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NOTE

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Absolute Configuration of Anti-HIV-1 Agent (−)-Concentricolide: Total Synthesis of (+)-(*R*)-Concentricolide†

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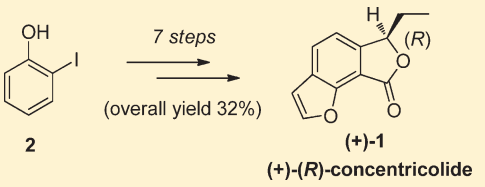
Supporting Information

ABSTRACT: The first enantioselective total synthesis of (+)-(*R*)-concentricolide, the enantiomer of an anti-HIV-1 agent isolated from *Daldinia concentrica*, from 2-iodophenol in 7 steps reveals the (*S*)-configuration for the natural form of the furanophthalide. The key features include an anionic ortho-Fries rearrangement to furnish 3-iodosalicylamide, facile construction of the benzofuran system employing the tandem Sonogashira coupling annulation reaction, directed ortho metalation to introduce a propanoyl group, as well as CBS reduction, establishing the stereocenter enantioselectively.

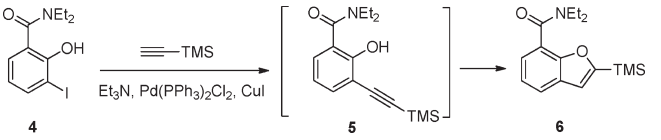


The devastating AIDS (Acquired Immunodeficiency Syndrome) in humans is caused by HIV (Human Immunodeficiency Virus) that attacks and gradually destroys the CD4 T-helper cells of the immune system. Depletion of the relevant T-lymphocytes predisposes invasion of opportunistic pathogens as well as incurrence of neurologic and neoplastic diseases from which death follows. Current therapy of AIDS targets primarily at the intervention of viral replication and entry into T cell. To this end, drugs for inhibiting reverse transcriptase, protease, integrase, viral absorption, viral uncoating, and viral fusion have been developed and some combinations are employed clinically.[1,2]

There have been active quests for anti-HIV agents from plant sources.[3] Constituents belonging to the alkaloid, coumarin, flavonoid, lignan, phenolic, quinone, saponin, terpenoid/sterol, xanthone, carbohydrate, peptide, and protein families have been identified. Several of them have proceeded to phase I or phase IIb stage of drug development.[4] As therapeutic agents are in urgent demand due to the emergence and transmission of drug-resistant variants, this search remains incessant to this day. Recently, (−)-concentricolide, a fungal metabolite of the Ascomycete *Daldinia concentrica*, was isolated (120 mg from 750 g of dried fruiting bodies) and its in vitro anti-HIV-1 activity was noted (EC_{50} 0.31 μg/mL in the inhibition of HIV-1-induced cytopathic effects; EC_{50} 0.83 μg/mL in the blockage of syncytium formation between HIV-1 infected cells and normal cells).[5] Although there have been a racemic synthesis[6] via a Diels−Alder reaction of furan-3-carbaldehyde and dihydrofuran-2(3*H*)-one and a discussion on the assignment of the configuration of (−)-concentricolide by DFT calculation,[7] the uncertainty of the absolute structure still remains; moreover, this tricyclic compound being the prototype of a new structural class deserves further study. Herein we describe a synthesis of (+)-concentricolide that also serves to establish its absolute configuration.

Our synthetic route started from commercially available 2-iodophenol (**2**) (Scheme 1). The hydroxy group was carbamated to afford **3** that was transformed into 3-iodosalicylamide **4** via anionic ortho-Fries rearrangement.[8] Treatment of **4** with trimethylsilylacetylene in the presence of 1 mol % of bis(triphenylphosphine)-palladium(II) chloride and 2 mol % of cuprous iodide in triethylamine−acetonitrile at 65 °C for 4 days gave benzofuran **6** in 88% yield. Significantly, higher reaction temperature decreased the turnover number of the catalyst system for the annulation from *Sonogashira* intermediate **5** to benzofuran **6** (Table 1 entries 1 and 2)[9] and consequently much higher catalyst loading with portionwise addition was required for the completion of the tandem reaction (Table 1 entry 3). Benzofuran **6** was then converted to a propanoyl derivative (**7**) by ortho-directed[10] lithiation and *N*-methoxy-*N*-methylpropionamide in 76%

Table 1. Optimization of the Tandem Sonogashira Coupling Annulation



entry	sovlent	temp, °C	$Pd(PPh_3)_2Cl_2$, mol %	CuI, mol %	time, h	products **5**/**6**[a]	yield,[c] %
1	CH_3CN	90	5	10	96	1/4	85
2[b]	toluene	100	10	20	96	1/7	85
3[b]	CH_3CN	90	10	20	70	>1/19	83
4	CH_3CN	65	1	2	2	4/1	80
5	CH_3CN	65	1	2	96	>1/19	88

[a] The product ratio of **5** and **6** was determined by ^{1}H NMR. [b] A second portion of 5 mol % of $Pd(PPh_3)_2Cl_2$ and 10 mol % of CuI was added after 48 h. [c] Yield of an inseparable mixture of **5** and **6**.

