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Total Syntheses of All Stereoisomers of Phenatic Acid B

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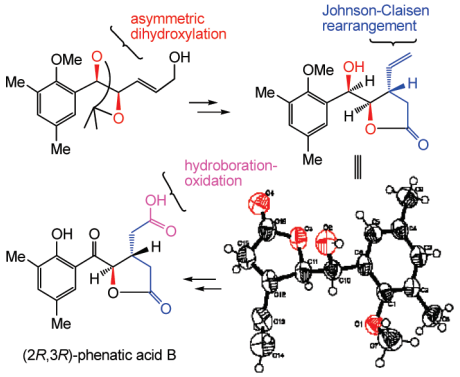


The total syntheses of all stereoisomers of phenatic acid B and determination of their absolute configuration are described. The synthetic strategy is based on an efficient combination of the Sharpless asymmetric dihydroxylation, the Johnson−Claisen rearrangement, and hydroboration−oxidation. It involves 11−12 steps and overall yield of 5−8%.

Fungal infections have aroused a major public concern in recent years.[1] Immune-deficient patients are prone to such infections, in particular of the fungi *Candida albicans*.[1] Given the urgency for new antifungal combination therapies for increased effectiveness in treatment, the search for new antifungal compounds with better and different mode of action is a research priority. Tomoda and co-workers[2] recently isolated two new 2,4-dimethyl phenols named phenatic acid A **1** and B **2** (Figure 1) from the culture of *Streptomyces* sp. K03-0132. Their structures were elucidated by NMR spectroscopy.[2] Related compounds such as actiphenol **4**, Nong-kang 101-G **5**, and 101 F **3** (Figure 1) were isolated long ago.[3] Compounds **1** and **2** showed miconazole activity against *Candida albicans*. Phenatic acid B also showed moderate activity against *Bacillus subtilis*, *Staphylococcus aureus*, *Bacteroides fragilis*, and *Acholeplasma laidlawii*.[2] The absolute and relative stereochemistry and syntheses of **1**−**5** are not yet known. Phenatic acid B **2** has four possible stereoisomers. Two of them have the 2,3-*anti*- and the others 2,3-*syn*-relative configurations (**2a**, **2b**, *ent*-**2a**, and *ent*-**2b**, Scheme 1).

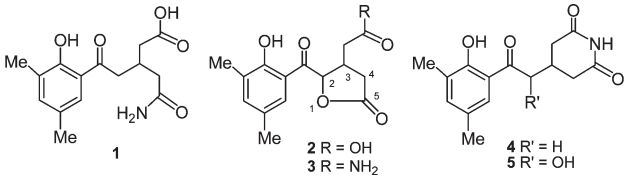
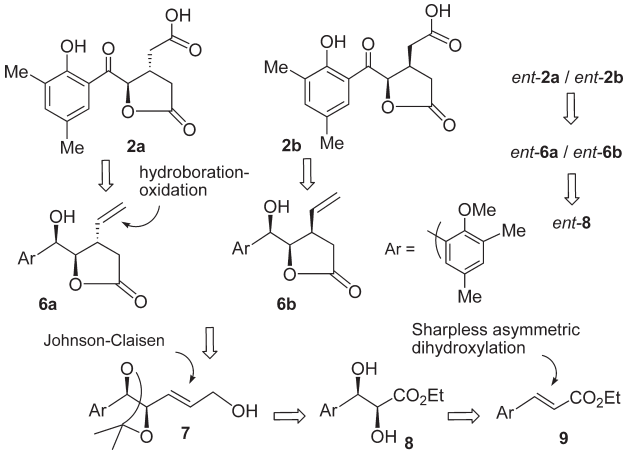


FIGURE 1. Phenatic acid A **1**, phenatic acid B **2**, actiphenol **4**, Nong-kang 101-G **5**, and 101-F **3**.

