A Direct Asymmetric Synthesis of Juglomycin A

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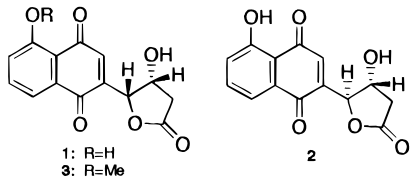
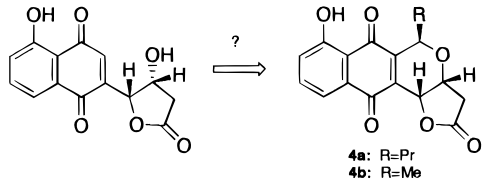
Juglomycin A has been synthesized in four steps from 5-methoxy-1-naphthol.

In 1971 Ono and co-workers isolated juglomycin A (**1**) and juglomycin B (**2**) from *Streptomyces* sp. 190−2.[1] The absolute configurations of **1** and **2** were confirmed by single crystal X-ray determination.[2] Syntheses of racemic **1** and **2** have been reported by Giles and co-workers.[3] A formal total synthesis of **1** has recently been reported.[4] No asymmetric synthesis of either **1** or **2** has been reported. According to the literature,[5] juglomycin A is readily converted into a mixture of juglomycin A and juglomycin B under acidic and weakly basic conditions. Both **1** and **2** exhibit modest antitumor activity as well

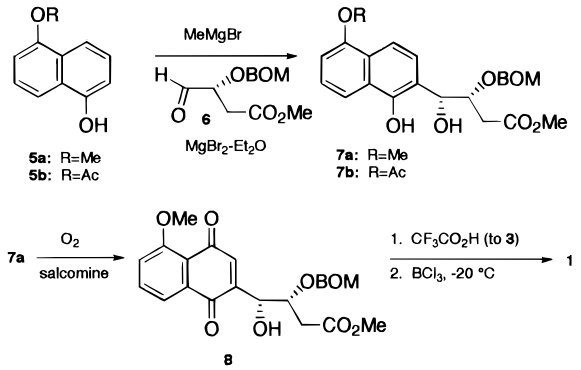


as antibacterial activity against both Gram-negative and Gram-positive bacteria.[1] Since juglomycin A is a fragment of the anticoccidial agent frenolicin B (**4a**) and the antifungal agent kalafungin (**4b**), a synthesis of juglomycin A could in principle be a stepping stone to a versatile synthesis of pyranonaphthoquinones. We report herein an efficient asymmetric synthesis of juglomycin A.



After a few unsuccessful approaches, our synthetic efforts focussed on the reaction of a naphthol anion with a chiral aldehyde. This reaction has been studied with simple phenols by Casiraghi and co-workers.[6] Our synthesis of **1** began with naphthol **5a** which was deprotonated using methyl magnesium bromide and then treated with aldehyde **6**[7] derived from D-malic acid. Diastereomer **7a** was produced as the major isomer of a 24:1 mixture (determined by ^{1}H NMR integration of phenol OH) in 67% isolated yield. This reaction was also conducted with 5-acetoxy-1-naphthol (**5b**). In this case, the ratio of diastereomers was only 12:1 and the yield was 57%.

The construction of the naphthoquinone subunit was achieved by treating **7a** with phenyliodine(III) bis(trifluoroacetate). Quinone **8** was produced in only 34% yield. Alternatively, quinone **8** could be generated using salcomine and molecular oxygen in 72% yield.[8] After several unsuccessful experiments using aqueous acids (HCl, HBr), the transformation of **8** into hydroxy lactone **3** was effected using anhydrous trifluoroacetic acid in methylene chloride. Both lactonization and deprotection of the BOM group were achieved. Attempts to produce a lactone from hydroxy ester **7** using either acid or base catalysis led to extensive epimerization of the benzylic alcohol, possibly by way of a quinone methide intermediate. Deprotection of **3** using boron trichloride in methylene chloride at −20 °C afforded **1** in 49% yield from **8** without significant epimerization at the benzylic position. Significant epimerization had previously been observed using aluminum chloride.[3] The spectral data (IR, ^{1}H NMR) for synthetic **1** were identical to those reported for the natural substance.



Juglomycin A has been synthesized from naphthol **5a** in four steps. This direct and flexible synthetic route will permit further evaluation of this novel compound. We are presently studying the conversion of juglomycin A into kalafungin.