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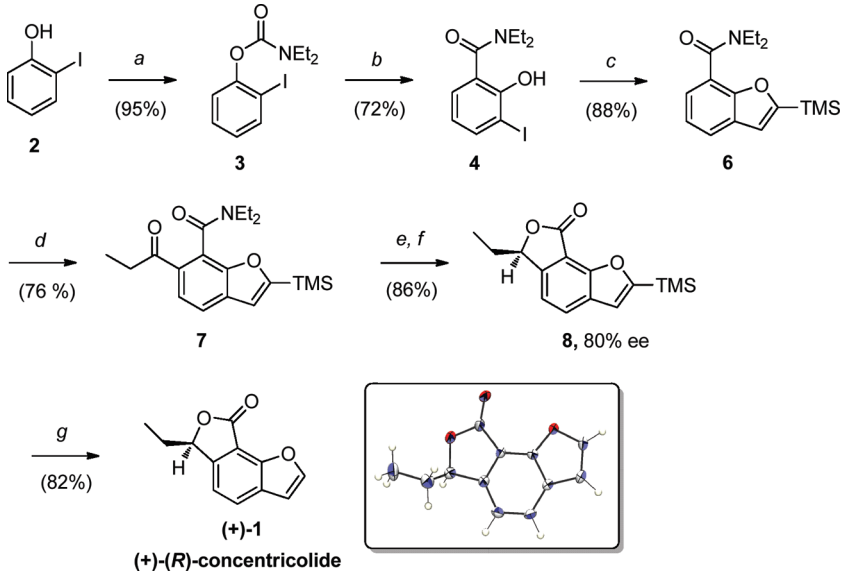
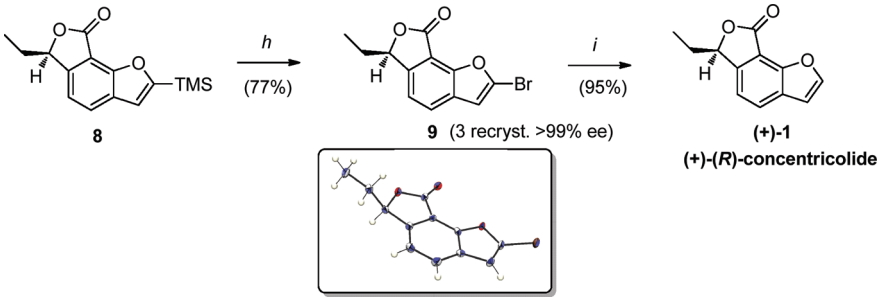
Scheme 1. Synthesis of (+)-(*R*)-Concentricolide[a]



[a] Reagents and conditions: (a) K_2CO_3, *N*,*N*-diethylchloroformamide, CH_3CN, reflux, 2 h; (b) LDA, THF, −60 °C; (c) trimethylsilylacetylene, Et_3N, $Pd(PPh_3)_2Cl_2$ (1 mol %), CuI (2 mol %), CH_3CN, 65 °C, 96 h; (d) TMEDA, *t*-BuLi, THF, −80 °C, 1.5 h; *N*-methoxy-*N*-methylpropionamide; (e) (*S*)-*B*-^{n}Bu-CBS catalyst (0.5 equiv), BH_3−THF, 0 °C; (f) KOAc, *o*-xylene, 130 °C, 1 h; (g) TBAF, AcOH, rt, 10 min.

