Supporting Information

for

Angew. Chem. Int. Ed. Z18944

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69451 Weinheim, Germany
First Enantioselective Total Synthesis of
Angucyclinone-Type Antibiotics Rubiginones A$_2$ and C$_2$

M. Carmen Carreño, María Ribagorda, Álvaro Somoza, Antonio Urbano

Experimental Section

**General:** Melting points were obtained in open capillary tubes and are uncorrected. $^1$H- and $^{13}$C-NMR spectra were recorded in CDCl$_3$ at 300 and 75 MHz, respectively. Diastereoisomeric ratios were established by integration of well-separated signals of both diastereomers in the crude reactions mixtures. All reactions were monitored by thin-layer chromatography that was performed on precoated sheets of silica gel 60, and flash column chromatography was done with silica gel 60 (230-400 mesh) of Merck. Eluting solvents are indicated in the text. The apparatus for inert atmosphere experiments was flame-dried under a stream of dry argon. CH$_2$Cl$_2$ was dried over P$_2$O$_5$. Dry THF was distilled from sodium/benzophenone ketyl. Diisopropylamine was distilled from KOH. All other reagent quality solvents were used without purification. For routine workup, hydrolysis was carried out with water, extractions with CH$_2$Cl$_2$, and solvent drying with MgSO$_4$.

[(S)S]-4-Hydroxy-4-[(p-tolylsulfinyl)methyl]-cyclohexa-2,5-dienone (3). To a solution of freshly distilled diisopropylamine (20.7 mL, 147.8 mmol) in THF (250 mL), n-butyllythium 2.4 M (56 mL, 135.5 mmol) was added under argon at -78 °C. After stirring for 30 min, a solution of (SS)-methyl-p-tolylsulfoxide (19.0 g, 123.2 mmol) in
THF (200 mL) was added at -78ºC. After 30 min, a solution of 4,4-
dimethoxy-2,5-cyclohexadienone (19.9 g, 129.4 mmol) in THF (430
mL) was slowly added and the mixture was stirred for two hours at
-78 ºC. Then, the mixture was hydrolyzed with an aqueous saturated
solution of ammonium chloride (40 mL) and the organic layer was
extracted with EtOAc. After workup, the crude product was
dissolved in THF (80 mL) and a solution of oxalic acid (1.16 g,
12.9 mmol) in water (20 mL) was added. After stirring for 2 h,
hydrolysis with saturated solution of NaHCO₃, extraction with EtOAc
and workup, the residue was crystallized from EtOAc/hexane
isolating compound 3 as a white solid in 76% yield: M.p. 142-144
ºC; [α]D²⁰ = -177 (c = 1 in CHCl₃); ¹H NMR: δ = 7.54 and 7.36
(AA’BB’ system, 4H), 7.25 (dd, J = 10.2 and 3.2 Hz, 1H), 7.00 (dd,
J = 10.2 and 3.2 Hz, 1H), 6.30 (dd, J = 10.2 and 1.8 Hz, 1H), 6.18
(dd, J = 10.1 and 1.9 Hz, 1H), 4.93 (s, 1H), 3.16 and 2.85 (AB
system, J = 13.3 Hz, 2H), 2.43 (s, 3H); ¹³C NMR: δ = 184.9, 149.2,
149.1, 142.2, 139.6, 130.1 (2C), 128.1, 127.6, 123.9 (2C), 68.0,
67.1, 21.3; elemental analysis calcd (% for C₁₄H₁₄O₃S (262.3): C
64.10, H 5.38, S 12.22; found C 63.91, H 5.48, S 12.47.

