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Total Synthesis of the Angucylinone Antibiotic (+)-Rubiginone B_2[1]

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Abstract: A new chiral synthesis of (+)-rubiginone B_2 is reported. The intramolecular cobalt-mediated [2+2+2]-cycloaddition of a triyne precursor, synthesized from (+)-citronellal, afforded a chiral anthracene, which led after a two-step oxidation to the angucyclinone antibiotic.

Key words: angucyclinone antibiotics, benz[*a*]anthraquinones, natural products, catalysis, cobalt, cycloaddition

The rubiginones (Figure 1),[2] isolated from the strain of *Streptomyces griseorubiginosus*, exhibit potential vincristine-induced cytotoxicity against multi-drug-resistant tumor cells. They feature the typical benz[*a*]anthraquinone structure of the angucyclinone antibiotics, a growing class of secondary metabolites with remarkable biological properties.[3] While several racemic syntheses of these angucyclinones have been achieved,[4] only a few asymmetric total syntheses have been reported.[5] The only known total synthesis of (+)-rubiginone B_2 has been reported by Carreño and co-workers based on the Diels–Alder reaction between an enantiopure substituted naphthoquinone and a racemic vinylcyclohexene through the kinetic resolution of the diene. The natural product was synthesized with 80% ee and 9% overall yield for the longest sequence.[6]

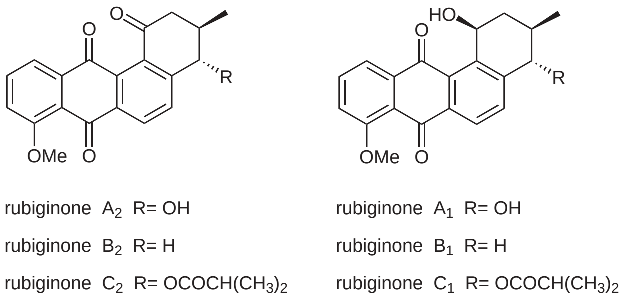
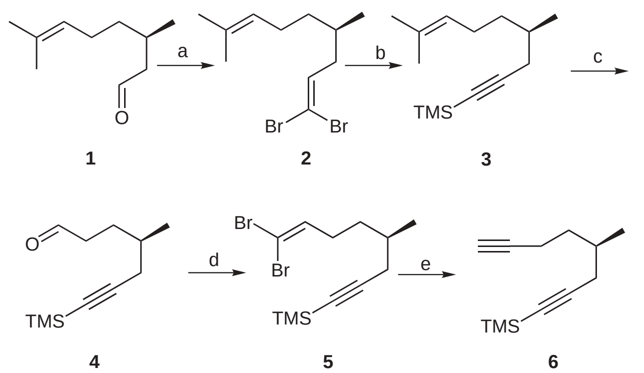


Figure 1

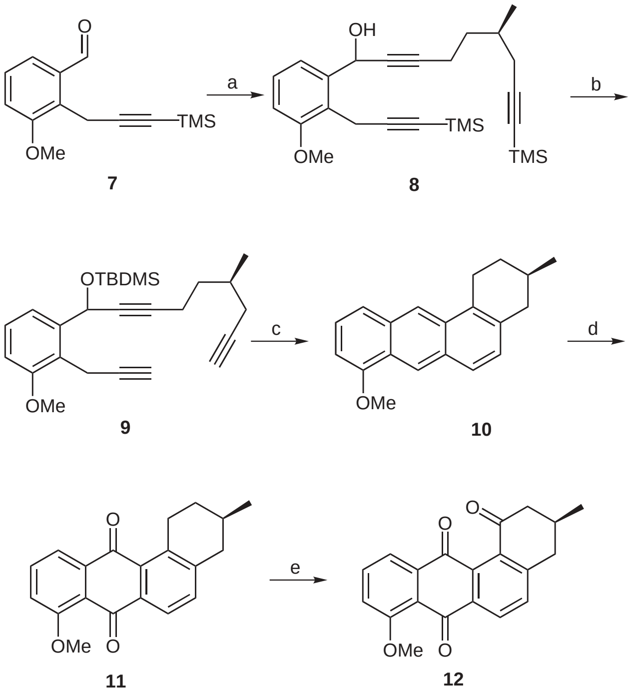
We have recently reported a new method[1] for the construction of the angucyclinone core via an intramolecular cobalt-mediated [2+2+2]-cycloaddition of a triyne.[7] Herein, we describe a new asymmetric access to the angucyclinone antibiotic (+)-rubiginone B_2 **12**. Starting from commercially available *R*-(+)-citronellal ($[\alpha]_D^{20}$ +13.0, neat, 92% ee)[8] we have synthesized the chiral diyne **6** (Scheme 1). By employing our previously reported method[1] we used **6** for the synthesis of the triyne **9**, which after cyclization and two-step oxidation led to (+)-rubiginone B_2 **12** (Scheme 2).

