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Synthesis of (1R,2S)-1-(3'-Chloro-4'-methoxyphenyl)-1,2-propanediol (Trametol) and (1R,2S)-1-(3',5'-Dichloro-4'-methoxyphenyl)-1,2-...

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Note

Synthesis of (1*R*,2*S*)-1-(3′-Chloro-4′-methoxyphenyl)-1,2-propanediol (Trametol) and (1*R*,2*S*)-1-(3′,5′-Dichloro-4′-methoxyphenyl)-1,2-propanediol, Chlorinated Fungal Metabolites in the Natural Environment†

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(1*R*,2*S*)-1-(3′-Chloro-4′-methoxyphenyl)-1,2-propanediol (Trametol, 3), a metabolite of the fungus *Trametes* sp. IVP-F640 and *Bjerkandera* sp. BOS55, was synthesized by employing Sharpless asymmetric dihydroxylation as the key step. Similarly, the (1*R*,2*S*)-isomer of 1-(3′,5′-dichloro-4′-methoxyphenyl)-1,2-propanediol (4), another metabolite of *Bjerkandera* sp. BOS55, was synthesized by asymmetric dihydroxylation.

Key words: asymmetric dihydroxylation; *Bjerkandera* sp.; chlorinated *p*-anisylpropanoid; optically active *p*-anisylpropanoid; white rot fungus

Although chlorinated organic compounds are largely regarded by the public as undesirable synthetic pollutants, they are produced in a huge quantity by many marine organisms and some terrestrial ones.[1)] It has been reported that the conversion of chlorophenols to dioxins occurs in fresh garden compost piles and sewage sludge.[1,2)] *Bjerkandera* sp. BOS55 is one of white-rot fungi (basidiomycetes) which are the most active lignin degraders in nature. This fungus is known to produce such chlorinated aromatics as 3-chloro-4-methoxybenzaldehyde (**1**, Fig. 1),[2)] 3-chloro-4-methoxybenzyl alcohol,[2)] 3,5-dichloro-4-methoxybenzaldehyde (**2**)[3)] and 3,5-dichloro-4-methoxylbenzyl alcohol.[3)] These chlorinated aromatics are produced in substantial amounts, and a concentration up to 37 mg/l has been detected in the culture broth of *Bjerkandera* sp. It is estimated that about 75 mg of chlorinated anisyl metabolites are produced per kg of wood or litter; if their biotoxification to chlorinated dioxins is efficient enough, it may create an environmental problem. The structures and ecological fate of natural chlorinated compounds are therefore worth studying.

In 1995, de Pava and his co-workers isolated (−)-1-(3′-chloro-4′-methoxyphenyl)-1,2-propanediol (**3**) from the fungus *Trametes* sp. IVP-F640, named the compound (−)-trametol, and assigned its (1*R*,2*S*)-absolute configuration.[4)] The basis for the assigned (1*R*,2*S*)-configuration of (−)-**3** was its synthesis by treating 3-chloroanisaldehyde (**1**) with fermenting baker's yeast. This biological C_2-homologation is empirically known to give an *erythro*-isomer with (1*R*,2*S*)-configuration. Soon afterwards in 1998, in the course of their study on the metabolites of *Bjerkandera* sp. BOS55, Wijnberg and his co-

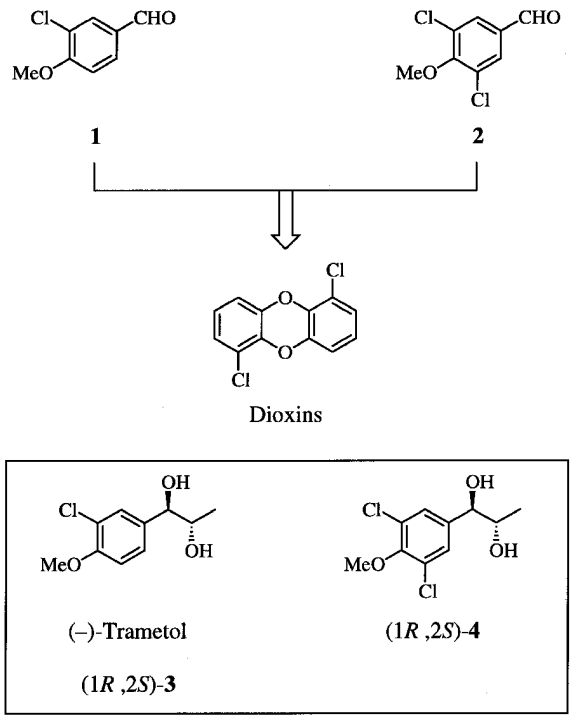

Fig. 1. Structures of the Target Molecules (**3** and **4**) and Related Compounds.

