Formal synthesis of piperazinomycin, a novel antifungal antibiotic

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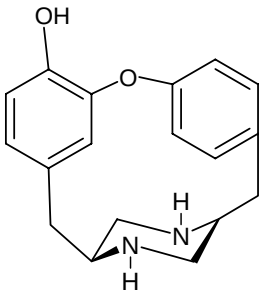
Abstract

An alternative synthesis of piperazinomycin is disclosed. The approach is based on an intramolecular *O*-arylation of arylboronic acid with phenol for formation of the macrocyclic biaryl ether.

Keywords: Piperazinomycin, antifungal, arylboronic acid, *O*-arylation

Introduction

Piperazinomycin **1**, constitutes the simplest naturally occurring agent possessing the parent 14-membered para- and metacyclophane diary1 ether structural subunit found in bouvardin,[1] deoxybouvardin,[1] RA-I-X,[2] OF4949-I-OF494-IV,[3] and K-13.[4] This has renewed the interest in the synthesis and evaluation of piperazinomycin and structurally related agents since **1** and notably **2.** However, efforts to critically examine the importance of the cycloisodityrosine subunit have been hampered by the synthetic inaccessibility of such systems.



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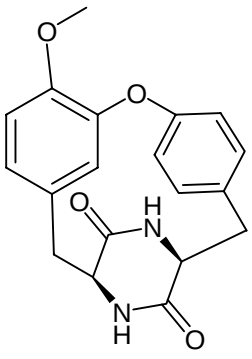

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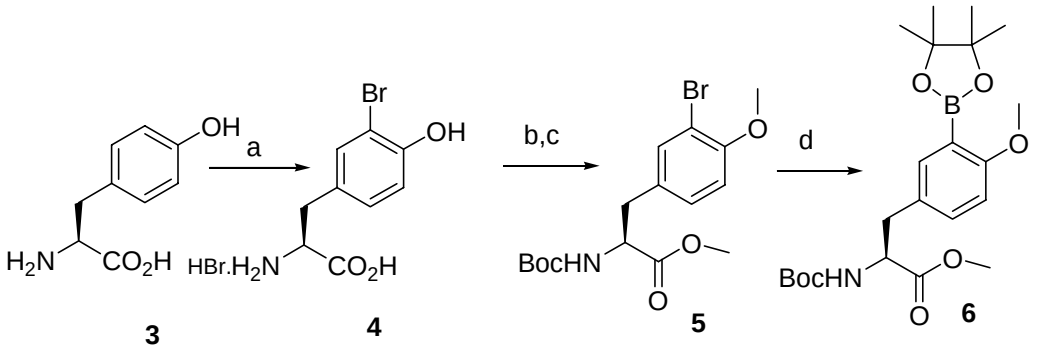
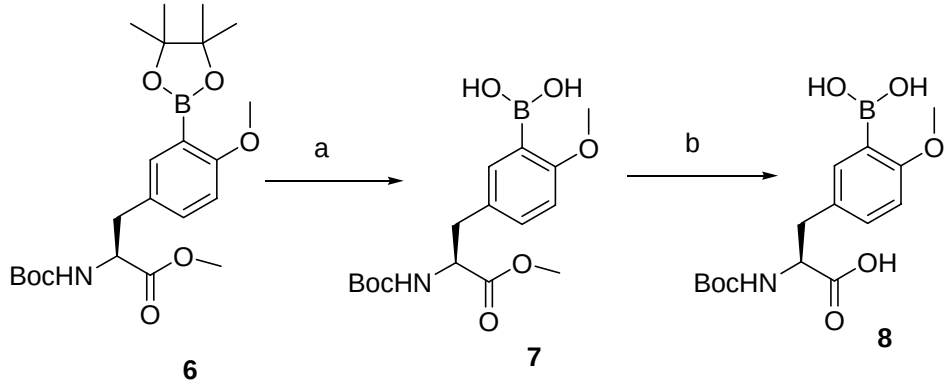
Results and Discussion

