JOC The Journal of Organic Chemistry

ARTICLE

pubs.acs.org/joc

Synthesis of the Azaphilones (+)-Sclerotiorin and (+)-8-*O*-Methylsclerotiorinamine Utilizing (+)-Sparteine Surrogates in Copper-Mediated Oxidative Dearomatization

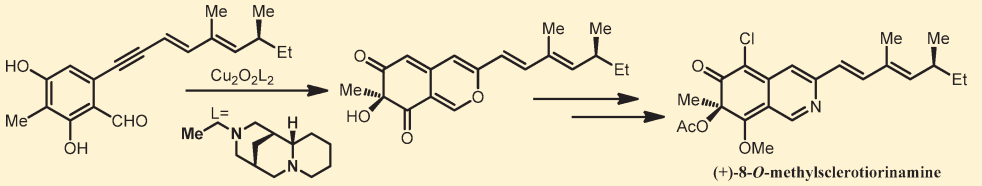
Andrew R. Germain,[†] Daniel M. Bruggemeyer,[†] Jianglong Zhu,[†] Cedric Genet,[‡] Peter O'Brien,[‡] and John A. Porco, Jr.*[,†]

[†]Department of Chemistry, Center for Chemical Methodology and Library Development (CMLD-BU), Boston University, 590 Commonwealth Avenue, Boston, Massachusetts 02215, United States

[‡]Department of Chemistry, University of York, Heslington, York YO105DD, U.K.

Supporting Information

ABSTRACT:



Enantioselective syntheses of the azaphilone natural products (+)-sclerotiorin and (+)-8-*O*-methylsclerotiorinamine that possess the natural *R*-configuration at the quaternary center are reported. The syntheses were accomplished using copper-mediated asymmetric dearomatization employing bis-μ-oxo copper complexes prepared from readily available (+)-sparteine surrogates. Of note, site-selective *O*-methylation of a vinylogous pyridone was used to access the isoquinolin-6(7*H*)-one core of (+)-8-*O*-methylsclerotiorinamine.

INTRODUCTION

The azaphilones[1] are a structurally diverse family of natural products containing a highly oxygenated bicyclic core and a quaternary center. Our group has previously reported the enantioselective synthesis of the azaphilone natural product S-15183a **1** (Figure 1) bearing a (*R*)-quaternary center.[2] The synthesis was achieved utilizing enantioselective oxidative dearomatization[3] mediated by a $[(-)\text{-sparteine}]_2Cu_2O_2$ complex.[4] A number of azaphilone natural products including (+)-sclerotiorin **2** and 8-*O*-methylsclerotiorinamine **3** possess the opposite stereochemistry at C7 compared to **1** (Figure 1).[5] Since (+)-sparteine is not readily available or readily synthesized,[6] it was necessary to identify an appropriate (+)-sparteine surrogate for use in asymmetric oxidative dearomatization. In this Article, we report the first asymmetric syntheses of (+)-**2** and (+)-**3** employing readily available (+)-sparteine surrogates[7] in copper-mediated oxidative dearomatization.

RESULTS AND DISCUSSION

In our initial studies, we investigated the utility of (+)-sparteine surrogates **5**−**8** developed by O'Brien and co-workers[7] for formation of $L_2Cu_2O_2$ complexes **9** to mediate oxidative dearomatization of alkynylbenzaldehyde **10**[2] in the presence of *N*,*N*-diisopropylethylamine (DIEA) as base and 4-dimethylaminopyridine (DMAP) as additive (Table 1). Gratifyingly, (+)-sparteine surrogates **5**−**7** were found to be suitable for this transformation and provided the desired (*S*)-enantiomer **11** in good to excellent enantiomeric excess (Table 1).[8] *N*-Ethyl-(+)-sparteine mimic **6** was found to be the optimal ligand to afford azaphilone core **11** in 70% yield and 95% ee (entry 3, Table 1) and was therefore employed in syntheses of (+)-sclerotiorin **2** and (+)-8-*O*-methylsclerotiorinamine **3** (*vide infra*). Use of (+)-sparteine surrogate **7** bearing an *N*-isopropyl substituent decreased both the yield and ee of azaphilone **11** (entry 4, Table 1). Likewise, ligand **8** bearing an *N*-neopentyl group was not effective, likely due to steric hindrance in the formation of the putative bis-μ-oxo complexes (entry 5, Table 1).

(+)-Sparteine surrogates were also found to be more susceptible to oxidative modification[8,9] under the reaction conditions than the alkaloid (−)-sparteine, which may explain the slightly lower yields observed relative to those using (−)-sparteine. Through mass spectrometry analysis, we determined that the (+)-sparteine surrogates are oxidized preferentially on the interior ring system and not on the *N*-alkyl side chain.[8]

Following development of an efficient route to the *S*-azaphilone core, we initiated studies toward the synthesis of (+)-sclerotiorin **2** and 8-*O*-methylsclerotiorinamine (**3**, Figure 1). Azaphilone **2** was the first azaphilone reported in the literature[5a]

Received: December 10, 2010
Published: March 14, 2011

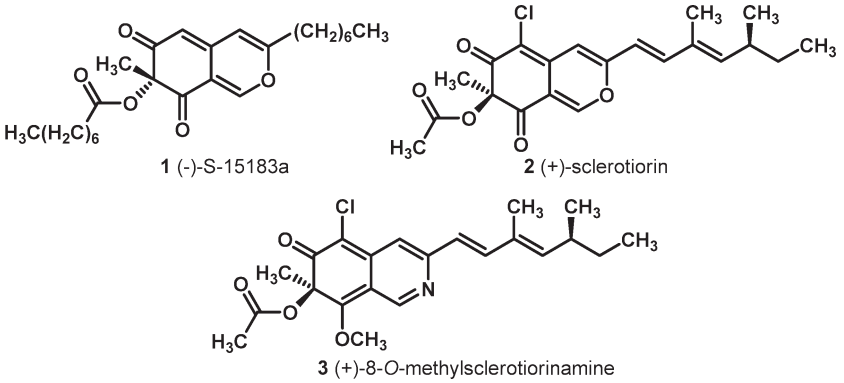
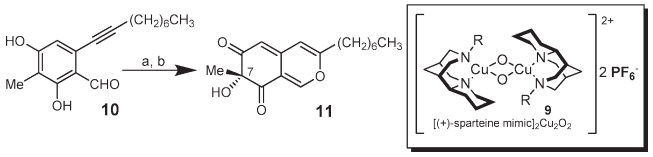
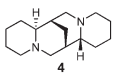
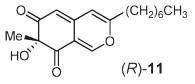
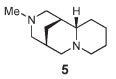
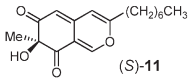
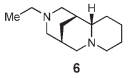
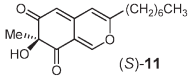
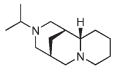
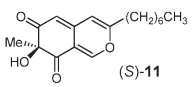
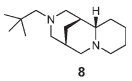
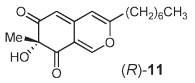


Figure 1. Azaphilone natural products.