Scheme 2. Preparation of (+)-1[a]



[a] Reagents and conditions: (h) Br_2, CH_2Cl_2, rt, 10 min; (i) Zn, AcOH, H_2O, 100 °C, 1 h.

yield.[11] This manipulation allowed us to gain access to a chiral intermediate and hence optically active concentricolide, enabling us to determine the absolute configuration of **1**. Thus, upon reduction of **7** by the CBS protocol[12] the resulting rotamers[13] were treated with potassium acetate in hot xylene without purification to generate phthalide **8** in 86% yield with 80% ee. Slightly to our disappointment, endeavors to further improve the enantioselectivity of CBS reduction were not promising. This would be attributed to the participation of the anilide group in the pretransition state of the borane-CBS catalyst−ketone assembly whose conformers interconvert sufficiently slowly and erode the facial selectivity. After desilylation with tetrabutylammonium fluoride buffered with acetic acid[14] for the prevention of the chirality loss, the final product (+)-**1** (Scheme 2) with opposite optical rotation to the natural product was obtained in 86% yield ($[\alpha]^{25}_D$ +26.1 (*c* 0.81, CH_3OH)),[5] of which structure was confirmed by NMR,[15] IR, mass spectra, and X-ray crystallography. Remarkably, the absolute configuration (*R*) of (+)-**1** was assigned by the application of the mechanistic model of CBS reduction as well as the X-ray diffraction analysis of its bromo derivative **9**, which was prepared from **8** by simple treatment with bromine in methylene chloride at room temperature. Recrystallization from ethyl acetate−hexane afforded **9** of >99% ee, mp 155−156 °C. Exposure of bromide **9** to 10 equiv of zinc powder in acetic acid/water at 100 °C gave enantiopure (+)-(*R*)-concentricolide: >99% ee, mp 89−90 °C (petroleum ether/acetone); mp 116−117 °C (ethyl acetate/hexane), $[\alpha]^{25}_D$ +34.8 (*c* 0.48, CH_3OH). All data for (+)-(*R*)-**1** were in good agreement with those reported by Liu et al. except optical rotation, which had been confirmed several times in two different polarimeters.[16]

In summary, the efficient and expeditious synthesis of (+)-(*R*)-concentricolide was accomplished enantioselectively in a linear sequence of 7 steps and an overall yield of 32% from easily accessible starting materials. The absolute configuration of the natural chiral form of concentricolide was affirmed as (*S*).

EXPERIMENTAL SECTION

***O*-(2-Iodophenyl)-*N*,*N*-diethylcarbamate (3):**[17] A mixture of 2-iodophenol (10.8 g, 49.1 mmol), K_2CO_3 (20.3 g, 147.3 mmol), and

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N,N-diethylchloroformamide (7.5 mL, 58.9 mmol) in CH_3CN (100 mL, ACS grade for direct use) was heated to reflux for 2 h. Upon cooling, the resulting mixture was filtered and washed by ethyl acetate (3 × 100 mL). The filtrate was concentrated in vacuo to give the residue, which was directly subjected to flash column chromatography (EtOAc−hexanes, 1:4) to afford *O*-(2-iodophenyl)-*N,N*-diethylcarbamate as an amber oil (14.8 g, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (1H, d, J = 8 Hz), 7.31−7.35 (1H, m), 7.17 (1H, d, J = 8 Hz), 6.92 (1H, t, J = 7.6 Hz), 3.52 (2H, q, J = 6.8 Hz), 3.39 (2H, q, J = 6.8 Hz), 1.32 (3H, t, J = 6.8 Hz), 1.22 (3H, t, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 151.7, 139.1, 129.1, 126.8, 123.3, 121.7, 90.8, 42.3, 42.0, 14.3, 13.3.

***N,N*-Diethyl-2-hydroxy-3-iodobenzamide (4):**[18] To a solution of diisopropylamine (169 μL, 1.20 mmol) in THF (1.2 mL) was slowly added *n*-BuLi (2.42 M in *n*-hexanes, 0.50 mL, 1.21 mmol) at −60 °C under nitrogen within 5 min. After the mixture was stirred for 20 min at −60 °C, a solution of *O*-(2-iodophenyl)-*N,N*-diethylcarbamate (**3**) (319 mg, 1.0 mmol) in THF (1.2 mL) was added within 5 min. The reaction mixture was stirred at −60 °C for 30 min, then allowed to warm to room temperature and stirred for another 2 h. The reaction was quenched with saturated NH_4Cl solution (10 mL). After removal of the organic solvent, the aqueous layer was acidified with 1 N HCl to pH 3 and the resulting residue was extracted with EtOAc (3 × 30 mL). The combined extract was washed with brine (10 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc−hexanes, 1:4) to afford *N,N*-diethyl-2-hydroxy-3-iodobenzamide as an amber oil (0.24 g, 72% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.42 (1H, s), 7.73 (1H, d, J = 7.4 Hz), 7.22 (1H, d, J = 7.3 Hz), 6.61 (1H, t, J = 7.3 Hz), 3.46 (4H, q, J = 6.7 Hz), 1.22 (6H, t, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 156.8, 141.3, 127.4, 120.3, 118.8, 86.2, 42.1, 13.2.