Our synthesis began with a Corey–Fuchs olefination[9] of (+)-citronellal **1**. The resulting dibromoalkene **2** was used without further purification and converted to the protected alkyne **3** by treatment with *n*-BuLi and then TMS-Cl[10] (76% yield, 2 steps). Ozonolysis of **3** (Me_2S workup) afforded **4** in quantitative yield, which was transformed without purification via another Corey–Fuchs olefination into the dibromoalkene **5**. Treatment of **5** with *n*-BuLi and hydrolysis of the resulting lithiated acetylene gave the diyne **6** (74% yield, 3 steps).



Scheme 1 *Reaction Conditions*: (a) 2 equiv CBr_4, 4 equiv PPh_3, CH_2Cl_2, 0 °C, 30 min, then **1**, 25 °C, 2 h. (b) i. 2 equiv *n*-BuLi, THF, –80 °C, 1 h, ii. 2 equiv TMS-Cl, –80 °C to r.t., 18 h (76%, 2 steps). (c) i. O_3, CH_2Cl_2, –80 °C, 15 min, ii. Me_2S, AcOH, –80 °C to r.t., 18 h. (d) 2 equiv CBr_4, 4 equiv PPh_3, CH_2Cl_2, 0 °C, 30 min, then **4**, 25 °C, 2 h. (e) i. 2 equiv *n*-BuLi, THF, –80 °C, 1 h, ii. H_2O, –80 °C to r.t., 2 h (74%, 3 steps).

After addition of the lithiated diyne **6** to the benzaldehyde **7**[1] and deprotection of the triple bonds of the resulting triyne **8** with NH_4F,[11] the hydroxy group of the obtained triyne was protected with TBDMSOTf.[12] Cyclization of **9** with 10% $CpCo(CO)_2$[13] in refluxing toluene under irradiation (tungsten-lamp) gave the anthracene **10** in 74% yield. By using 5% $CpCo(CO)_2$ **10** was obtained in 61% yield. The use of the expensive $CpCo(ethene)_2$[14] for the cyclization (see ref.[1]) of the triyne **9** was not necessary. Oxidation with $[Ag(Py)_2]MnO_4$[15] led to the anthraquinone **11** (62% yield), which was converted via photooxidation[4c] to (+)-rubiginone B_2 **12** (67% yield).[16] The spectroscopic data of synthetic (+)-rubiginone B_2 **12** coincided with those of the natural compound.[2] The structure of **12** was proven by two-dimensional NMR experiments (ROESY-, H,H-COSY-spectra, see the H,H-correlations in Figure 2). Additionally, the observed optical rotation value $[\alpha]_D^{25}$ +71.64 (*c* 0.275, $CHCl_3$, 92% ee) agreed satisfactory with the reported value $[\alpha]_D^{25}$ +78.00 (c 0.5, $CHCl_3$) for the natural product.



Scheme 2 *Reaction Conditions*: (a) *n*-BuLi, **6**, THF, –80 °C, 1 h, then **7**, –80 °C to –30 °C, 4 h (93%), (b) i. NH_4F, Bu_4NHSO_4, CH_2Cl_2, r.t., 48 h (96%), ii. TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 25 °C, 2 h (95%) (c) 10% $CpCo(CO)_2$, toluene, reflux, hν, 4 h (74%). (d) 8 equiv $[Ag(Py)_2]MnO_4$, CH_2Cl_2, 25 °C, 8 h (62%). (e) hν, air, $CHCl_3$, 25 °C, 18 h (67%).

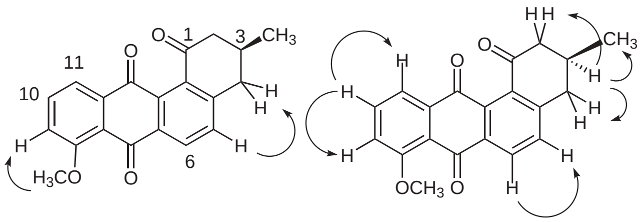


Figure 2 H,H-correlations in ROESY- and H,H-COSY-Spectra

In summary, a new effective chiral synthesis of (+)-rubiginone B_2 has been achieved starting from commercially available *R*-(+)-citronellal in 11 steps and 15% overall yield. Applications to the asymmetric synthesis of other angucyclinone antibiotics using the reported methodology[1] are currently under investigation.