SCHEME 1. Retrosynthetic Analysis of Phenatic Acid B Stereoisomers



In continuation of our research efforts in the asymmetric synthesis of natural products,[4,5] we have recently demonstrated that chiral vicinal diols are good platforms for separable diastereomers in the Johnson−Claisen rearrangement.[5] We envisioned a similar strategy to synthesize the stereoisomers of phenatic acid B **2** (Figure 1) and elucidate their absolute configurations. Our retrosynthetic plan is shown in Scheme 1. From compound **6a**, we planned to have **2a** through a three-step sequence, viz. hydroboration−oxidation of terminal olefin, hydroxyl oxidation, and demethylation. Compound **6a** would be produced as a C-4 diastereomer mixture with **6b** after the Johnson−Claisen rearrangement of **7** followed by lactonization. We have demonstrated earlier that such C-4 diastereomers based on vicinal diols are separable.[5] The allyl alcohol **7** could be derived from **8**, and the latter can be prepared from the olefin **9** through the Sharpless asymmetric dihydroxylation. The diastereomer **6b** would give **2b**. Similarly, *ent*-**2a** and *ent*-**2b** can be synthesized using *ent*-**8** through *ent*-**6a** and *ent*-**6b**, respectively.

(1) Nishiyama, Y.; Yamaguchi, H. *Antibiot. Chemother.* **2000**, *16*, 19–26.
(2) Fukuda, T.; Matsumoto, A.; Takahashi, Y.; Tomoda, H.; Omura, S. *J. Antibiot.* **2005**, *58*, 252–259.
(3) Hua, J. C.; Xie, Y. Y. *Hua Hsueh Hsueh Pao* **1980**, *38*, 275–282.
(4) (a) Fernandes, R. A.; Chavan, V. P.; Ingle, A. B. *Tetrahedron Lett.* **2008**, *49*, 6341–6343. (b) Fernandes, R. A.; Chavan, V. P. *Tetrahedron Lett.* **2008**, *49*, 3899–3901. (c) Fernandes, R. A. *Tetrahedron: Asymmetry* **2008**, *19*, 15–18. (d) Fernandes, R. A. *Eur. J. Org. Chem.* **2007**, 5064–5070.
(5) Fernandes, R. A.; Ingle, A. B. *Tetrahedron Lett.* **2009**, *50*, 1122–1124.

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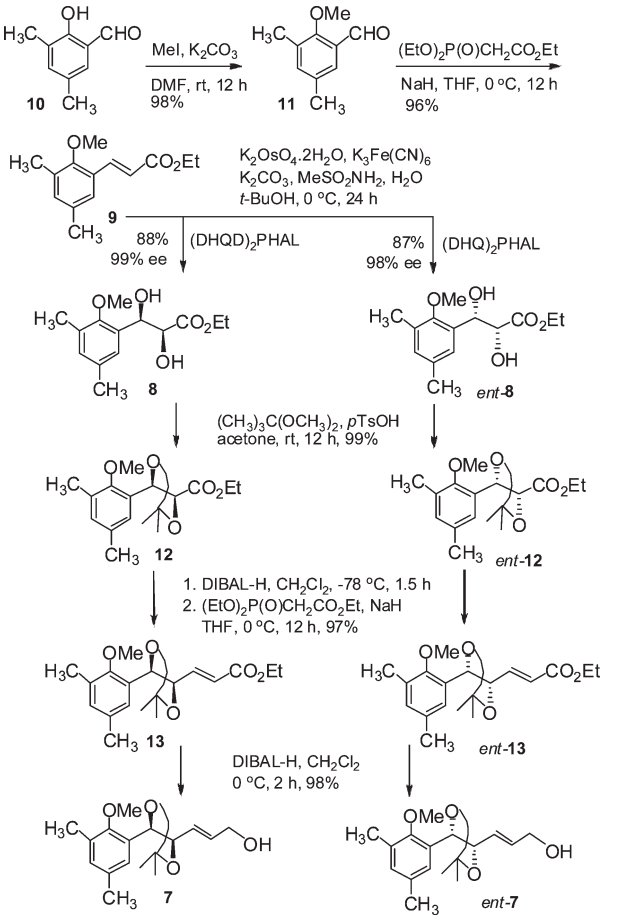
The synthesis of **7** and *ent*-**7** is shown in Scheme 2. The phenol **10**[6] was methylated to **11** (98%), and subsequent Wittig−Horner reaction afforded the olefin **9** in excellent yield (96%). The Sharpless asymmetric dihydroxylation[7]