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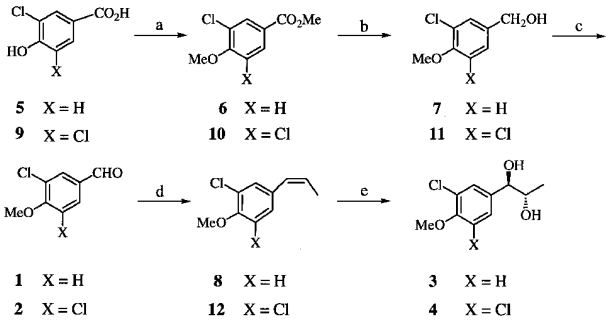
workers also identified (−)-trametol (**3**), and synthesized (±)-**3**.[5] At the same time, they newly isolated *erythro*-1-(3′,5′-dichloro-4′-methoxyphenyl)-1,2-propanediol (**4**), and prepared (±)-**4**.[5] Unfortunately, the specific rotation values for Wijnberg's **3** and **4** have not been reported. We became interested in unambiguously synthesizing (1*R*,2*S*)-**3** and -**4** by employing an asymmetric dihydroxylation reaction[6] whose steric course is now well-established. Our synthesis of (1*R*,2*S*)-**3** verifies the (1*R*,2*S*)-stereochemistry assigned to (−)-trametol (**3**).

Scheme 1 summarizes our syntheses of (1*R*,2*S*)-**3** and -**4**. The key step was the final one to dihydroxylate (*Z*)-alkenes **8** and **12** to target molecules (1*R*,2*S*)-**3** and -**4**. Although the enantioselectivity of this reaction is known to be low [20–80% ee for (*Z*)-alkenes; cf. 90–99% ee for (*E*)-alkenes], we were optimistic about purifying the products. To prepare (*Z*)-alkenes **8** and **12**, known aldehydes **1**[2,4,7] and **2**[5] had to be synthesized. An examination of their previous preparative methods[2,4,5,7] prompted us to develop a more efficient (although conventional) method for the syntheses of **1** and **2** by starting from commercially available acids **5** and **9**. The synthesis of (1*R*,2*S*)-trametol (**3**) will be discussed first.

3-Chloro-4-hydroxybenzoic acid (**5**) was doubly methylated to give corresponding methyl ether-methyl ester **6**. Reduction of **6** with lithium aluminum hydride furnished benzyl alcohol **7**. This was oxidized with pyridinium chlorochromate (PCC) to give aldehyde **1** in an 87% yield based on **5**. In the past, this oxidation step has been achieved with pyridinium dichromate[2] or active manganese dioxide;[7] de Pava oxidized **7** with PCC to give **1**, but no experimental details were reported.[4]

(*Z*)-Selective Wittig olefination of **1**, using sodium hexamethyldisilazide (NaHMDS) as the base under the conditions reported by Bestmann *et al.*,[8] yielded a mixture of **8** and its (*E*)-isomer (*E*/*Z* = 1:7 by a ^{1}H-NMR analysis) in a 94% yield. Rigorous purification of **8** was achieved by MPLC to give pure **8** in a 39% yield based on **1**. Asymmetric dihydroxylation (AD) of (*Z*)-alkene **8** with AD-mix-*β*®[6] yielded crude **3** (*ca.* 45% ee as estimated by a chiral GC analysis on Chirasil-DEX CB®) in an 89% yield. Recrystallization of crude **3** from ethyl acetate/hexane gave (±)-**3**, mp 120–121°C (lit.[5] mp 117–118°C), as the first crop. The desired (1*R*,2*S*)-trametol (**3**) could be recovered from the mother liquor in a 17% yield to give colorless needles, mp 80.5–82°C, $[\alpha]_D^{25}$ −34.0 (*c* 1.40, $CHCl_3$) [lit.[4] mp 74°C, $[\alpha]_D$ −29.2 (*c* 1.40, $CHCl_3$)]. The spectral properties of our synthesized (−)-**3** were in good agreement with the data reported for (−)-**3**[4] and (±)-**3**.[5] The enantiomeric purity of synthetic (−)-**3** was 94.7% ee as determined by the chiral GC analysis. A comparison of the $[\alpha]_D$ values for natural **3** and synthetic (−)-**3** suggested that the natural (−)-trametol (**3**) was the (1*R*,2*S*)-isomer with 81% ee. The overall yield of (−)-**3** was 6.2% based on **5** (5 steps).