Table 1. Oxidative Dearomatization Employing Sparteine Surrogates[a]



entry	ligand	product	yield[b] (ee)
1	 4	 (*R*)-**11**	84% (98%)[2]
2	 5	 (*S*)-**11**	63% (92%)
3	 6	 (*S*)-**11**	70% (95%)
4	 7	 (*S*)-**11**	54% (74%)
5	 8	 (*R*)-**11**	33% (11%)

[a] Conditions: (a) 2.2 equiv of $Cu(CH_3CN)_4PF_6$, 2.4 equiv of ligand, 1.6 equiv of DIEA, 2.4 equiv of DMAP, O_2, −78 to −10 °C; (b) aq H_2PO_4/K_2HPO_4 buffer (pH 7.2), CH_3CN, RT. DIEA = *N*,*N*-diisopropylethylamine, DMAP = 4-(dimethylamino)pyridine. [b] Isolated yield after silica gel chromatography.

and has been shown to be an inhibitor of several important protein targets.[10] Azaphilone **3** has been shown to significantly inhibit binding between the Grb2-SH2 domain and the phosphopeptide derived from the Shc protein.[5d] According to our retrosynthetic analysis (Figure 2), we anticipated that 8-*O*-methylsclerotiorinamine **3** could be obtained by amination and methylation of sclerotiorin **2**, which itself could be derived from acylation and chlorination of **12**. Azaphilone core structure **12** may be obtained *via* diastereoselective oxidative dearomatization[3] of alkynylbenzaldehyde **13** followed by cycloisomerization.[2]

Synthesis of the requisite alkynyl benzaldehyde substrate **13** was initiated with preparation of an iodo-diene side-chain fragment (Scheme 1). Swern oxidation of the commercially available chiral alcohol **14**, followed by treatment of the intermediate aldehyde with (carbethoxyethylidene)triphenylphosphorane, afforded allylic ester **15** (85% yield, >20:1 *E*:*Z* selectivity).[11] DIBAL-H reduction of **15** provided alcohol **16** (55%) which was cleanly oxidized with manganese dioxide to produce enal **17**.[12] Chlorous chromium-mediated Takai olefination[13] of **17** produced iodo-diene **18** (65% yield over two steps, 10:1 *E*:*Z* selectivity).

For expedient access to the Sonogashira coupling partner for **18**, we developed an optimized route to iodobenzaldehyde **19** (Scheme 2).[14] We have previously reported a six step route to the corresponding bromobenzaldehyde involving installation of a nitro group to 3-methyl-2,4-dimethoxybenzaldehyde **20** to allow for *ortho*-halogenation of the aldehyde.[15] A more concise route was developed utilizing the directed lithiation conditions originally reported by Comins and co-workers.[16] Treatment of **20** with *N*,*N*,*N*′-trimethylethylenediamine, followed by *ortho*-lithiation of the amino-alkoxide intermediate with *n*-butyl lithium and subsequent treatment with 1,2-diiodoethane, produced the desired protected iodobenzaldehyde. Deprotection using boron tribromide proceeded smoothly to yield iodobenzaldehyde **19** (33% yield, three steps) using a single purification step. Sonogashira coupling of iodobenzaldehyde **19** with trimethylsilylacetylene, followed by silyl deprotection, afforded alkynylbenzaldehyde **21** (80% yield, Scheme 3).[17] Alkynylbenzaldehyde **21** was subjected to Sonogashira conditions with vinyl iodide **18** providing alkynylbenzaldehyde **13** in 55% yield.

(+)-Sclerotiorin **2** was obtained in four steps (49% yield) from alkynylbenzaldehyde substrate **13** (Scheme 4). Copper-mediated, diastereoselective oxidative dearomatization of **13** afforded azaphilone **12** (76% yield, dr = 12:1) with (*S*)-stereochemistry at C-7 based on the sign of the optical rotation ($[\alpha]^{22}_D$ = +163) after conversion to **2** (lit. reported $[\alpha]^{22}_D$ = +133)[5a] utilizing the *N*-ethyl (+)-sparteine surrogate **6** to access the desired $L_2Cu_2O_2$ complex.[7b,8] Since the optical rotation of the final product 8-*O*-methylsclerotiorinamine (+)-**3** was consistent with that reported in the literature (*vide infra*, $[\alpha]^{22}_D$ = +104, lit. reported $[\alpha]^{22}_D$ = +102),[5d] the apparent erosion in stereoselectivity in the formation of (+)-**12** in comparison to the formation of (+)-**11** may be an artifact of an inseparable impurity (*vida infra*). Azaphilone **12** was acylated (Ac_2O/DMAP) and

dx.doi.org/10.1021/jo102448n |*J. Org. Chem.* 2011, 76, 2577–2584

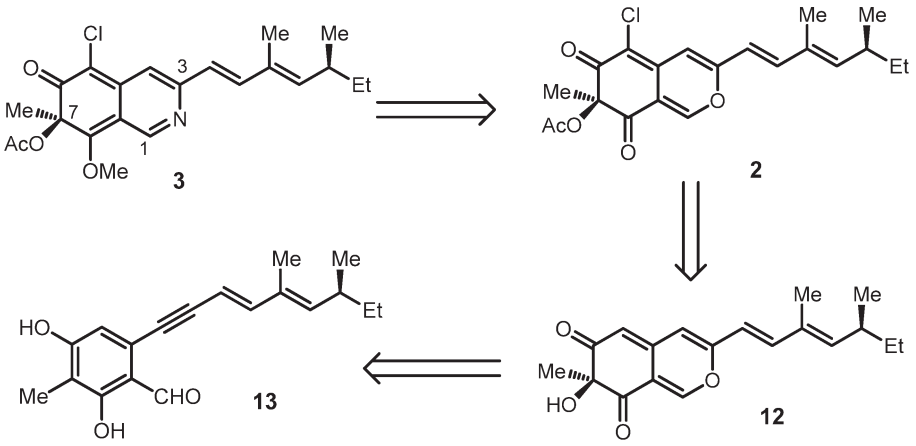
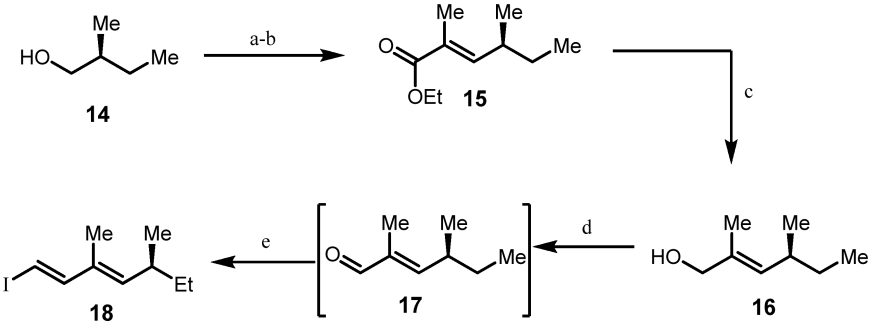