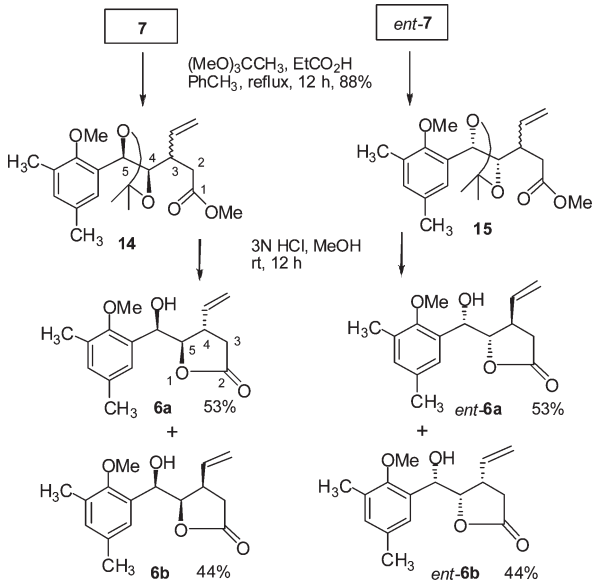
SCHEME 2. Enantioselective Synthesis of Allyl Alcohols 7 and *ent*-7



reaction on olefin **9** was performed following standard procedure: with $(DHQD)_2$-PHAL as the stereoinducing ligand, we obtained the diol (2*S*,3*R*)-**8** (88%) and with $(DHQ)_2$-PHAL ligand the diol (2*R*,3*S*)-*ent*-**8** (87%). Enantioselectivities were excellent (99 and 98% ee, respectively) as revealed by chiral HPLC.[8] Sequential acetonide protection of diol **8** to **12** (99%), DIBAL-H reduction to the aldehyde, and Wittig−Horner reaction afforded the α,β-unsaturated ester **13** (97%). Similarly, *ent*-**8** led to *ent*-**13**. Further, the DIBAL-H reduction of the ester groups in **13** and *ent*-**13** furnished the allyl alcohols **7** and *ent*-**7**, respectively, the precursors for the anticipated Johnson−Claisen rearrangement.[9]

The Johnson−Claisen rearrangement of **7** with trimethylorthoacetate and catalytic propionic acid gave the diastereomeric mixture **14** in 88% yield (*ent*-**7** provided **15**, Scheme 3). ^{1}H NMR of the crude product **14** indicated a 55:45 C-3 diastereomeric mixture. Acetonide deprotection of **14** with 3 N HCl resulted in concomitant lactonization to give **6a** and **6b** (**15** led to *ent*-**6a** and *ent*-**6b**). As expected,

SCHEME 3. Johnson−Claisen Rearrangement of 7 and *ent*-7



these diastereomers could easily be separated by silica gel flash column chromatography as crystalline solids. The *syn*-product **6b** (44%) was eluted first followed by **6a** (53%). Similarly *ent*-**6a** (53%) and *ent*-**6b** (44%) were separated. The relative configuration of **6a** and **6b** is based on the comparison of the ^{1}H NMR chemical shifts of H_b protons in the lactones (Figure 2). In **6a**, the H_b proton is *syn* to the vinyl group and is shielded to δ 4.38 as compared to H_b (δ 4.70) in **6b**. This was further ascertained by a single-crystal X-ray diffraction analysis of **6a** and **6b**.[10] Asymmetric