Scheme 1. Syntheses of (1*R*,2*S*)-**3** and **4**.
Reagents: (a) K_2CO_3, MeI, dry acetone (96% for **6**; 99% for **10**). (b) $LiAlH_4$, Et_2O (98% for **7**; 99% for **11**). (c) PCC, CH_2Cl_2 (99% for **1**; 97% for **2**). (d) $Ph_3P^+EtBr^-$, NaHMDS, hexane, then MPLC purification (39% for **8**; 32% for **12**). (e) AD-mix-*β*®, $MeSO_2NH_2$, *tert*-BuOH, H_2O (17% for **3**; 29% for **4**).

In exactly the same manner, commercially available 3,5-dichloro-4-hydroxybenzoic acid (**9**) was converted *via* **10**, **11**, **2** and **12** into (1*R*,2*S*)-(−)-(3′,5′-dichloro-4′-methoxyphenyl)-1,2-propanediol (**4**), mp 46–47°C, $[\alpha]_D^{24}$ −23.5 (*c* 1.45, $CHCl_3$), whose enantiomeric purity was estimated as 97.8% ee by a chiral GC analysis. Its spectral data matched those reported for (±)-**4**;[5] unfortunately, neither the mp nor $[\alpha]_D$ values for natural **4** have been recorded.[5]

In conclusion, the absolute configuration of (−)-trametol (**3**) was verified as 1*R*,2*S* by its enantioselective synthesis, and an authentic sample of (1*R*,2*S*)-(−)-**4** could be secured.

Experimental

^{1}H-NMR: Jeol JNM-AL300 (300 MHz), JNM-AL400 (400 MHz), JNM-AL500 (500 MHz) (TMS at $\delta = 0.00$, $CHCl_3$ $\delta = 7.26$ as an internal standard). ^{13}C-NMR: Jeol JNM-AL300 (75 MHz), JNM-AL400 (100 MHz), JNM-AL500 (126 MHz) (TMS at $\delta = 0.00$, $CHCl_3$ $\delta = 77.0$ as an internal standard). IR: Jasco FT/IR-410. GC: Shimadzu GC-17A gas chromatograph. $[\alpha]_D$: Jasco P-1020. n_D: Atago NAR-1T. Mp: Yanaco MP-S3.

Methyl 3-chloro-4-methoxybenzoate (6). 3-Chloro-4-hydroxybenzoic acid (**5**, 1.00 g, 5.79 mmol) was dissolved in dry acetone (46 ml), to which was added K_2CO_3 (2.40 g, 17.4 mmol). After adding methyl iodide (2.47 ml, 17.4 mmol), the mixture was stirred under reflux for 16 h. The solvent was removed *in vacuo*, and the resulting residue was diluted with ether. The solution was successively washed with water, 1 N NaOH and brine, dried with anhydrous $MgSO_4$, and concentrated *in vacuo* to afford crude **6** (1.11 g, 96%) which was recrystallized from hexane to give **6** as colorless needles, mp 94–96°C (lit.[7] mp 97–99°C). IR

ν_{max} (KBr) cm^{-1}: 1705 (s, C=O), 1600 (m, Ar), 1505 (m, Ar). NMR δ_H (400 MHz, $CDCl_3$): 3.90 (3H, s, OCH_3), 3.97 (3H, s, CO_2CH_3), 6.95 (1H, d, J=11.0 Hz, 5′-H), 7.94 (1H, dd, J=2.7 and 11.0 Hz, 6′-H), 8.06 (1H, d, J=2.7 Hz, 2′-H).