***N,N*-Diethyl-2-trimethylsilylbenzofuran-7-carboxamide (6):** A solution of *N,N*-diethyl-2-hydroxyl-3-iodobenzamide (280 mg, 0.88 mmol), trimethylsilylacetylene (0.19 mL, 1.32 mmol), and Et_3N (0.92 mL, 3.52 mmol) in CH_3CN (1.76 mL) in a Schlenk tube was degassed by two freeze−pump−thaw cycles and charged with $Pd(PPh_3)_2Cl_2$ (6.2 mg, 8.8 μmol) and CuI (1.2 mg, 11.6 μmol) under nitrogen. The resulting mixture was stirred at 65 °C for 96 h. Upon completion of conversion (monitored by ^{1}H NMR), the solution was concentrated and directly purified by flash column chromatography (EtOAc−hexanes, 1:9) to afford *N,N*-diethyl-2-trimethylsilylbenzofuran-7-carboxamide as an amber oil (223 mg, 88% yield). IR (film) 2965, 2935, 2899, 1633, 1534, 1430, 1481, 1380, 1346, 1284, 1250, 1121, 1067, 910, 845, 752, 634 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (1H, dd, J = 7.7, 1.3 Hz,), 7.28 (1H, dd, J = 7.3, 1.3 Hz), 7.21 (1H, t, J = 7.5 Hz), 6.96 (1H, s), 3.66 (2H, q, J = 7.1 Hz), 3.20 (2H, q, J = 7.1 Hz), 1.31 (3H, t, J = 7.1 Hz), 1.05 (3H, t, J = 7.1 Hz), 0.32 (s, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 164.1, 153.2, 128.4, 122.9, 122.6, 121.8, 121.4, 116.0, 42.9, 38.9, 14.0, 12.8, −1.9; HRMS (FAB+) calcd for $C_{16}H_{23}NO_2Si$ [(M + H)$^+$] 290.1580, found 290.1576.

***N,N*-Diethyl-6-propionyl-2-trimethylsilylbenzofuran-7-carboxamide (7):** To a solution of *N,N*-diethyl-2-trimethylsilylbenzofuran-7-carboxamide (**6**) (190 mg, 0.66 mmol) and tetramethylethylenediamine (TMEDA) (156 μL, 1.05 mmol) in THF (2.2 mL) at −80 °C was added slowly a solution of *t*-BuLi (1.44 M in pentane, 0.69 mL, 0.99 mmol). The color of the solution turned to deep-blue gradually and reached a stable state while the lithiation reagent was added. The resulting solution was kept at −80 °C for 1 h and the neat *N*-methoxy-*N*-methylpropionamide (120 mg, 0.99 mmol) was added slowly at the same temperature. After another 1 h of stirring at −80 °C, the reaction was quenched with saturated NH_4Cl solution (5 mL). THF was removed and the residue was diluted with EtOAc (15 mL), washed with 1 N HCl (2 × 10 mL) and brine (10 mL), dried over $MgSO_4$, concentrated, and purified by column chromatography (EtOAc−hexanes, 1:4) to afford *N,N*-diethyl-6-propionyl-2-trimethylsilylbenzofuran-7-carboxamide as an amber oil (173 mg, 76% yield). IR (film) 2975, 2937, 2901, 2877, 1720, 1683, 1640, 1606, 1579, 1523, 1484, 1432, 1348, 1361, 1314, 1279, 1246, 1224, 1106, 1066, 912, 881, 844, 759, 633 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (1H, d, J = 8.2 Hz), 7.57 (1H, d, J = 8.2 Hz), 6.97 (1H, s), 3.70 (2H, s), 3.12 (2H, q, J = 7.1 Hz), 3.03 (2H, s), 1.38 (3H, t, J = 7.1 Hz), 1.23 (3H, t, J = 7.2 Hz), 0.98 (3H, t, J = 7.1 Hz), 0.32 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.3, 168.1, 166.8, 131.9, 131.0, 123.3, 122.0, 120.4, 115.7, 43.0, 38.9, 33.4, 13.4, 12.5, 8.3, −2.0; HRMS (FAB+) calcd for $C_{19}H_{27}NO_3Si$ [(M + H)$^+$] 346.1838, found 346.1839.

