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First Total Synthesis of the Alkaloid Polycitrin B

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Abstract—Starting from 3,5-dibromo-4-methoxy-phenylacetic acid methyl ester **2**, a first total synthesis of the marine alkaloid polycitrin B is reported, based on the Pd catalyzed coupling reaction of the triflate **4** with the (4-methoxymethoxy-phenyl)tributylstannane.

Polycitrin A **(la)** and B (**lb**) are alkaloids that contain a maleimide unit with two aromatic residues at positions 3 and 4, and the nitrogen atom substituted with a (4-hydroxy-phenyl)ethyl residue. Their isolation from the marine Ascidian Polycitor sp. and structure elucidation were reported in 1994 by Kashman and coworkers.[1] In 1995, Steglich and coworkers[2] reported the biomimetic synthesis of Polycitrin A. We now report a total synthesis of polycitrin B based on a Pd catalyzed cross coupling reaction, and starting from 4-methoxyphenylacetic acid methyl ester.

The dibromo ester **2** was prepared by bromination of 4-methoxyphenylacetic acid methyl ester following the method reported for the bromination of the corresponding acid.[4,5] Condensation of the ester **2** with dimethyl oxalate gave compound **3** as a 1:1 mixture of keto- and enol forms (the ^{1}H NMR spectra recorded in DMSO, showed the enol form only). The triflate **4** was obtained from **3** by reaction with trifluoromethanesulfonic anhydride and in the presence of Hunig's base.[3]

The coupling reaction between triflate **4** and tributyl-(4-methoxymethoxy-phenyl)-stannane[6] was unsatisfactory when carried out according to the classical Stille conditions [$Pd(PPh_3)_4$, THF at reflux][7], the coupling product **5** being obtained in a very low yield. A dramatic improvement was achieved when the reaction was carried out in DMF at 70–75°C with Pd_2dba_3 [tris(dibenzylideneacetone)dipalladium] as the catalyst and in the presence of triphenylphosphine. Using these conditions, **5** was obtained in 81% yield (Scheme 1).

Removal of the methoxymethyl ether in **5** was achieved with trimethyl silyl chloride-sodium iodide[8] giving phenol **6**. Basic hydrolysis of the ester groups then provided anhydride **7**, which was brominated with bromine in glacial acetic acid to give **8**.

Polycitrin B was obtained by heating a mixture of compound **8** with tyramine, Hunig's base and phenol at 140°C.[2] Using these conditions, polycitrin B and polycitrin A were both obtained in a 3:2 ratio. This result was rationalized in terms of an S_NAr reaction path[9] with water as the nucleophile, addition being assisted by the presence of strongly electron withdrawing groups on the aromatic ring. Better results were obtained working in the presence of activated molecular sieves. In this case a considerable improvement was observed in favour of the polycitrin B and the yield of polycitrin A was diminished.

The spectral data for the polycitrin B is in agreement with those reported in literature.[1] Only 2 mg of the compound were isolated from the natural source as a yellowish fluorescent oil. By the synthetic path, the compound was obtained in a good yield and crystallized from CH_2Cl_2-pentane as yellow crystals.

Experimental

Melting points were determined on a Büchi 510 apparatus and are uncorrected. IR spectra were recorded on a JASCO IR Report 100 instrument, in Nujol mull for solids and as liquid films for oils. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini 200 or a Bruker AVANCE DRX 300 spectrometer. Chemical shifts are expressed in ppm (δ) relative to TMS. UV spectra were recorded on a UVICON 943 Kontron instrument. Mass spectra were obtained by electron impact ionization at 70 eV from a MD 800 Finnigan instrument using the direct exposure probe (DEP). Column chromatography was performed on Kieselgel Merck 60, 0.063–0.2 mm. Organic extracts were

