has to contain suitable masked functionality to develop into the final pyran ring later in the synthesis, and therefore the new dioxolane containing diene **24** was prepared as shown in Scheme 4. Following monoprotection of acetylacetone as its mono ketal,[23] olefination gave **23** as an inconsequential mixture of geometric isomers, and treatment of this ester with LDA and TMSCl gave the diene **24**, the reaction being readily conducted on a 20 g scale. Reaction of this diene with the Boc-protected aminobenzoquinone **11** gave the expected 2-aminonaphthoquinone derivative **25**, with the incorrect regiochemistry for a synthesis of **3**. However, as planned, the introduction of a halogen into the quinone dienophile reversed the regioselectivity of the Diels–Alder reaction. Thus reaction of diene **24** with the chlorobenzoquinone **15** gave the regioisomeric 3-aminonaphthoquinone derivative **26** (Scheme 4), the structure of which was confirmed by X-ray crystallography (see Supporting Information), and is a potential precursor to the naturally occurring pyranonaphthoquinone **3**. Likewise, 2-acetamido-5-chlorobenzoquinone **13** gave regioselectively the corresponding 3-acetamidonaphthoquinone **27** (Scheme 4). Although the structure of naphthoquinone **26** was confirmed unambiguously using X-ray crystallography, there is again a very large difference in the chemical shift of the 8-hydroxy proton in the otherwise very similar ^{1}H NMR spectra of the two regioisomers **25** (δ11.38) and **26** (δ12.32), which allows their rapid differentiation.

The origin of the ability of halogen atoms to direct Diels–Alder reactions of benzoquinone dienophiles, although known for more than two decades, remains obscure. Ab initio calculations performed by Grunwell and co-workers in their investigation of conjugate addition of transoid dienes to 2- and 3-bromo-5-hydroxy-1,4-naphthoquinones showed essentially no difference in LUMO coefficients for the C-2 and C-3 atoms for either system despite the fact that a very strong preference for addition to the unhalogenated carbon was observed.[24] Our own preliminary calculations on **13** again indicate only an insignificant difference between the LUMO coefficients of C-5 and C-6 (and also the coefficients of these atoms in **9**) that cannot explain the extremely high levels of regioselectivity observed.

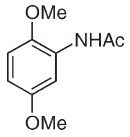
CONCLUSION

In conclusion, we have demonstrated that iodine(III) reagents are uniquely suitable for the oxidation of a range of protected 2,5-dimethoxyanilines to the corresponding 2-aminobenzoquinones. The method is convenient, rapid, operationally simple, uses inexpensive organic oxidants, and is amenable to use on multigram scale. A range of nitrogen protecting groups are tolerated giving access to a number of novel aminobenzoquinones that were subsequently used in highly regioselective Diels–Alder reactions to give aminonaphthoquinones. This method for the preparation of 2-aminonaphthoquinones such as **17** also obviates the problem of introducing the amino functionality into an existing quinone, classically performed by displacement of a suitable leaving group with ammonia in a sealed tube. Importantly, the regiochemical outcome of the Diels–Alder reaction is completely controlled by the presence, or absence, of a 5-halogen substituent on the 2-aminobenzoquinone dienophile, hence giving selective access to 2- or 3-aminonaphthoquinones as building blocks for the synthesis of the aminonaphthoquinone antibiotics.

EXPERIMENTAL SECTION

General Experimental Details. Commercially available reagents were used throughout without purification unless otherwise stated. Anhydrous solvents were used as supplied unless otherwise stated. Tetrahydrofuran was distilled from sodium benzophenone ketyl under nitrogen atmosphere. Dichloromethane was distilled from calcium hydride under a nitrogen atmosphere. Light petroleum refers to the fraction with bp 40–60 °C. Ether refers to diethyl ether. Reactions were routinely carried out under a nitrogen or argon atmosphere. Analytical thin layer chromatography was carried out on aluminum backed plates coated with silica gel and visualized under UV light at 254 and/or 360 nm and/or potassium permanganate or ethanolic vanillin dip. Chromatography was carried out on silica gel. Fully characterized compounds were chromatographically homogeneous. Infrared spectra were recorded in the range 4000–600 cm^{-1} as solutions in chloroform or as a solid in attenuated total reflectance (ATR) mode. NMR spectra were recorded NMR spectra were recorded at the frequencies stated. Chemical shifts are quoted in ppm and J values in Hz. Chemical shift values are referenced against residual proton in the deuterated solvents. In the ^{13}C NMR spectra, signals corresponding to CH, CH_2, or CH_3 are assigned from DEPT-90 and -135 spectra; all others are quaternary C. High and low resolution mass spectra were recorded on a time-of-flight spectrometer.

N-(2,5-Dimethoxyphenyl)acetamide



Acetyl chloride (11.13 mL, 156.68 mmol) was added to a solution of 2,5-dimethoxyaniline (20.0 g, 130.57 mmol) and triethylamine

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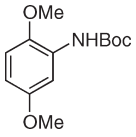
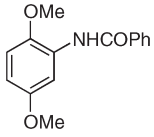
(21.75 mL, 156.68 mmol) in dichloromethane (500 mL) at 0 °C. The resulting solution was warmed to rt over 30 min and then washed with water (3 × 100 mL), saturated aqueous sodium hydrogen carbonate solution (200 mL) and brine (200 mL), and then dried ($MgSO_4$) and concentrated to give the title compound as a brown crystalline solid (24.19 g, 95%) that did not require further purification; mp 88−89 °C (lit.,[25] mp 91−92 °C). (Found: C, 61.3; H, 6.7; N, 7.2%. $C_{10}H_{13}NO_3$ requires C, 61.5; H, 6.7; N, 7.2%.). (Found: [M + Na^+], 218.0784. $C_{10}H_{13}NNaO_3^+$ requires 218.0788.) ν_{max} ($CHCl_3$)/cm^{-1} 3426, 3011, 1688, 1601, 1531, 1479, 1425, 1240, 1046. δ_H (400 MHz; $CDCl_3$) 8.12 (1 H, d, *J* 3.2), 7.81 (1 H, s), 6.80 (1 H, d, *J* 9.0), 6.60 (1 H, dd, *J* 3.2, 9.0), 3.86 (3 H, s), 3.80 (3 H, s) 2.22 (3 H, s). δ_C (100 MHz; $CDCl_3$) 168.2 (C), 153.9 (C), 141.8 (C), 128.4 (C), 110.6 (C), 108.3 (CH), 106.0 (CH), 56.2 (Me), 55.8 (Me), 25.0 (Me).