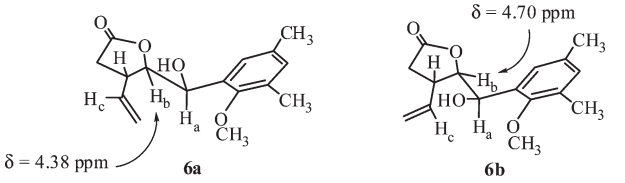


FIGURE 2. Comparison of chemical shifts of H_b proton in **6a** and **6b**.

dihydroxylation ascertains the C-2 and C-3 configurations in **8** to be (2*S*,3*R*). These centers will have the configuration carried in **6a** and **6b**. Since **6a** has the C-4/C-5 *anti*-relative configuration in the lactone (as revealed by X-ray

(6) Knight, P. D.; O'Shaughnessy, P. N.; Munslow, I. J.; Kimberley, B. S.; Scott, P. *J. Organomet. Chem.* **2003**, *683*, 103–113.

(7) Reviews: (a) Zaitsev, A. B.; Adolfsson, H. *Synthesis* **2006**, 1725–1756. (b) Bolm, C.; Hildebrand, J. P.; Muniz, K. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp 399−428. (c) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.

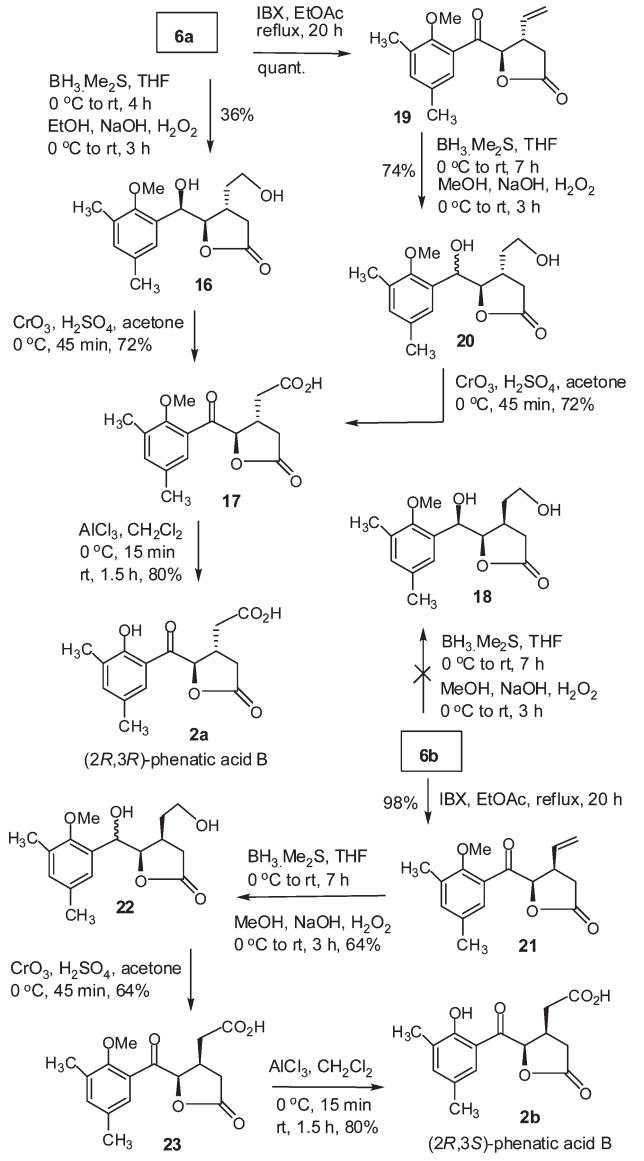
(8) Enantiomeric excess was determined by chiral HPLC. Column: Chiralpak IA. Eluent: *n*-hexane/*i*-PrOH (95:5); flow rate = 0.5 mL/min; UV detector = 240 nm; t_R = 20.53 min for **8**, 24.21 min for *ent*-**8**.