[4R,5R, (S) S]-4-Hydroxy-5-methyl-4-[(p-tolylsulfinyl)methyl]-2-
cyclohexen-1-one (4). To a solution of Me₃Al 2M in heptane (3.8 mL,
7.6 mmol) in CH₂Cl₂ (10 mL) was added a solution of 3 (500 mg, 1.9
mmol) in CH₂Cl₂ (10 mL) under argon at -78 ºC. After 4 h at the
same temperature, the excess organoaluminum reagent was destroyed
with methanol, and the mixture was poured into an Erlenmeyer
containing EtOAc and a saturated solution of sodium potassium
tartrate and stirred vigorously for 30 min. The organic layer was
washed with brine and dried over MgSO₄. After workup and flash chromatography (eluent EtOAc/hexane 1:1), compound 4 was obtained as a white solid in 65% yield: M.p. 120-121 ºC (EtOAc/hexane); \([\alpha]_D^{20} = -245 \) (c = 1 in CHCl₃); \(^1\)H NMR: \(\delta = 7.56 \) and 7.37 (AA′BB′ system, 4H), 7.25 (d, \(J = 10.2\) Hz, 1H) 6.10 (dd, \(J = 10.2\) Hz, 1H), 4.85 (s, 1H), 3.22 and 2.92 (AB system, \(J = 12.2\) Hz, 2H), 2.62-2.22 (m, 3H), 2.44 (s, 3H), 1.10 (d, \(J = 7.0\) Hz, 3H); \(^{13}\)C NMR: \(\delta = 198.3, 149.7, 142.4, 139.7, 130.3\) (2C), 129.0, 123.8 (2C), 71.6, 64.9, 41.7, 38.8, 21.3, 14.2; elemental analysis calcd (%) for C₁₅H₁₈O₃S (278.4): C 64.72, H 6.52, S 11.52; found C 64.69, H 6.85, S 11.89.

(4R,5R)-4-Hydroxy-5-methyl-4-[((p-tolylsulfonyl)methyl]-2-cyclohexen-1-one (5). To a solution of 4 (3.8 g, 13.8 mmol) in CH₂Cl₂ (45 mL) at 0 ºC, a solution of m-CPBA (6.2 g, 17.9 mmol) in CH₂Cl₂ (60 mL) was added dropwise. After stirring at 0 ºC for 30 min, the mixture was hydrolyzed with an aqueous saturated solution of Na₂SO₃, extracted with CH₂Cl₂, and the organic layer washed with an aqueous saturated solution of NaHCO₃. After workup and crystallization (EtOAc/hexane) compound 5 was obtained as a white solid in 96% yield: M.p. 145-146 ºC; \([\alpha]_D^{20} = -65 \) (c = 1 in acetone); \(^1\)H NMR: \(\delta = 7.80 \) and 7.39 (AA′BB′ system, 4H), 7.05 (dd, \(J = 10.2\) and 0.9 Hz, 1H), 5.95 (d, \(J = 10.2\) Hz, 1H), 4.08 (br s, 1H), 3.50 and 3.45 (AB system, \(J = 14.2\) Hz, 2H), 2.62-2.37 (m, 3H), 2.47 (s, 3H), 1.09 (d, \(J = 6.6\) Hz, 3H); \(^{13}\)C NMR: \(\delta = 198.3, 149.7, 142.4, 139.9, 130.2\) (2C), 129.1, 123.8 (2C), 71.7, 64.9,
41.7, 38.9, 21.4, 14.3; elemental analysis calcd (%) for C\textsubscript{15}H\textsubscript{18}O\textsubscript{4}S (294.4): C 61.20, H 6.16, S 10.89; found C 61.12, H 6.19, S 11.24.