In the present paper, we describe a practical and short synthetic route to compound **2** from commercially available L-tyrosine by a coupling reaction of arylboronic acid with phenol originally developed by Chan, [5] Evans,[6] and Lam.[7, 8]



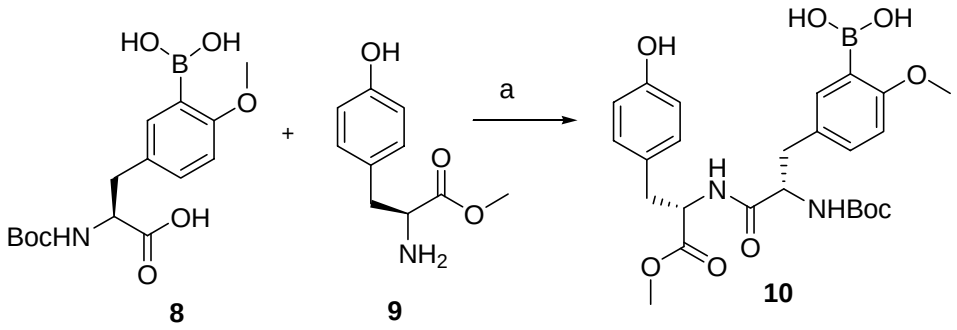
Scheme 1. (a) Br_2/AcOH, HBr/AcOH, RT, 6h, 95%; (b) $(Boc)_2O$, $NaHCO_3$, MeOH, EtOAc, RT, 4h (c) Me_2SO_4, K_2CO_3, Acetone, RT, 12h, 96% (from 4 to 5) (d) Bis(pinacolato)diboron, KOAc, $PdCl_2$(dppf), DME,110^{0}C, 18 h, 90 %.

Commercially obtained L-tyrosine **3** was brominated at 3-position with bromine in acetic acid and hydrobromic acid in acetic acid at room temperature to afford 3-bromo- L-tyrosine hydrobromide **4**[9] in 95 % yield from **3**. Compound **4** was *N*-protected with a Boc group and methylated with dimethyl sulphate (2.5 eq.) in presence of potassium carbonate (3 eq.) in acetone to afford protected bromotyrosine **5** in 96% yield from **4**. Compound **5** was treated with bis (pinacolato) diboron (1.3 eq.), potassium acetate (3 eq.) and $PdCl_2$ (dppf) (0.05 eq.), as a catalyst, in 1, 2-dimethoxy ethane (DME) at 110^{0}C for 18 h to afford compound **6** in 90 % yield.



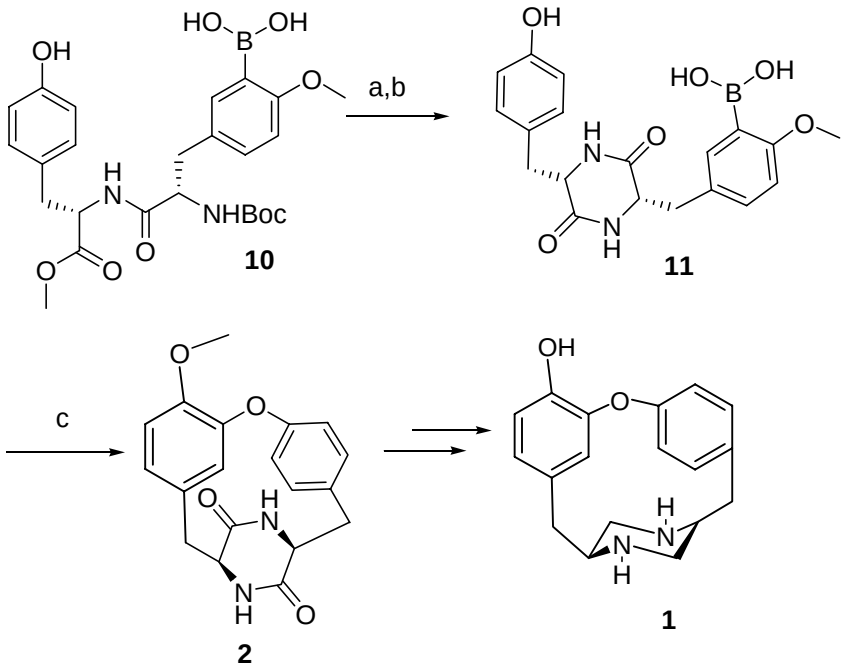
Scheme 2. (a) $NaIO_4$, acetone, 0.1 N aq. NH_4OAc, RT, 16 h, 90 %.(b) LiOH, MeOH, H_2O, RT, 30 min, 96 %.

