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Heteroatom-Directed Reverse Wacker Oxidations. Synthesis of the Reported Structure of (−)-Herbaric Acid

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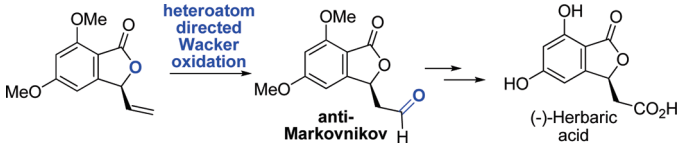
Received August 22, 2010



A microwave-assisted chemoenzymatic resolution has been used to install the C3 stereocenter of the reported structure of the fungal metabolite herbaric acid in high enantiomeric excess. The synthesis and stereochemical assignment was accomplished using a completely regioselective anti-Markovnikov addition of water to vinylphthalide **3**, achieved using a heteroatom-directed Wacker oxidation that proceeds with retention of stereochemistry. These results establish that so-called "reverse" Wacker oxidations are a viable alternative to hydroboration/oxidation procedures.

Introduction

The phthalide [1(3*H*)-isobenzofuranone] moiety is present in a rich and diverse group of natural products.[1] A smaller subset of this class are phthalides that contain a chiral C3-substituent, many of which possess a vast array of biological activities. Representative examples include spirolaxine methyl ether,[2a] hydrastine,[2b] vermastatin,[2c] alcyopterosin,[2d] typhaphthalide,[2e] 3-butylphthalide,[2f] and herbaric acid[2g] (Figure 1).

Significant effort has been directed toward the synthesis of phthalides bearing 3-alkyl substituents. Existing asymmetric methods primarily involve the use of chiral auxiliaries[3] and chiral organometallics,[4] but recently reported organocatalytic[5] and hydroacylation[6] methodologies have provided elegant additions to the synthetic repertoire. Nonetheless, efficient new methods for the asymmetric synthesis of this medicinally important motif are highly sought after. Herein, we report a procedure for the efficient installation of the phthalide C-3 stereocenter using an operationally simple microwave-assisted enzymatic resolution. Furthermore, an entirely regioselective anti-Markovnikov hydroxypalladation of the chiral 3-vinylphthalide intermediate used herein demonstrates that heteroatom-directed Wacker oxidations are a useful alternative for the synthesis of aldehydes from terminal alkenes.[7] The synthetic utility of these methodologies is further exemplified by the synthesis and stereochemical assignment of the reported structure of the fungal metabolite (−)-herbaric acid **1**.

Results and Discussion

Our initially planned retrosynthesis of herbaric acid is shown in Scheme 1, involving oxidation and deprotection of aldehyde **2**. It was envisaged that upon subjecting vinylphthalide **3** to Wacker oxidation conditions, the bridging oxygen

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Published on Web 09/27/2010 DOI: 10.1021/jo1016585

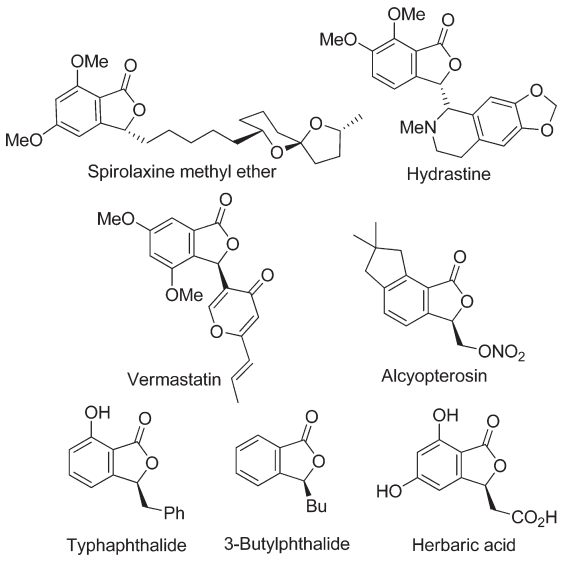
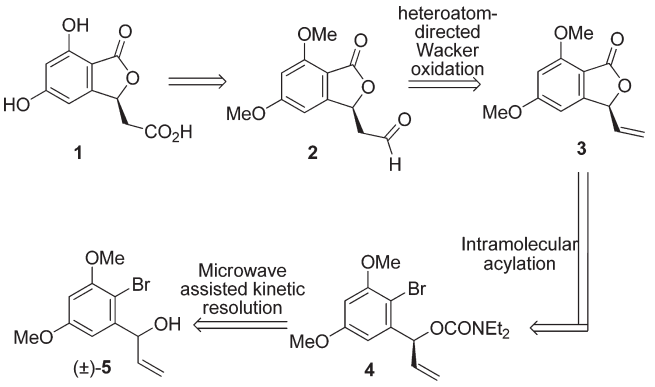


FIGURE 1. Phthalide natural products.