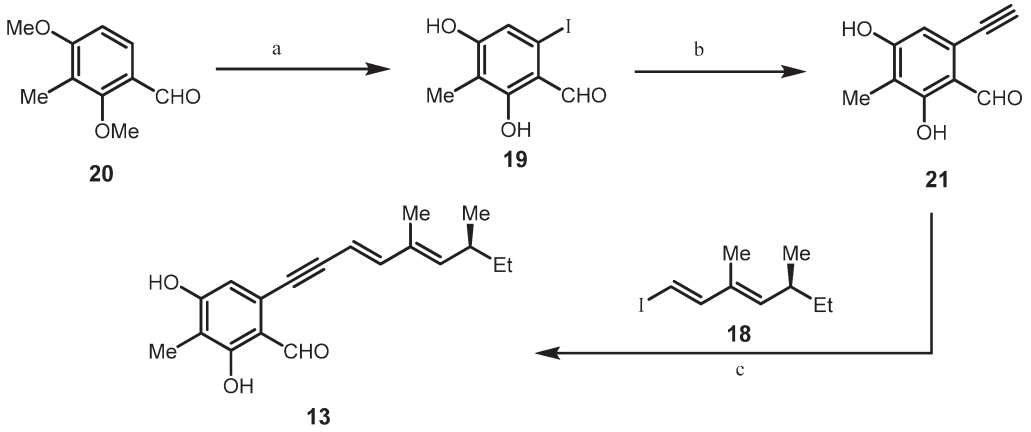
Figure 2. Retrosynthetic analysis for 8-*O*-methylsclerotiorinamine **3**.

Scheme 1. Synthesis of Iodo Diene 18[a]



[a] Conditions: (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2 0 °C, 3 h; (b) (carboethoxyethylidene)triphenylphosphorane, reflux, 12 h, 85%, 20:1 *E*:*Z*; (c) DIBAl-H, CH_2Cl_2,rt, 2 h, 55%; (d) MnO_2, THF, 24 h; (e) $CrCl_2$, CHI_3, dioxane/THF 6:1, 2 h, 0 °C, 65% yield 2 steps, 10:1 *E*:*Z*.

Scheme 2. Synthesis of Alkynylbenzaldehyde 13[a]



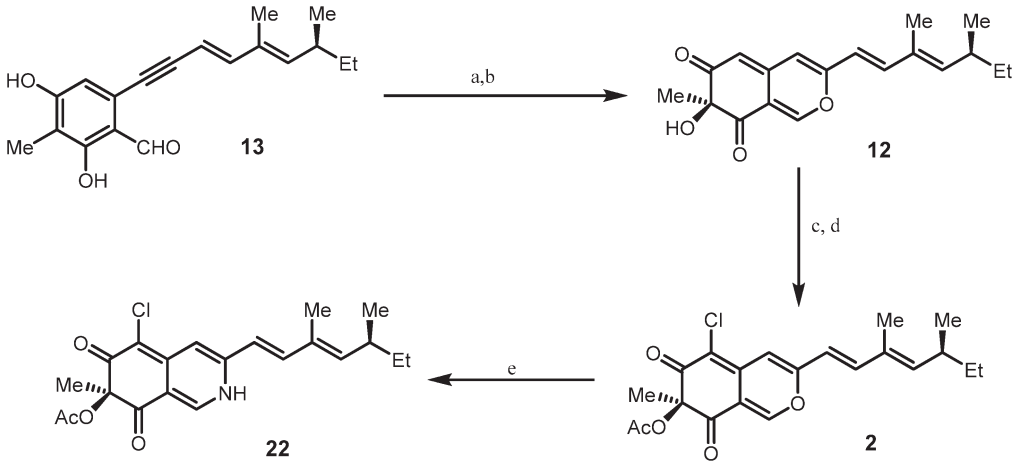
[a] Conditions: (a) *N*,*N*,*N*′-trimethylethylenediamine, *n*-BuLi, THF, 0 °C 30 min; *n*-BuLi, THF, −20 °C, 16 h, then 1,2-diiodoethane; BBr_3, CH_2Cl_2, 18 h (33% yield 3 steps; (b) CuI, trimethylsilylacetylene, $(t\text{-Bu})_3P\text{-}HBF_4$, $PdCl_2(CH_3CN)_4$, diisopropylamine, rt, 12 h, then K_2CO_3, MeOH, rt, 1 h 80%, 2 steps; (c) $Pd(PPh_3)_4$, CuI, Et_3N, 12 h, rt, 55%.

chlorinated (*N*-chlorosuccinimide, NCS) to afford the natural product sclerotiorin **2** (65% yield for two steps). Amination of **2** with ammonium acetate provided the vinylogous pyridone sclerotiorinamine **22** (60% yield).[18]

During the synthesis of (+)-sclerotiorin **2**, we found that the azaphilone core **12** was formed as a mixture of two compounds in a ∼10:1 ratio after silica gel purification. On the basis of comparison with related azaphilones such as isochromophilone I and II that contain the same dienyl side chain, we determined that the minor compound was the azaphilone containing a *Z*-double bond at C11−C12.[19] The minor isomer is generally seen as a minor component during isolation; however, the two olefin

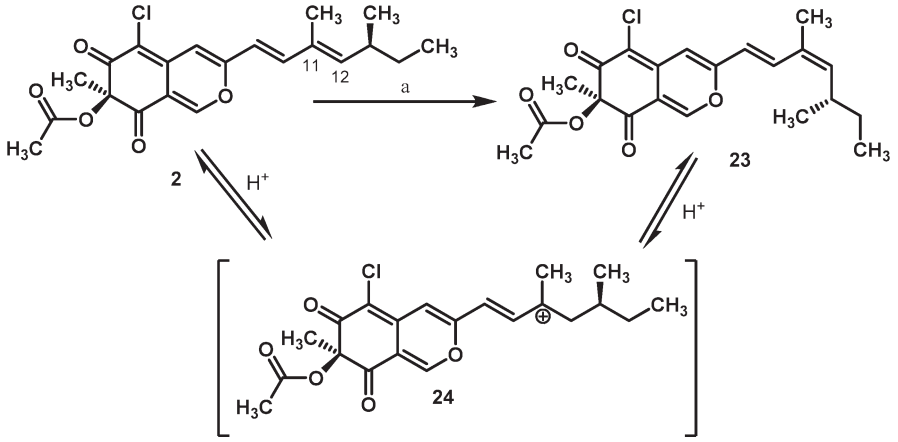
dx.doi.org/10.1021/jo102448n |*J. Org. Chem.* 2011, 76, 2577–2584