(9) For the Johnson−Claisen rearrangement see: (a) Ziegler, F. *Chem. Rev.* **1988**, *88*, 1423–1452. (b) Chan, K.-K.; Cohen, N.; De Noble, J. P.; Specian, A. C. Jr.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3497–3505. (c) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.-T.; Faulkner, D. J.; Peterson, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741–743.

(10) See Supporting Information for the ORTEP diagrams. CCDC 725576 (**6a**) and CCDC 725575 (**6b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

crystallography analysis), the absolute configuration will be (4*S*,5*R*); **6b** has the C-4/C-5 *syn*-relative configuration and hence will have (4*R*,5*R*) absolute configuration. Similarly, *ent*-**6a** should have (4*R*,5*S*) and *ent*-**6b** the (4*S*,5*S*) configurations. With these separated stereoisomers in hand, the stage was now set to finally target all the stereoisomers of phenatic acid B (Schemes 4 and 5).

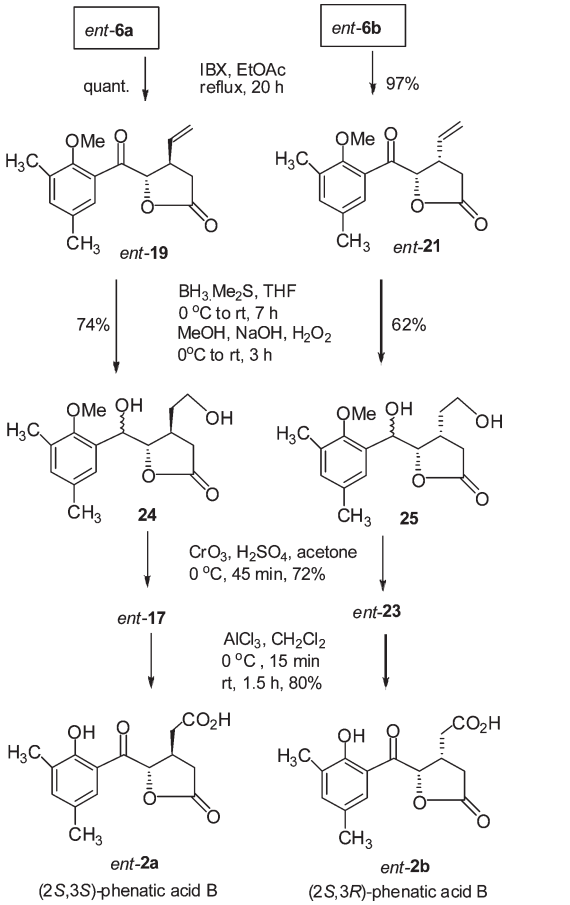
SCHEME 4. Synthesis of Phenatic Acid B Stereoisomers 2a and 2b



The hydroboration reaction on **6a** (Scheme 4) with $BH_3 \cdot Me_2S$ followed by oxidative workup afforded the diol **16** in 36% optimized yield.[11] The oxidation of both hydroxyl groups in **16** led to the keto-acid **17** in 72% yield. The hydroboration−oxidation of **6b** (Scheme 4) with $BH_3 \cdot Me_2S$ failed to deliver the diol **18**.[11] We believed that the free hydroxyl group in **6a** or **6b** might be complexing with the borane reagent during hydroboration and provided diminished yields. To check this hypothesis, the hydroxyl group in **6a** was oxidized with IBX[12] to give the keto-compound **19** in quantitative yield (Scheme 4). Further hydroboration−oxidation of **19** led to the diastereomeric mixture **20** (74%), which on subsequent oxidation afforded the acid **17** in 72% yield. Overwhelmingly, this three-step sequence gave improved yield of **17** from **6a** (overall 48%) as compared to the two-step conversion of **6a** to **17** (23%) via **16**. Finally, demethylation of **17** with $AlCl_3$ cleanly provided (2*R*,3*R*)-phenatic acid B **2a** in 80% yield. Similarly, the ketone **21** obtained from **6b** was converted to the diol **22** (64%) and further oxidized to the acid **23** (64%) and demethylated to provide (2*R*,3*S*)-phenatic acid B **2b** (80%). Thus a stereodivergent synthesis of both diastereomers **2a** and **2b** was achieved from a single stereoisomer **7** (although there was lack of stereoselectivity in the Johnson−Claisen rearrangement). In a similar sequence of reactions, *ent*-**6a** (→ *ent*-**19** → **24** → *ent*-**17** → *ent*-**2a**) and *ent*-**6b** (→ *ent*-**21** → **25** → *ent*-**23** → *ent*-**2b**) led to (2*S*,3*S*)-phenatic acid B *ent*-**2a** and (2*S*,3*R*)-phenatic acid B *ent*-**2b**, respectively (Scheme 5).