\textbf{(1R,4S,6R)-6-Methyl-1-[(p-tolylsulfonyl)methyl]-2-cyclohexen-1,4-diol (6).} To a solution of DIBALH 1 M in hexanes (39.8 mL 39.8 mmol) in THF (130 mL), a solution of 5 (3.9 g, 13.3 mmol) in THF (45 mL) was added dropwise under argon at -78 ºC. After 30 min at the same temperature, the excess organoaluminum reagent was destroyed with methanol, and the mixture was poured into an Erlenmeyer containing ethyl acetate and a saturated solution of sodium potassium tartrate and stirred vigorously for 30 min. The organic layer was washed with brine and dried over MgSO\textsubscript{4}. After workup, compound 6 was obtained in 99% yield as a white solid, which could be used without further purification: M.p. 96-97 ºC (EtOAc/hexane); [α]\textsubscript{D}\textsuperscript{20} = -56 (c = 1 in acetone); \textsuperscript{1}H NMR: δ = 7.79 and 7.36 (AA’BB’ system, 4H), 6.17 (dd, J = 10.1 and 2.0 Hz, 1H), 5.85 (dt, J = 10.1 and 1.8 Hz, 1H), 4.5 (s, 1H), 4.23 (m, 1H), 3.46 and 3.25 (AB system, J = 14.3 Hz, 2H), 2.46 (s, 3H), 1.85 (m, 2H), 1.68-1.51 (m, 2H), 1.01 (d, J = 6.7 Hz, 3H); \textsuperscript{13}C NMR: δ = 144.9, 138.2, 134.6, 130.0, 129.9 (2C), 127.7 (2C), 70.3, 67.2, 63.3, 36.1 (2C), 21.6, 14.9; elemental analysis calcd (%) for C\textsubscript{15}H\textsubscript{20}O\textsubscript{4}S (296.1): C 60.79, H 6.80, S 10.82; found C 60.46, H 7.14, S 10.56.

\textbf{(1R,4S,6R)-4-[(tert-Butyldimethylsilyl)oxy]-6-methyl-1-[(p-tolylsulfonyl)methyl]-2-cyclohexen-1-ol (7).} To a solution of 6 (1.8 g, 6.0 mmol) in dry CH\textsubscript{2}Cl\textsubscript{2} (20 mL) at 0 ºC, 2,6-lutidine (1.8 mL, 14.9 mmol) and TBDMSOTf (1.8 mL, 25.3 mmol) were added under
argon. After 2 h, the mixture was hydrolyzed with 10% HCl, extracted with CH₂Cl₂ and the organic layer washed with brine. After workup, compound 7 was obtained as a yellowish oil, which could be used without further purification in the next step. An analytical sample was obtained after purification by flash chromatography (EtOAc/hexane 1:3) and crystallization in ethyl ether/hexane, to afford 7 as a white solid: M.p. 107-108 °C; [α]D²⁰ = +41 (c = 1 in acetone); ¹H NMR: δ = 7.78 and 7.36 (AA’BB’ system, 4H), 6.04 (dd, J = 10.1 and 2.0 Hz, 1H), 5.76 (dt, J = 10.1 and 2.0 Hz, 1H), 4.23 (m, 1H), 3.44 and 3.29 (AB system, J = 14.2 Hz, 2H), 2.59 (s, 1H), 2.45 (s, 3H), 1.91 (m, 1H), 1.74-1.53 (m, 2H), 1.01 (d, J = 6.9 Hz, 3H), 0.89 (s, 9H), 0.08 and 0.07 (2s, 6H); ¹³C NMR: δ = 144.8, 138.1, 135.9, 129.9 (2C), 129.8, 127.7 (2C), 70.3, 67.7, 63.2, 36.4, 35.7, 25.8 (3C), 21.6, 18.1, 15.0, -3.6, -3.7; MS (FAB): calcd. for C₂₁H₃₄OSSi: 411.1947, found 411.2026 [M+H]+; m/z (%): 411 (7) [M+H]+, 393 (100), 371 (46).