(+)-(*R*)-2-Trimethylsilylconcentricolide (8): To a solution of *N,N*-diethyl-6-propionyl-2-trimethylsilylbenzofuran-7-carboxamide (**7**) (104 mg, 0.30 mmol) and (*S*)-*B*-^{n}Bu-CBS catalyst[19] (0.15 mmol) at 0 °C with vigorous stirring was added BH_3−THF (1.0 M in THF, 0.45 mL, 0.45 mmol) slowly along the side wall of the reaction flask by a syringe pump over 5 h. After completion of the addition and another 1 h of stirring at 0 °C, KOAc (294 mg, 3.0 mmol) and *o*-xylene (2 mL) were added to the flask followed by the removal of THF under reduced pressure. The resulting mixture was directly heated at 140 °C for 1 h. Upon cooling, water (10 mL) was added and a bilayer solution was then extracted with EtOAc (3 × 10 mL). The combined extracts were washed with brine (5 mL), dried over $MgSO_4$, concentrated, and column chromatographied (EtOAc−hexanes, 1:19) to furnish 2-trimethylsilylconcentricolide as a colorless oil (71 mg, 86% yield, 80% ee). $[\alpha]^{25}_D$ +13.9 (*c* 0.92, $CHCl_3$, 80% ee); IR (film) 2966, 2936, 1760, 1635, 1596, 1528, 1462, 1328, 1251, 1283, 1178, 1150, 1109, 1056, 955, 844, 792, 758, 685 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (1H, d, J = 7.9 Hz), 7.21 (1H, d, J = 7.9 Hz), 7.05 (1H, s), 5.54 (1H, dd, J = 7.5, 4.5 Hz), 2.24−2.06 (1H, m), 1.91−1.78 (1H, m), 0.99 (1H, t, J = 7.3 Hz), 0.38 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.2, 166.2, 153.2, 147.9, 129.8, 127.5, 115.8, 115.4, 110.8, 82.6, 27.9, 8.7, −1.83; HRMS (EI+) calcd for $C_{15}H_{18}O_3Si$ (M^+) 274.1025, found 274.1033; enantioselectivity was determined by HPLC analysis (Chiralpak-AD, 1.0 mL/min, 220 nm, hexanes/*i*-PrOH 99/1); retention times were 11.8 (enantiomer) and 13.1 min (major).

(+)-(*R*)-Concentricolide (1): To a solution of 2-trimethylsilylconcentricolide (**8**) (63 mg, 0.23 mmol, 80% ee) and AcOH (14 μL, 0.23 mmol) in THF (2 mL) was added tetra-*n*-butylammonium fluoride (TBAF, 1 M in THF, 0.25 mL, 0.25 mmol) at room temperature. Upon completion of the conversion, the resulting solution was concentrated and purified by flash column chromatography (EtOAc−hexanes, 1:9) to afford concentricolide as a white solid (52 mg, 82% yield, 80% ee). Mp 89−90 °C (petroleum ether/acetone); mp 116−117 °C (ethyl acetate/hexane) [lit. mp 89−90 °C, petroleum ether/acetone]; $[\alpha]^{25}_D$ +26.1 (*c* 0.81, CH_3OH); IR (film) 2970, 2933, 1761, 1640, 1595, 1536, 1435, 1321, 1204, 1109, 1061, 976, 837, 768, 665 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (1H, d, J = 8.0 Hz,), 7.80 (1H, d, J = 2.1 Hz), 7.27 (1H, d, J = 8.0 Hz), 6.90 (1H, d, J = 2.1 Hz), 5.57 (1H, dd, J = 7.0, 4.2 Hz), 2.20−2.18 (1H, m), 1.86−1.83 (1H, m), 1.01 (3H, t, J = 7.4 Hz); ^{1}H NMR (500 MHz, $CDOD_3$) δ 8.02 (1H, d, J = 8.0 Hz), 7.94 (1H, d, J = 2.2 Hz), 7.41 (1H, d, J = 8.0 Hz), 7.03 (1H, d, J = 2.2 Hz), 5.66 (1H, dd, J = 6.9, 4.1 Hz), 2.24−2.17 (1H, m), 1.88−1.80 (1H, m), 0.95 (3H, t, J = 7.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 149.8, 147.9, 146.6, 129.0, 127.9, 116.1, 111.1, 106.6, 82.9, 27.9, 8.8; ^{13}C NMR (125 MHz, $CDOD_3$) δ 170.1, 151.0, 149.7, 148.1, 130.6, 129.6, 117.6, 111.6, 107.9, 84.7, 28.7, 8.9; HRMS (EI+) calcd for $C_{12}H_{10}O_3$ (M^+) 202.0630, found 202.0633; enantioselectivity was determined by HPLC analysis (Chiralpak-AD, 1.0 mL/min, 220 nm, hexanes/*i*-PrOH 99/1); retention times were 48.7 (major) and 55.4 min (enantiomer).