The absolute and relative stereochemistry of the naturally isolated phenatic acid B is not known.[2] The C-2 proton for

SCHEME 5. Synthesis of Phenatic Acid B Stereoisomers *ent*-2a and *ent*-2b



(11) Other variations of hydroboration−oxidation using $Cy_2 \cdot BH$ or 9-BBN or changes in reagent to substrate ratio, solvents, and temperature did not improve the reaction either.

(12) IBX applications: (a) Nicolaou, K. C.; Mathison, C. J. N.; Montagnon, T. *J. Am. Chem. Soc.* **2004**, *126*, 5192–5201. (b) Nicolaou, K. C.; Baran, P. S.; Kranich, R.; Zhong, Y.-L. *Angew. Chem., Int. Ed.* **2001**, *40*, 202−206. Reviews: (c) Stang, P. J. *J. Org. Chem.* **2003**, *68*, 2997–3008. (d) Zhdankin, V. V.; Stang, P. *J. Chem. Rev.* **2002**, *102*, 2523–2584.

the natural product appears at δ 5.70 ppm in the ^{1}H NMR.[2] The synthetic *syn*-stereoisomers (**2b** and *ent*-**2b**) had the C-2 proton appearing at δ 6.05 ppm, while the *anti*-stereoisomers (**2a** and *ent*-**2a**) had the same proton at δ 5.69 ppm.[13] From this observation, we believe the natural isolate to be the *anti*-stereoisomer (relative configuration) and should have either (2*R*,3*R*) or (2*S*,3*S*) absolute configurations. Due to a large difference in optical rotation value of synthetic (−115.7 for **2a** and +109.8 for *ent*-**2a**) in comparison to natural isolate (−2.2), we could not make the assignment of absolute configuration unambiguously to the natural phenatic acid B at this stage. Also, the natural isolate was not available for further studies.

In summary, we have achieved the first total syntheses of all stereoisomers of phenatic acid B. The synthetic strategy is based on an efficient combination of the Sharpless asymmetric dihydroxylation, Johnson−Claisen rearrangement, and hydroboration−oxidation as the key steps. The synthesis of phenatic acid B stereoisomers is completed in high enantio- and diastereoselectivity in 11−12 steps and overall yield of 5−8%. We have also established the absolute configurations of all stereoisomers of phenatic acid B. The naturally isolated product is an *anti*-stereoisomer, while the absolute stereochemistry could be (2*R*,3*R*) or (2*S*,3*S*). The synthetic strategy is flexible and will potentially allow us to synthesize the other members of the phenatic acid family (Figure 1). Work in this direction is in progress.