SCHEME 1. Retrosynthetic Analysis of Herbaric Acid 1



present in the lactone would provide an anchor enabling chelation to palladium, thereby facilitating delivery of water to the methylene carbon and affording the desired aldehyde **2**. The successful realization of this heteroatom-directed Wacker oxidation would provide a basis for a convenient and mild alternative to hydroboration/oxidation, a harsh procedure traditionally used for the synthesis of aldehydes from terminal alkenes.[8] The chiral vinylphthalide **3** would be constructed by lactonization of carbamate **4**, which in turn is accessed using our recently described microwave-assisted kinetic resolution[9] of benzylic alcohol (±)-**5**.

With these ideas in mind, the synthesis of the enantioenriched alkene **3** was initiated (Scheme 2). Smooth Grignard addition of vinylmagnesium bromide to the readily available benzaldehyde[10] **6** provided (±)-benzylic alcohol **5**, the substrate for the key kinetic resolution (Table 1). Previous experience in our laboratory has established that the optimum conditions for this microwave-assisted chemoenzymatic resolution used toluene and *p*-chlorophenyl acetate **7** as the solvent and acyl donor, respectively.[9] Preliminary screening of the conversion of (±)-**5** to (*S*)-**5** and (*R*)-**8** using several solvents and acyl donors confirmed these conditions as the most promising, and further optimization of these baseline conditions is shown in Table 1. Conventional heating (entry 1) led to disappointing enantioselectivities, as did the use of microwave heating in an open vessel (entry 2). After much experimentation, it was eventually found that microwave irradiation using a closed vessel (entries 3−5) was vital for the success of this reaction, as was the careful monitoring of the total reaction time. Gratifyingly, conducting the resolution for 48 h led to a 50% yield of (*S*)-**5** with good enantioselectivity. The resolution showed no appreciable drop in yield or enantioselectivity upon scale-up and was routinely conducted on a 2 g scale. The stereochemistry of the products was evaluated according to Kazlauskas' rule,[11] and the resolved products were unequivocally assigned as (*S*)-**5** and (*R*)-**8**.

SCHEME 2. Synthesis of Vinylphthalide 3

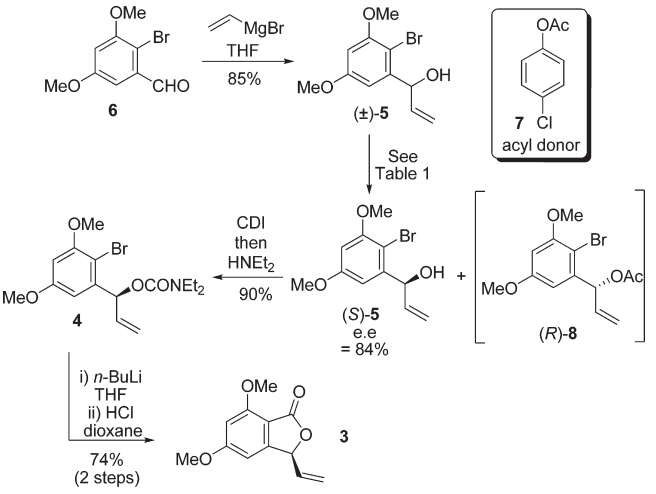


TABLE 1. Chemoenzymatic Resolution of (±)-5[a]

entry	heating[b]	time (h)	ee (*S*)-**5** (%)[c]	yield (%)
1	conventional	24	50	62
2	microwave; open vessel	24	59	54
3	microwave; closed vessel	24	74	46
4	**microwave; closed vessel**	**48**	**84**	**50**
5	microwave; closed vessel	60	66	50

[a]Conditions: Novozyme 435, *p*-chlorophenyl acetate **7**, toluene, 55 °C. [b]All microwave reactions were conducted at 300 W. [c]Enantiomeric excess calculated by HPLC [Chiralcel OD-H, hexanes/*i*-PrOH (93:7)] (see Experimental Section section and Supporting Information for full details).