The arylboronate **6** was easily converted into arylboronic acid **7** [10] using sodium metaperiodate (3 eq.) in acetone (20 Vol) in presence of 0.1M NH_4OAc aq. solution at room temperature for 16 h. in 90 % yield. Compound **7** was hydrolyzed with lithium hydroxide in methanol and water at room temperature for 30 min to afford compound **8** in 96 % yield.



Scheme 3. (a) EDCI, HOBt, DIPEA, DCM, RT, 2h, 85%.

Compound **8** was coupled with compound **9** using 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride and *N*-hydroxy benzotriazol in presence of diisopropyl ethyl amine in dichloromethane at room temperature to afford dipeptide **10** in 85 % yield.



Scheme-4. (a) 2N HCl, EtOAc, RT, 30 min, 96 %, (b) 0.1M AcOH-iPrOH, NMM, 4h, reflux, 90 %. (c) Cu $(OAc)_2$, Et_3N, DMF, powdered 4 A^0 molecular sieves, 72 h, 33 %.

Compound **10** was *N*-deprotected using 2N HCl in ethyl acetate to yield the corresponding hydrochloride salt which was then treated with 0.1M acetic acid in isopropyl alcohol in presence of *N*-methylmorpholine to afford compound **11** in 90 % yield. Key ring closure of **11** to **2** [11] via the intramolecular *O*-arylation of phenol with arylboronic acid **11** smoothly proceeded using cupric acetate (1.3 eq.) and triethyl amine (5 eq.) in *N*,*N*-dimethyl formamide in presence of powered 4 A^0 molecular sieves for 72 h at room temperature in 33% yield. The conversion of compound **2** to compound **1** has already been reported in the literature.[12]

Conclusions

Our methods described above provide new and shorter routes for the synthesis of piperazinomycin from commercially available L-tyrosine.

Experimental Section

General Procedures. All solvents and reagents were purchased from the suppliers and used without further purification. All non-aqueous reactions were performed in dry glassware under dry nitrogen atmosphere. Organic solutions were concentrated under reduced pressure. Thin layer chromatography was performed on Merck precoated Silica-gel $60F_{254}$ plates. ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini 400 MHz FT NMR spectrometer using DMSO-d_6 and $CDCl_3$ as a solvent. The chemical shifts were reported in δ ppm relative to TMS. The mass spectra were recorded on Shimadzu LCMS-QP 800 LC-MS and AB-4000 Q-trap LC-MS/MS. Melting points were obtained by using the open capillary method and are uncorrected.