Experimental Section

(4*S*,5*R*)-5-[(*R*)-Hydroxy-(2-methoxy-3,5-dimethylphenyl)methyl]-4-vinyldihydrofuran-2(3*H*)-one (6a) and (4*R*,5*R*)-5-[(*R*)-Hydroxy-(2-methoxy-3,5-dimethylphenyl)methyl]-4-vinyldihydrofuran-2(3*H*)-one (6b): To a solution of allyl alcohol **7** (1.3 g, 4.45 mmol) in toluene (15 mL) were added trimethylorthoacetate (5.34 g, 5.6 mL, 44.46 mmol, 10 equiv) and $EtCO_2H$ (cat, 5 drops), and the solution was refluxed for 12 h. After cooling to room temperature, the volatile material was removed under reduced pressure and the residue was purified by silica gel flash column chromatography using petroleum ether/EtOAc (95:5) as eluent to provide **14** (1.36 g, 88%) as a colorless oil. Analysis of crude **14** by ^{1}H NMR indicated calcd 55:45 C-3 diastereomeric mixture.

To a solution of **14** (1.36 g, 3.9 mmol) in MeOH (25 mL) was added 3 N HCl (3 mL) and stirred for 12 h at room temperature. It was then quenched with powdered $NaHCO_3$ (1.0 g) and filtered. The filtrate was concentrated and the residue purified by silica gel flash column chromatography using petroleum ether/EtOAc (85:15) as eluent to provide **6b** (0.475 g, 44%) as white crystalline solid. Further elution gave **6a** (0.57 g, 53%) as colorless crystalline solid. Data for **6b**: mp 144−146 °C; $[\alpha]^{25}_D$ = −135.7 (*c* = 0.14, $CHCl_3$); IR (KBr film) ν = 3458, 2991, 2954, 2826, 1753, 1475, 1409, 1350, 1313, 1249, 1213, 1188, 1136, 1069, 1012, 930, 803, 672 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ = 7.0 (s, 1H), 6.95 (s, 1H), 6.02−6.12 (m, 1H), 5.21−5.33 (m, 2H), 5.11−5.16 (m, 1H), 4.70 (dd, *J* = 8.2, 2.1 Hz, 1H), 3.75 (s, 3H), 3.28−3.37 (m, 1H), 3.01 (br s, 1H, *OH*), 2.84 (dd, *J* = 17.2, 10.2 Hz, 1H), 2.58 (dd, *J* = 17.4, 9.1 Hz, 1H), 2.27 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.0, 153.7, 134.8, 133.7, 132.0 (2C), 130.7, 126.0, 118.9, 84.8, 69.4, 61.0, 43.0, 34.4, 20.8, 16.1; HRMS (ESI+) calcd for $[C_{16}H_{20}O_4 + Na]^+$ 299.1259, found 299.1247. Data for **6a**: mp 84−86 °C; $[\alpha]^{25}_D$ = −50.0 (*c* = 0.16, $CHCl_3$); IR (KBr film) ν = 3429, 2997, 2926, 2831, 1752, 1479, 1355, 1273, 1214, 1167, 1139, 1100, 1041, 1009, 876, 794, 667 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ = 7.04 (s, 1H), 6.95 (s, 1H), 5.5−5.6 (m, 1H), 4.98−5.04 (m, 3H), 4.38 (dd, *J* = 7.6, 4.2 Hz, 1H), 3.75 (s, 3H), 3.18−3.23 (m, 1H), 2.97 (br s, 1H, *OH*), 2.79 (dd, *J* = 17.2, 9.5 Hz, 1H), 2.45 (dd, *J* = 17.2, 9.5 Hz, 1H), 2.27 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.7, 153.8, 135.8, 133.7, 132.1, 131.3, 130.7, 125.7, 117.3, 87.5, 69.5, 61.0, 41.2, 35.0, 20.8, 16.1; HRMS (ESI+) calcd for $[C_{16}H_{20}O_4 + Na]^+$ 299.1259, found 299.1252.