Experimental Section

Optical rotations were measured with a DIP-370 polarimeter using a 10 cm cell. H:EA refers to hexanes:ethyl acetate solvent mixtures for thin layer chromatography and silica gel flash chromatography (sgc). Infrared spectra (IR) were recorded on a FTS-7 spectrophotometer. Proton NMR spectra were measured at 300 MHz with tetramethylsilane as an internal standard. ^{13}C NMR spectra were recorded in $CDCl_3$ at 75 MHz. High resolution mass spectra (HRMS) were EI spectra obtained by a Kratos MS50 magnetic sector mass spectrometer.

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Methyl (*R*)-4-Oxo-3-((phenylmethoxy)methoxy)butanoate (6). To a stirred solution of (*R*)-malic acid dimethyl ester (3.69 g, 22.8 mmol) and diisopropylethylamine (4.76 mL, 27.4 mmol) in anhydrous CH_2Cl_2 (30 mL) at 0 °C was added dropwise chloromethyl benzyl ether (6.34 mL, 45.6 mmol). The reaction mixture was stirred at rt for 72 h and then quenched with H_2O. After concentration in vacuo, the aqueous layer was separated and extracted with CH_2Cl_2. The combined organic portions were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by sgc (H:EA = 6:1) to afford 5.40 g (84%) as a colorless oil: $[\alpha]^{25}_D$ + 40.9° (c = 1.83, $CHCl_3$); R_f = 0.24 (H:EA = 6:1); IR (neat) 1743 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.81 (d, J = 6.3 Hz, 2H), 3.70 (s, 3H), 3.73 (s, 3H), 4.55−4.75 (m, 3H), 4.85 (d, J = 7.2 Hz, 1H), 4.88 (d, J = 7.2 Hz, 1H), 7.20−7.40 (m, 5H); HRMS exact mass calcd for $C_{13}H_{15}O_5$ (M − OCH_3) 251.09195, found 251.09176.

A solution of dimethyl (*R*)-2-((phenylmethoxy)methoxy)-butanedioate (4.70 g, 16.7 mmol) and magnesium bromide etherate (4.74 g, 18.4 mmol) in anhydrous CH_2Cl_2 (50 mL) was stirred at rt for 30 min and then cooled to −90 °C. Diisobutylaluminum hydride (18.4 mL of a 1.0 M solution in hexane, 18.4 mmol) was then added dropwise via syringe pump (one drop every 5 s). After addition was complete, anhydrous MeOH (18 mL) was added via syringe pump, and the reaction was allowed to warm to rt. Saturated Rochelle salts (200 mL) was added, the solution was stirred for 2 h, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$. The residue was purified by sgc using (H:EA = 4:1) to afford 2.77 g (66%) of **6** as a colorless oil: $[\alpha]^{25}_D$ +16.8° (c = 2.50, $CHCl_3$); R_f = 0.26 (H:EA = 3:1); IR (neat) 1738 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.75 (dd, J = 16.5 and 6.7 Hz, 1H), 2.83 (dd, J = 16.5 and 4.8 Hz, 1H), 3.70 (s, 3H), 4.37 (dd, J = 6.7 and 4.8 Hz, 1H), 4.65 (d, J = 11.7 Hz, 1H), 4.69 (d, J = 11.7 Hz, 1H), 4.91 (s, 2H), 7.20−7.40 (m, 5H), 9.76 (s, 1H). HRMS exact mass calcd for $C_{11}H_{13}O_3$ (M − CO_2Me) 193.08647, found 193.08640.