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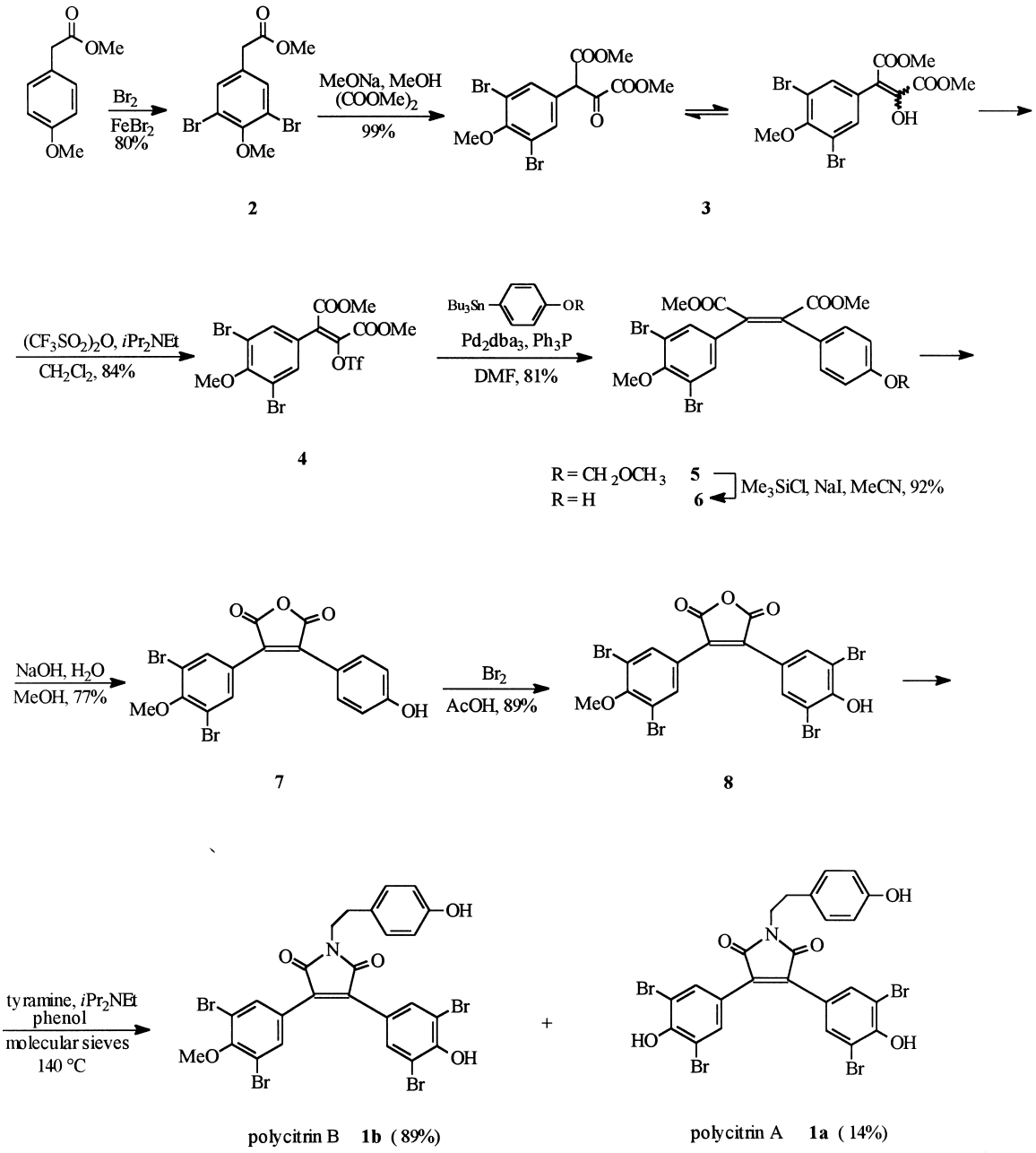

Scheme 1.

dried with Na_2SO_4. Evaporation of the solvent was carried out under vacuum on a rotary evaporator.

3,5-Dibromo-4-methoxy-phenyl acetic acid methyl ester 2. To a solution of 4-methoxy-phenyl acetic acid methyl ester (9.18, 50 mmol) in anhydrous chloroform (90 mL), $FeBr_2$ was added (1.72 g, 7.9 mmol). A solution of bromine (7.8 mL, 150 mmol) in chloroform (15 mL) was added dropwise to the reaction vessel. After the mixture was stirred for 48 h at room temperature, additional bromine (4 mL, 77 mmol) and $FeBr_2$, (400 mg, 1.85 mmol) were added. The solution was stirred for 48 h, then poured carefully into an excess of 5% aqueous $NaHSO_3$, and extracted with Et_2O (2×50 mL). The combined ethereal extracts were washed with H_2O and then dried. Removal of the solvent afforded the crude product which was purified by silica gel column chromatography (pentane–CH_2CI_2 1:1) to give the compound **2** (12.5 g, 80%) as white crystals, mp 39–40°C (hexane), (lit.[5] mp 36°C from MeOH).

2-(3,5-Dibromo-4-methoxy-phenyl)-3-hydroxy-but-2-enedioic acid dimethyl ester 3. To a methanolic solution of sodium methoxide, formed by adding Na (1.38 g, 60 mmol) to anhydrous methanol (130 mL), compound **2** (10 g, 30 mmol) and dimethyloxalate (5.3 g, 45 mmol) were added. The mixture was heated under reflux for 5 h, then the solvent was evaporated and the residue diluted with 4% HCl (70 mL) and extracted with CH_2CI_2 (2×50 mL). The organic layer was dried, filtered and evaporated. The crude product was purified by silica gel column chromatography (pentane–CH_2C1_2 2:1) to give compound **3** as an oil in quantitative yield; $C_{13}H_{12}Br_2O_6$ requires C, 36.82; H, 2.85.