tert-Butyl 2,5-Dimethoxyphenylcarbamate



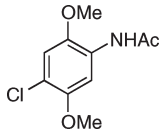
Di-*tert*-butyl dicarbonate (8.55 g, 39.2 mmol) was added to 2,5-dimethoxyaniline (5.0 g, 32.6 mmol) in THF (20 mL), and the resulting solution was heated to reflux and stirred for 16 h and then cooled to rt and concentrated. The residue was purified by flash column chromatography on silica gel eluting with ethyl acetate−light petroleum (1:20) to give the title compound as a colorless oil (7.51 g, 91%). (Found: C, 61.5; H, 7.6; N, 5.3%. $C_{13}H_{19}NO_4$ requires C, 61.6; H, 7.6; N, 5.5%.) (Found: [M + Na^+], 276.1211. $C_{13}H_{19}NNaO_4^+$ requires 276.1206.) ν_{max} ($CHCl_3$)/cm^{-1} 3429, 3011, 2982, 1723, 1603, 1529, 1480, 1239, 1157, 1051. δ_H (400 MHz; $CDCl_3$) 7.83 (1 H, br s), 7.12 (1 H, br), 6.78 (1 H, d, *J* 8.9), 6.51 (1 H, dd, *J* 3.0, 8.9) 3.84 (3 H, s), 3.80 (3 H, s), 1.55 (9 H, s). δ_C (100 MHz; $CDCl_3$) 154.1 (C), 152.6 (C), 141.7 (C), 128.9 (C), 110.8 (CH), 107.1 (CH), 104.3 (CH), 80.3 (C), 56.2 (Me), 55.8 (Me), 28.4 (Me).

N-(2,5-Dimethoxyphenyl)benzamide



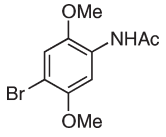
Benzoyl chloride (2.74 mL, 23.50 mmol) was added dropwise to 2,5-dimethoxyaniline (3.0 g, 19.58 mmol) and triethylamine (3.26 mL, 23.50 mmol) in dichloromethane (40 mL) at 0 °C. The brown solution was stirred for 1 h, warming to rt, then washed with saturated aqueous sodium hydrogen carbonate solution (50 mL), hydrochloric acid (1 M; 20 mL), and water (50 mL). The organic phase was dried (Na_2SO_4) and concentrated to give a gray solid that was purified by flash column chromatography on silica gel, eluting with ethyl acetate−light petroleum (1:9−1:3) to give the title compound as off-white solid (4.60 g, 92%); mp 84−85 °C (lit.,[26] mp 82−84 °C). (Found: C, 69.8; H, 5.9; N, 5.7%. $C_{15}H_{15}NO_3$ requires C, 70.0; H, 5.9; N, 5.4%.) (Found: [M + Na^+], 280.0950. $C_{15}H_{15}NNaO_3^+$ requires 280.0944.) ν_{max} ($CHCl_3$)/cm^{-1} 3426, 3011, 2888, 1673, 1602, 1531, 1478, 1426, 1045. δ_H (400 MHz; $CDCl_3$) 8.61 (1 H, br s), 8.32 (1 H, d, *J* 3.0), 7.93−7.91 (2 H, m), 7.58−7.51 (3 H, m), 6.86 (1 H, d, *J* 8.8), 6.65 (1 H, dd, *J* 3.0, 8.8), 3.92 (3 H, s), 3.85 (3 H, s). δ_C (100 MHz; $CDCl_3$) 165.2 (C), 154.0 (C), 142.4 (C), 135.2 (C), 131.8 (CH), 128.9 (CH), 128.5 (C), 127.0 (CH), 110.8 (CH), 108.9 (CH), 105.9 (CH), 56.4 (Me), 55.9 (Me).

N-(4-Chloro-2,5-dimethoxyphenyl)acetamide



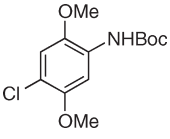
Acetyl chloride (0.91 mL, 12.79 mmol) was added to a solution of 4-chloro-2,5-dimethoxyaniline (2.0 g, 10.66 mmol) and triethylamine (1.78 mL, 12.79 mmol) in dichloromethane (50 mL) at 0 °C. The brown solution was warmed to rt over 30 min and poured into water (100 mL). The layers were separated, and the aqueous phase was extracted with dichloromethane (3 × 50 mL). The combined extracts were washed with water (100 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated to a brown crystalline solid (2.31 g, 95%) that did not require further purification; mp 116−117 °C (lit.,[27] mp 118 °C). (Found: C, 52.2; H, 5.3; N, 5.9%. $C_{10}H_{12}ClNO_3$ requires C, 52.3; H, 5.3; N, 6.1%.) (Found: [M + Na^+], 252.0402. $C_{10}H_{12}{}^{35}ClNNaO_3^+$ requires 252.0398.) ν_{max} ($CHCl_3$)/cm^{-1} 3426, 3011, 1689, 1597, 1521, 1483, 1465, 1450, 1401, 1244, 1038. δ_H (300 MHz; $CDCl_3$) 9.25 (1 H, s), 7.75 (1 H, br s), 6.89 (1 H, s), 3.89 (3 H, s), 3.85 (3 H, s), 2.21 (3 H, s). δ_C (75 MHz; $CDCl_3$) 168.3 (C), 149.1 (C), 141.6 (C), 127.1 (C), 115.5 (C), 112.2 (CH), 104.8 (CH), 56.7 (Me), 56.3 (Me), 25.0 (Me).

N-(4-Bromo-2,5-dimethoxyphenyl)acetamide



Bromine (0.55 mL, 10.76 mmol) in dichloromethane (5 mL) was added dropwise to 2,5-dimethoxyacetanilide (2.0 g, 10.24 mmol) in dichloromethane (50 mL) at rt. The brown solution was stirred for 6 h and then washed with saturated aqueous sodium thiosulfate solution (50 mL), saturated aqueous sodium bicarbonate solution (50 mL), water (50 mL), and brine (50 mL). The organic phase was dried (Na_2SO_4) and concentrated to give the title compound as a crystalline pale-brown solid (2.80 g, 100%) that did not require further purification; mp 110−111 °C (lit.,[28] mp 123 °C). (Found: [M + Na^+], 295.9899. $C_{10}H_{12}{}^{79}BrNNaO_3^+$ requires 295.9893.) ν_{max} ($CHCl_3$)/cm^{-1} 3425, 3008, 1689, 1518, 1397, 1243, 1036. δ_H (400 MHz; $CDCl_3$) 8.23 (1 H, s), 7.77 (1 H, br s), 7.04 (1 H, s), 3.87 (3 H, s), 3.84 (3 H, s), 2.21 (3 H, s). δ_C (75 MHz; $CDCl_3$) 168.3 (C), 150.1 (C), 141.9 (C), 127.7 (C), 114.9 (CH), 104.6 (CH), 103.8 (C), 56.8 (Me), 56.4 (Me), 25.0 (Me). ^{13}C Spectrum matches that reported (^1H not reported).[13]

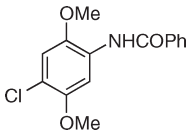
tert-Butyl 4-Chloro-2,5-dimethoxyphenylcarbamate