Scheme 3. Synthesis of (+)-Sclerotioin 2[a]



[a] Conditions: (a) 2.2 equiv of $Cu(CH_3CN)_4PF_6$, 2.4 equiv of *N*-ethyl-(+)-sparteine mimic **6**, 1.6 equiv of DIEA, 2.4 equiv of DMAP, O_2, −78 °C to −10 °C; (b) aq H_2PO_4/K_2HPO_4 buffer (pH 7.2), CH_3CN, rt 76% over two steps; (c) acetic anhydride, DMAP, DIEA, 0 °C, 30 min; (d) NCS, CH_3CN, rt, 24 h 65% over two steps; (e) NH_4OAc, MeOH, 30 min, 60%.

Scheme 4. Isomerization of the C11−C12 Olefin[a]



[a] Conditions: (a) SiO_2, ethyl acetate, 1 h.

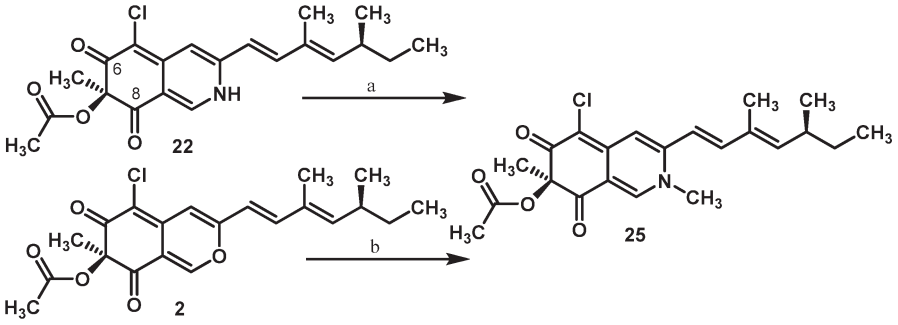
isomers have been reported to interconvert.[20] Through analyses of the isolation procedures of azaphilones containing the dienyl side chain, it was determined that the minor *E,Z* isomer (*cf.* Scheme 4) is present in compounds that have been purified using silica gel chromatography. Accordingly, we suspected that azaphilones bearing dienyl side chains were prone to mild acid-catalyzed olefin isomerization. The latter was confirmed by treating a natural sample of (+)-sclerotiorin **2** with silica gel which resulted in a mixture of **2**:**23** in ~10:1 ratio (Scheme 4). We believe that the facile isomerization results from protonation of **2** to afford the stabilized carbocation **24**, which allows for equilibration between **2** and **23**.[8] The minor isomer **23** may affect the optical rotation of (+)-sclerotiorin, limiting comparison of optical rotations of synthetic ($[\alpha]^{22}_D$ = +163) and natural samples ($[\alpha]^{22}_D$ = +133).

With a sample of sclerotiorinamine **22** in hand, we next investigated conditions for *O*-methylation[21] to access the congener 8-*O*-methylsclerotiorinamine. After screening of various reported methylation procedures, it was found that selective *N*-methylation could be obtained upon treatment of **22** with trimethyloxonium tetrafluoroborate (Me_3OBF_4) with diisopropylamine as base (0 °C) to afford *N*-methylsclerotiorinamine **25** (Scheme 5) (85% yield). The selectivity for *N*-methylation was confirmed by alternative synthesis of **25** by treatment of (+)-sclerotiorin **2** with methylamine (>95%).[22] Interestingly, methylation of **22** with Me_3OBF_4 and 2,6-di-*tert*-butylpyridine (DTBP) as base led to apparent methylation of the C6-oxygen based on the crude NMR spectra. However, the presumed 7,8-dihydroisoquinoline was found to be unstable to purification and isolation. It is possible that utilization of a weaker base may alter the selectivity from *N*- to *O*-methylation by not significantly deprotonating the N−H of the vinylogous amide until activation by *O*-alkylation. Other attempts to employ alternant electrophilic methylating agents (e.g., methyl triflate) and various weak bases did not result in isolable products.

A related method for *O*-methylation of amides involves treatment with diazomethane (CH_2N_2).[23] These reactions generally proceed without the need for base, likely arising from methylation of the enol tautomer of the amide. Gratifyingly, treatment of vinylogous pyridine **22** with trimethylsilyldiazomethane[24] in a mixture of

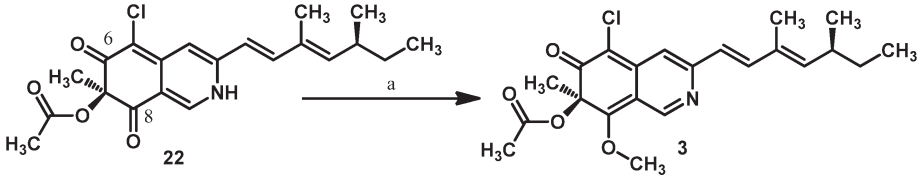
dx.doi.org/10.1021/jo102448n |*J. Org. Chem.* 2011, 76, 2577–2584

Scheme 5. Synthesis of *N*-Methylsclerotiorinamine 25[a]



[a] Conditions: (a) Me_3OBF_4, *i*Pr_2NH, THF, 85%; (b) methylamine, THF, >95%

Scheme 6. Synthesis of (+)-8-*O*-Methylsclerotiorinamine 3[a]



[a] Conditions: (a) $TMSCHN_2$, CH_2Cl_2:MeOH 9:1, quantitative.

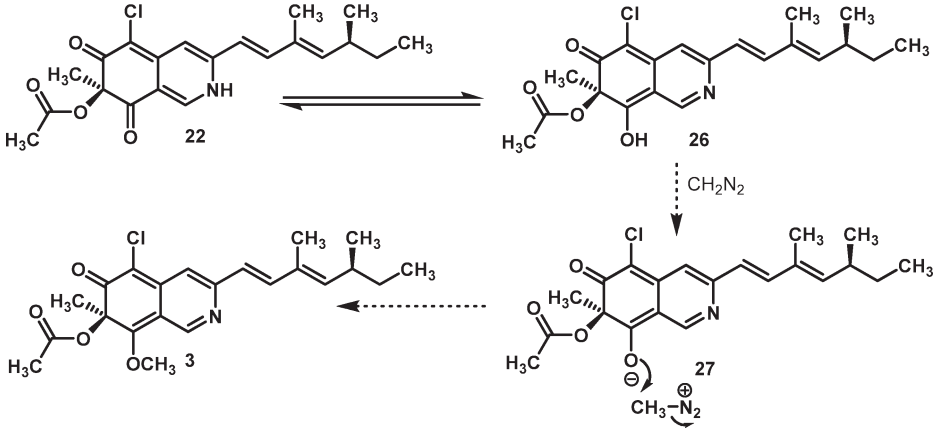


Figure 3. Proposed mechanism for *O*-methylation.

