Synthesis of Simple 3,4-Diarylpyrrole-2,5-dicarboxylic Acids and Lukianol A by Oxidative Condensation of 3-Arylpyruvic Acids with Ammonia

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Abstract: Several derivatives of 3,4-diaryl- and 3,4-diindolylpyrrole-2,5-dicarboxylic acids including lycogalic acid A and two Halomonas metabolites were synthesized by oxidative dimerization of arylpyruvic acids or arylpyruvates in the presence of ammonia. The reaction can be applied for a short synthesis of lukianol A.

Key words: biomimetic synthesis, pyrroles, lycogalic acid, 3,4-diarylpyrrole-2,5-dicarboxylic acids

Lycogalic acid A (1) (Figure 1) has been isolated from the slime mould Lycogala epidendrum1,2 and from cultures of Chromobacterium violaceum (chromopyrrolic acid).3 Recently it was demonstrated that 1 is a key intermediate in the biosynthesis of the indolocarbazole antibiotics staurosporin and rebeccamycin.4 The close relationship between both types of compounds is also suggested by the co-occurrence of lycogalic acids with staurosporinone and arcyriaflavin A (7) in L. epidendrum.1,5 Recently, two phenyl analogues of lycogalic acid A, designated as HPPD-1 (3) and HPPD-2 (2) (Figure 1), have been found in cultures of a marine Halomonas bacterium.6 Both metabolites show effective antitumor activities.

Some time ago we discovered that lycogalic acid A dimethyl ester (4) is formed by treatment of methyl 3-(indol-3-yl)pyruvate with iodine in methanolic ammonia (Scheme 1).1a We reasoned that a similar protocol could be applied for the synthesis of 4,5-diarylpyrrole-2,5-dicarboxylic acid diesters. In this case, however, partial hydrolysis of the ester functions took place, and the crude product had to be re-esterified with diazomethane. In this manner methyl 3-(4-hydroxyphenyl)pyruvate afforded the bis(4-methoxyphenyl) derivative 5a in 60% yield (Scheme 2).

In the same fashion, the corresponding diphenyl derivative 5b was obtained from methyl 3-phenylpyruvate (Scheme 2). Interestingly, the reaction proceeded more sluggishly, and the mixture had to be heated under reflux for four hours to achieve a reasonable yield. Finally, diester 5a could be obtained in one step and with 67% yield from methyl 3-(4-methoxyphenyl)pyruvate by adding 4 Å molecular sieves to the refluxing reaction mixture. This prevented hydrolysis of the ester groups by the water formed during the pyrrole condensation.

Free 3,4-diarylpyrrole-2,5-dicarboxylic acids can be obtained from arylpyruvic acids under anhydrous conditions. This was first demonstrated in the total synthesis of polycitrin A,7 in which a solution of 3-(4-methoxyphenyl)pyruvic acid in anhydrous tetrahydrofuran at -78 °C was treated with two equivalents of n-butyllithium followed by 0.5 equivalent of iodine. After saturation of the solution with gaseous ammonia and stirring for 12 hours with 4 Å molecular sieves or titanium(IV) chloride at ambient temperature, 3,4-bis-(4-methoxyphenyl)pyrrole-2,5-dicarboxylic acid8 was obtained in 72% yield. Oxidative cyclization of a 1:1 mixture of 3-(4-hydroxyphenyl)pyruvic acid and 3-phenylpyruvic acid in tetrahydrofuran with five equivalents of n-butyllithium following the same procedure afforded a mixture of 25% 2 and 5% 3 (Scheme 3). None of the symmetrical diphenyl derivative 6 could be
detected. This can be explained by formation of a reactive quinone methide intermediate from 3-(4-hydroxyphenyl)pyruvate and iodine, which is able to react with the enolates of both reaction partners. The higher proportion of the bis(4-hydroxyphenyl) derivative 2 reflects the greater reactivity of the (4-hydroxyphenyl)pyruvate trianion as compared to the dianion formed from phenylpyruvate. The two dicarboxylic acids 2 and 3 could be easily separated by HPLC. Their spectroscopic data agreed with those reported for the *Halomonas* metabolites HPPD-2 and HPPD-1.