Di-*tert*-butyl dicarbonate (4.19 g, 19.19 mmol) was added to 4-chloro-2,5-dimethoxyaniline (3.0 g, 15.99 mmol) in THF (15 mL), and the resulting solution was heated to reflux and stirred for 16 h and then cooled to rt and concentrated. The residue was purified by flash column chromatography on silica gel eluting with ethyl acetate−light petroleum (1:9) to give the title compound as an off-white crystalline solid (3.87 g, 94%); mp 101−102 °C. (Found: C, 54.1; H, 6.3; N, 4.8%. $C_{13}H_{18}ClNO_4$ requires C, 54.3; H, 6.3; N, 4.9%). (Found: [M + Na^+], 310.0825. $C_{13}H_{18}{}^{35}ClNNaO_4^+$ requires 310.0817.) ν_{max} ($CHCl_3$)/cm^{-1} 3429, 3010, 1721, 1598, 1521, 1481, 1403, 1369, 1241, 1154, 1069, 1039. δ_H (400 MHz; $CDCl_3$) 7.83 (1 H, br s), 7.36 (1 H, s), 6.88

(1 H, s), 3.92 (3 H, s), 3.85 (3 H, s), 1.55 (9 H, s). δ_C (100 MHz; $CDCl_3$) 152.5 (C), 149.3 (C), 141.5 (C), 127.6 (C), 114.1 (C), 112.3 (CH), 103.3 (CH), 80.7 (C), 56.7 (Me), 56.4 (Me), 28.1 (Me).

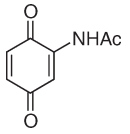
N-(4-Chloro-2,5-dimethoxyphenyl)benzamide



Benzoyl chloride (2.23 mL, 19.19 mmol) was added dropwise to 4-chloro-2,5-dimethoxyaniline (3.0 g, 15.99 mmol) and triethylamine (2.7 mL, 19.19 mmol) in dichloromethane (50 mL) at 0 °C. The brown solution was stirred for 1 h, warming to rt, then washed with saturated aqueous sodium hydrogen carbonate solution (50 mL), hydrochloric acid (1 M; 20 mL), and water (50 mL). The organic phase was dried (Na_2SO_4) and concentrated to give the title compound as a gray solid (4.06 g, 87%) that did not require further purification; mp 97−98 °C. (Found: C, 61.7; H, 5.0; N, 4.8%. $C_{15}H_{14}ClNO_3$ requires C, 61.8; H, 4.8; N, 4.8%.) (Found: [M + Na^+], 314.0550. $C_{15}H_{14}{}^{35}ClNNaO_3{}^+$ requires 314.0554.) ν_{max} ($CHCl_3$)/cm^{-1} 3427, 3011, 1673, 1597, 1522, 1480, 1402, 1261, 1038. δ_H (400 MHz; $CDCl_3$) 8.56 (1 H, br s), 8.54 (1 H, s), 7.92−7.89 (2 H, m), 7.60−7.51 (3 H, m), 6.97 (1 H, s). δ_C (100 MHz; $CDCl_3$) 165.3 (C), 149.2 (C), 142.2 (C), 134.8 (C), 132.0 (CH), 128.9 (CH), 127.1 (C), 127.0 (CH), 115.9 (C), 112.3 (CH), 104.9 (CH), 56.8 (Me), 56.5 (Me).

Quinones. *General Procedure for Oxidation.* Diacetoxyiodobenzene or bis(trifluoroacetoxy)iodobenzene (1.2−2.5 mmol) was added to a stirred suspension of the protected dimethoxyaniline derivative (1 mmol) in water (5 mL) and MeOH (125 μL). The resulting suspension was stirred for the indicated time and then diluted with water (15 mL) and extracted with dichloromethane (3 × 10 mL). The combined extracts were washed with water, dried (Na_2SO_4), and concentrated, and the residue was purified by flash column chromatography to give the protected aminobenzoquinone.

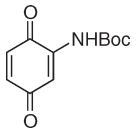
*2-Acetamido-1,4-benzoquinone (**9**)*



Diacetoxyiodobenzene (483 mg, 1.5 mmol) was added to 2,5-dimethoxyacetanilide (195 mg, 1.0 mmol) in water (5 mL)−MeOH (125 μL). The resulting suspension was stirred for 2 h then diluted with water (15 mL) and extracted with dichloromethane (3 × 10 mL). The combined extracts were washed with water (30 mL), saturated aqueous sodium hydrogen carbonate solution (30 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate−toluene (1: 2) to give the title compound as a golden-yellow solid (121 mg, 73%); mp 145−146 °C, (lit.,[29] mp 146−148 °C). (Found: C, 58.1; H, 4.3; N, 8.4%. $C_8H_7NO_3$ requires C, 58.2; H, 4.3; N, 8.5%.) (Found: [M + Na^+], 188.0318. $C_8H_7NNaO_3{}^+$ requires 188.0318.) ν_{max} ($CHCl_3$)/cm^{-1} 3375, 3011, 1718, 1673, 1659, 1578, 1506, 1324, 1096. δ_H (400 MHz; acetone-d_6) 8.92 (1 H, br s), 7.51 (1 H, d, J 2.3), 6.88 (1 H, d, J 10.0), 6.76 (1 H, dd, J 10.0, 2.3), 2.29 (3 H, s). δ_C (100 MHz; acetone-d_6) 188.1 (C), 182.6 (C), 170.3 (C), 139.5 (C), 137.5 (CH), 133.8 (CH), 113.8 (C), 23.8 (Me). NMR data matches those reported.[14]

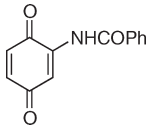
This reaction was also performed on a much larger scale (10.0 g, 51.2 mmol), giving essentially the same yield of **9** (6.0 g, 71%).

*2-tert-Butoxycarbonylamino-1,4-benzoquinone (**11**)*



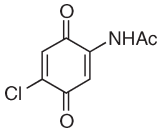
Diacetoxyiodobenzene (805 mg, 2.5 mmol) was added to *tert*-butyl 2,5-dimethoxyphenylcarbamate (253 mg, 1.0 mmol) in water (5 mL)−MeOH (125 μL). The resulting suspension was stirred for 2 h and then diluted with water (15 mL) and extracted with dichloromethane (3 × 10 mL). The combined extracts were washed with water (30 mL), dried (Na_2SO_4), and concentrated, and the residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate−light petroleum (5:95) to give the title compound as a yellow solid (130 mg, 58%); mp 91−92 °C. (Found: C, 59.0; H, 5.8; N, 6.1%. $C_{11}H_{13}NO_4$ requires C, 59.2; H, 5.9; N, 6.3%.) (Found: [M + Na^+], 246.0737. $C_{11}H_{13}NNaO_4{}^+$ requires 246.0737.) ν_{max} ($CHCl_3$)/cm^{-1} 3378, 3012, 1739, 1671, 1507, 1342, 1145, 1019. λ_{max} (CH_2Cl_2)/nm 216 (log ε 4.05), 257 (3.88), 388 (3.16). δ_H (400 MHz; $CDCl_3$) 7.42 (1 H, br s), 7.22 (1 H, d, J 2.4), 6.76 (1 H, d, J 10.2), 6.73 (1 H, dd, J 10.2, 2.5) 1.53 (9 H, s). δ_C (100 MHz; $CDCl_3$) 187.4 (C), 182.4 (C), 151.1 (C), 139.3 (C), 138.2 (CH), 133.1 (CH), 112.5 (CH), 82.7 (C), 28.1 (Me).