(4S,6R)-4-[(tert-Butyldimethylsilyl)oxy]-6-methyl-2-cyclohexen-1-one (8). To a solution of 7 in CH₃CN (60 mL), Cs₂CO₃ (3.9 g, 12 mmol) was added at room temperature. After stirring for 17 h, the reaction mixture was hydrolyzed with water and extracted with EtOAc. The organic layer was washed with brine and dried over MgSO₄. After workup and purification by flash chromatography (EtOAc/hexane 1:12), compound 8 was obtained as a colorless oil in 87% yield for the two last steps: [α]D²⁰ = -76 (c = 1 in acetone); ¹H NMR: δ = 6.77 (dt, J = 10.1 and 2.0 Hz, 1H), 5.91 (dd, J = 10.1 and 2.4 Hz, 1H), 4.59 (m, 1H), 2.38 (m, 1H), 2.20 (m, 1H), 1.77
(4S,6R)-2-Bromo-4-[(tert-butyldimethylsilyl)oxy]-6-methyl-2-cyclohexen-1-one (9). To a solution of 8 (72 mg, 0.30 mmol) in CCl₄ (3 mL), a solution of bromine (15 µL, 0.30 mmol) in CCl₄ (3 mL) was added dropwise at 0 ºC. When no starting material was observed, tryethylamine (0.15 mL, 1.1 mmol) was added and the mixture was stirred at room temperature for 32 h. The reaction mixture was quenched with aqueous saturated solution of Na₂SO₃ and extracted with CH₂Cl₂. After workup and flash chromatography (EtOAc/hexane 1:120), compound 9 was obtained as a white solid in 80% yield: M.p. 40-41 ºC; [α]D²⁰ = -38 (c = 1 in acetone); ¹H NMR: δ = 7.22 (m, 1H), 4.59 (m, 1H), 2.46 (m, 1H), 2.25 (m, 1H), 1.87 (m, 1H), 1.21 (d, J = 6.7 Hz, 3H), 0.91 (s, 9H), 0.13 and 0.12 (2s, 6H); ¹³C NMR: δ = 193.1, 154.3, 123.4, 69.0, 41.6, 40.0, 25.7 (3C), 18.0, 15.6, -3.4, -3.6; elemental analysis calcd (%) for C₁₃H₂₃BrO₂Si (319.3): C 48.90, H 7.26; found C 48.88, H 7.56.

(1S,4S,6R)-2-Bromo-4-[(tert-Butyldimethylsilyl)oxy]-6-methyl-2-cyclohexen-1-ol (10). To a solution of 7 (163 mg, 0.51 mmol) in THF (17 mL) at -100 ºC, a solution of LiAlH₄ (31 mg, 0.76 mmol) in THF (25 mL) was added under argon. After 30 min at same temperature, the reaction was hydrolyzed with methanol, and the
mixture was poured into an erlenmeyer containing ethyl acetate and a saturated solution of sodium potassium tartrate and stirred vigorously for 30 min. The organic layer was washed with brine and dried over MgSO₄. After workup, compound 10 was isolated as a 93:7 diastereoisomeric ratio which could be used without further purification. An analytical sample of the major diastereoisomer could be isolated by HPTLC as a white solid: M.p. 88-89 ºC; [α]₂₀° = -67 (c = 1 in CHCl₃); ¹H NMR: δ = 6.05 (d, J = 1.6 Hz, 1H), 4.29 (m, 1H), 3.82 (m, 1H), 2.24 (d, J = 3.6 Hz, 1H), 1.90 (m, 1H), 1.78 (m, 1H), 1.45 (m, 1H), 1.15 (d, J = 6.5 Hz, 3H), 0.89 (s, 9H), 0.08 and 0.07 (2s, 6H); ¹³C NMR: δ = 136.4, 128.4, 75.8, 68.9, 39.9, 36.3, 25.8 (3C), 19.0, 18.1, -3.5, -3.6; elemental analysis calcd (%) for C₁₃H₂₅BrO₂Si (321.33): C 48.59, H 7.84; found C 48.33, H 7.54.