Methyl (3*R*,4*R*)-4-Hydroxy-4-(1-hydroxy-5-methoxynaphthyl)-3-((phenylmethoxy)methoxy)butanoate (7a). To a solution of 5-methoxy-1-naphthol (1.50 g, 8.62 mmol) in anhydrous Et_2O (40 mL) was added a solution of MeMgBr (3.14 mL of a 3.0 M solution in Et_2O, 9.41 mmol) at 0 °C, and the reaction mixture was allowed to warm to rt. The ether was removed in vacuo, and anhydrous CH_2Cl_2 (40 mL) was added. This solution was cooled to −78 °C. To a stirred solution of **6** (2.07 g, 8.21 mmol) in CH_2Cl_2 (40 mL) was added magnesium bromide etherate (2.54 g, 9.80 mmol). The suspension was stirred for 1 h and cooled to −78 °C. This suspension was added to the above solution at −78 °C, and the reaction mixture was stirred at rt for 4 h in sonication bath. The reaction was quenched with saturated aqueous NH_4Cl. The aqueous layer was separated and extracted with CH_2Cl_2. The combined organic portions were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by sgc (H:EA = 3:1) to afford 2.36 g (67%) of **7a** as a syrup: $[\alpha]^{25}_D$ −64.5° (c = 0.62, $CHCl_3$); R_f = 0.32 (H:EA = 3:1); IR (neat) 3325 (br), 1737 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.37 (dd, J = 16.2 and 4.0 Hz, 1H), 2.52 (dd, J = 16.2 and 8.2 Hz, 1H), 3.58 (s, 3H), 3.98 (s, 3H) 4.32 (dt, J = 8.2 and 4.0 Hz, 1H), 4.64 (d, J = 11.9 Hz, 1H), 4.72 (J = 11.9 Hz, 1H), 4.90 (s, 1H), 4.94 (s, 2H), 5.09 (s, 1H), 6.82 (d, J = 7.5 Hz, 1H), 7.06 (d, J = 8.7 Hz, 1H), 7.28−7.45 (m, 6H), 7.72 (d, J = 8.7 Hz, 1H), 7.84 (d, J = 7.5 Hz, 1H), 9.03 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 12.4, 37.4, 51.7, 55.4, 70.6, 77.8, 81.6, 96.3, 104.6, 113.3, 114.5, 116.1, 125.3, 126.4, 126.6, 128.0, 128.1, 128.6, 136.5, 151.8, 155.0, 171.3; HRMS exact mass calcd for $C_{24}H_{26}O_7$ 426.16785, found 426.16883. Anal. Calcd for $C_{24}H_{26}O_7$: C 67.59, H 6.15. Found: C 67.65, H 6.29.

Methyl (3*R*,4*R*)-4-(5-Acetoxy-1-hydroxynaphthyl)-4-hydroxy-3-((phenylmethoxy)methoxy)butanoate (7b). The same procedures were used as for **7a** starting from 5-acetoxy-1-naphthol (1.95 g, 9.65 mmol) and **6** (2.36 g, 9.37 mmol). The crude product was purified by sgc (H:EA = 5:2) to afford 2.41 g (57%) of **7b** as a thick syrup: $[\alpha]^{25}_D$ −40.1° (c = 1.01, $CHCl_3$); R_f = 0.22 (H:EA = 5:2); IR (neat) 3310 (br), 1767, 1738 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.38 (dd, J = 16.2 and 4.2 Hz, 1H), 2.44 (s, 3H), 2.50 (dd, J = 16.2 and 7.8 Hz, 1H), 3.56 (s, 3 H), 4.31 (dt, J = 7.8 and 4.2 Hz, 1H), 4.63 (d, J = 11.8 Hz, 1H), 4.71 (d, J = 11.8 Hz, 1H), 4.91 (s, 1H), 4.93 (s, 2H), 5.10 (s, 1H), 7.11 (d, J = 8.6 Hz, 1H), 7.23 (d, J = 7.5 Hz, 1H), 7.26−7.41 (m, 6H), 7.44 (t, J = 7.5 Hz, 1H), 8.17 (d, J = 8.7 Hz, 1H), 9.16 (s, 1H); HRMS exact mass calcd for $C_{25}H_{26}O_8$ 454.16277, found 454.16303. Anal. Calcd for $C_{25}H_{26}O_8$: C 66.07, H 5.77. Found: C 65.78, H 5.96.

Methyl (3*R*,4*R*)-4-Hydroxy-4-(5-methoxy-1,4-naphthoquinon-2-yl)-3-((phenylmethoxy) methoxy)butanoate (8). To a stirred solution of **7a** (0.40 g, 0.94 mmol) in dry DMF (20 mL) was added bis(salicylidene)ethylenediiminocobalt (II) (30 mg, 0.092 mmol). The dark suspension was stirred under an oxygen atmosphere for 15 min. To the reaction mixture were added H_2O and AcOEt. The organic layer was washed with H_2O five times followed by brine and dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by sgc (H:EA = 1:1) to afford 1.11 g (72%) of **8** as a yellow syrup: $[\alpha]^{25}_D$ −36.1° (c = 0.91, $CHCl_3$); R_f = 0.26 (H:EA = 1:1); IR (neat) 3470 (br), 1734, 1652 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.71 (dd, J = 15.9 and 5.5 Hz, 1H), 2.79 (dd, J = 15.9 and 7.2 Hz, 1H), 3.49 (d, J = 6.9 Hz, 1H), 3.67 (s, 3H), 3.98 (s, 3H), 4.35−4.43 (m, 1H), 4.47 (s, 2H), 4.70 (d, J = 7.0 Hz, 1H), 4.77 (d, J = 7.0 Hz, 1H), 4.86−4.94 (m, 1H), 7.00 (d, J = 1.5 Hz, 1H), 7.15−7.30 (m, 6 H), 7.60−7.73 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 37.4, 51.8, 56.3, 69.6, 69.9, 77.2, 95.0, 117.8, 119.1, 119.3, 127.2, 127.4, 128.2, 134.2, 134.8, 136.9, 137.4, 146.9, 159.3, 171.4, 184.1, 184.8; HRMS exact mass calcd for $C_{24}H_{24}0_8$ 440.14712, found 440.14724.