*2-Benzamido-1,4-benzoquinone (**12**)*



Diacetoxyiodobenzene (805 mg, 2.5 mmol) was added to *N*-(2,5-dimethoxyphenyl)benzamide (257 mg, 1.0 mmol) in water−MeOH (125 μL). The resulting suspension was stirred for 2 h and then diluted with water (10 mL) and extracted with dichloromethane (3 × 10 mL). The combined extracts were washed with water (30 mL), dried (Na_2SO_4), and concentrated, and the residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate−light petroleum (1:3−1:2) to give the title compound as a yellow solid (170 mg, 75%); mp 109−110 °C. (Found: [M + Na^+], 250.0473 $C_{13}H_9NNaO_3{}^+$ requires 250.0475.) ν_{max} ($CHCl_3$)/cm^{-1} 3378, 3011, 1668, 1658, 1511, 1490, 1327, 1240, 1100. λ_{max} (CH_2Cl_2)/nm 198 (log ε 3.85), 254 (3.62), 386 (2.74). δ_H (400 MHz; $CDCl_3$) 8.86 (1 H, br s), 7.92−7.89 (2 H, m), 7.78 (1 H, d, J 2.5), 7.66−7.61 (1 H, m), 7.58−7.51 (2 H, m), 6.86 (1 H, d, J 10.2), 6.80 (1 H, dd, J 10.2, 2.5). δ_C (100 MHz; $CDCl_3$) 187.9 (C), 182.9 (C), 165.8 (C), 138.43 (C), 138.40 (CH), 133.2 (CH), 133.1 (CH), 129.1 (CH), 128.8 (C), 127.3 (CH), 114.9 (CH).

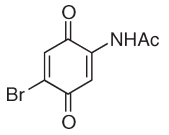
*2-Acetamido-5-chloro-1,4-benzoquinone (**13**)*



Bis(trifluoroacetoxy)iodobenzene (483 mg, 1.5 mmol) was added to 4-chloro-2,5-dimethoxyacetanilide (230 mg, 1.0 mmol) in water (5 mL)−MeOH (125 μL). The resulting suspension was stirred for 2 h and then diluted with water (15 mL) and extracted with dichloromethane (3 × 10 mL). The combined extracts were washed with water (30 mL), dried (Na_2SO_4), and concentrated, and the residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate−toluene (1:2) to give the title compound as a golden-yellow solid (146 mg, 68%); mp 183−185 °C (lit.,[30] mp 168−169 °C). (Found: C, 48.0; H, 3.0; N, 6.8%. $C_8H_6ClNO_3$ requires C, 48.1; H, 3.0;

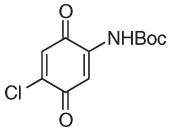
N, 7.0%.) (Found: [M + Na^+], 252.0400. $C_8H_6{}^{35}ClNO_3{}^+$ requires 252.0398.) ν_{max} ($CHCl_3$)/cm^{-1} 3374, 1721, 1670, 1593, 1500, 1335, 1312, 1183. δ_H (300 MHz; $CDCl_3$) 8.09 (1 H, br s), 7.73 (1 H, s), 7.01 (1 H, s), 2.27 (3 H, s). δ_C (75 MHz; $CDCl_3$) 180.8 (C), 179.7 (C), 169.3 (C), 146.4 (C), 138.5 (C), 130.4 (CH), 114.2 (CH), 24.9 (Me).

*2-Acetamido-5-bromo-1,4-benzoquinone (**14**)*



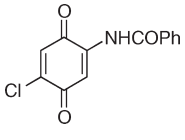
Bis(trifluoroacetoxy)iodobenzene (560 mg, 1.3 mmol) was added to *N*-(4-bromo-2,5-dimethoxyphenyl)acetamide (244 mg, 1.0 mmol) in water (5 mL)−MeOH (125 μL). The resulting suspension was stirred for 30 min and then diluted with water (10 mL) and extracted with dichloromethane (3 × 10 mL). The combined extracts were washed with water (30 mL), dried (Na_2SO_4), and concentrated, and the residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate−toluene (1:4−3:7) to give the title compound as an orange solid (130 mg, 53%); mp 184−185 °C (lit.,[30] mp 190−192 °C). (Found: C, 39.5; H, 2.4; N, 5.5%. $C_8H_6BrNO_3$ requires C, 39.4; H, 2.5; N, 5.7%.) (Found: [M + Na^+], 265.9427. $C_8H_6{}^{79}BrNNaO_3{}^+$ requires 265.9423.) ν_{max} ($CHCl_3$)/cm^{-1} 3374, 3012, 1721, 1668, 1593, 1503, 1331, 1167. λ_{max} (CH_2Cl_2)/nm 202 (log ε 4.65), 288 (4.03), 422 (2.99). δ_H (400 MHz; $CDCl_3$) 8.05 (1 H, br s), 7.78 (1 H, s), 7.31 (1 H, s), 2.27 (3 H, s). δ_C (100 MHz; $CDCl_3$) 180.4 (C), 179.7 (C), 169.2 (C), 140.6 (C), 138.4 (C), 134.7 (CH), 114.0 (CH), 24.9 (Me).

*2-tert-Butoxycarbonylamino-5-chloro-1,4-benzoquinone (**15**)*



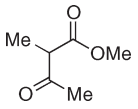
Bis(trifluoroacetoxy)iodobenzene (645 mg, 1.5 mmol) was added to *tert*-butyl 4-chloro-2,5-dimethoxyphenylcarbamate (258 mg, 1.0 mmol) in water (5 mL)−MeOH (125 μL). The resulting suspension was stirred for the indicated time and then diluted with water (15 mL) and extracted with dichloromethane (3 × 10 mL). The combined extracts were washed with water (30 mL), dried (Na_2SO_4), and concentrated, and the residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate−toluene (1:9) to give the title compound as a golden-yellow solid (174 mg, 66%); mp 92−93 °C. (Found: C, 51.3; H, 4.7; N, 5.3%. $C_{11}H_{12}ClNO_4$ requires C, 51.3; H, 4.7; N, 5.4%.) (Found: [M + Na^+], 280.0358. $C_{11}H_{12}{}^{35}ClNNaO_4{}^+$ requires 280.0347.) ν_{max} ($CHCl_3$)/cm^{-1} 3378, 2984, 1739, 1671, 1506, 1145, 1019. λ_{max} (CH_2Cl_2)/nm 223 (log ε 4.75), 280 (4.68), 406 (3.70). δ_H (300 MHz; $CDCl_3$) 7.43 (1 H, br s), 7.35 (1 H, s), 6.98 (1 H, s), 1.53 (9 H, s). δ_C (75 MHz; $CDCl_3$) 184.5 (C), 179.1 (C), 150.8 (C), 146.4 (C), 139.7 (C), 130.4 (CH), 111.9 (CH), 83.1 (C), 28.0 (Me).