(+)-(*R*)-2-Bromoconcentricolide (9): To a solution of 2-trimethylsilylconcentricolide (**8**) (106 mg, 0.39 mmol, 80% ee) in CH_2Cl_2 (3 mL) was added slowly a solution of bromine in CH_2Cl_2 (0.6 M in CH_2Cl_2, 1.3 mL, 0.78 mmol) at room temperature. After 10 min, the reaction was treated with Et_3N (0.2 mL) and concentrated to obtain the crude product. The residue was purified by flash column chromatography

(CH_2Cl_2−EtOAc−hexanes, 1:1:8) to obtain 2-bromoconcentricolide as a white solid (84 mg, 77% yield, 80% ee). The solid 2-bromoconcentricolide with 80% ee was recrystallized three times from EtOAc−hexanes (1:4) to give a colorless needle (48 mg, 58% yield, >99% ee,). Mp 155−156 °C; $[\alpha]^{25}_D$ +22.4 (*c* 0.82, $CHCl_3$); IR (film) 2970, 2931, 1759, 1643, 1538, 1428, 1328, 1299, 1113, 1057, 952, 907, 842 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.80 (1H, d, J = 8.0 Hz), 7.28 (1H, d, J = 8.0 Hz), 6.85 (1H, s), 5.53 (1H, dd, J = 7.0, 4.2 Hz), 2.18−2.12 (1H, m), 1.83−1.80 (1H, m), 0.98 (3H, t, J = 7.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.3, 150.3, 147.5, 130.2, 130.11, 126.5, 116.8, 110.7, 108.5, 82.8, 27.8, 8.7; HRMS (FAB+) calcd for $C_{12}H_9BrO_3$ [$(M + H)^+$] 280.9813, found 280.9814; enantioselectivity was determined by HPLC analysis (Chiralcel-OJ, 1.0 mL/min, 220 nm, hexanes/*i*-PrOH 4/1); retention times were 16.6 (enantiomer) and 25.1 min (major).

Enantiopure (+)-(*R*)-Concentricolide (1) Prepared from 2-Bromoconcentricolide (9): Zinc powder (37.5 mg, 0.5 mmol) was added portionwise to a mixture of 2-bromoconcentricolide (**9**) (14 mg, 0.05 mmol, >99% ee) in a mixed solvent of AcOH (0.3 mL) and water (0.1 mL) at 100 °C. After 1 h of heating at 100 °C, the reaction mixture was cooled to room temperature, filtered, and washed with EtOAc (3 × 5 mL). To this filtrate was added saturated $NaHCO_3$ (5 mL) slowly, followed by extraction with EtOAc (2 × 5 mL). The combined extracts were washed with brine (5 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (EtOAc−hexanes, 1:9) to afford (+)-concentricolide (9.6 mg, 95% yield, >99% ee) as a white solid. Mp 89−90 °C (petroleum ether/acetone); mp 116−117 °C (ethyl acetate/hexane); $[\alpha]^{25}_D$ +34.8 (*c* 0.48, CH_3OH); $[\alpha]^{25}_D$ +36.7 (*c* 0.60, $CHCl_3$).

■ ASSOCIATED CONTENT

Supporting Information. Copies of ^1H and ^{13}C NMR spectra for all new compounds and the X-ray crystallographic data of (+)-(*R*)-concentricolide and compound **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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DEDICATION

†This paper is dedicated to Professor Tse-Lok Ho on the occasion of his 73rd birthday.

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(15) The comparison of the ^1H and ^{13}C NMR between synthetic concentricolide and reported data is summarized in the Supporting Information. The solvent ($CDCl_3$) used for taking NMR spectra in ref 5 was mistaken for CD_3OD.
(16) Shortly before the acceptance of this paper, the natural form (−)-(*S*)-concentricolide [99% ee, mp 87−88 °C (petroleum ether/acetone); $[\alpha]^{25}_D$ −35.1 (*c* 0.48, CH_3OH); $[\alpha]^{25}_D$ −37.5 (*c* 1.0, $CHCl_3$)] was synthesized by using the same reagents and procedures except (*R*)-CBS catalyst was employed.
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