3-Chloro-4-methoxybenzyl alcohol (7). To a stirred suspension of $LiAlH_4$ (0.30 g, 7.96 mmol) in dry ether (45 ml) was added dropwise a solution of **6** (2.00 g, 9.95 mmol) in dry ether (6 ml) at 0°C. The mixture was stirred for 1 h at room temperature. Excess $LiAlH_4$ was then destroyed by carefully adding a few drops of water and then 0.5 N HCl (16 ml). The mixture was extracted with ether, and the resulting extract was successively washed with water, saturated aq. $NaHCO_3$ and brine, dried with anhydrous $MgSO_4$, and the solvent was removed *in vacuo*. The residue was chromatographed on silica gel (40 g; hexane/ethyl acetate, 5:1) to give 1.68 g (98%) of **7**[7] as a colorless oil, n_D^{23}=1.3512. IR ν_{max} (film) cm^{-1}: 3325 (m, O–H), 1605 (m, Ar), 1505 (m, Ar). NMR δ_H (400 MHz, $CDCl_3$): 1.58 (1H, s, OH), 3.91 (3H, s, OCH_3), 4.61 (2H, d, J=5.4 Hz, CH_2O), 6.92 (1H, d, J=8.4 Hz, 5′-H), 7.22 (1H, dd, J=1.7 and 8.4 Hz, 6′-H), 7.40 (1H, d, J=1.7 Hz, 2′-H).

3-Chloro-4-methoxybenzaldehyde (1). To a suspension of PCC (2.24 g, 10.4 mmol), MS 4 Å (0.72 g) and Celite (0.36 g) in dry dichloromethane (37 ml) was added dropwise a solution of **7** (1.20 g, 6.93 mmol) in dry dichloromethane (10 ml). The mixture was stirred for 1 h at room temperature and then filtered through silica gel (24 g). The filtrate was concentrated *in vacuo* to give 1.18 g (99%) of crude **1**, which was recrystallized from dichloromethane/hexane to give colorless needles, mp 56.0–56.5°C. (lit.[3] mp 61–62°C). IR ν_{max} (film) cm^{-1}: 1695 (s, CHO), 1595 (m, Ar), 1505 (m, Ar). NMR δ_H (500 MHz, $CDCl_3$): 4.00 (3H, s, OCH_3), 7.05 (1H, d, J=8.6 Hz, 5′-H), 7.78 (1H, dd, J=1.5 and 8.6 Hz, 6′-H), 7.92 (1H, d, J=1.5 Hz, 2′-H), 9.86 (1H, s, CHO).

(Z)-2-Chloro-4-(1′-propenyl)anisole (8). Ethyl bromide was heated with triphenylphosphine for 12 h at 80°C to give the phosphonium salt. To a stirred suspension of this phosphonium salt (14.1 g, 38.0 mmol) in dry hexane (138 ml) was added a solution of NaHMDS (a 0.6 M solution in toluene, 63.3 ml, 38.0 mmol) under argon. The mixture was stirred under reflux for 3 h, before being cooled to −20°C and diluted with dry THF (130 ml). The supernatant solution was transferred to another flask under argon. To this solution was added dropwise a solution of **1** (3.24 g, 19.0 mmol) in dry THF (17.3 ml) while stirring at −78°C. Stirring was continued for 12 h at room temperature, and the mixture was then filtered. The filtrate was successively washed with water and brine, dried with anhydrous $MgSO_4$, and the solvent was removed *in vacuo*. The residue was chromatographed on silica gel (65 g, hexane/ethyl acetate, 100:1) to give **8** (E/Z=1:7 by a ^{1}H-NMR analysis, 3.27 g, 94%). The E/Z mixture was separated by repeated MPLC to give 1.36 g (39%) of **8** as a colorless oil, n_D^{23}=1.5163. IR ν_{max} (film) cm^{-1}: 1645 (w, C=C), 1600 (m, Ar), 1500 (m, Ar). NMR δ_H (500 MHz, $CDCl_3$): 1.88 (3H, dd, J=1.8 and 7.0 Hz, 3′-H), 3.90 (3H, s, OCH_3), 5.74 (1H, dq, J=7.0 and 11.5 Hz, 2′-H), 6.31 (1H, dd, J=1.8 and 11.5 Hz, 1′-H), 6.89 (1H, d, J=8.5 Hz, 6-H), 7.16 (1H, dd, J=1.8 and 8.5 Hz, 5-H), 7.33 (1H, d, J=1.8 Hz, 3-H). NMR δ_C (100 MHz, $CDCl_3$): 14.5 (C-3′), 56.1 (OCH_3), 111.6 (C-5), 121.9 (C-2), 126.4 (C-2′), 128.1 (C-6), 128.2 (C-1′), 130.4 (C-3), 131.1 (C-4), 153.4 (C-1). *Anal.* Found: C, 65.84; H, 6.17%. Calcd. for $C_{10}H_{11}ClO$: C, 65.76; H, 6.07%.