*2-Benzamido-5-chloro-1,4-benzoquinone (**16**)*



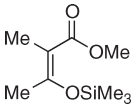
Bis(trifluoroacetoxy)iodobenzene (645 mg, 1.5 mmol) was added to *N*-(4-chloro-2,5-dimethoxyphenyl)benzamide (292 mg, 1.0 mmol) in water (5 mL)−MeOH (125 μL). The resulting suspension was stirred for 2 h and then diluted with water (10 mL) and extracted with dichloromethane (3 × 10 mL). The combined extracts were washed with water (30 mL), dried (Na_2SO_4), and concentrated, and the residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate−light petroleum (1:4) to give the title compound as a yellow solid (165 mg, 73%); mp 148−149 °C. (Found: C, 59.4; H, 3.1; N, 5.2%. $C_{13}H_8ClNO_3$ requires C, 59.7; H, 3.1; N, 5.4%.) (Found: [M + Na^+], 284.0096. $C_{13}H_8{}^{35}ClNNaO_3{}^+$ requires 284.0085.) ν_{max} ($CHCl_3$)/cm^{-1} 3377, 1703, 1666, 1601, 1509, 1480, 1339, 1311, 1173, 994. λ_{max} (CH_2Cl_2)/nm 201 (log ε 4.26), 273 (3.45), 426 (2.69). δ_H (400 MHz; $CDCl_3$) 8.88 (1 H, br s), 7.93−7.90 (3 H, m), 7.68−7.63 (1 H, m), 7.59−7.53 (3 H, m), 7.09 (1 H, s). δ_C (100 MHz; $CDCl_3$) 181.0 (C), 179.6 (C), 165.7 (C), 146.7 (C), 138.8 (C), 133.3 (CH), 132.8 (C), 130.5 (CH), 129.2 (CH), 127.4 (CH), 114.3 (CH).

Methyl 2-Methyl-3-oxobutanoate



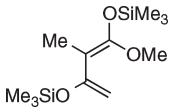
A mixture of methyl acetoacetate (21.6 mL, 200 mmol) and iodomethane (12.5 mL, 200 mmol) was cooled to 0 °C, and anhydrous potassium carbonate (41.4 g, 300 mmol) was slowly added. The reaction mixture was stirred at 0 °C for 2 h and then at rt overnight. Ether (200 mL) was added, and the suspension was filtered under reduced pressure, washing with ether (200 mL). The filtrate was washed with brine (200 mL) and concentrated to a colorless oil that was purified by flash column chromatography, eluting with ethyl acetate−light petroleum (1:9) to give the title compound as a colorless oil (20.3 g, 78%). δ_H (300 MHz, $CDCl_3$) 3.65 (3 H, s), 3.49 (1 H, q, *J* 7.3), 2.11 (3 H, s), 1.31 (3 H, d, *J* 7.3). δ_C (75 MHz; $CDCl_3$) 203.6 (C), 171.0 (C), 53.5 (CH), 52.4 (Me), 28.5 (Me), 12.8 (Me). NMR data matched those reported.[31]

Methyl 2-Methyl-3-(trimethylsiloxy)but-2-enoate



A solution of methyl 2-methyl-3-oxobutenoate (7.0 g, 53.8 mmol) and imidazole (550 mg, 8.1 mmol) in hexamethyldisilazane (12.5 mL, 59.2 mmol) was heated to 100 °C and stirred at this temperature for 2 h and then cooled to rt and stirred overnight. Distillation under reduced pressure (water aspirator) gave the title compound as a colorless oil (10.2 g, 93%); bp 140−145 °C (lit.,[21] bp 60−62 °C/0.6 mmHg). (Found: [M + H^+], 203.1089. $C_9H_{19}O_3Si$ requires 203.1098.) ν_{max} ($CHCl_3$)/cm^{-1} 3581, 3308, 1739, 1662, 1631, 1586, 1427, 1398, 1368, 1255, 1098. δ_H (400 MHz; $CDCl_3$) 3.71 (3 H, s), 2.29 (3 H, d, *J* 1.2), 1.78 (3 H, d, *J* 1.2), (9 H, s). δ_C (100 MHz; $CDCl_3$) 170.2 (C), 161.7 (C), 108.8 (C), 51.1 (Me), 21.6 (Me), 12.4 (Me), 0.5 (Me).

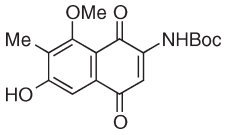
*1-Methoxy-2-methyl-1,3-bis(trimethylsiloxy)-1,3-butadiene (**19**)*



n-Butyllithium (2.5 M in hexanes; 35 mL, 89.0 mmol) was added to a solution of diisopropylamine in THF (175 mL) at 0 °C. The solution was warmed to rt, stirred for 5 min, and then cooled to −78 °C. Chlorotrimethylsilane (13.8 mL, 108.7 mmol) was added, followed by a solution of methyl 2-methyl-3-(trimethylsiloxy)but-2-enoate (10.0 g, 49.4 mmol) in THF (15 mL). The reaction mixture was stirred at −78 °C for 1 h, then warmed to rt over 30 min. Solvents were removed in vacuo at rt, and dry *n*-pentane (150 mL) was added. The resulting suspension was filtered repeatedly until no salts remained, then

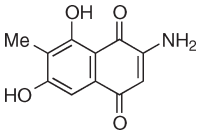
concentrated in vacuo to give a pale-yellow oil (14 g, >100%) that was not purified further and was stored in the freezer. δ_H (300 MHz; $CDCl_3$) 4.42 (1 H, s), 4.29 (1 H, s), 3.56 (3 H, s), 1.65 (3 H, s), 0.24 (9 H, s) 0.20 (9 H, s). NMR data matches those reported.[21]

*2-tert-Butoxycarbonylamino-6-hydroxy-8-methoxy-7-methyl-1,4-naphthoquinone (**20**)*