Compound (*S*)-**5** was treated with 1,1′-carbonyldiimidazole and diethylamine to furnish the carbamate **4**, which upon treatment with *n*-BuLi led to smooth intramolecular acylation and subsequent acid-mediated lactonization to deliver the key vinylphthalide **3**. A similar intramolecular Parham-type cyclization served us[12] and others[13] well during the total syntheses of the spirolaxine antibiotics and was

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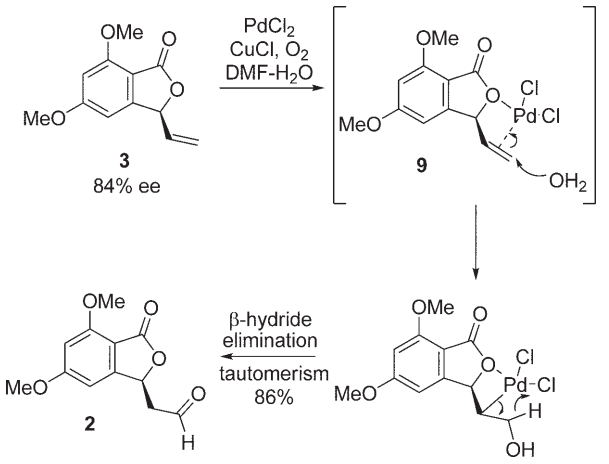
employed in this instance, especially since the aryllithium derived from **4** readily underwent protonation when quenched with external electrophiles (e.g., DMF), even under strictly anhydrous conditions.

With multigram quantities of vinylphthalide **3** secured, attention turned toward the pivotal Wacker oxidation step. Upon Wacker oxidation, terminal alkenes predominantly form methylketones, inferring that hydroxypalladation takes place following Markovnikov's rules.[14] A reliable procedure for the anti-Markovnikov addition of nucleophiles during the Wacker oxidation of terminal alkenes would greatly enhance the synthetic utility of this widely employed reaction. Currently, the few successful examples of so-called "reverse" Wacker transformations are controlled by heteroatoms[15] and π-complexation,[16] and studies involving the anti-Markovnikov addition of nucleophiles to styrenes using Wacker conditions exist.[17] To the best of our knowledge this reaction has not found any use in natural product synthesis, primarily due to the rarely observed[7,18] total reversal of regioselectivity, with the resulting product mixtures (aldehyde and methylketone) rendering the reaction unattractive.

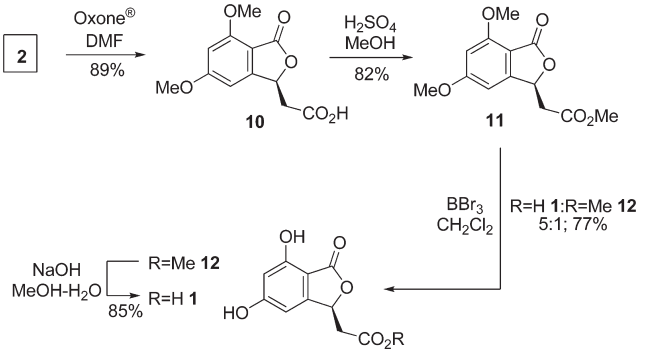
Upon exposure of **3** to standard Wacker oxidation conditions, TLC analysis indicated clean consumption of the starting material within 2 h. We were delighted to find that the sole product obtained from this reaction was the desired aldehyde **2** in excellent yield, with no methylketone observed in the ^{1}H NMR spectrum of the crude reaction mixture. This remarkable regioselectivity has been rationalized to result from intramolecular coordination of the lactone oxygen to the palladium (cf. **9**) that polarizes the palladium to the central vinylic carbon, thereby encouraging nucleophilic attack of water exclusively at the methylene carbon (Scheme 3). Gratifyingly, the stereochemical integrity present in alkene **3** was completely retained during the oxidation process, as determined by ^{19}F NMR analysis of the Mosher's ester of the alcohol derived from aldehyde **2** (See Supporting Information).

Given the successful reverse Wacker oxidation process, the final stages of the synthesis of herbaric acid **1** were initiated. Aldehyde **2** underwent smooth oxidation with Oxone affording acid **10**, which underwent facile methyl ester formation to facilitate purification, thus delivering enantioenriched lactone ester **11**. Gratifyingly, smooth demethylation with concomitant ester hydrolysis was effected by boron tribromide, delivering (−)-herbaric acid **1** in excellent overall yield along with a small quantity of herbaric acid methyl ester **12** in a 5:1 ratio favoring **1**. The latter ester underwent facile saponification to provide further amounts of **1** (Scheme 4).