Acknowledgment

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(13) **Experimental Procedure:** A solution of $CpCo(CO)_2$ (25.00 mg, 0.142 mmol, 10 mol%) in 2 mL toluene was added via canula to a solution of triyne **9** (0.58 g, 1.42 mmol) in 120 mL toluene and the mixture was heated to reflux and irradiated with a tungsten-lamp (osram vitalux 300 W) for 4 h. The organic phase was then concentrated in vacuo. Chromatography on silica gel (Et_2O–petroleum ether, 1:200) provided anthracene **10** (0.29 g, 1.051 mmol, 74% yield) as a white solid.

Mp 136–138 °C. $[\alpha]_D^{22}$ +86.43 (*c* 0.14, $CHCl_3$). R_f = 0.31 (Et_2O–petroleum ether, 1:100). IR (CCl_4): 2935–2810 [C–H (OCH_3)] cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 1.16 (d, ^3J = 6.6 Hz, 3 H, 3-CH_3), 1.58 (m, 1 H, H-2), 2.00 (m, 1 H, H-3), 2.14 (m, 1 H, H-2), 2.60 (dd, ^2J = 16.5 Hz, ^3J =10.5 Hz, 1 H, H-4), 2.95 (dd, ^2J = 16.5 Hz, ^3J = 3.9 Hz, 1 H, H-4), 3.14 (m, 1 H, H-1), 3.40 (d, ^2J = 16.5 Hz, 1 H, H-1), 4.09 (s, 3 H, OCH_3), 6.73 (d, J_o = 8.0 Hz, 1 H, H-9), 7.18 (d, J_o = 8.6 Hz, 1 H, H-5), 7.37 (t, J_o = 8.0 Hz, 1 H, H-10), 7.62 (d, J_o = 8.0 Hz, 1 H, H-11), 7.82 (d, J_o = 8.6 Hz, 1 H, H-6), 8.44 (s, 1 H, H-12), 8.78 (s, 1 H, H-7). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.79 (3-CH_3), 25.83 (C-1), 28.88 (C-3), 31.35 (C-2), 39.14 (C-4), 55.45 (OCH_3), 101.34 (C-9), 120.75 (C-12), 120.83 (C-11), 121.35 (C-7), 125.06 (C-10), 126.58 (C-6), 128.05 (C-5), 124.09, 130.34, 131.42, 132.64, 133.57, 155.38 (C_{quart}-arom.). EI-MS (70 eV): *m/z* = 276 (100%, M^+), 261 (15%, $M^+ - CH_3$), 246 (7%, 261 – CH_3), 233 (77%, 261 – C_2H_4). HRMS: calcd 276.1514 for $C_{20}H_{20}O$, found 276.1508.

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(16) **Experimental Procedure:** Anthraquinone **11** (60.00 mg, 0.195 mmol) was dissolved in 5 mL $CHCl_3$ and irradiated with a tungsten-lamp (osram vitalux 300 W) over 18 h. The organic layer was then removed in vacuo. Chromatography on silica gel (petroleum ether–Et_2O, 1:2) provided (+)-rubiginone B_2 **12** (42.00 mg, 0.131 mmol, 67% yield) as a yellow solid.
Mp > 262 °C (dec.). $[\alpha]_D^{25}$ +71.64 (*c* 0.275, $CHCl_3$, recrystallized from petroleum ether–$CHCl_3$, 2:1). R_f = 0.14 (Et_2O–petroleum ether, 1:4). IR (CCl_4): 1673, 1677, 1708 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.20 (d, ^3J = 6.4 Hz, 3 H, 3-CH_3), 2.45 (m, 1 H, H-3), 2.55 (dd, ^2J = 15.6 Hz, ^3J = 11.0 Hz, 1 H, H-2), 2.67 (dd, ^2J = 16.4 Hz, ^3J = 11.0 Hz, 1 H, H-2), 2.98 (m, 2 H, H-1 and H-4), 4.04 (s, 3 H, OCH_3), 7.24 (d, J_o = 8.2 Hz, 1 H, H-9), 7.45 (d, J_o = 8.0 Hz, 1 H, H-5), 7.65 (t, J_o = 8.2 Hz, J_o = 7.8 Hz, 1 H, H-10), 7.71 (d, J_o = 7.8 Hz, 1 H, H-11), 8.20 (d, J_o = 8.0 Hz, 1 H, H-6). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 21.43 (3-CH_3), 30.82 (C-3), 38.33 (C-4), 47.55 (C-2), 56.50 (OCH_3), 117.15 (C-9), 119.68 (C-11), 129.60 (C-6), 132.99 (C-5), 135.34 (C-10), 120.56, 134.98, 135.07, 137.67, 149.13, 159.81 (C_{quart}-arom.), 181.59, 184.51, 198.89 (C=O). EI-MS (70 eV): *m/z* = 320 (100%, M^+), 305 (15%, $M^+ - CH_3$), 292 (35%, M^+– CO), 291 (15%, M^+ – HCO), 261 (27%, 292 – OCH_3), 233 (24%, 261 – CO).