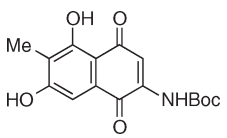
1-Methoxy-2-methyl-1,3-bis(trimethylsiloxy)-1,3-butadiene (**19**) (565 mg, 2.0 mmol) was added dropwise to 2-*tert*-butoxycarbonylamino-1,4-benzoquinone (**11**) (223 mg, 1.0 mmol) in toluene (5 mL). The green solution was stirred at room temperature for 2 h and then poured into hydrochloric acid (1 M; 15 mL) and ethyl acetate (10 mL). The layers were separated, and the aqueous phase was extracted with ethyl acetate (2 × 10 mL). Silica (ca. 5 g) was added to the combined extracts and the suspension stirred under air at rt for 24 h. Concentration and flash column chromatography eluting with ethyl acetate−toluene (1:2) gave the title compound, which was recrystallized from toluene to give a yellow powder (212 mg, 64%); mp >280 °C decomp. (Found: $[M + Na^+]$, 356.1103. $C_{17}H_{19}NNaO_6^+$ requires 356.1105.) ν_{max} ($CHCl_3$)/cm^{-1} 3582, 3367, 3008, 1737, 1662, 1582, 1501, 1313, 1149, 1111. λ_{max} (CH_2Cl_2)/nm 219 (log ε 4.22), 272 (4.10), 314 (4.01). δ_H (300 MHz; DMSO-d_6) 11.18 (1 H, br s), 8.44 (1 H, s), 7.25 (1 H, s), 7.07 (1 H, s), 3.71 (3 H, s), 2.09 (3 H, s), 1.49 (9 H, s). δ_C (75 MHz; DMSO-d_6) 184.4 (C), 177.1 (C), 162.8 (C), 161.0 (C), 151.9 (C), 143.0 (C), 132.9 (C), 124.7 (C), 115.1 (C), 112.3 (CH), 109.0 (CH), 82.1 (C), 60.9 (Me), 28.2 (Me), 9.2 (Me).

*2-Amino-6,8-dihydroxy-7-methyl-1,4-naphthoquinone (**17**)*



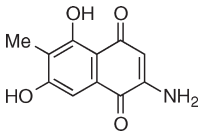
Magnesium bromide (276 mg, 1.5 mmol) was added to a solution of 2-*tert*-butoxycarbonylamino-6-hydroxy-8-methoxy-7-methyl-1,4-naphthoquinone (**20**) (50 mg, 0.15 mmol) in toluene (10 mL), and the mixture was heated to reflux and stirred for 18 h. The reaction mixture was poured into hydrochloric acid (1 M; 5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined extracts were washed with water (10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated to give the title compound as a red powder (33 mg, 99%) that did not require further purification; mp >300 °C decomp. (Found: $[M + Na^+]$, 242.0430. $C_{11}H_9NNaO_4^+$ requires 242.0424.) ν_{max} ($CHCl_3$)/cm^{-1} 3464, 3349, 1598, 1563, 1326, 1273, 1127, 1072. λ_{max} (CH_2Cl_2)/nm 225 (log ε 4.72), 267 (3.67), 275 (3.65), 341 (3.62). δ_H (400 MHz; DMSO-d_6) 12.22 (1 H, s), 11.15 (1 H, br s), 7.21 (1 H, br s), 7.00 (1 H, s), 5.66 (1 H, s), 2.02 (3 H, s). δ_C (100 MHz; DMSO-d_6) 184.6 (C), 181.4 (C), 163.9 (C), 162.2 (C), 151.3 (C), 133.1 (C), 114.2 (C), 107.6 (C), 107.3 (CH), 102.0 (CH), 8.2 (Me).

*3-tert-Butoxycarbonylamino-6,8-dihydroxy7-methyl-1,4-naphthoquinone (**21**)*



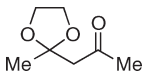
1-Methoxy-2-methyl-1,3-bis(trimethylsiloxy)-1,3-butadiene (**19**) (564 mg, 2.0 mmol) was added dropwise to 2-chloro-5-*tert*-butoxycarbonylamino-1,4-benzoquinone (**15**) (258 mg, 1.0 mmol) and pyridine (160 μL, 2.0 mmol) in toluene (5 mL). The green solution was stirred at room temperature for 2 h and then poured into hydrochloric acid (1 M; 15 mL) and ethyl acetate (10 mL). The layers were separated, and the aqueous phase was extracted with ethyl acetate (2 × 10 mL). Silica gel (ca. 5 g) was added to the combined extracts and the suspension stirred under air at rt for 24 h. Concentration and flash column chromatography eluting with ethyl acetate−toluene (1:2) gave the title compound as an orange powder (137 mg, 43%); mp >300 °C decomp. (Found: $[M + Na^+]$, 342.0938. $C_{16}H_{17}NNaO_6^+$ requires 342.0948.) ν_{max} ($CHCl_3$)/cm^{-1} 3691, 1605, 3376, 3001, 1736, 1632, 1603, 1507, 1325, 1150, 1054, 1029, 1011. λ_{max} (CH_2Cl_2)/nm 224 (log ε 4.21), 263 (3.81), 318 (3.78), 449 (3.38). δ_H (400 MHz; DMSO-d_6) 12.81 (1 H), 11.00 (1 H, s), 8.73 (1 H, s), 7.12 (1 H, s), 7.10 (1 H, s), 2.06 (3 H, s), 1.50 (9 H, s). δ_C (100 MHz; DMSO-d_6) 189.9 (C), 179.7 (C), 161.8 (C), 161.2 (C), 152.1 (C), 142.8 (C), 129.1 (C), 126.9 (C), 118.7 (C), 114.1 (CH), 107.9 (CH), 82.3 (C), 28.2 (Me), 9.2 (Me). A small amount of the 8-methoxy-6-hydroxy- compound (30 mg, 9%) was also formed.

*3-Amino-6,8-dihydroxy-7-methyl-1,4-naphthoquinone (**22**)*



Magnesium bromide (276 mg, 1.5 mmol) was added to a solution of 3-*tert*-butoxycarbonylamino-6,8-dihydroxy7-methyl-1,4-naphthoquinone (**21**) (20 mg, 0.06 mmol) in toluene (5 mL), and the mixture was heated to reflux and stirred for 18 h. The reaction mixture was poured into hydrochloric acid (1 M; 5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined extracts were washed with water (10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography on silica gel eluting with ethyl acetate−toluene (1:2) to give a dark-red powder (11 mg, 80%); mp >300 °C decomp. (Found: $[M - H^+]$, 218.0455. $C_{11}H_8NO_4^-$ requires 218.0459.) ν_{max} (ATR)/cm^{-1} 3432, 3337, 3291, 1609, 1567, 1480, 1386, 1354, 1308, 1262, 1105. λ_{max} (CH_2Cl_2)/nm 210 (log ε 3.93), 224 (3.83), 270 (3.88), 338 (3.55), 399 (3.05). δ_H (400 MHz; DMSO-d_6) 13.71 (1 H, s), 10.57 (1 H, br s), 7.33 (1 H, br s), 7.07 (1 H, s), 5.64 (1 H, s), 2.03 (3 H, s). δ_C (100 MHz; DMSO-d_6) 188.7 (C), 181.8 (C), 160.9 (C), 160.2 (C), 151.5 (C), 129.1 (C), 119.0 (C), 107.6 (C), 106.8 (CH), 100.7 (CH), 8.7 (Me).