(S)-Methyl 3-(3-bromo-4-methoxyphenyl)-2-(tert-butoxycarbonyl) propanoate (5). To a solution of compound **4** (5 g, 14.66 mmol) in MeOH (30 mL) and EtOAc (30 mL) at room temperature was added $NaHCO_3$ (2.45 g, 29.32 mmol) and H_2O (20 mL) followed by $(Boc)_2O$ (4.8 g, 22 mmol). The reaction mixture was stirred at same temperature for 4 h. To the reaction mixture heptane (50 mL) was added and diluted with water (20 mL). The organic layer was separated and aqueous layer was washed with heptane (40 mL) one more time. Then the aqueous layer was acidified with 10 % aqueous citric acid solution (20 mL) to make the PH~ 4-5. The aqueous layer was extracted with EtOAc (2X50 mL) and concentrated under vacuum to afford corresponding Boc-protected compound (5.2 g). To a solution of Boc-protected compound (5.2 g, 14.44 mmol) in acetone (50 mL) was added K_2CO_3 (6 g, 43.33 mmol) and Me_2SO_4 (4.5 g, 36.11 mmol) at room temperature. The reaction mixture was stirred at same temperature for 12 h. The reaction mixture was filtered through pad of Celite and washed with acetone (50 mL). The acetone layer was concentrated under vacuum. Purification by column chromatography (silica, 7:3 hexane/EtOAc) provided arylbromide **5** as an off white solid (on storing at rt slowly became

solid) (5.5 g, 96% yield), R_f = 0.6 (7:3 ; heptanes/EtOAc), mp 66-70 °C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.40 (s, 1H), 7.25 (d, J = 8.4 Hz, 1H), 7.18 (dd, J= 8.4 Hz, 1H), 6.99 (d, J = 8.4 Hz, 1H), 4.08 (m, 1H), 3.76 (s, 3H), 3.57 (s, 3H), 2.89 (m, J = 5.2 Hz, 1H), 2.75 (m, J = 10 Hz, 1H), 1.28 (s, 9H)); ^{13}C NMR (400 MHz, DMSO-d_6): δ 170.9, 158.9, 155.1, 134.2, 131.0, 130.6, 114.5, 113.1, 79.9, 56.7, 53.5, 53.3, 35.4, 34.8; ESIMS: m/z calcd [M+]: 388; found: 287.94 [M+].

(S)-Methyl 2-(tert-butoxycarbonyl)-3-(4-methoxy-3-(4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl) phenyl) propanoate (6). Aryl bromide **5** (5 g, 12.88 mmol), bis (pinacolato) diboron (4.23 g, 16.75 mmol), KOAc (3.78 g, 38.65 mmol) and $PdCl_2$ (dppf) (0.525 g, 0.644 mmol) were suspended in dry 1, 2-dimethoxyethane (50 mL, degassed by sparging with N_2), and heated to 110 ºC for 18 h. Water (30 mL) and EtOAc (30 mL) were added. The layers were separated, and the aqueous layer was extracted with EtOAc (2x50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuum. Purification by column chromatography (silica, 7:3 hexane/EtOAc) provided aryl boronate **6** as an off white solid (on storing at rt slowly became solid) (5 g, 90% yield), R_f = 0.5 (7:3 ; heptanes/EtOAc), mp 92-95 °C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.21-7.33 (m, 3H), 6.82 (d, J = 8.8Hz, 1H), 4.00 (m, J = 8.8Hz, 1H), 3.66 (s, 3H), 3.56 (s, 3H), 2.77-2.88 (m, 2H), 1.29 (s, 6H), 1.19 (s, 6H), 1.03 (s, 9H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 172.9, 160.0, 155.1, 133.3, 131.9, 131.3, 123.3, 111.2, 85.3, 80.8, 56.9, 55.3, 51.3, 36.8, 29.3, 24.8, 23.9; ESIMS: m/z calcd [M+]: 435; found: 436 [M+H+]; HRMS (ESI): *m*/*z* calcd [M+]: 435.3188; found: 435.3165 [M +].