SCHEME 3. Regioselective Reverse Wacker Oxidation



SCHEME 4. Synthesis of Reported Structure of (−)-Herbaric Acid 1



Comparison of the ^{1}H and ^{13}C spectra of synthetic **1** (d_6-DMSO) and the spectroscopic data supplied[2g] for natural herbaric acid clearly showed several significant differences. After some initial confusion, communication with the authors of the isolation paper confirmed that the solvent used to collect the NMR data of natural herbaric acid was in fact d_4-methanol and not d_6-DMSO as stated in the original report.[2g] Disappointingly, our synthetic sample of **1** was not sufficiently soluble in d_4-methanol to obtain anything other than a poor quality ^{1}H NMR spectrum. Nevertheless, we are confident our synthetic sample is indeed (−)-herbaric acid **1** and there is a subtle difference between the synthetic and natural samples that is contributing to their respective solubility. Unfortunately, the researchers who isolated herbaric acid **1** no longer have any natural material remaining for direct comparison with our synthetic material.

Next we set out to assign the absolute configuration of (−)-herbaric acid. The optical rotations of our synthetic sample (84% ee) $[\alpha]^{20}_D$ −21.7 (*c* 0.18, MeOH) and the reported value[2g] for natural **1** $[\alpha]^{20}_D$ −27.0 (*c* 0.18, MeOH) were in good agreement. We therefore conclude that (−)-herbaric acid possesses (*S*)-stereochemistry.

In conclusion, we have reported a novel chemoenzymatic method for the synthesis of chiral substituted phthalides. Furthermore, we have uncovered an entirely regioselective anti-Markovnikov addition of water during the Wacker oxidation of a vinylphthalide, which provided the key step in the first synthesis and structural assignment of the reported

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structure of (−)-herbaric acid. This heteroatom-directed Wacker process provides a mild alternative to hydroboration/oxidation protocols that are traditionally used for the anti-Markovnikov addition of water to terminal alkenes. Further exploration of this fascinating heteroatom-directed Wacker oxidation using other substituted alkenes is currently in progress.

Experimental Section

General. All reactions were carried out in oven-dried or flame-dried glassware under a nitrogen atmosphere unless otherwise stated. Analytical thin layer chromatography was performed using aluminum-backed silica plates, and compounds were visualized under 365 nm ultraviolet irradiation followed by staining with either alkaline permanganate or ethanolic vanillin solution. Infrared spectra were recorded on an FTIR spectrometer, in the range 4000−600 cm^{-1} as neat samples in attenuated total reflectance (ATR) mode. Optical rotations were measured using a polarimeter at $\lambda = 598$ nm and are given in 10^{-1} deg cm^2 g^{-1}. Melting points were recorded on an electrothermal melting point apparatus and are uncorrected. NMR spectra were recorded at 300 and 400 MHz (^{1}H frequencies, corresponding ^{13}C frequencies 75, 100, and 125 MHz). Chemical shifts are quoted in ppm and are referenced to residual H in the deuterated solvent as the internal standard. ^{13}C NMR values are reported as chemical shift δ, multiplicity, and assignment. ^{1}H NMR shift values are reported as chemical shift δ, relative integral, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant (J in Hz), and assignment. Assignments are made with the aid of DEPT 135, COSY, NOESY and HSQC experiments. High resolution mass spectra were recorded on a mass spectrometer at a nominal accelerating voltage of 70 eV. For all microwave-assisted reactions a single mode microwave synthesis system was used, resulting in formation of a homogeneous field pattern surrounding the sample. The reaction temperatures were measured using a surface sensor.

(±)-1-(2-Bromo-3,5-dimethoxyphenyl)prop-2-en-1-ol (±)-5. A solution of vinylmagnesium bromide (20.6 mL, 1 M in THF, 20.6 mmol) was added dropwise to a solution of 2-bromo-3,5-dimethoxybenzaldehyde **6**[10] (2.5 g, 10.3 mmol) in dry THF (10 mL) cooled to −78 °C. The reaction mixture was stirred at −78 °C overnight before quenching *via* the slow addition of 1 M HCl (30 mL). The reaction mixture was extracted with ethyl acetate (3 × 25 mL), and the combined organic layers were washed with saturated sodium bicarbonate solution (15 mL) and brine (15 mL) and dried over magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography using hexanes/ethyl acetate (5:1) as eluent to afford the title compound as a yellow oil (2.4 g, 8.7 mmol, 85%); TLC (hexanes/ethyl acetate 4:1) $R_f = 0.24$; ν_{max} (neat)/cm^{-1} 3398, 2938, 2839, 1584, 1452, 1417, 1321, 1198, 1157, 1019, 927, 836, 601; δ_H (300 MHz; $CDCl_3$) 2.72 (1 H, br s, O*H*), 3.76 (3 H, s, OCH_3), 3.86 (3 H, s, OCH_3), 5.15 (1 H, dt, J = 10.5, 1.5, 9-Hα), 5.34 (1 H, dt, J = 17.4, 1.5, 9-Hβ), 5.59 (1 H, t, J = 1.5, 7-H), 5.96 (1 H, m, 8-H), 6.36 (1 H, d, J = 3.0, 4-H), 6.68 (1 H, d, J = 3.0, 6-H); δ_C (75 MHz; $CDCl_3$) 55.4 (CH_3, OCH_3), 56.2 (CH_3, OCH_3), 73.2 (CH, C-7), 99.0 (CH, C-4), 102.7 (C, C-2), 103.5 (CH, C-6), 115.4 (CH_2, C-9), 138.1 (CH, C-8), 143.5 (C, C-1), 156.3 (C, C-3), 159.8 (C, C-5); m/z (EI) 295 (21%, MH^+ + Na), 273 (4), 257 (21), 190 (1), 176 (100) and 161 (2); HRMS (EI, MH^+ + Na) found 294.9927, calcd for $C_{11}H_{13}BrNaO_3$ 294.9940.