1-(2-Methyl-1,3-dioxolan-2-yl)propan-2-one



p-Toluenesulfonic acid (43 mg, 0.23 mmol) was added to a solution of acetylacetone (20.0 g, 200 mmol) and ethylene glycol (14.2 g, 200 mmol) in benzene (40 mL). The mixture was heated to reflux, and the solution was stirred overnight with azeotropic removal of water using a Dean−Stark trap. Benzene was carefully removed under reduced pressure, and the remaining liquid was fractionally distilled twice through a 30 cm Vigreux column under reduced pressure (water aspirator). The title compound (19.1 g, 66%) was obtained along with some minor impurities which did not affect subsequent reactions; bp 122−124 °C/5 mmHg (lit.,[23] bp 120 °C/5 mmHg). ν_{max} ($CHCl_3$)/cm^{-1} 2989, 2888, 1709, 1790, 1361, 1241, 1054. δ_H (400 MHz; $CDCl_3$) 3.97−3.94 (4 H, m), 2.75 (2 H, s), 2.20 (3 H, s), 1.39 (3 H, s). δ_C (100 MHz; $CDCl_3$) 205.9 (C), 107.8 (C), 64.6 (CH_2), 64.2 (CH_2), 52.5 (CH_2), 31.6 (Me), 24.3 (Me).

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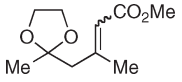
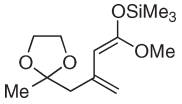
*Methyl 3-Methyl-4-(2-methyl-1,3-dioxolan-2-yl)but-2-enoate (**23**)*



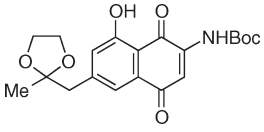
Sodium hydride (60% in mineral oil; 8.32 g, 208.1 mmol) was washed with dry *n*-pentane (30 mL), dried under vacuum, suspended in THF (250 mL), and cooled to 0 °C. Methyl diethyl phosphonoacetate (38.2 mL, 208.1 mmol) was added dropwise, and the reaction mixture was slowly heated to reflux. 1-(2-Methyl-1,3-dioxolan-2-yl)propan-2-one (20.0 g, 138.7 mmol) in THF (50 mL) was added dropwise and the suspension stirred for 6 h then cooled to rt. Ether (100 mL) and brine (200 mL) were added, and the aqueous phase was extracted with ether (3 × 100 mL). The combined ethereal extracts were washed with water (2 × 200 mL) and brine (2 × 200 mL), dried, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel eluting with ether−light petroleum (1:25) to give the title compound as a colorless oil (20.2 g, 73%) as a 2.2:1 mixture of geometric isomers which were used directly in the next reaction. ν_{max} ($CHCl_3$)/cm^{-1} 2989, 2952, 2888, 1712, 1646, 1437, 1380, 1155, 1055. Major: δ_H (400 MHz; $CDCl_3$) 5.78 (1 H, d, *J* 0.7), 3.96−3.94 (4 H, m), 3.71 (3 H, s), 2.48 (2 H, s), 2.26 (3 H, d, *J* 1.5), 1.34 (3 H, s); δ_C (100 MHz; $CDCl_3$) 166.9 (C), 155.5 (C), 119.2 (CH), 109.4 (C), 64.7 (CH_2), 50.8 (Me), 49.5 (CH_2), 24.3 (Me), 20.1 (Me). Minor: δ_H (400 MHz; $CDCl_3$) 5.81 (1 H, d, *J* 0.7), 3.96−3.94 (4 H, m), 3.70 (3 H, s), 3.10 (2 H, s) 2.00 (3 H, d, *J* 1.5), 1.36 (3 H, s); δ_C (100 MHz; $CDCl_3$) 166.8 (C), 154.9 (C), 118.8 (CH), 109.9 (C), 64.5 (CH_2), 50.8 (Me), 41.1 (CH_2), 26.5 (Me), 24.0 (Me).

*1-Methoxy-3-[(2-methyl-1,3-dioxolan-2-yl)methyl]buta-1,3-dienyloxytrimethylsilane (**24**)*



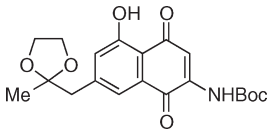
n-Butyllithium (2.5 M in hexanes; 52.0 mL, 129.9 mmol) was added to a 0 °C solution of diisopropylamine (18.3 mL, 129.9 mmol) in THF (300 mL). The solution was warmed to rt, stirred for 5 min, and then cooled to −78 °C. Chlorotrimethylsilane (20.3 mL, 159.8 mmol) was added, followed by dropwise addition of methyl 3-methyl-4-(2-methyl-1,3-dioxolan-2-yl)but-2-enoate (**23**) (20.0 g, 99.9 mmol) in THF (30 mL). The resulting solution was stirred at −78 °C for 90 min and then warmed to rt and concentrated without heating in vacuo. The residue was diluted with dry *n*-pentane (50 mL) and careful filtration under nitrogen followed by concentration gave the title compound as a colorless oil (27.0 g, quant.) that was used without further purification, and stored in the freezer. (Found [M + Na^+] 295.1322. $C_{13}H_{24}NaO_4Si^+$ requires 295.1336.) ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2962, 2888, 1707, 1646, 1598, 1254, 1097, 1050, 976. δ_H (400 MHz; $CDCl_3$) 5.26 (1 H, d, *J* 2.5), 4.81 (1 H, d, *J* 2.5), 4.24 (1 H, s), 3.97−3.95 (4 H, m), 3.58 (3 H, s), 2.50 (2 H, s), 1.37 (3 H, s), 0.26 (9 H, s). δ_C (100 MHz; $CDCl_3$) 157.7 (C), 138.3 (C), 110.9 (CH_2), 110.2 (C), 79.2 (CH), 64.4 (CH_2), 55.0 (CH), 47.3 (CH_2), 23.8 (Me), 0.5 (Me).