(1S,4S,6R)-2-Bromo-4-[((tert-butyldimethylsilyl)oxy]-6-methyl-2-cyclohexen-1-yl isobutyrate (11). To a solution of the above obtained mixture containing 10 in CH₂Cl₂ (1 mL), isobutyryl chloride (76 µL, 0.71 mmol) and 4-dimethylaminopyridine (135 mg, 1.1 mmol) were added. The reaction mixture was stirred for 1 h, hydrolyzed with water and extracted with CH₂Cl₂. After workup and flash chromatography (EtOAc/hexane 1:50), compound 11 was obtained as a colorless oil in 79% yield for the two last steps: ¹H NMR: δ = 6.14 (dd, J = 3.6 and 1.6 Hz, 1H), 5.32 (m, 1H), 4.32 (m, 1H), 2.61 (sept, J = 7.1 Hz, 1H), 1.92 (m, 2H), 1.52 (m, 1H), 1.21 (d, J = 6.9 Hz, 3H), 1.20 (d, J = 7.1 Hz, 3H), 0.99 (d, J = 6.5 Hz, 3H), 0.88 (s, 9H), 0.07 and 0.06 (2s, 6H); ¹³C NMR: δ = 176.4,
(1S,4S,6R)-4-[(tert-Butyldimethylsilyl)oxy]-6-methyl-2-vinyl-2-cyclohexen-1-yl isobutyrate (2). A mixture of 11 (583 mg, 1.5 mmol), tetrakistriphenylphosphine palladium (0) (207 mg, 0.18 mmol) and tributylvinylstannane (0.58 mL, 0.18 mmol) in toluene (7.5 mL) was heated at 90 °C for 24 h. The reaction was hydrolyzed with water and extracted with CH2Cl2. After workup and flash chromatography (EtOAc/hexane 1:60), compound 2 was obtained as colorless oil in 78% yield: 1H NMR: δ = 6.13 (dd, J = 17.8 and 10.9 Hz, 1H), 5.84 (m, 1H), 5.46 (m, 1H), 5.13 (d, J = 17.8 Hz, 1H), 4.99 (d, J = 10.9 Hz, 1H), 4.45 (m, 1H), 2.51 (sept, J = 6.9 Hz, 1H), 1.90 (m, 2H), 1.45 (m, 1H), 1.14 (d, J = 6.9 Hz, 3H), 1.12 (d, J = 6.9 Hz, 3H), 1.01 (d, J = 6.9 Hz, 3H), 0.89 (s, 9H), 0.08 and 0.07 (s, 3H); 13C NMR: δ = 177.0, 135.8, 135.7, 135.0, 114.2, 72.7, 66.9, 38.3, 34.2, 33.7, 25.8, 19.0, 18.9, 18.4, 18.1, −3.5, −3.6; MS (FAB): calcd for C15H27OSi: 251.1831; found: 251.1829 [M−C4H7O2]⁺; m/z (%): 265 (9) [M−C3H5O2]⁺, 251 (100) [M−C4H7O2]⁺, 235 (52), 227 (10), 219 (37), 207 (22).

(1S,3R,4S,12bR)-1-[(tert-Butyldimethylsilyl)oxy]-8-methoxy-3-methyl-7,12-dioxo-1,2,3,4,6,12b-hexahydrobenz[a]anthracen-4-yl isobutyrate (12). A solution of 2-(p-tolylsulfinyl)-5-methoxy-1,4-naphthoquinone 1 (37 mg, 0.12 mmol) and diene 2 (16 mg, 0.048
mmol) in dry CH₂Cl₂ (1 mL) was refluxed under argon for 24 h. After elimination of the solvent and flash chromatography (elucent EtOAc/hexane 1:9), compound 12 was obtained as a yellowish solid in 52% yield): M.p. 88-89 °C; [α]₀⁰₂⁰ = -85 (c = 0.25 in CHCl₃); ¹H NMR: δ = 7.71 (dd, J = 7.7 and 1.4 Hz, 1H), 7.64 (t, J = 7.9 Hz, 1H), 7.25 (dd, J = 8.3 and 1.4 Hz, 1H), 5.60 (m, 1H), 4.88 (m, 1H), 4.01 (s, 3H), 3.81 (m, 1H), 3.49 (ddt, J = 24.7, 4.0 and 2.2 Hz, 1H), 3.38 (m, 1H), 3.05 (ddt, J = 24.5, 4.6, and 2.2 Hz, 1H), 2.68 (sept, J = 6.9 Hz, 1H), 1.97 (dd, J = 8.9 and 3.8 Hz, 1H) 1.69 (m, 2H), 1.26 (d, J = 1.2 Hz, 3H), 1.23 (d, J = 1.2 Hz, 3H), 1.01 (d, J = 5.9 Hz, 3H) 0.73 (s, 9H), -0.12 and -0.37 (2s, 6H); ¹³C NMR: δ = 183.7, 183.6, 176.1, 159.3, 142.9, 141.6, 135.2, 135.1, 134.5, 119.5, 116.9, 113.2, 77.3, 76.4, 56.4, 43.0, 42.9, 37.5, 34.3, 25.6 (3C), 25.1, 19.2, 19.1, 18.3, 17.8, -3.2, -3.3; MS (EI): calcd for C₃₅H₄₀O₆Si: 524.2594; found: 524.2573 [M⁺]; m/z (%): 526 (62) [M+2]⁺, 524 (54) [M⁺], 509 (57), 499 (41), 483 (100), 483 (100), 481 (71).