(S)-5-(2-(tert-butoxycarbonyl)-3-methoxy-3-oxopropyl)-2-methoxyphenylboronic acid (7). To a stirred solution of the arylboronate **6** (5 g, 11.5 mmol) in acetone (100 mL) was added NH_4OAc (aq.) (125 mL, 0.lN) and $NaIO_4$ (7.34 g, 34.48 mmol) at room temperature. The mixture was stirred at room temperature for 24 h. To the reaction mixture ethyl acetate (50 ml) was added and organic layer was separated and concentrated. Purification by column chromatography (silica, 5:5 hexane/EtOAc) provided arylboronic acid **7** as an off white solid (on storing at rt slowly became solid) (3.6 g, 90% yield), R_f = 0.3 (5:5 ; heptanes/EtOAc), mp 95-100 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (s, 1H), 7.16 (d, J = 8.4 Hz, 1H), 6.79 (d, J= 8.8 Hz, 1H), 6.28 (s, 2H), 4.50 (m, 1H), 3.82 (s, 3H), 3.67 (s, 3H), 3.02 (m, J = 5.6 Hz, 2H), 1.36 (s, 9H)); ^{13}C NMR (400 MHz, $CDCl_3$): δ 172.4, 163.6, 155.0, 137.7, 133.4, 133.3, 128.4, 110.0, 79.8, 55.5, 54.5, 52.2, 37.4, 28.9; ESIMS: m/z calcd [M+]: 353; found: 354 [M+1].

(S)-3-(3-borono-4-methoxyphenyl)-2-(tert-butoxycarbonyl)propanoic acid (8). To a stirred solution of the arylboronic acid **7** (3.6 g, 10.2 mmol) in MeOH (20 mL) and H_2O (20 mL) was added LiOH (0.73 g, 30.6 mmol) at room temperature. The reaction mixture was stirred at same temperature for 30 min. To the reaction mixture heptane (30 mL) was added and stirred for another 15 min. The aqueous layer was separated and acidified with 10 % aq. citric acid solution to make PH ~ 4. The aqueous layer was extracted with EtOAc (3X30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuum to afford compound **8** as an off white solid (on storing at rt slowly became solid) (3.3 g, 96% yield), mp 98-102 °C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.22 (s, 2H), 7.37 (s, 1H), 7.19 (m, J= 8 Hz, 1H), 6.98 (d, J = 8.4

Hz, 1H), 6.82 (d, J = 8 Hz, 1H), 3.95 (m, 1H), 3.70 (s, 3H), 2.86 (m, 1H), 2.70 (m, 1H), 1.24 (s, 9H)); ^{13}C NMR (400 MHz, DMSO-d_6): δ 174.0, 162.7, 155.8, 136.6, 132.6, 131.5, 129.9, 110.5, 79.5, 56.4, 55.7, 36.0, 28.5; ESIMS: m/z calcd [M+]: 339; found: 340 [M+1].

5-((S)-2-(tert-butoxycarbonyl)-3-((S)-3-(4-hydroxyphenyl)-1-methoxy-1-oxopropan-2-ylamino)-3-oxopropyl)-2-methoxyphenylboronic acid (10). A suspension of **8** (3 g, 6.89 mmol) in dry DCM (50 mL) was added compound **9** (1.35 g, 6.89 mmol), EDCI (1.97 g, 10.34 mmol), HOBt (0.93g, 6.89 mmol) and DIPEA (1.33 g 10.34 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with water and neutralized with 10 % aq. citric acid solution and dichloromethane layer was separated and concentrated to get a residue. The residue was purified by column chromatography (silica, 5:5; heptanes / EtOAc) to afford compound **10** as an off white solid (3.00 g, 85% yield) as a white solid. R_f = 0.2 (5:5 ; Heptane/EtOAc), mp 90-95 °C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.21 (s, 1H), 8.24 (d, J = 7.56Hz, 1H), 7.65 (s, 2H), 7.49 (s, 1H), 6.64-7.23 (m, 7H), 4.41 (q, 1H), 4.09 (q, 1H), 3.77 (s, 3H), 3.58 (s, 3H), 2.79-2.88 (m, 4H), 1.28 (s, 9H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 171.7, 171.6, 162.1, 155.9, 155.0, 136.3, 132.2, 129.9, 129.8, 128.0, 126.8, 114.9, 109.9, 77.9, 56.2, 55.8, 55.2, 53.6, 36.5, 36.0, 28.0; ESIMS: m/z calcd [M+]: 516; found: 517 [M+H+]; HRMS (ESI): *m*/*z* calcd [M+]: 516.3485; found: 516.3435 [M +].