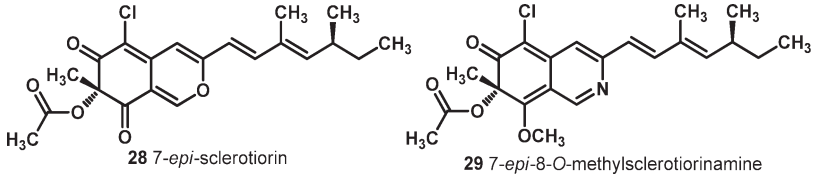


Figure 4. Epimers of the azaphilone natural products.

dichloromethane and methanol resulted in quantitative formation of 8-*O*-methylsclerotiorinamine **3** (Scheme 6), which had spectroscopic data consistent with that reported in the literature including the optical rotation ($[\alpha]^{22}_D = +104$, lit. reported $[\alpha]^{22}_D = +102$) (Scheme 7).[5d] In the case at hand, derived enol **26** may be deprotonated by CH_2N_2 to give ion pair **27**, which may expel nitrogen to yield **3** (Figure 3). Presumably, in this case selective methylation at C8 was observed[8] due to steric congestion around the C6 ketone.

7-*epi*-Sclerotiorin **28**, a naturally occurring diasteromer of (+)-sclerotiorin varying only at the C7 stereocenter[5c] and the analogous 7-*epi*-8-*O*-methylsclerotiorinamine **29** were synthesized using the same synthetic sequence described above[8] by substituting *N*-ethyl (+)-sparteine surrogate **6** for (−)-sparteine in the copper-mediated, oxidative dearomatization (Figure 4). Comparison of both diastereomers of the natural products with the rotation of the natural samples thus confirms the stereochemistry of 8-*O*-methylsclerotiorinamine.[8]

dx.doi.org/10.1021/jo102448n |*J. Org. Chem.* 2011, 76, 2577–2584

CONCLUSION

We have developed methodology to access azaphilone natural products containing the natural *S*-configuration at the quaternary center found in various members of this family utilizing (+)-sparteine surrogates. The methodology has been utilized in the asymmetric syntheses of the azaphilone natural products (+)-sclerotiorin **2** and (+)-8-*O*-methylsclerotiorinamine **3**. Further studies toward the synthesis of related natural products and biological evaluation of **2**, **3**, and related molecules will be reported in due course.

EXPERIMENTAL SECTION

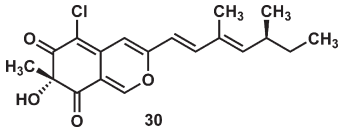
Azaphilone Core 11. Alkynylbenzaldehyde **10** (27 mg, 0.10 mmol) and *N*,*N*-diisopropylethylamine (DIEA) (28 μL, 0.16 mmol) in 400 μL of CH_2Cl_2 solution were added to the $Cu_2L_2O_2$ complex prepared from $Cu(CH_3CN)_4PF_6$ (82 mg, 0.22 mmol) and (−)-sparteine (56 μL, 0.24 mmol) in 1.6 mL of anhydrous CH_2Cl_2 under an oxygen atmosphere at −78 °C. After 5 min, 4-dimethylaminopyridine (29.2 mg, 0.24 mmol) in 400 μL of CH_2Cl_2 was added, and the mixture was warmed and stirred at −10 °C for 30 h under an oxygen atmosphere. The reaction was quenched at −10 °C with 2 mL of 10% sulfuric acid and 2 mL of satd brine. The mixture was extracted three times with EtOAc, and the combined extracts were concentrated *in vacuo*. The crude residue was dissolved in 2.0 mL of CH_3CN, and 1.0 mL of 1:1.6 aqueous KH_2PO_4/K_2HPO_4 buffer (pH 7.2, prepared by dissolving 1.7 g KH_2PO_4 and 3.5 g K_2HPO_4 in 50 mL of distilled water) was added to the solution. The resulting heterogeneous mixture was stirred at room temperature for 1 h. 10% H_2SO_4 was added dropwise to the reaction mixture to adjust the pH to 2−3. The resulting mixture was extracted three times with EtOAc. The organic extracts were dried over anhydrous Na_2SO_4, concentrated, and purified on silica gel (hexane/EtOAc = 10:1 to 2:1) to afford azaphilone core **11**. The ^{1}H, ^{13}C NMR, IR, and CIHRMS were found to be identical to those previously reported.[2] The enantiomeric excesses for **11** was determined using a HPLC (Chiralcel OD, 15% ^{i}PrOH in hexane, 1.0 mL/min) using UV detection at 320 nm and are listed in Table 1 corresponding to the ligand used.

2-Iodo-4,6-dihydroxy-5-methylbenzaldehyde 19. *N*,*N*,*N*′-Trimethylethylenediamine (4.0 mL, 30.5 mmol) was dissolved in 200 mL of THF. A solution of 1.9 M *n*BuLi (15 mL, 36.7 mmol) was added at 0 °C. After stirring for 15 min, the reaction was cooled to −20 °C, and a solution of benzaldehyde **20** (5.0 g, 27.7 mmol) in 50 mL of THF was added. The mixture was stirred for 30 min, and then a solution of 1.9 M *n*BuLi (45 mL, 73.3 mmol) was added dropwise. The reaction was stirred overnight. The solution was cooled to −40 °C, and a solution of diiodoethane (23.5 g, 83.2 mmol) in 50 mL of THF was added dropwise. After 5 min, the reaction was warmed to room temperature, and the reaction was quenched by addition of saturated ammonium chloride (100 mL), followed by saturated sodium thiosulfate (40 mL), and finally extracted three times with diethyl ether (3 × 120 mL). The organic layer was concentrated *in vacuo* and purified on silica (ethyl acetate/hexanes 1:10) to yield **19** (2.8 g, 33% yield, three steps) as a faint yellow powder. Mp 75−77 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.25 (1H, s), 6.91 (1H, s), 3.88 (3H, s), 3.79 (3H, s), 2.08 (3H, s); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 189.6, 162.7, 161.8, 124.0, 120.68, 120.65, 112.2, 62.3, 55.9, 8.1; IR (thin film) 2944, 1685, 1584, 1559, 1456, 1376, 1283, 1234, 1133, 1019, 816 cm^{-1}; CIHRMS M^+ calculated for $C_8H_7IO_3$ 278.9518, found 278.9520.