(*S*)-1-(2-Bromo-3,5-dimethoxyphenyl)prop-2-en-1-ol (−)-5. A mixture of (±)-1-(2-bromo-3,5-dimethoxyphenyl)prop-2-en-1-ol (±)-**5** (2.0 g, 7.4 mmol) and *p*-chlorophenyl acetate (2.5 g, 14.7 mmol) in toluene (50 mL) was purged with argon for 1 min followed by the addition of Novozyme 435 (Sigma-Aldrich) (100 mg). The resulting suspension was stirred at 55 °C in a microwave reactor (single mode CEM Discover Focused Microwave Synthesis System) at 300 W for 48 h. The reaction mixture was cooled to rt and filtered through cotton wool to remove the residual enzyme, and the solid was washed with dichloromethane (2 × 3 mL). The filtrate was concentrated under reduced pressure, and the residue was purified by flash chromatography using hexanes/ethyl acetate (9:1) as eluent to afford the title compound as a colorless oil (1.0 g, 3.68 mmol, 50%); $[\alpha]^{19}_D$ −33.3 (*c* 1.2, CH_2Cl_2, 84% ee). Spectroscopic data as described for (±)-**5**. Enantiomeric excess calculated by HPLC [Chiralcel OD-H, hexanes/*i*-PrOH (93:7)], see Supporting Information.

(*S*)-1-(2-Bromo-3,5-dimethoxyphenyl)allyl Diethylcarbamate (4). To a solution of 1-(2-bromo-3,5-dimethoxyphenyl)prop-2-en-1-ol (−)-**5** (0.75 g, 2.8 mmol) in dichloromethane (100 mL) was added *N*,*N*′-carbonyldiimidazole (1.64 g, 10.1 mmol), and the reaction mixture was stirred at rt for 1 h. Diethylamine (0.57 mL, 5.5 mmol) was added dropwise, and the reaction was stirred for a further 24 h. The reaction mixture was washed with water (30 mL) and brine (30 mL). The organic layer was dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by flash chromatography using hexane/ethyl acetate (4:1) as eluent to give the title compound as a colorless oil (0.92 g, 2.48 mmol, 90%); TLC (hexanes/ethyl acetate 4:1) $R_f = 0.30$; $[\alpha]^{19}_D$ −5.71 (*c* 1.4, CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2972, 1698, 1587, 1454, 1418, 1323, 1269, 1200, 1058, 995, 766; δ_H (300 MHz; $CDCl_3$) 1.01 (3 H, br s, NCH_2CH_3), 1.11 (3 H, br s, NCH_2CH_3), 3.22 (2 H, br s, NCH_2CH_3), 3.26 (2 H, br s, NCH_2CH_3), 3.68 (3 H, s, OCH_3), 3.72 (3 H, s, OCH_3), 5.15 (2 H, m, 9-H), 5.91 (1 H, m, 8-H), 6.32 (1 H, d, J = 2.8, 4-H), 6.47 (1 H, d, J = 1.6, 7-H), 6.49 (1 H, t, J = 2.8, 6-H); δ_C (75 MHz; $CDCl_3$) 13.0 (CH_3, NCH_2CH_3), 13.8 (CH_3, NCH_2CH_3), 40.9 (CH_2, NCH_2CH_3), 41.5 (CH_2, NCH_2CH_3), 54.9 (CH_3, OCH_3), 55.8 (CH_3, OCH_3), 75.0 (CH, C-7), 98.3 (CH, C-4), 102.4 (C, C-2), 103.6 (CH, C-6), 115.8 (CH_2, C-9), 135.0 (CH, C-8), 140.7 (C, C-1), 154.0 (C, C=O), 156.2 (C, C-3), 159.5 (C, C-5); m/z (EI) 394 (100%, M^+ + Na), 350 (6), 318 (3), and 140 (2); HRMS (EI, M^+ + Na) found 394.0624, calcd for $C_{16}H_{22}BrNNaO_4$ 394.0623.