(3R,4S)-8-Methoxy-3-methyl-1,7,12(2H)-trioxo-3,4-dihydrobenz[a]anthracen-4-yl isobutyrate (13), Rubiginone C₂. Compound 12 (42 mg, 0.08 mmol) was exposed under solvent-free conditions to the sun light for 16 h. After flash chromatography (elucent EtOAc/hexane 1:3) and crystallization (EtOAc), compound 13 (Rubiginone C₂) was obtained as a yellowish solid in 35% yield: M.p. 218-219 °C; [α]₀⁰₂⁰ = -57 (c = 0.5 in CHCl₃); ¹H NMR: δ = 8.35 (d, J = 8.3 Hz, 1H), 7.78 (dd, J = 7.7 and 1.4 Hz, 1H), 7.72 (t, J = 7.9 Hz, 1H) 7.59 (d, J = 8.3 Hz, 1H), 7.31 (dd, J = 8.1 and 1.2
Hz, 1H), 5.84 (d, J = 7.1 Hz, 1H), 4.04, (s, 3H), 3.17 (m, 1H),
2.75-2.56 (m, 3H), 1.24 (d, J = 5.5 Hz, 3H), 1.22 (d, J = 5.5 Hz,
3H), 1.12 (d, J = 6.5 Hz, 3H); $^{13}$C NMR: $\delta$ = 196.6, 184.0, 181.2,
176.4, 159.9, 145.9, 137.5, 136.1, 135.5, 134.8, 134.6, 131.5,
130.1, 120.6, 119.7, 117.3, 73.3, 56.5, 43.8, 35.1, 34.1, 19.0,
18.9, 18.0; MS (EI): calcd for C$_{24}$H$_{22}$O$_{6}$: 406.1416; found: 406.1421
$[M]^+$; m/z (%): 406 (61) $[M]^+$, 336 (68), 318 (100), 294 (90), 151
(25), 71 (92).

[3R,4S]-4-Hydroxy-8-methoxy-3-methyl-3,4-dihydrobenz[a]antracene-
1,7,12(2H)-trione (14), Rubiginone A$_2$. To a solution of 13 (4 mg,
9.8 $\mu$mol) in methanol (0.5 mL) and THF (0.5 mL), K$_2$CO$_3$ (10 mg, 72
$\mu$mol) was added. After stirring for 90 min, the mixture was
filtered through silica gel, and the solvent evaporated to give 14
(Rubiginone A$_2$) as a yellowish solid in 91% yield: M.p. (dec) >215
$^\circ$C (EtOAc); [$\alpha$]$_D^{20}$ = +78 (c = 0.2 in CHCl$_3$); $^1$H NMR: $\delta$ = 8.39, (d, J =
8.3 Hz, 1H), 8.02 (dd, J = 8.3 and 1.0 Hz, 1H), 7.78 (dd, J =
7.7 and 1.4 Hz, 1H), 7.72 (t, J = 7.9 Hz, 1H), 7.31 (dd, J = 8.3
and 1.4 Hz, 1H), 4.52 (m, 1H), 4.05 (s, 3H), 3.11 (dd, J = 16.6
and 5.7 Hz, 1H), 2.58 (dd, J = 16.6 and 10.7 Hz, 1H), 2.38 (m,
1H), 2.19 (d, J = 6.9 Hz, 3H); $^{13}$C NMR: $\delta$ = 197.2, 184.3, 181.5,
159.9, 150.4, 137.5, 135.6, 135.5, 134.4, 134.0, 130.4, 130.2,
120.6, 119.7, 117.3, 73.5, 56.5, 44.8, 38.3, 18.2; MS (FAB): calcd
for 337.1076: found 337.1069 $[M+1]^+$; m/z (%): 337 (13) $[M+1]^+$, 307
(10).