Vinyl Iodide 18. To $CrCl_2$ (5.4 g, 43.7 mmol) was added anhydrous THF (75 mL) at 0 °C. In a separate flask, unsaturated aldehyde **17** (1.0 g, 7.9 mmol) and iodoform (4.3 g, 11.0 mmol) were added to anhydrous THF (45 mL). The aldehyde mixture was added to the reaction mixture *via* cannula dropwise, and the resulting mixture was stirred for 1 h. The reaction was filtered through Celite and then washed with ether. The filtrate was finally washed with water and brine, and the organic layer was dried with sodium sulfate, filtered, and concentrated *in vacuo*. The concentrated material was passed through a plug of neutral alumina (hexanes) to afford vinyl iodide **18** as a light yellow oil 1.28 g (65% yield, 10:1 *E*:*Z* by ^{1}H NMR analysis). Due to stability issues, **18** was used immediately and was not fully characterized. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (1H, d, J = 15.3 Hz), 6.12 (1H, d, J = 15.3 Hz), 5.24 (1H, d, J = 10.2 Hz), 2.35 (1H, m), 1.70 (3H, s), 1.40 (2H, m), 0.95 (3H d), 0.83 (3H,t, J = 7.5 Hz).

Dienyne-benzaldehyde 13. An oven-dried round-bottom flask containing a mixture of vinyl iodide **18** (639 mg, 2.556 mmol), $PdCl_2(PPh_3)_2$ (60 mg, 0.084 mmol), and CuI (6.6 mg, 0.033 mmol) was evacuated and refilled with argon. Anhydrous triethylamine (6.0 mL, *x* mmol) was added dropwise, and the reaction was stirred at rt for 10 min. Alkynylbenzaldehyde **21** (300 mg, 1.70 mmol) in 3 mL of THF was added. The resulting mixture was stirred at room temperature until complete conversion of **21** was observed (TLC analysis). The reaction mixture was diluted with water, carefully neutralized with 0.1 N aqueous HCl, and extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification on silica gel (hexane/EtOAc = 10:1) provided 279 mg (55%) of enyne benzaldehyde **13** as a yellow solid. Mp 149−154 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.34 (1H, s), 10.21 (1H, s), 6.72 (1H, d, J = 16 Hz), 6.49 (1H, s), 5.69 (1H, d, J = 16 Hz), 5.44 (2H, ovrlp), 2.40 (1H, m), 2.10 (3H, s) 1.76 (3H, s), 1.36 (2H, m), 0.97 (3H, d, J = 6.8 Hz), 0.84 (3H, t, J = 7.6 Hz) ; ^{13}C NMR (75.0 MHz, acetone-d_6) δ 195.3, 163.3, 160.7, 148.8, 144.4, 132.6, 131.9, 128.7, 127.3, 114.3, 112.2, 104.0, 96.3, 85.5, 34.9, 30.4, 20.6, 12.3, 7.4; IR (thin film) 3161 (br), 2922, 2360, 1595, 1457, 1288, 1259 cm^{-1}; ESIHRMS $[M + H]^+$ calculated for $C_{19}H_{23}O_3$ 299.1667, found $C_{19}H_{23}O_3$ 299.1647. $[\alpha]^{22}_D$ = +14.0 (*c* 0.3, $CHCl_3$).

Azaphilone 12. Alkynylbenzaldehyde **13** (27 mg, 0.10 mmol) and *N*,*N*-diisopropylethylamine (DIEA) (28 μL, 0.16 mmol) in 400 μL of CH_2Cl_2 solution were added to the $Cu_2L_2O_2$ complex prepared from $Cu(CH_3CN)_4PF_6$ (82 mg, 0.22 mmol) and *N*-ethyl-(+)-sparteine mimic **6** (56 μL, 0.24 mmol) in 1.6 mL of anhydrous CH_2Cl_2 under an oxygen atmosphere at −78 °C. After 5 min, 4-dimethylaminopyridine (29 mg, 0.24 mmol) in 400 μL was added, and the mixture was warmed and stirred at −10 °C for 30 h under an oxygen atmosphere. The reaction was quenched at −10 °C with 2 mL of 10% sulfuric acid and 2 mL of satd brine. The mixture was extracted three times with EtOAc, and the combined extracts were concentrated *in vacuo*. The crude residue was dissolved in 2.0 mL of CH_3CN, and 1.0 mL of 1:1.6 aqueous KH_2PO_4/K_2HPO_4 buffer (pH 7.2, prepared by dissolving 1.7 g KH_2PO_4 and 3.5 g K_2HPO_4 in 50 mL of distilled water) was added to the solution. The resulting heterogeneous mixture was stirred at room temperature for 1 h. 10% H_2SO_4 was added dropwise to the reaction mixture to adjust the pH to 2−3. The resulting mixture was extracted three times with EtOAc. The organic extracts were dried over anhydrous Na_2SO_4, concentrated, and purified on silica gel (hexane/EtOAc = 10:1 to 2:1) to afford azaphilone core **12** as a red oil (76% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (1H, s), 6.95 (1H, d, J = 15.6 Hz), 6.13 (1H, s), 5.90 (1H, d, J = 15.6 Hz), 5.60 (1H, d, J = 9.6 Hz), 5.51 (1H, s), 3.88 (1H, s), 2.40 (2H, m) 1.75 (3H, s), 1.50 (3H, s), 1.33 (2H, m), 0.93 (3H, d, J = 6.4 Hz), 0.79 (3H, s); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 196.0, 156.9, 152.5, 148.3, 144.2, 142.1, 131.8, 115.9, 108.8, 105.5, 83.4, 35.1, 30.1, 28.7, 12.3, 12.0; IR (thin film) 3431 (br), 2961, 2360, 1616, 1540, 1172, 838 cm^{-1} $[\alpha]^{22}_D$ = +82.0 (*c* 0.1, $CHCl_3$).



30

7-*epi*-Azaphilone 30. Azaphilone **30** was synthesized following the same procedure as above for (+)-**12**, except for the replacement of

ligand **6** with (−)-sparteine **4**. All spectroscopic data was indistinguishable from (+)-**12**. $[\alpha]^{22}_{D} = -62.0$ (*c* 0.1, $CHCl_3$).