(1R,2S)-(3′-Chloro-4′-methoxyphenyl)-1,2-propanediol (Trametol) (3). AD-mix-β® (10.4 g) and $MeSO_2NH_2$ (0.71 g, 7.44 mmol) were added to a solution of **8** (1.36 g, 7.44 mmol) in *tert*-BuOH (37.1 ml) and H_2O (37.1 ml) at 0°C. The mixture was stirred for 24 h at 0°C. It was then quenched at 0°C by adding Na_2SO_3 (0.71 g, 88.9 mmol), warmed to room temperature, and stirred for 1 h. The organic layer was separated, and the aqueous layer was extracted several times with ethyl acetate. The resulting extract was washed with 2 N KOH, dried with anhydrous $MgSO_4$, and the solvent was removed *in vacuo*. The residue was purified by silica gel chromatography (27 g; hexane/ethyl acetate, 5:1). Crude **3** (1.43 g, 89%) was of *ca.* 45% ee. The product was recrystallized from hexane/ethyl acetate. The first crop (0.91 g) was (±)-**3**, mp 120–121°C (lit.[3] mp 117–118°C). The mother liquor was concentrated *in vacuo* to give 0.27 g (17%) of **3** as colorless needles (hexane/ethyl acetate), mp 80.5–82.0°C, $[\alpha]_D^{25}$ −34.0 (*c* 1.40, $CHCl_3$) [lit.[4] mp 74°C, $[\alpha]_D$ −29.2 (*c* 1.40, $CHCl_3$)]. GLC [Chirasil-DEX CB® column (0.25 mm × 25 m) at 80+5°C/min to 200°C; He carrier gas at 90 kPa] t_R=30.3 min (2.6%), t_R=30.5 min (97.3%). The enantiomeric purity of **1** was therefore 94.7% ee. IR ν_{max} (nujol) cm^{-1}: 3310 (m, O–H), 3230 (m, O–H), 2925 (s), 2725 (w), 2280 (w), 1870 (w), 1605 (m, Ar), 1505 (m, Ar), 1460 (s), 1380 (s), 1340 (m), 1290 (m), 1260 (m), 1200 (m), 1180 (m), 1145 (m), 1120 (m), 1080 (m), 1060 (m), 1040 (w), 1020 (m), 1000 (m), 945 (m), 895 (m), 885 (m), 835 (w), 810 (m), 790 (w), 720 (m), 705 (m), 695 (m), 650 (w), 605 (m). NMR δ_H (500 MHz, $CDCl_3$): 1.08 (3H, d, J=6.4 Hz, 3-H), 1.83 (1H, d, J=4.9 Hz, 2-OH), 2.32 (1H, d, J=3.5 Hz, 1-OH), 3.90 (3H, s, OCH_3), 4.00 (1H, m, 2-H), 4.60 (1H, seemingly t, J=3.5 Hz, 1-H), 6.92 (1H, d, J=8.2 Hz, 5′-H), 7.22 (1H, dd, J=2.2 and 8.2 Hz, 6′-H), 7.40 (1H, d, J=2.2 Hz, 2′-H) [lit.[5] NMR δ_H (250.1 MHz, $CDCl_3$): 1.07 (3H, d,

J=6.0 Hz, 3-H), 2.20 (2H, br, 1-OH and 2-OH), 3.90 (3H, s, OCH_3), 3.98 (1H, dq, J=4.2 and 6.0 Hz, 2-H), 4.61 (1H, d, J=4.2 Hz, 1-H), 6.92 (1H, d, J=8.5 Hz, 5′-H), 7.22 (1H, dd, J=8.5 and 2.0 Hz, 6′-H), 7.39 (1H, d, J=2.0 Hz, 2′-H)]. NMR δ_C (75 MHz, $CDCl_3$): 17.3 (C-3), 56.2 (OCH_3), 71.1 (C-2), 76.6 (C-1), 111.8 (C-5′), 122.4 (C-3′), 126.1 (C-6′), 128.5 (C-2′), 133.5 (C-1′), 154.5 (C-4′). These ^{13}C-NMR data are in good agreement with those reported for (±)-**3**.[5] *Anal.* Found: C, 55.45; H, 6.22%. Calcd. for $C_{10}H_{13}ClO_3$: C, 55.44; H, 6.05%.