For the synthesis of diester 9 containing two different aryl substituents, the sodium enolate of ethyl 3-(4-hydroxyphenyl)pyruvate was treated with ethyl 3-bromo-3-phenylpyruvate (8a) and the resulting 1,4-diketo intermediate cyclized with ammonia in situ (Scheme 5). This one-pot procedure afforded diester 9 in 14% yield.

Similarly, half ester 10 was obtained in 34% yield by reaction of 3-(4-methoxyphenyl)pyruvic acid with its 3-bromo ester derivative 8b (Scheme 6). Decarboxylation of compound 10 yielded Fürstner’s intermediate 11, a key compound in previous syntheses of lukianol A (14). Usually, 11 is N-alkylated with 4-methoxyphenacyl bromide to yield ketone 12, which is then transformed into lukianol A trimethyl ether (13) by cleavage of the ester group followed by cyclization with Ac₂O/NaOAc. We were able cyclize 12 in one step by applying Otera’s distannoxane catalyst. Lukianol A trimethyl ether (13) was thereby obtained in 79% yield, considering the recovery of 26% of the starting material. For an alternative approach to lukianol A, see ref. 13.

In conclusion, we have shown that simple 3,4-diaryl- and 2,4-diindolylpyrrole-2,5-carboxylic acids can be easily obtained from ary(indolyl)pyruvic acids and ammonia.
Melting points (uncorrected): Büchi SMP 535 apparatus. IR spectra: PerkinElmer FT-IR Spectrum 1000. Abbreviations: s: strong; m: medium; w: weak; br: broad. Mass spectra (EI, 70 eV): Finnigan MAT 90 and Finnigan MAT 95Q, High-resolution mass spectra (EI, 70 eV): Finnigan MAT 95Q. NMR spectra: Bruker ARX 300, Bruker AMX 600, and Varian VX 400S. The spectra were recorded in CDCl3 or DMSO-d6 using the residual solvent peak as the internal standard (CDCl3, δH = 7.26 and δC = 77.1; DMSO-d6, δH = 2.49 and δC = 39.5). Elemental analyses were carried out by the Microanalytical Laboratory of the Department Chemie, Universität München. Flash chromatography (FC): Merck Kieselgel 60 (0.040-0.063 mm). TLC: Aluminum foils, silica gel 60 F254 (Merck). HPLC: Waters 717Plus Autosampler. Column: Nucleosil 100 RP 18, 5 μm (4 × 250 mm). Solvents for chromatography were distilled before use.

**Lycogal Acid A Dimethyl Estor (4)**

A solution of NaOMe in MeOH (30% w/w, 5 mL) was added at 0 °C under argon to a solution of methyl 3-(indol-3-yl)pyruvate (0.20 g, 0.92 mmol) in anhyd MeOH (40 mL). The mixture was stirred for 15 min and then treated dropwise with a solution of I2 (0.12 g, 0.46 mmol) in MeOH (20 mL). After warming to r.t., concd aq ammonia (5 mL) was added and the stirring continued for 30 min. The reaction was completed by heating the solution under reflux for 1 h. After addition of EtOAc (100 mL) and neutralization with 10% aq citric acid, the aq layer was extracted with EtOAc (2 × 100 mL). The combined organic phases were washed with brine (100 mL), dried (MgSO4) and concentrated under reduced pressure. Purification of the residue by FC (hexanes–EtOAc, 1:1) afforded 4 (0.08 g, 42%) as a yellowish resin, which crystallized from MeOH by addition of H2O. Pale yellow needles, mp 126–127 °C (dec.).

**3-(4-Hydroxyphenyl)pyruvic Acid (0.24 g, 1.24 mmol) in MeOH (50 mL) was then added and the mixture was heated under reflux for 2 h at r.t., then concd aq NH4 (5 mL) was added and the solution heated under reflux for 4 h. Re-esterification of the crude mixture with diazomethane and work-up as usual yielded 5b (0.15 g, 52%) as colorless needles; mp 194–195 °C; Rf = 0.70 (hexanes–EtOAc, 1:1).