[(2*R*,3*R*)-2-(2-Hydroxy-3,5-dimethylbenzoyl)-5-oxotetrahydrofuran-3-yl]acetic acid (Phenatic Acid B, 2a): To a solution of **17** (0.13 g, 0.42 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C was added $AlCl_3$ (0.198 g, 1.48 mmol, 3.5 equiv) in portions, and the reaction mixture was stirred for 15 min. The ice bath was removed and stirring continued at room temperature for 1.5 h. It was then quenched with water (5 mL), and the solution was extracted with CH_2Cl_2 (5 × 25 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel flash column chromatography using petroleum ether/EtOAc (1:1) as eluent to provide **2a** (0.099 g, 80%) as a white solid: mp 185−187 °C; $[\alpha]^{25}_D$ = −115.7 (*c* = 0.2, MeOH); IR (KBr pallet) ν = 3445, 3231, 2925, 2853, 1783, 1756, 1705, 1645, 1474, 1414, 1376, 1321, 1290, 1193, 1177, 1091, 1056, 1019, 919, 860, 787, 767, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ = 11.8 (s, 1H), 7.48 (s, 1H), 7.25 (s, 1H), 5.69 (d, *J* = 3.0 Hz, 1H), 3.1−3.15 (m, 1H), 2.85 (dd, *J* = 17.7, 8.5 Hz, 1H), 2.75 (dd, *J* = 17.1, 7.9 Hz, 1H), 2.64 (dd, *J* = 17.1, 6.7 Hz, 1H), 2.32 (dd, *J* = 17.7, 3.7 Hz, 1H), 2.27 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 198.5, 175.9, 175.2, 159.9, 140.0, 128.0, 127.7, 126.8, 115.8, 80.5, 37.0, 34.5, 33.0, 20.4, 15.4; HRMS (ESI+) calcd for $[C_{15}H_{16}O_6 + H]^+$ 293.1025, found 293.1035.

[(2*R*,3*S*)-2-(2-Hydroxy-3,5-dimethylbenzoyl)-5-oxotetrahydrofuran-3-yl]acetic acid (Phenatic Acid B, 2b): The title compound was prepared from **23** (0.028 g, 0.091 mmol) by a similar procedure as described for the conversion of **17** to **2a** with $AlCl_3$ to give **2b** (0.0214 g, 80%) as white solid: mp 188−190 °C; $[\alpha]^{25}_D$ = −103.3 (*c* = 0.3, MeOH); IR (thin film) ν = 3395, 3134, 2923, 2854, 1790, 1750, 1725, 1634, 1474, 1422, 1282, 1262, 1227, 1173, 1143, 1100, 1053, 1041, 978, 845, 796, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ = 11.9 (s, 1H), 7.28 (s, 1H), 7.27 (s, 1H), 6.05 (d, *J* = 7.9 Hz, 1H), 3.32−3.38 (m, 1H), 2.79 (dd, *J* = 17.4, 8.5 Hz, 1H), 2.56 (dd, *J* = 17.4, 10.4 Hz, 1H), 2.38−2.41 (m, 2H), 2.26 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 199.7, 175.4, 175.2, 159.9, 140.4, 128.2, 128.1, 126.2, 116.9, 77.0, 35.4, 33.9, 32.7, 20.5, 15.4; HRMS (ESI+) calcd for $[C_{15}H_{16}O_6 + H]^+$ 293.1025, found 293.1031.

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Supporting Information Available: General information and experimental procedures for preparation and compound characterization data of **11**, **9**, **8**, *ent*-**8**, **12**, *ent*-**12**, **13**, *ent*-**13**, **7**, *ent*-**7**, *ent*-**6a**, *ent*-**6b**, **16**, **17**, **19**, **20**, **21**, **22**, **23**, *ent*-**19**, *ent*-**21**, **24**, **25**, *ent*-**17**, *ent*-**23**, *ent*-**2a**, and *ent*-**2b**, copies of NMR spectra for all new compounds. Crystallographic data for compounds **6a** and **6b**. This material is available free of charge via the Internet at http://pubs.acs.org.

(13) See Supporting Information for a comparison.