*2-tert-Butoxycarbonylamino-8-hydroxy-6-[(2-methyl-1,3-dioxolan-2-yl)methyl]-1,4-naphthoquinone (**25**)*



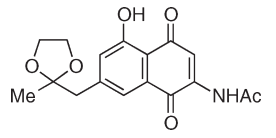
1-Methoxy-3-((2-methyl-1,3-dioxolan-2-yl)methyl)buta-1,3-dienyloxytrimethylsilane (**24**) (410 mg, 1.5 mmol) was added dropwise to 2-*tert*-butoxycarbonylamino-1,4-benzoquinone (**11**) (223 mg, 1.0 mmol) in dichloromethane (10 mL). The green solution was stirred at rt for 2 h and then poured into hydrochloric acid (1 M; 15 mL) and ethyl acetate (10 mL). The layers were separated, and the aqueous phase was extracted with ethyl acetate (2 × 10 mL). The combined organic extracts were treated with silica gel (ca. 5 g), and the suspension stirred under air for 16 h. Concentration and flash column chromatography on silica gel eluting with ethyl acetate−toluene (1:9−1:4) gave the title compound as an orange powder (250 mg, 64%); mp 120−121 °C. (Found: [M + Na^+], 412.1356. $C_{20}H_{23}NNaO_7^+$ requires 412.1367.) ν_{max} ($CHCl_3$)/cm^{-1} 3381, 3011, 1736, 1639, 1614, 1506, 1383, 1294, 1148, 1049. λ_{max} (CH_2Cl_2)/nm 211 (log ε 5.06), 228 (4.09), 304 (3.75), 409 (3.30). δ_H (400 MHz; $CDCl_3$) 11.38 (1 H, s), 7.69 (1 H, br s), 7.55 (1 H, d, *J* 1.6), 7.42 (1 H, s), 7.15 (1 H, d, *J* 1.6), 3.92−3.90 (2 H, m), 3.84−3.82 (2 H, m), 2.98 (2 H, s), 1.55 (9 H, s), 1.33 (3 H, s). δ_C (100 MHz; $CDCl_3$) 184.4 (C), 184.1 (C), 161.4 (C), 151.1 (C), 148.6 (C), 140.9 (C), 138.7 (C), 124.7 (CH), 121.8 (CH), 115.5 (CH), 112.2 (C), 109.1 (C), 82.7 (C), 64.9 (CH_2), 44.6 (CH_2), 28.1 (Me), 24.5 (Me).

*3-tert-Butoxycarbonylamino-8-hydroxy-6-[(2-methyl-1,3-dioxolan-2-yl)methyl]-1,4-naphthoquinone (**26**)*



. 1-Methoxy-3-((2-methyl-1,3-dioxolan-2-yl)methyl)buta-1,3-dienyloxytrimethylsilane (**24**) (410 mg, 1.5 mmol) was added dropwise to 5-chloro-2-*tert*-butoxycarbonylamino-1,4-benzoquinone (**15**) (258 mg, 1.0 mmol) and pyridine (160 μL, 2.0 mmol) in dichloromethane (10 mL). The green solution was stirred at rt for 4 h and then silica gel (ca. 5 g) was added, and the suspension stirred under air for 16 h. Concentration and flash column chromatography on silica gel eluting with ethyl acetate−toluene (1:9−1:4) gave the title compound as an orange powder, which was recrystallized from toluene−hexane (ca. 1:2) to give red crystals (193 mg, 49%); mp 135−137 °C. (Found: C, 61.7; H, 5.9; N, 3.5%. $C_{20}H_{23}NO_7$ requires C, 61.7; H, 6.0; N, 3.6%.) (Found: [M + Na^+], 412.1358. $C_{20}H_{23}NNaO_7^+$ requires 412.1367.) ν_{max} ($CHCl_3$)/cm^{-1} 3373, 2986, 1738, 1673, 1635, 1613, 1504, 1372, 1325, 1278, 1150. λ_{max} (CH_2Cl_2)/nm 210 (log ε 4.23), 252 (4.02), 304 (4.81), 436 (3.55). δ_H (400 MHz; $CDCl_3$) 12.32 (1 H, s), 7.78 (1 H, br s), 7.57 (1 H, d, *J* 1.6), 7.39 (1 H, s), 7.23 (1 H, d, *J* 1.6), 3.95−3.92 (2 H, m), 3.82−3.80 (2 H, m), 2.98 (2 H, s), 1.56 (9 H, s), 1.35 (3 H, s). δ_C (100 MHz; $CDCl_3$) 190.5 (C), 180.1 (C), 160.9 (C), 151.1 (C), 145.6 (C), 141.7 (C), 129.4 (C), 127.4 (CH), 121.9 (CH), 114.3 (CH), 112.2 (C), 109.2 (C), 82.8 (C), 64.9 (CH_2), 45.4 (CH_2), 28.0 (Me), 24.3 (Me).

*3-Acetamido-8-hydroxy-6-[(2-methyl-1,3-dioxolan-2-yl)methyl]-1,4-naphthoquinone (**27**)*



1-Methoxy-3-((2-methyl-1,3-dioxolan-2-yl)methyl)buta-1,3-dienyloxytrimethylsilane (**24**) (220 mg, 0.81 mmol) was added dropwise to 2-acetamido-5-chloro-1,4-benzoquinone (**13**) (100 mg, 0.54 mmol) in dichloromethane (5 mL). The solution was stirred at rt for 2 h, and then silica gel (ca. 3 g) was added and the resulting suspension was stirred for 18 h under air. Concentration and flash column chromatography on silica gel eluting with ethyl acetate−toluene (1:2−1:1), followed by recrystallization from toluene−hexane (ca. 1:1), gave the product as an orange−brown solid (97 mg, 54%); mp 164−165 °C. (Found: C, 61.4;

dx.doi.org/10.1021/jo201320g |*J. Org. Chem.* 2011, 76, 7872–7881

H, 5.2; N, 4.1%. $C_{17}H_{17}NO_6$ requires C, 61.6; H, 5.2; N, 4.2%.) (Found: [M + Na^+], 354.0948. $C_{17}H_{17}NNaO_6^+$ requires 354.0948.) ν_{max} ($CHCl_3$)/cm^{-1} 3368, 2989, 2888, 1717, 1670, 1637, 1612, 1503, 1382, 1319, 1277, 1047. λ_{max} (CH_2Cl_2)/nm 212 (log ε 4.07), 253 (3.86), 302 (3.66), 435 (3.39). δ_H (400 MHz; $CDCl_3$) 12.26 (1 H, s), 8.41 (1 H, br s), 7.80 (1 H, s), 7.61 (1 H, d, *J* 1.7), 7.27 (1 H, d, *J* 1.7), 3.98−3.94 (2 H, m), 3.83−3.79 (2 H, m), 3.01 (2 H, s), 2.31 (3 H, s), 1.37 (3 H, s). δ_C (100 MHz; $CDCl_3$) 191.1 (C), 180.4 (C), 169.5 (C), 160.9 (C), 146.0 (C), 140.5 (C), 129.2 (C), 127.6 (CH), 122.3 (CH), 116.7 (CH), 112.7 (C), 109.1 (C), 65.0 (CH_2), 45.5 (CH_2), 25.1 (Me), 24.6 (Me).

■ ASSOCIATED CONTENT

Supporting Information. Copies of ^1H and ^{13}C NMR spectra, X-ray structure of compound **26**, and associated .cif file for the X-ray structure. This material is available free of charge via the Internet at http://pubs.acs.org.

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