**3,4-Bis(3-hydroxyphenyl)pyrrole-2,5-dicarboxylic Acid (2) and 3-(4-Hydroxyphenyl)pyrrole-2,5-dicarboxylic Acid (3)**

n-BuLi (2.5 M solution in hexane, 9.8 mL, 24.4 mmol) was added at –78 °C to a solution of 3-phenylvinylic acid (1.00 g, 6.09 mmol) and 3-(4-hydroxyphenyl)pyrrole-2,5-dicarboxylic acid (1.10 g, 6.09 mmol) in anhyd THF (200 mL), and the mixture was stirred for 20 min. I2 (1.55 g, 6.09 mmol) dissolved in anhyd THF (20 mL) was then added and the mixture warmed to r.t. After stirring for 1 h, the solution was saturated with gaseous ammonia in the presence of 4 Å molecular sieves (2.5 g), and the stirring was continued for 12 h. The turbid solution was made alkaline by addition of 2 N NaOH, washed with EtOAc (3 × mL), acidified with concd HCl to pH 4, and extracted with EtOAc (3 × 100 mL). The combined organic extracts were dried (Na2SO4) and concentrated under reduced pressure. The resulting mixture was separated by preparative HPLC (eluent A: H2O–MeCN, 9:1; eluent B: MeCN; gradient: start 100% A, 60 min; 100% B; flow rate: 5 mL/min) to yield 3 (100 mg, 5%) and 2 (256 mg, 25%) as yellow-orange solids. 2 (HPPD-2)

Mp 93 °C; Rf = 0.21 (toluene–HCO2Et-HCO2H, 10:5:3).

IR (KBr): 3271 (s, br), 2924 (s), 1694 (s), 1614 (m), 1555 (m), 1538 (s), 1461 (m), 1360 (m). 1H NMR (400 MHz, CDCl3): δ = 3.73 (s, 6 H, 2 × OCH3), 7.08–7.14 (m, 4 H), 7.16–7.21 (m, 6 H), 9.94 (br s, 1 H, NH). 13C NMR (100 MHz, CDCl3): δ = 51.8 (CH3), 121.3 (C-3), 127.0 (CH’-4’), 127.3 (CH’-3’), 130.8 (CH2-’*), 131.5 (C-2’), 132.9 (C-1’), 160.8 (* signals may be interchanged). 1H NMR (400 MHz, CDCl3): δ = 3.73 (s, 6 H, 2 × OCH3), 7.08–7.14 (m, 4 H), 7.16–7.21 (m, 6 H), 9.94 (br s, 1 H, NH). 13C NMR (100 MHz, CDCl3): δ = 51.8 (CH3), 121.3 (C-3), 127.0 (CH’-4’), 127.3 (CH’-3’), 130.8 (CH2-’*), 131.5 (C-2’), 132.9 (C-1’), 160.8 (* signals may be interchanged). 1H NMR (400 MHz, CDCl3): δ = 3.73 (s, 6 H, 2 × OCH3), 7.08–7.14 (m, 4 H), 7.16–7.21 (m, 6 H), 9.94 (br s, 1 H, NH). 13C NMR (100 MHz, CDCl3): δ = 51.8 (CH3), 121.3 (C-3), 127.0 (CH’-4’), 127.3 (CH’-3’), 130.8 (CH2-’*), 131.5 (C-2’), 132.9 (C-1’), 160.8 (* signals may be interchanged).
EL-MS: m/z (%): 339 (3, [M]+), 295 (4), 277 (7), 251 (100), 223 (7), 178 (7), 165 (9), 117 (6), 107 (8), 77 (6), 44 (42).

HRMS: m/z calc'd for C_{18}H_{13}NO_{6}: 339.0743; found: 339.0760.

3 (HPDP-1)

Mp 84 °C; R_{f} = 0.29 (toluene–HCO\textsubscript{2}Et–HCO\textsubscript{2}H, 10:5:3).

IR (KBr): 3414 (br s), 2961 (m), 1690 (s), 1613 (m), 1554 (m), 1485 (s), 1421 (m), 1374 (m), 1286 (s), 1232 (m), 1157 (m), 1140 (s), 1125 (s), 1072 (s), 1020 (m), 963 (s), 869 (m), 784 (s), 697 (s), 650 (m), 605 (w), 476 (w).