Methyl 3,5-dichloro-4-methoxybenzoate (10). In the same manner as that described for the preparation of **6**, **9** (1.00 g, 4.83 mmol) was converted to crude **10** (1.14 g, 99%) which was recrystallized from hexane to give colorless needles, mp 78–79°C (lit.[3] 82–83°C). IR ν_{max} (film) cm^{-1}: 1735 (s, C=O), 1555 (m, Ar), 1480 (m, Ar), 1290 (s, C–O–C). NMR δ_H (500 MHz, $CDCl_3$): 3.92 (3H, s, OCH_3), 3.96 (3H, s, CO_2CH_3), 7.98 (2H, s, 2′-H, 6′-H).

3,5-Dichloro-4-methoxybenzyl Alcohol (11). In the same manner as that described for the preparation of **7**, **10** (17.4 g, 73.5 mmol) was converted to 15.3 g (99 %) of **11** as colorless needles, mp 44–46°C (lit.[3] 46–47°C). IR ν_{max} (film) cm^{-1}: 3305 (m, O–H), 1560 (m, Ar), 1480 (m, Ar). NMR δ_H (400 MHz, $CDCl_3$): 1.74 (1H, t, J=5.6 Hz, OH), 3.90 (3H, s, OCH_3), 4.63 (2H, d, J=5.6 Hz, CH_2O), 7.31 (2H, s, 2′-H, 6′-H).

3,5-Dichloro-4-methoxybenzaldehyde (2). In the same manner as that described for the preparation of **1**, **11** (2.70 g, 12.9 mmol) was converted to 2.60 g (97%) of **2** which was recrystallized from hexane to give colorless needles, mp 62°C (lit.[3] 63–65°C). IR ν_{max} (film) cm^{-1}: 1695 (s, CHO), 1585 (m, Ar), 1555 (m, Ar). NMR δ_H (500 MHz, $CDCl_3$): 3.99 (3H, s, OCH_3), 7.83 (2H, s, 2′-H, 6′-H), 9.87 (1H, s, CHO).

(Z)-2,6-Dichloro-4-(1′-propenyl)anisole (12). In the same manner as that described for the preparation of **8**, **2** (5.86 g, 26.9 mmol) was converted to 5.85 g (E/Z=1:2 by a ^{1}H-NMR analysis, 95%) of **12**. The E/Z mixture was separated several times by MPLC to give 1.85 g (32%) of **12** as a colorless oil, n_D^{24}= 1.5161. IR ν_{max} (film) cm^{-1}: 1645 (w, C=C), 1590 (m, Ar), 1540 (m, Ar). NMR δ_H (300 MHz, $CDCl_3$): 1.88 (3H, dd, J=1.8 and 6.0 Hz, 3′-H), 3.90 (3H, s, OCH_3), 5.83 (1H, dq, J=6.0 and 12.0 Hz, 2′-H), 6.26 (1H, dd, J=1.8 and 12.0 Hz, 1′-H), 7.20 (2H, s, 3-H, 5-H). NMR δ_C (100 MHz, $CDCl_3$): 14.5 (C-3′), 60.7 (OCH_3), 127.1 (C-1′), 128.7 (C-2′), 128.8 (C-2, C-6), 129.0 (C-3, C-5), 135.0 (C-4), 150.5 (C-1). *Anal.* Found: C, 55.46; H, 4.91%. Calcd. for $C_{10}H_{10}Cl_2O$: C, 55.33; H, 4.64%.