Found: C, 36.70; H, 2.80. ν_{max} 3450, 1725, 1642 cm^{-1}; δ_H (300 MHz DMSO-d_6) 3.60 (3H, s, OMe), 3.78 (3H, s, OMe), 3.81 (3H, s, OMe), 7.54 (2H, s, aryl-H), 12.40 (1H, s, exchange with D_2O, OH).

2-(3,5-Dibromo-4-methoxy-phenyl)-3-(trifluoromethanesulfonyloxy)-but-2-enedioic acid dimethyl ester 4. Compound **3** (5.6 g, 13.2 mmol) was dissolved in dry dichloromethane (70 mL) and *N*,*N*-diisopropylethylamine (3.4 mL, 19.8 mmol) was added. The reaction mixture was cooled at 0°C and a solution of trifluoromethanesulfonic anhydride (2.82 mL, 17 mmol) in CH_2Cl_2 (10 mL) was added dropwise with stirring. The mixture was kept at 0°C for 15 min, then warmed to room temperature and washed with water (2×40 mL). The organic layer was dried, filtered and evaporated and the residue purified by silica gel column chromatography (hexane–CH_2Cl_2 1:1) to give **4** (6.9 g, 84%) as white solid, mp 107–108°C (pentane–Et_2O); $C_{14}H_{11}Br_2F_3O_8S$ requires C, 30.24; H, 1.99. Found: C, 30.41; H, 1.96; ν_{max} 1722, 1717, 1620 cm^{-1}; δ_H (200 MHz $CDCl_3$) 3.92 (3H, s, OMe), 3.93 (3H, s, OMe), 3.95 (3H, s, OMe), 7.68 (2H, s, aryl-H).

2-(3,5-Dibromo-4-methoxy-phenyl)-3-(4-methoxymethoxy-phenyl)-but-2-enedioic acid dimethyl ester 5. Compound **4** (1.7 g, 34 mmol) and tributyl-(4-methoxymethoxy-phenyl)-stannane[6] (2.18 g, 51 mmol) were dissolved in DMF (10 mL). Pd_2dba_3 (155 mg, 0.17 mmol) and Ph_3P (96 mg, 0.36 mmol) were added to this solution and the mixture was heated at 70–75°C for 1 h. After this time, the solution was poured into a saturated NaCl–H_2O solution (150 mL) and extracted with Et_2O (2×50 mL). The organic layer was dried, filtered and evaporated and the residue purified by crystallization giving **5** (1.52 g, 81%) as white crystals, mp 133–134°C (Et_2O); $C_{21}H_{20}Br_2O_7$ requires C, 46.35; H, 3.70. Found: C, 46.21; H, 3.66; ν_{max} 1721, 1699, 1583 cm^{-1}; δ_H (200 MHz $CDCl_3$) 3.44 (3H, s, OMe), 3.82 (3H, s, OMe), 3.85 (3H, s, OMe), 3.86 (3H, s, OMe), 5.15 (2H, s, CH_2O), 6.90 (2H, d, J=9.0 Hz, aryl-H), 7.01 (2H, d, J=9.0 Hz, aryl-H), 7.24 (2H, s, aryl-H).

2-(3,5-Dibromo-4-methoxy-phenyl)-3-(4-hydroxy-phenyl)-but-2-enedioic acid dimethylester 6. To a solution of compound **5** (1.8 g, 3.3 mmol) in dry acetonitrile (40 mL) at −20°C, NaI (600 mg, 4 mmol) and trimethylsilyl chloride (0.85 mL, 6.6 mmol) were added. After stirring at this temperature for 20 min., the mixture was allowed to warm to room temperature. The acetonitrile was then removed in vacuo and the residue extracted with Et_2O (2×30 mL). The organic phase was dried, filtered and evaporated and the crude product purified by silica gel column chromatography (CH_2Cl_2–Et_2O 20:1) to give **6** (1.52 g, 92%) as white crystals, mp 167°C (pentane–Et_2O); $C_{19}H_{16}Br_2O_6$ requires C, 45.63; H, 3.22. Found: C, 45.48; H 3.19; ν_{max} 3220br, 1699, 1583 cm^{-1}; δ_H (200 MHz $CDCl_3$) 3.82 (3H, s, OMe), 3.85 (3H, s, OMe), 3.86 (3H, s, OMe), 5.07 (1H, s, exchange with D_2O, OH), 6.70 (2H d, J=8.7 Hz, aryl-H), 6.96 (2H, d, J=8.7 Hz, aryl-H), 7.24 (2H, s, aryl-H).