1H NMR (300 MHz, CD\textsubscript{3}OD): δ = 6.56, 6.89 (d each, J = 8.6 Hz, 2 H), 7.03–7.18 (m, 5 H), 9.19 (s, 1 H), 11.6 (s, 1 H), 12.6 (br s, 2 H), 130.1, 130.3, 130.9 (2 CH\textsubscript{2}), 131.8 (2 CH\textsubscript{2}), 134.5, 156.0, 161.6, 161.7.

FAB-MS: (m-NA): m/z (%): 324 (98, [M + H\textsuperscript{+}]), 323 (99, [M\textsuperscript{+}]), 238 (100).

FAB-HRMS: m/z calc'd for C_{18}H_{13}NO_{6}: 339.0743; found: 339.0760.

Lycogalic Acid A (1)

From 3-(indol-3-yl)pyruvic acid (1.00 g, 4.9 mmol), n-ButLi (2.5 M solution in hexane, 5.9 mL, 14.7 mmol), I\textsubscript{2} (0.62 g, 2.45 mmol), and gaseous NH\textsubscript{3} in the presence of 4 Å molecular sieves (5 g) was obtained as a pale yellow powder (yield not determined); mp >200 °C. Identical with an authentic sample (UV, 1H NMR, EI MS, TLC comparison).\textsuperscript{14}

1H NMR (300 MHz, CD\textsubscript{3}OD): δ = 6.68 (ddd, J\textsubscript{1} = 7.9 Hz, J\textsubscript{2} = 7.0 Hz, J\textsubscript{3} = 1 Hz, 2 H), 6.77 (s, 2 H), 6.84 (ddd, J\textsubscript{1} = 8.1 Hz, J\textsubscript{2} = 7.0 Hz, J\textsubscript{3} = 1 Hz, 2 H), 7.06 (dd, J\textsubscript{1} = 7.9, J\textsubscript{2} = 1 Hz, 2 H), 7.11 (dd, J\textsubscript{1} = 8.1 Hz, J\textsubscript{2} = 1 Hz, 2 H).

13C NMR (75 MHz, CD\textsubscript{3}OD): δ = 110.2, 111.7, 119.4 (CH\textsubscript{2}), 121.1 (CH\textsubscript{2}), 121.6 (CH), 125.0, 125.85 (CH), 125.90, 129.4 (CH), 130.8 (2 CH\textsubscript{2}), 134.3, 156.0, 161.6, 161.7.

EI-MS: m/z (%): 385 (5, [M]+), 368 (40), 267 (31), 175 (36), 148 (79), 147 (21), 140 (18), 133 (14), 130 (100), 117 (31), 90 (12).

FAB-OrNative: m/z calc'd for C_{18}H_{13}NO_{6}: 339.0743; found: 339.0760.

Methyl 3-Bromo-3-(4-methoxyphenyl)pyruvate (8b)

To a solution of ethyl 3-(4-methoxyphenyl)pyruvate (3.80 g, 18.0 mmol)\textsuperscript{34} in anhyd CH\textsubscript{2}Cl\textsubscript{2} (200 mL), was added NBS (2.70 g, 15.0 mmol), and the mixture was irradiated for 20 min with a halogen lamp (500 W). After cooling to 0 °C, the suspension was filtered and the orange solution concentrated under reduced pressure. The crude ester 8b (~5.0 g) was used for the next step without further purification.

1H NMR (300 MHz, CD\textsubscript{3}OD): δ = 3.68 (s, 3 H), 3.80 (s, 3 H), 6.14 (s, 1 H), 6.82, 7.31 (d each, J = 8.6 Hz, 2 H), 11.95 (s, 1 H).

1C NMR (75 MHz, CD\textsubscript{3}OD): δ = 48.8 (CH\textsubscript{3}), 52.5 (CH\textsubscript{2}), 54.3 (CH\textsubscript{3}), 113.5 (2 CH\textsubscript{2}), 123.7, 130.1 (2 CH\textsubscript{2}), 159.5, 182.4.