(+)-Sclerotiorin 2. To azaphilone (+)-**12** (120 mg, 0.41 mmol) in 3 mL of methylene chloride at 0 °C were added acetic anhydride (77 μL, 0.82 mmol) and *N*, *N*-diisopropylethylamine (80 μL, 0.45 mmol). The resulting mixture was stirred at 0 °C for 30 m. The reaction mixture was quenched with water, extracted three times with ethyl acetate, washed with 1 N HCl, washed three times with water, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was dissolved in acetonitrile (3 mL) and *N*-chlorosuccinimide (129 mg, 0.96 mmol) was added. The reaction vessel was covered with aluminum foil and stirred at room temperature until ^{1}H NMR analysis indicated completion of the reaction. The reaction mixture was diluted with ethyl acetate, washed with water, the organic extracts dried over anhydrous Na_2SO_4, concentrated, and purified on silica gel (hexane/EtOAc = 10:1 to 2:1) to yield sclerotiorin **2** as a red oil (65%, two steps). The synthetic sample matched the ^{1}H, ^{13}C, and mass spectrum of the natural product. However due to the presence of a small amount of olefin isomer the optical rotations were not comparable. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (1H, s), 7.05 (1H, d, *J* = 15.6 Hz), 6.62 (1H, s), 6.07 (1H, d, *J* = 15.6 Hz), 5.69 (1H, d, *J* = 9.6 Hz), 2.45 (1H, m), 2.15 (3H, s), 1.82 (3H, s) 1.54 (3H, s), 1.39 (2H, m), 1.33 (2H, m), 0.99 (3H, s), 0.85 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 196.0, 186.2, 170.3, 158.3, 152.9, 149.1, 143.1, 138.9, 132.2, 115.9, 114.7, 111.0, 106.6, 84.8, 35.3, 30.3, 22.7, 20.4, 20.3, 12.6, 12.2; IR (thin film) 3438 (br), 2924, 2853, 1631 cm^{-1} CIHRMS M^+ calculated for $C_{21}H_{24}O_5Cl$ 391.1312, found 391.1333. $[\alpha]^{22}_{D} = +163.0$ (*c* 0.1, EtOH), lit. reported $[\alpha]^{22}_{D} = +133.0°$ (*c* 0.3, EtOH).

***7-epi*-Sclerotiorin 28.** Starting from **30**, the same procedure employed to prepare (+)-**2** was followed. All spectroscopic data was undistinguishable from (+)-**2**. $[\alpha]^{22}_{D} = -103.0$ (*c* 0.1, EtOH).

Sclerotiorinamine (+)-22. To sclerotiorin (+)-**2** (217 mg, 0.59 mmol) in THF (6 mL) was added ammonium acetate (54.8 mg, 0.71 mmol). The reaction mixture was stirred at room temperature until TLC indicated completion of the reaction. The mixture was diluted with water, extracted three times with ethyl acetate, washed with water, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to yield sclerotiorinamine **22** as an orange oil (229 mg, 100%) which was used directly in the next step without further purification.

***N*-Methylsclerotiorinamine (+)-25.** Sclerotiorinamine (+)-**22** (4.3 mg, 0.01 mmol) in CH_2Cl_2 (200 μL) was cooled to 0 °C. Trimethyloxonium tetrafluoroborate (3.6 mg, 0.24 mmol) was added, followed by the slow addition of diisopropylamine (4.2 μL, 0.02 mmol). The reaction was stirred at 0 °C until completion of the reaction was observed (TLC analysis). Purification over silica (EtOAc) provided *N*-methylsclerotiorinamine (+)-**25** as a red oil (3.4 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (1H, s), 7.04 (1H, s), 6.97 (1H, d, 15.6 Hz), 6.12 (1H, d, 15.6 Hz), 5.72 (1H, d, 9.8 Hz), 3.62 (3H, s), 2.46 (1H, m), 2.17 (3H, s), 1.86 (3H, s), 1.54 (3H, s), 1.43 (1H, ovrlp), 1.34 (1H, ovrlp), 1.01 (3H, d, 6.9 Hz), 0.88 (3H, t, 7.5 Hz); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ194.0, 184.6, 170.4, 148.7, 146.3, 145.3, 145.0, 142.1, 131.9, 114.8, 114.7, 111.4, 102.4, 85.0, 42.1, 35.3, 30.3, 23.5, 20.6, 20.5, 12.8, 12.3; IR (thin film) 2961, 2922, 2360, 1734, 1703, 1593, 1500, 1253, 1201 cm^{-1} CIHRMS M^+ calculated for $C_{22}H_{26}NO_4Cl$ 404.1629, found 404.1625. $[\alpha]^{22}_{D} = +114$ (lit. reported = +112)[5d] (*c* 0.1, CH_3OH).

(+)-8-*O*-Methylsclerotiorinamine (+)-3. To sclerotiorinamine **22** (25 mg, 0.064 mmol) in CH_2Cl_2:MeOH 9:1 (5 mL) was added trimethylsilyldiazomethane (2.0*M* in diethylether) (160 μL, 0.3 mmol). The reaction was stirred at rt for 1 h. Purification using silica gel chromatography (ether/hexanes 2:3) provided (+)-8-*O*-methylsclerotiorinamine **3** as an orange gum (26 mg, >95%.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (1H, s), 7.55 (1H, s), 7.5 (1H, d, *J* = 15.9 Hz), 6.60 (1H, d, 16 Hz), 5.71 (1H, d, 9.6 Hz), 4.01 (3H, s), 2.49 (1H, m), 2.10 (3H, s), 1.84 (3H, s), 1.55 (3H, s), 1.43 (2H, m), 1.34 (1H, m), 0.99 (3H, d, *J* = 9.6 Hz), 0.87 (3H, t, *J* = 7.5 Hz); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ192.7, 170.1, 162.4, 159.6, 149.5, 146.6, 143.1, 132.5, 130.5, 124.6, 119.1, 115.5, 111.5, 80.7, 61.9, 34.9, 30.2, 23.1, 20.4, 20.4, 12.6, 12.0; IR (thin film) 2961, 2871, 1742, 1696, 1611, 1579, 1279, 1248 cm^{-1} CIHRMS M^+ calculated for $C_{22}H_{26}NO_4Cl$ 404.1629, found 404.1635. $[\alpha]^{22}_{D} = +104$ (lit. reported = +102) (*c* 0.1, CH_3OH). All spectroscopic data matched those reported in the literature.[5d]

***7-epi*-8-*O*-Methylsclerotiorinamine 29.** Starting from (−)-sclerotiorinamine **30**, the same procedure to synthesize (+)-**22** and (+)-**3** was followed to produce **29**. All spectroscopic data were indistinguishable from (+)-**3**. ($[\alpha]^{22}_{D} = -80$ (*c* 0.1, CH_3OH).

■ ASSOCIATED CONTENT

Supporting Information. Complete experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
*E-mail: porco@bu.edu.

■ ACKNOWLEDGMENT

This work was generously supported by the National Institutes of Health (GM-073855), Wyeth Research, and Merck Research Laboratories. We also thank the NSF (CHE-0443618) for the high resolution mass spectrometer used in this work.