(*S*)-5,7-Dimethoxy-3-vinylisobenzofuran-1(3*H*)-one (3). (*S*)-1-(2-bromo-3,5-dimethoxyphenyl)allyl diethylcarbamate **4** (1.0 g, 2.7 mmol) was taken up in dry THF (8 mL). The solution was cooled to −78 °C, and *n*-BuLi (3.71 mL, 1.6 M in hexanes, 5.9 mmol) was added dropwise. The resulting yellow solution was stirred at −78 °C for 1 h and warmed to rt. The reaction was quenched with water (10 mL) and extracted with ethyl acetate (3 × 20 mL). The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The crude mixture was dissolved in freshly distilled dioxane (15 mL), and anhydrous HCl (5 mL, 4 M in dioxane, 20 mmol) added dropwise. The solution was stirred for 12 h and concentrated under reduced pressure. The residue was purified by flash chromatography using hexane/ethyl acetate (7:3) as eluent to give the title compound as a colorless solid (0.44 g, 2.0 mmol, 74%); mp = 84 °C; TLC (hexanes/ethyl acetate 1:1) $R_f = 0.45$; $[\alpha]^{19}_D$ +21.1 (*c* 0.57, CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3093, 2951, 2842, 1751, 1596, 1417, 1461, 1330, 1213, 1156, 1050, 837, 690; δ_H (300 MHz; $CDCl_3$) 3.86 (3 H, s, OCH_3), 3.92 (3 H, s, OCH_3), 5.36 (2 H, dt, J = 1.2, 10.2, 2′-H), 5.61 (1 H, d, J = 7.2, 3-H), 5.79 (1 H, m, 1′-H), 6.37 (1 H, s, 6-H), 6.40 (1 H, s, 4-H); δ_C (75 MHz; $CDCl_3$) 55.9 (CH_3, OCH_3), 55.9 (CH_3, OCH_3), 80.6 (CH, C-3), 98.0 (CH, C-4), 99.0 (CH, C-6), 106.1 (C, C-7a), 119.4 (CH_2, C-2′), 133.6 (CH, C-1′), 153.5 (C, C-3a), 159.5 (C, C-7), 166.8 (C, C-5), 167.9 (C, C=O); m/z (EI) 221 (22%, MH^+), 178 (8), 162 (9); HRMS (EI, MH^+) found 221.0805, calcd for $C_{12}H_{13}O_4$ 221.0808.

(*S*)-2-(4,6-Dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)-acetaldehyde (2). A solution of (*S*)-5,7-dimethoxy-3-vinylisobenzofuran-1(3*H*)-one **3** (100 mg, 0.45 mmol) in DMF (3 mL)

was added to a slurry of palladium(II) chloride (40 mg, 0.23 mmol) and copper(I) chloride (58 mg, 0.59 mmol) in DMF (3 mL) and water (1 mL). Oxygen gas was bubbled through the solution for 2 h. The reaction mixture was filtered through silica, and the residue was washed with ethyl acetate (100 mL) and hexane (50 mL). The volatile solvents were removed *in vacuo*, and the DMF was removed under high vacuum at 40 °C. The residue was purified by flash chromatography using dichloromethane/methanol (50:1) as eluent to give the title compound as an oil (92 mg, 0.36 mmol, 86%); TLC (dichloromethane/methanol 50:1) R_f = 0.35; $[\alpha]^{19}_D$ −9.1 (*c* 0.44, CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2929, 2848, 1749, 1601, 1334, 1212, 1200, 1158, 1026, 839, 731, 699; δ_H (300 MHz; $CDCl_3$) 2.97 (2 H, m, CH_2) 3.85 (3 H, s, OCH_3), 3.91 (3 H, s, OCH_3), 5.74 (1 H, t, *J* = 6.0, C*H*), 6.40 (1 H, d, *J* = 3.0, 5-H), 6.44 (1 H, d, *J* = 3.0, 7-H), 9.81 (1 H, t, *J* = 3.0, C*H*O); δ_C (75 MHz; $CDCl_3$) 48.2 (CH_2, C-2′), 55.9 (CH_3, OCH_3), 56.0 (CH_3, OCH_3), 74.1 (CH, C-1), 97.8 (CH, C-5), 99.1 (CH, C-7), 106.2 (C, C-3a), 153.8 (C, C-7a), 159.7 (C, C-4), 167.0 (C, C-6), 167.5 (C, C-3), 198.0 (C, C=O); *m*/*z* (EI) 259 (18%, M^+ + Na), 237 (2), 193 (9), 172 (7), 135 (2); HRMS (EI, M^+ + Na) found 259.0581, calcd for $C_{12}H_{12}NaO_5$ 259.0577.