5-O-Methyljuglomycin A (3). To a stirring solution of **8** (200 mg, 0.46 mmol) in anhydrous CH_2Cl_2 (4 mL) at 0 °C was added dropwise trifluoroacetic acid (3.2 mL). The reaction mixture was stirred at rt for 5 h, and the solvents were evaporated in vacuo. To the residue were added H_2O and AcOEt. The black precipitate generated was filtered by suction. The organic layer separated in the filtrate was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (H:EA = 2:3) to afford 83 mg (63%) of **3** as a yellow solid: mp 170−173 °C (decomp) (from CH_2Cl_2−hexane); $[\alpha]^{25}_D$ −57.5° (c = 0.20, MeOH); R_f = 0.16 (H:EA = 1:2); IR (KBr) 3450 (br), 1791, 1656, 1587 cm^{-1}; ^1H NMR (acetone-d_6) δ 2.50 (d, J = 17.4 Hz, 1H), 3.15 (dd, J = 17.4 and 5.1 Hz, 1H), 3.97 (s, 3H), 4.73 (br, 1H), 4.87−4.94 (m, 1H), 5.66 (dd, J = 3.6 and 1.5 Hz, 1H), 6.77 (d, J = 1.5 Hz, 1H), 7.55 (dd, J = 8.4 and 1.0 Hz, 1H), 7.68 (dd, J = 7.6 and 1.0 Hz, 1H), 7.80 (dd, J = 8.4 and 7.6 Hz, 1H); HRMS exact mass calcd for $C_{15}H_{12}O_6$ 288.06339, found 288.06416.

Juglomycin A (1). To a stirring solution of **3** (42 mg, 0.146 mmol) in 12 mL of anhydrous CH_2Cl_2 at −78 °C was added a solution of BCl_3 (0.44 mL of a 1.0 M solution in CH_2Cl_2, 1.32 mmol), and the reaction mixture was allowed to warm to −20 °C which was maintained for 15 min. The mixture was poured into a mixture of ice and AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by preparative thin layer chromatography (CH_2Cl_2:MeOH= 95:5) to afford 31 mg (78%) of **1** as a yellow solid: mp 175−177 °C (decomp.) (from CH_2Cl_2); lit.,[5] mp 172 °C (decomp); $[\alpha]^{25}_D$ −49.0° (c = 0.10, DMSO); lit.,[5] $[\alpha]^{25}_D$ −51.9° (c = 0.42, DMSO); R_f = 0.39 (CH_2Cl_2:MeOH = 95:5); IR (KBr) 3400 (br), 1781, 1671, 1646, 1621 cm^{-1}; ^1H NMR (acetone-d_6) δ 2.52 (d, J = 17.4 Hz, 1 H), 3.17 (dd, J = 17.4 and 5.4 Hz, 1 H), 4.78 (d, J = 3.9 Hz, 1 H), 4.92 (m, 1 H), 5.71 (dd, J = 3.6 and 1.5 Hz, 1 H), 6.95 (d, J = 1.5 Hz, 1 H), 7.35 (dd, J = 8.4 and 1.2 Hz, 1 H), 7.62 (dd, J = 7.5 and 1.2 Hz, 1 H), 7.79 (dd, J = 8.4 and 7.5 Hz, 1 H). Anal. Calcd for $C_{14}H_{10}O_6$: C 61.32, H 3.68. Found: C 60.96, H 3.78.

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Supporting Information Available: Copies of ^1H NMR spectra of all title compounds and integrated spectra for ratios of **7a** and **7b** (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the Journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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