3-(3,5-Dibromo-4-methoxy-phenyl)-4-(4-hydroxy-phenyl)-furan-2,5-dione 7. To a solution of compound **6** (1.66 g, 3.3 mmol) in MeOH (60 mL) was added a solution of sodium methoxide (from Na 536 mg, 23.3 mmol in MeOH, 20 mL). The reaction mixture immediately turned red. Water (1.2 mL) was then added and the mixture was heated under reflux for 2 h. After solvent evaporation, the residue was diluted with 4% HCl and extracted with CH_2C1_2 (2×40 mL). The combined organic layers were dried, filtered and evaporated and the crude product purified by silica gel column chromatography (CH_2C1_2–Et_2O 20:1) to give **7** (1.16 g, 77%) as yellow solid, mp 181–183°C (hexane–CH_2C1_2); $C_{17}H_{10}Br_2O_5$ requires C, 44.97; H, 2.22. Found: C, 45.02; H, 2.19; ν_{max} 3420, 1820, 1750, 1739 cm^{-1}; δ_H (200 MHz $CDCl_3$) 3.95 (3H, s, OMe), 5.25 (1H, bs, exchange with D_2O, OH), 6.90 (2H, d, J=9.0 Hz, aryl-H), 7.53 (2H, d, J=9.0 Hz, aryl-H), 7.71 (2H, s, aryl-H).

3-(3,5-Dibromo-4-methoxy-phenyl)-4-(3,5 dibromo-4-hydroxy-phenyl)-furan-2,5-dione 8. To a stirred solution of **7** (883 mg, 1.94 mmol) in glacial acetic acid (30 mL) a solution of bromine (0.6 mL, 11.64 mmol) in acetic acid (10 mL) was added dropwise at room temperature in 10 min. After stirring for 1 h, the solution was poured into Na_2SO_3–H_2O solution to give a yellow precipitate. The solid was filtered off, washed with cool water and dried in vacuo. Recrystallization from pentane–Et_2O yielded **8** (1.09 g, 89%) as yellow crystals; mp 191–193°C; $C_{17}H_8Br_4O_5$ requires C, 33.37; H, 1.32. Found: C, 33.42; H, 1.26; ν_{max} 3400, 1820, 1740 cm^{-1}; δ_H (300 MHz $CDCl_3$) 3.97 (3H, s, OMe), 6.30 (1H, bs, exchange with D_2O, OH), 7.75 (4H, s, aryl-H).

Polycitrin B 1b. A mixture of **8** (300 mg, 0.49 mmol), phenol (1.2 g), *N*,*N*-diisopropylethylamine (0.7 mL), tyramine (140 mg, 1 mmol) and activated molecular sieves, 4 Å, powder (1 g) (Aldrich) was heated with vigorous stirring under argon for 2 h at 140°C. The brown melt was cooled, dissolved in CH_2Cl_2 (30 mL), filtered and the filtered washed with 4% HCl (40 mL). The organic layer was dried, filtered and evaporated. The crude mixture was chromatographed on silica gel (eluent pentane–CH_2Cl_2 2:1 to CH_2Cl_2 to CH_2C1_2-Et_2O 20:1), giving polycitrin B (320 mg, 89%); mp 140–142°C (CH_2C1_2–pentane) (lit.[1] oil); $C_{25}H_{17}Br_4NO_5$ requires C, 41.08; H, 2.34; N, 1.92. Found: C, 41.22; H, 2.58; N, 2.05; UV (CH_3OH): λ_{max} (ϵ)=208 (61028), 273 (19861), 490 (10278); ν_{max} 3350 br, 1842, 1678 cm^{-1}; δ_H (300 MHz acetone-d_6) 2.88 (2H, t, J=7.6 Hz, CH_2), 3.77 (2H, bs, exchange with D_2O, OH), 3.79 (2H, t, J=7.6 Hz, CH_2), 3.94 (3H, s, OMe), 6.79 (2H, d, J=8.4 Hz, aryl-H), 7.11 (2H, d, J=8.4 Hz, aryl-H), 7.73 (2H, s, aryl-H), 7.78 (2H, s, aryl-H); δ_C (300 MHz acetone–d_6) 33.70, 40.29, 60.74, 110.95, 115.73, 118.26, 122.97, 127.94, 129.35, 130.15, 133.00, 134.22, 134.47, 134.66, 152.74, 155.61, 156.48, 169.78, 169.86; *m/z* (EI) 733 (2), 731 [M^+] (3), 729 (2), 613 (4), 611 (6), 609 (4), 527 (4), 525 (6), 523 (4), 339 (3), 337 (6), 335 (3), 279 (3), 277 (6), 275 (3), 177 (3), 163 (4), 161 (4), 148 (7), 120 (100); and polycitrin A (51 mg, 14%); mp 170–172°C (CH_2C1_2–pentane) (lit.[2] mp 180–181°C from $CHC1_3$–MeOH).

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