(*S*)-2-(4,6-Dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)-acetic Acid (10). To a solution of (*S*)-2-(4,6-dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)acetaldehyde **2** (100 mg, 0.42 mmol) in DMF (5 mL) was added Oxone (260 mg, 0.42 mmol), and the reaction mixture was stirred at rt for 6 h. The reaction mixture was diluted with 1 M HCl (15 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography using dichloromethane/methanol (10:1) as eluent to give the title compound as a colorless solid (95 mg, 0.38 mmol, 89%); mp = 201 °C; TLC (dichloromethane/methanol 5:1) R_f = 0.32; $[\alpha]^{19}_D$ −14.3 (*c* 0.21, EtOH); ν_{max} (neat)/cm^{-1} 3171, 2983, 1738, 1711, 1601, 1330, 1225, 1204, 1164, 1060, 1009, 836, 694; δ_H (400 MHz; d_6-DMSO) 2.57 (1 H, dd, *J* = 8.4, 16.8, 2′-Hα), 3.07 (1 H, dd, *J* = 3.6, 16.8, 2′-Hβ), 3.84 (3 H, s, OCH_3), 3.85 (3 H, s, OCH_3), 5.61 (1 H, q, *J* = 4.0, C*H*), 6.57 (1 H, d, *J* = 1.6, 5-H), 6.78 (1 H, t, *J* = 1.2, 7-H); δ_C (100 MHz; d_6-DMSO) 39.5 (CH_2, C-2′), 56.3 (CH_3, OCH_3), 56.5 (CH_3, OCH_3), 76.2 (CH, C-1), 99.2 (CH, C-5), 99.3 (CH, C-7), 106.1 (C, C-3a), 154.5 (C, C-7a), 159.4 (C, C-4), 166.8 (C, C-6), 167.3 (C, C-3), 171.3 (C, C=O); *m*/*z* (EI) 253 (41%, MH^+), 235 (5), 227 (2), 193 (10); HRMS (EI, MH^+) found 253.0708, calcd for $C_{12}H_{13}O_6$ 253.0707.

(*S*)-Methyl 2-(4,6-Dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)acetate (11). To a solution of (*S*)-2-(4,6-dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)acetic acid **10** (200 mg, 0.79 mmol) in methanol (10 mL) was added concentrated H_2SO_4 (1 mL). The reaction mixture was stirred at rt for 12 h and concentrated under reduced pressure. The residue was purified by flash chromatography using dichloromethane/methanol (20:1) as eluent to give the title compound as a colorless solid (173 mg, 0.65 mmol, 82%); mp = 145 °C; TLC (dichloromethane/methanol 10:1) R_f = 0.55; $[\alpha]^{19}_D$ −13.0 (*c* 0.23, EtOH); ν_{max} (neat)/cm^{-1} 2952, 2848, 1736, 1601, 1434, 1336, 1200, 1156, 1054, 1012, 838, 733, 689; δ_H (400 MHz; $CDCl_3$) 2.83 (2 H, m, CH_2) 3.74 (3 H, s, COOCH_3) 3.86 (3 H, s, OCH_3), 3.93 (3 H, s, OCH_3), 5.69 (1 H, t, *J* = 6.8, C*H*), 6.42 (1 H, d, *J* = 2.0, 5-H), 6.46 (1 H, t, *J* = 0.8, 7-H); δ_C (100 MHz; $CDCl_3$) 39.6 (CH_2, C-2′), 52.1 (CH_3, OCH_3), 55.9 (CH_3, OCH_3), 56.0 (CH_3, OCH_3), 75.5 (CH, C-1), 97.8 (CH, C-5), 99.1 (CH, C-7), 106.5 (C, C-3a), 153.7 (C, C-7a), 159.7 (C, C-4), 166.9 (C, C-6), 167.6 (C, C-3), 169.8 (C, C=O); *m*/*z* (EI) 267 (70%, MH^+), 226 (5), 193 (18), 149 (2), 130 (4); HRMS (EI, MH^+) found 267.0858, calcd for $C_{13}H_{15}O_6$ 267.0863.