5-(((2S,5S)-5-(4-hydroxybenzyl)-3,6-dioxopiperazin-2-yl)methyl)-2-methoxyphenylboronic acid (11). A solution of **10** (2.5 g, 6.00 mmol) in 2 M HCl-EtOAc (50 mL) was stirred at room temperature for 30 min. The volatiles were removed in vacuum and the residue was dried thoroughly under vacuum to afford the corresponding amine hydrochloride salt as an off white solid. A suspension of the hydrochloride salt in 0.1 M HOAc-iPrOH (30 ml) was treated with *N*-methylmorpholine (NMM, 0.64 g, 6.34 mmol, 1.3 equiv) at room temperature**,** and the resulting weakly acidic reaction mixture was heated at reflux for 4 h. The diketopiperazine began to crystallize from the hot reaction solution. The mixture was cooled at 0^0C (4 h) and filtered, and the collected product was washed with Et_20 (3 X 30 mL) to afford compound **11** (1.67 g, 90% yield) as an off white solid. mp 222-225 °C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.23 (s, 1H), 7.80 (s, 2H), 7.61(s, 2H), 7.35 (s, 1H), 6.82-7.04 (m, 4H), 6.64 (d, J = 8 Hz, 2H), 3.86 (m, 2H), 3.68 (s, 3H), 3.02 (m, 2H), 2.64 (m, 2H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 166.2, 166.1, 162.5, 156.0, 136.9, 133.0, 130.7, 128.1, 126.4, 114.9, 113.6, 110.1, 55.7, 55.3, 52.7, 38.9, 38.5; ESIMS: m/z calcd [M+]: 384; found: 385.11 [M+H+], 406.92 [M+ +Na]; HRMS (ESI): *m*/*z* calcd [M+]: 384.1908; found: 384.1935 [M +].

(3S, 6S)-11-Methoxy–5, 21–dioxo-13–oxa–4, 20 – diazatetracyclo- [12.2.2.2$^{3,\ 6}$.1$^{8,\ 12}$] heniecosa-8, 10, 12(19), 14, 16, 17-hexaen (2). To a stirred suspension of compound **11** (1g , 2.60 mmol), anhydrous $Cu(OAc)_2$ (0.611 g, 3.38 mmol) and activated 4 Å molecular sieves (2 g) in dry DMF (50 mL) was added triethyl amine (1.8 ml, 13.02 mmol) at room temperature. The mixture was stirred vigorously for 74 h at room temperature , then filtered through a pad of Celite, and washed with water (15 mL) and 10 % MeOH-$CHCl_3$ (20 ml). The organic layer was separated and dried over $MgSO_4$ and was evaporated to dryness in vacuum. The residue was subjected to column chromatography (silica, 2-10% $CH_3OH/CHCl_3$) to afford compound **2** (0.29

g, 33%) as a white solid: R_f = 0.3 (9:1 ; $CHCl_3$/MeOH) ; mp 280-282^{0}C, $[\alpha]^{25}_D$ +182 (c 0.05, MeOH) ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.09 (s, 1H), 7.89 (s, 1H), 6.45-7.40 (m, 6H), 4.27 (m, 1H), 4.20 (m, 1H), 4.14 (d, 1H), 3.83 (s, 3H), 3.05-3.48 (m, 2H), 2.87-2.72 (m, 2H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 166.9, 166.3, 157.8, 153.1, 145.8, 133.5, 133.0, 131.8, 128.9, 125.0, 114.9, 112.7, 56.0, 55.0, 51.7, 36.5, 31.4; ESIMS: m/z calcd [M+]: 338; found: 339 [M+H+]; HRMS (ESI): *m*/*z* calcd [M+]: 338.3572; found: 338.3385 [M +].

Acknowledgements

We are grateful to Indian Association for Cultivation Sciences, Jadavpur for analytical support, Pfizer Ltd, and SVNIT, Surat, India.

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