3,4-Bis(4-methoxyphenyl)pyrrole-2,5-dicarboxylic Acid

Monomethyl Ester (10)

n-ButLi (2.5 M solution in hexane, 20 mL, 50 mmol) was added at –78 °C to a solution of 3-(4-methoxyphenyl)pyruvic acid (4.85 g, 25 mmol) in anhyd THF (400 mL), and the mixture was stirred for 20 min. A solution of freshly prepared 8b (7.18 g, 25 mmol) in anhyd THF (300 mL) was then added dropwise, and after warming the mixture to r.t, the stirring was continued for 1 h. The mixture was then saturated with gaseous NH\textsubscript{3} in the presence of 4 Å mol sieves (5 g) and stirred for 12 h. The turbid solution was made alkaline by addition of aq 2 N NaOH, washed with EtO\textsubscript{Ac} (3 × 100 mL), acidified with concd HCl to pH 4, and extracted with EtO\textsubscript{Ac} (3 × 200 mL). The combined organic extracts were dried (Na\textsubscript{2}SO\textsubscript{4}), concentrated under reduced pressure, and purified by FC to yield 10 (320 g, 34%) as colorless crystals; mp 292–295 °C.

1H NMR (300 MHz, CDCl\textsubscript{3}): δ = 3.60 (s, 3 H), 3.70 (s, 6 H), 6.73 (d, J = 8.8 Hz, 4 H), 6.94, 6.96 (d each, J = 8.8 Hz, 2 H), 11.95 (s, 1 H, NH).

13C NMR (75 MHz, CDCl\textsubscript{3}): δ = 52.1 (CH\textsubscript{3}), 55.7 (2 CH\textsubscript{2}), 113.5 (2 CH\textsubscript{2}), 114.7 (2 x), 126.5 (4 x), 126.7, 131.1, 131.6, 132.5 (CH\textsubscript{2}), 132.6 (CH), 158.6, 158.7, 161.2, 162.3.

EI-MS: m/z (%): 382 (22, [M + H\textsuperscript{+}]), 381 (100, [M\textsuperscript{+}]), 363 (30, [M – CO\textsuperscript{+}]), 349 (18), 305 (20), 304 (20), 262 (16).

Anal. Calc'd for C\textsubscript{21}H\textsubscript{19}NO\textsubscript{6}: C, 66.14; H, 5.02; N, 3.67. Found: C, 66.49; H, 5.06; N, 3.64.

Methyl 3,4-Bis(4-methoxyphenyl)pyrrole-2-carboxylate (11)

To a solution of 10 (1.96 g, 5.14 mmol) in freshly distilled quinoline (40 mL) was added a small portion of Cu chromite, and the mixture was heated for 10 min at 200 °C. After cooling to r.t., EtO\textsubscript{Ac} (200 mL) was added and the solution washed with sat. aq NaHCO\textsubscript{3} (3 × 100 mL), 2 N HCl (4 × 150 mL), and brine (100 mL), dried (MgSO\textsubscript{4}) and concentrated. Purification of the residue by FC (Et\textsubscript{2}O–hexanes, 1:1) yielded 11 (1.28 g, 75%) as a yellow oil (Lit.\textsuperscript{35} mp 238–240 °C).
169–171 °C). The spectroscopic data agreed with those reported in the literature.

**Lukianol A Trimethyl Ether (13)**

Ketone 12 was prepared from 11 according to the literature.9 Compound 12 (109 mg, 224 μmol), 1-hydroxy-3-(isothiocyanato)tetrahydrodistannoxane12 (228 mg, 224 μmol), and a crystal of DMAP were dissolved in anhyd benzene (100 mL), and the resulting mixture was refluxed for 16 h using a Soxhlet extractor charged with 4 Å molecular sieves (50 g). Compound 13 (59 mg) was separated from starting material 12 (28 mg, 26%) by FC (Et2O–hexanes, 1:1). The yield of 13 was 79%, considering the recovered starting material. Colorless crystals, mp 206-207 °C (Lit. 10 mp 206–207 °C). The derived spectroscopic data were in good agreement with those reported in the literature.10

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**References**