■ REFERENCES

(1) Osmanova, N.; Schultze, W.; Ayoub, N. *Phytochem. Rev.* **2010**, *9*, 3115.
(2) Zhu, J.; Grigoriadis, N.; Lee, J. P.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2005**, *127*, 9342.
(3) Dong, S.; Zhu, J.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2008**, *130*, 2738.
(4) Funahashi, Y.; Nakaya, K.; Hirota, S.; Yamauchi, O. *Chem. Lett.* **2000**, 1172.
(5) Sclerotiorin: (a) MacCurtin, T.; Reilly, J. *Nature* **1940**, *146*, 335. (b) Eade, R. A.; Page, H.; Robertson, A.; Turner, K.; Whalley, W. B. *J. Chem. Soc.* **1957**, 4913. (c) Whalley, W. B.; Ferguson, G.; Marsh, W. C.; Restivo, R. J. *J. Chem. Soc., Perkin 1* **1976**, *13*, 1366. 8-*O*-Methylsclerotiorinamine:(d) Nam, J.-Y.; Kim, H.-K.; Kwon, J-Y; Han, M. Y.; Son, K-H; Lee, U. C.; Choi, J.-D.; Kwon, B.-M. *J. Nat. Prod.* **2000**, *63*, 1303.
(6) (a) Ebner, T.; Eichelbaum, M.; Fischer, P.; Meese, C. O. *Arch. Pharm. (Weinheim)* **1989**, *322*, 399. (b) Smith, B. T; Wendt, J. A.; Aube, J. *Org. Lett.* **2002**, *4*, 2577.
(7) (a) Dearden, M. J.; Firkin, C. R.; Hermet, J.-P.; O'Brien, P. *J. Am. Chem. Soc.* **2002**, *124*, 11870. (b) Dearden, M. J.; McGrath, M. J.; O'Brien, P. *J. Org. Chem.* **2004**, *69*, 5789. (c) Ebner, D. C.; Trend, R. M.; Genet, C.; McGrath, M. J.; O'Brien, P.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 6367. (d) O'Brien, P. *Chem. Commun.* **2008**, 655. (e) Bilke, J. L.; Moore, S. P.; O'Brien, P.; Gilday, J. *Org. Lett.* **2009**, *11*, 1935. (f) Stead, D.; Carbone, G.; O'Brien, P.; Campos, K. R.; Sanderson, A. *J. Am. Chem. Soc.* **2010**, *132*, 7260. (g) Carbone, G.; O'Brien, P.; Hilmersson, G. *J. Am. Chem. Soc.* **2010**, *132*, 15445.
(8) See Supporting Information for complete experimental details.
(9) For representative examples of internal oxidation of ligands in $L_2Cu_2O_2$ complexes, see: (a) Mahapatra, S.; Halfen, J. A.; Tolman, W. B. *J. Am. Chem. Soc.* **1994**, *116*, 9785. (b) Mahadevan, V.; Hou, Z.; Cole, A. P.; Root, D. E.; Lal, T. K.; Solomon, E. I.; Stack, T. D. *J. Am. Chem. Soc.* **1997**, *119*, 11996. (c) Itoh, S.; Nakao, H.; Berreau, L. M.; Kondo, T.; Komatsu, M.; Fukuzumi, S. *J. Am. Chem. Soc.* **1998**, *120*, 2890.

(10) Lipoxygenase: (a) Nam, J.-Y.; Son, K.-H.; Kim, H.-Y.; Han, M.-Y.; Kim, S.-U.; Choi, J.-D.; Kwon, B.-M. *J. Microbiol. Biotechnol.* **2000**, *10*, 544. (b) Chidananda, C.; Rao, L.; Jagan, M.; Sattur, A. P. *Biotechnol. Lett.* **2006**, *28*, 1633. Grb2-Shc: (c) Chidananda, C.; Sattur, A. P. *J. Agric. Food. Chem.* **2007**, *55*, 2879. Aldose reductase: cholesteryl ester transfer protein:(d) Tomoda, H.; Matsushima, C.; Tabata, N.; Namatame, I.; Tanaka, H.; Bamberger, M. J.; Arai, H.; Fukazawa, M.; Inoue, K.; Omura, S. *J. Antibiot.* **1999**, *52*, 160.

(11) Zelle, R. E.; Deninno, M. P.; Selnick, H. G.; Danishefsky, S. J. *J. Org. Chem.* **1986**, *51*, 5032.

(12) Ramamoorthy, G.; Acevedo, C. M.; Alvira, E.; Lipton, M. A. *Tetrahedron: Asymmetry* **2008**, *19*, 2546.

(13) Couladouros, E. A.; Bouzas, E. A.; Magos, A. D. *Tetrahedron* **2006**, *62*, 5272.

(14) For a related route to the bromide congener of **19**, see: Clark, R. C.; Lee, S. Y.; Boger, D. L. *J. Am. Chem. Soc.* **2008**, *130*, 12355.

(15) Zhu, J.; Germain, A. R.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2004**, *43*, 1239.

(16) Lang, M.; Steglich, W. *Synthesis* **2005**, 1019.

(17) Zhu, J.; Porco, J. A., Jr. *Org. Lett.* **2006**, *8*, 5169.

(18) Natsume, M.; Takahashi, Y.; Marumo, S. *Agric. Biol. Chem.* **1988**, *52*, 307.

(19) (a) Fujimoto, H.; Matsudo, T.; Yamaguchi, A.; Yamazaki, M. *Heterocycles* **1990**, *30*, 607. (b) Matsuzaki, K.; Tanaka, H.; Omura, S. *J. Antibiot.* **1995**, *48*, 708.

(20) Matsuzaki, K.; Ikeda, H.; Masuma, R.; Tanaka, H.; Omura, S. *J. Antibiot.* **1995**, *48*, 703.

(21) For *N*- and *O*-methylation of pyridones, see: Chung, N. M.; Tieckelmann, H. *J. Org. Chem.* **1970**, *35*, 2517.

(22) For formation of vinylogous pyridones from azaphilones, see: Wei, W.-G.; Yao, Z.-J. *J. Org. Chem.* **2005**, *70*, 4585.

(23) Lei, Y. X.; Rappoport, Z. *J. Org. Chem.* **2002**, *67*, 6971.

(24) (a) Aoyama, T.; Terasawa, S.; Sudo, K.; Shioiri, T. *Chem. Pharm. Bull.* **1984**, *32*, 3759. (b) Kuhnel, E.; Laffan, D. D. P.; Lloyd-Jones, G. C.; Martinez, T.; Shepperson, I. R.; Slaughter, J. L. *Angew. Chem., Int. Ed.* **2007**, *119*, 7205.