(*S*)-Methyl 2-(4,6-Dihydroxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)acetate (12) and (*S*)-2-(4,6-Dihydroxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)acetic Acid (Herbaric Acid; 1). To a solution of (*S*)-methyl-2-(4,6-dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)acetate **11** (11 mg, 0.04 mmol) in dichloromethane (3 mL) was added BBr_3 (0.04 mL, 0.41 mmol) at 0 °C. The solution was stirred at 0 °C for 2 h, then at rt for 72 h. The reaction mixture was slowly quenched with 1 M HCl (3 × 5 mL) and extracted with ethyl acetate (3 × 10 mL). The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography using dichloromethane/methanol (5:1) as eluent to give the title compounds **12** as a colorless solid followed by **1** as a colorless solid.

Data for (*S*)-methyl 2-(4,6-dihydroxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)acetate (12): (1 mg, 0.005 mmol, 12%); mp = 164−166 °C; TLC (dichloromethane/methanol 5:1) R_f = 0.31; $[\alpha]^{19}_D$ −10.5 (*c* 0.19, MeOH); ν_{max} (neat)/cm^{-1} 3265, 1720, 1614, 1477, 1440, 1336, 1216, 1163, 1071, 1016, 850, 692, 656; δ_H (400 MHz; MeOH) 2.75 (1 H, dd, *J* = 8.0, 16.5, 2′-Hα), 2.97 (1 H, dd, J 3.8, 16.4, 2′-Hβ), 3.71 (3 H, s, COOCH_3), 5.68 (1 H, t, *J* = 8.0, C*H*), 6.29 (1 H, s, 5-H), 6.39 (1 H, s, 7-H); δ_C (100 MHz; $CDCl_3$) 40.3 (CH_2, C-2′), 52.5 (CH_3, OCH_3), 78.0 (CH, C-1), 101.7 (CH, C-5), 103.8 (CH, C-7), 104.5 (C, C-3a), 154.5 (C, C-7a), 159.8 (C, C-6), 167.1 (C, C-4), 171.4 (C, C-3), 171.7 (C, C=O); *m*/*z* (EI) 239 (100%, MH^+), 225 (10), 207 (2), 179 (7), 165 (35), 149 (4); HRMS (EI, MH^+) found 239.0544, calcd for $C_{11}H_{11}O_6$ 239.0550.

Data for (*S*)-2-(4,6-dihydroxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)acetic acid (Herbaric Acid, 1): (6 mg, 0.027 mmol, 65%); mp = 190 °C; TLC (dichloromethane/methanol 5:1) R_f = 0.09; $[\alpha]^{19}_D$ −21.7 (*c* 0.18, MeOH); ν_{max} (neat)/cm^{-1} 3201, 2959, 1707, 1612, 1474, 1399, 1366, 1336, 1251, 1216, 1160, 1076, 1012, 823, 737, 693; δ_H (400 MHz; d_6-DMSO) 2.65 (1 H, br s, CH_2), 2.73 (1 H, br s, CH_2), 5.55 (1 H, br s, C*H*), 6.30 (1 H, br s, 5-H), 6.44 (1 H, br s, 7-H); δ_C (100 MHz; d_6-DMSO) 77.0 (CH, C-1), 101.0 (C, C-3a), 103.0 (CH, C-5), 103.2 (CH, C-7), 154.6 (C, C-7a), 158.6 (C, C-6), 165.3 (C, C-4), 168.2 (C, C-3), 172.1 (C, C=O), 1 x CH_2 obscured by d_6-DMSO; *m*/*z* (EI) 225 (86%, MH^+), 207 (3), 165 (56), 149 (12); HRMS (EI, MH^+) found 225.0400, calcd for $C_{10}H_9O_6$ 225.0394.

(*S*)-2-(4,6-Dihydroxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)-acetic Acid (Herbaric Acid; 1). A solution of (*S*)-methyl-2-(4,6-dihydroxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)acetate **12** (5 mg, 0.021 mmol) in 2 M NaOH (3 mL) was stirred at rt for 2 h. The reaction mixture was acidifed to pH = 2−3 with 1 M HCl (10 mL) and extracted with ethyl acetate (3 × 10 mL). The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography using dichloromethane/methanol (5:1) as eluent to give the title compound as a colorless solid (4 mg, 0.018 mmol, 85%); spectroscopic data as described previously.

Acknowledgment. The authors thank the Royal Society of New Zealand Marsden fund for financial support. Professor Peter Proksch (University of Düsseldorf) is thanked for helpful discussions.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra and HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.