(1R,2S)-(3′,5′-Dichloro-4′-methoxyphenyl)-1,2-propanediol (4). In the same manner as that described for the preparation of **3**, **12** (1.85 g, 8.52 mmol) was converted to 1.13 g (53%) of (±)-**4**, mp 98.5–107°C (lit.[3] mp 100–102°C) and 0.63 g (29%) of (−)-**4** as colorless needles, mp 46–47°C, $[\alpha]_D^{24}$ −23.5 (*c* 1.45, $CHCl_3$). IR ν_{max} (nujol) cm^{-1}: 3270 (m, O–H), 3200 (m, O–H), 2925 (s), 2855 (s), 2360 (m), 1555 (m, Ar), 1480 (m, Ar), 1460 (m), 1425 (m), 1400 (m), 1375 (m), 1265 (m), 1210 (m), 1135 (m), 1095 (m), 1065 (m), 1020 (m), 1000 (m), 905 (w), 825 (m), 810 (m), 780 (m), 750 (m), 690 (m). GLC (Chirasil-DEX CB® column (0.25 mm×25 m) at 80°C+1.5°C/min to 200°C, He carrier gas at 90 kPa) t_R=59.3 min (98.9%), t_R=59.8 min (1.1%). The enantiomeric purity of **1** was therefore 97.8% ee. NMR δ_H (500 MHz, $CDCl_3$): 1.07 (3H, d, J=6.4 Hz, 3-H), 2.02 (1H, d, J=3.4 Hz, 2-OH), 2.65 (1H, d, J=3.4 Hz, 1-OH), 3.87 (3H, s, OCH_3), 3.99 (1H, m, 2-H), 4.60 (1H, seemingly t, J=3.4 Hz, 1-H), 7.29 (2H, s, 2′-H, 6′-H). NMR δ_C (125 MHz, $CDCl_3$): 17.1 (C-3), 60.7 (OCH_3), 70.9 (C-2), 76.0 (C-1), 127.1 (C-2′, C-6′), 129.1 (C-3′, C-5′), 138.0 (C-1′), 151.4 (C-4′). These ^{1}H- and ^{13}C-NMR data are in good agreement with those reported for (±)-**4**.[5] *Anal.* Found: C, 47.98; H, 4.74%. Calcd. for $C_{10}H_{12}Cl_2O_3$: C, 47.83; H, 4.82%.

Acknowledgments

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References

1) Gribble, G. W., Naturally occurring organohalogen compounds. *Acc. Chem. Res.*, **31**, 141–152 (1998).
2) de Jong, E., Field, J. A., Dings, J. A. F. M., Wijnberg, J. B. P. A., and de Bont, J. A. M., *De-novo* biosynthesis of chlorinated aromatics by the white-rot fungus *Bjerkandera* sp. BOS55. Formation of 3-chloroanisaldehyde from glucose. *FEBS Lett.*, **305**, 220–224 (1992).
3) de Jong, E., Field, J. A., Spinnler, H.-E., Wijnberg, J. B. P. A., and de Bont, J. A. M., Significant biogenesis of chlorinated aromatics by fungi in natural environments. *Appl. Environ. Microbiol.*, **60**, 264–270 (1994).
4) Brambilla, U., Nasini, G., and de Pava, O. V., Secondary mold metabolites, Part 49. Isolation, structural elucidation, and biomimetic synthesis of trametol, a new 1-arylpropane-1,2-diol produced by the fungus *Trametes* sp. *J. Nat. Prod.*, **58**, 1251–1253 (1995).
5) Swarts, H. J., Verhagen, F. J. M., Field, J. A., and Wijnberg, J. B. P. A., Identification and synthesis of novel chlorinated *p*-anisylpropanoid metabolites from *Bjerkandera* species. *J. Nat. Prod.*, **61**, 1110–1114 (1998).
6) Kolb, H. C., VanNieuwenhze, M. S., and Sharpless, K. B., Catalytic asymmetric dihydroxylation. *Chem.*

Rev., **94**, 2483–2547 (1994).
7) Riggs, R. M., Nichols, D. E., Foreman, M. M., and Truex, L., Evaluation of isomeric 4-(chlorohydroxyphenyl)-1,2,3,4-tetrahydroisoquinolines as dopamine D-1 antagonists. *J. Med. Chem.*, **30**, 1887–1891 (1987).
8) Bestmann, H. J., Stransky, W., and Vostrowsky, O., Reaktionen mit Phosphinalkylenen, XXXIII. Darstellung lithiumsalzfreier Ylidlösungen mit Natrium-bis(trimethylsilyl)amide als Base. *Chem. Ber.*, **109**, 1694–1700 (1976).