Total synthesis of antibacterial dibromotyrosine derived alkaloid purpuramine-K

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The first total synthesis of a dibromotyrosine derived alkaloid purpuramine K reported for possible anti-bacterial activity against gram-positive bacteria viz: Staphylococcus aureus, Bacillus subtilis, Bacillus sphaericus and gram-negative bacteria like Chromobacterium violaceum, Klebsiella aerogenes and Pseudomonas aeruginosa.

To confirm the structure derived from the NMR assignment of purpuramine K as well as to scale-up availability and to prepare its analogues, which can be helpful for further activity studies, the total synthesis of purpuramine K has been undertaken and achieved by using simple starting materials and using lucid chemical transformations.

Results and Discussion

The retrosynthetic analysis of purpuramine K 1 revealed that it could be disconnected into three units: the western propyl amine 6, the central dibromotyramine unit 13, and the eastern unit, monobromo oxime acid chain 17. The synthesis of western part originated from 3-amino-1-propanol 3, which was reacted with ethyl formate to give N-formyl alcohol 3, followed by reduction with lithium aluminum hydride in dry THF to give the corresponding N-methyl alcohol 4. Compound 4 was further converted into 3-hydroxypropyl methyl carbamate 5 by reaction with methyl chloroformate in the presence of K$_2$CO$_3$ in dry acetone. The alcohol 5 was treated with PBr$_3$ to give the corresponding bromo compound 6 (Scheme 1).

For the synthesis of the central unit 13, the methyl ester of 4-hydroxyphenyl acetic acid 7 was dibrominated by using 2 equivalents of NBS in dry THF to give the dibromo compound 8. The phenolic group of compound 8 was protected as its TBDMS ether 9. The ester group in compound 8 was reduced...
with LAH to yield the corresponding alcohol 10, which was converted to the Boc protected 3,5-dibromotyramine 13 via four conventional steps with an overall yield of 83% (Scheme II).

The eastern unit 17 (Ref. 10) was synthesized in good yield by treating 4-hydroxyphenyl pyruvic acid 16, with O-tetrahydropyranyl oxime in ethanol at reflux temperature.

Finally, the western 6 and central 13 units were coupled using K2CO3 in acetone at reflux temperature to obtain compound 14. After deprotection of the Boc group in compound 14, it was coupled with the eastern unit 4-hydroxyphenylpyruvic acid oxime 17 (Ref. 10), using EDCI/HOBt10 to give compound 18. This was then subjected to careful mono bromination using one equivalent of NBS in dry THF followed by O-methylation of the phenolic hydroxyl group to get the target molecule purpuramine K as the THP ether 19 (Scheme III).

Experimental Section

All air or moisture sensitive reactions were carried out under nitrogen atmosphere. Solvents were freshly distilled before use. THF and ether were dried over Na/benzophenone, DCM over P2O5 followed by CaH2, and DMF and DIPA (Diisopropylamine) over NH2 OH

\[ \text{Scheme I} \]

\[ \text{Scheme II} \]
Thin layer chromatography was performed with pre-coated silica gel plates. Column chromatography was carried out over silica gel (100-200 mesh) and hexane and ethyl acetate mixtures as eluent, unless otherwise mentioned. Melting points were determined on a Mel-Temp apparatus and are uncorrected. IR spectra were recorded on Perkin-Elmer 240-C instrument, the $^1$H and $^{13}$C NMR spectra were recorded on 300 MHz (Bruker), and 200 MHz (Varian) instruments using TMS as internal standard. Chemical shifts are reported in $\delta$ (ppm) and coupling constants ($J$) are expressed in Hz. The MS were recorded on a VG Auto Spec-M instrument.

**Methyl 3-hydroxypropyl methyl carbamate (5):** A mixture of compound 4 (800 mg, 9 mmole), methyl chloroformate (2.8 mL, 36 mmole), and K$_2$CO$_3$ (7.45 g, 54 mmole) was taken in dry acetone (100 mL) and refluxed for 12 hr. After completion of the reaction, the solvent was removed under reduced pressure, water was added (20 mL) and extracted into ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give crude product, which was subjected to silica gel column chromatography using hexane:ethyl acetate (25:75) as eluent to give yellowish gummy liquid 5 (1.175 g, 7.99 mmole) in 89% yield. IR (KBr): 3414, 2951, 1689, 1491, 1398, 1264, 1215, 1151, 1061 and 772 cm$^{-1}$; $^1$H NMR (CDCl$_3$): $\delta$ 3.69 (3H, s, OMe), 3.53 (2H, t, $J = 7.1$ Hz), 3.40 (2H, t, $J = 6.4$ Hz, N-CH$_2$), 2.89 (3H, s, N-CH$_3$), 1.70 (2H, quintet); LCMS: m/z 148 (M$^+$+H), 143, 134, 130, 116, 102, 88, 73 and 59.

**Methyl 3-bromopropyl methyl carbamate, 6:** To a cooled (0°C) solution of compound 5 (300 mg, 2.04 mmole) in dry ether (20 mL) was added phosphorus tri-bromide (PBr$_3$) (0.09 mL, 0.9 mmole). The reaction was stirred for 30 min at RT. After completion of the reaction, saturated potassium bromide solution was added dropwise at 0°C, and the mass extracted with ether to give crude product 6. The crude product was chromatographed over silica-gel using hexane and ethyl acetate as eluent to afford pure compound 6 (411 mg, 1.96 mmole) in 96% yield.

**Methyl 2-(3,5-dibromo-4-hydroxyphenyl) acetate, 8:** To a solution of compound 7 (2.6 g, 15.66 mmoles) in dry tetrahydrofuran (THF) (100 mL), N-bromo succinamide (NBS) (5.6 g, 31.28 mmoles) was added and stirred for 30 min. After completion of the reaction, the reaction was quenched with saturated Na$_2$S$_2$O$_3$ solution, and the solvent removed under reduced pressure. The reaction mass was then extracted into ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give crude dibromo compound 8. The crude product was chromatographed over silica gel column using hexane:ethyl acetate mixture as eluent to afford pure dibromo compound 8 (4.97 g, 15.34 mmole) in 98% yield. IR (KBr): 3364, 3018, 2957, 1720, 1553, 1481, 1410, 1288, 1235, 1142, 999, 906 and 753 cm$^{-1}$; $^1$H NMR...
264, 262, 243, 199, 163, and 113.

3.42 (2H, s); LCMS: m/z 324, 323, 322, 283, 266, 15 min. To this was then added (399.9 mg, 5.88 mmoles) and the mixture stirred for 15 min. To this was then added tert-butyl-dimethylsilyl chloride (TBDMS chloride) (534 mg, 3.52 mmoles) and the stirring continued at RT for 90 min. After completion of the reaction, the solvent was evaporated under reduced pressure, water was added (10 mL) and the mass extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give crude alcohol which was added Boc anhydride [(BOC)2O] (0.5 mL, 2.3 mmoles) and the stirring continued for another 4 hr. After completion of the reaction, the solvent was evaporated under reduced pressure, water (15 mL) was added, and the mass extracted with ethyl acetate. The organic layer was concentrated under reduced pressure to give crude amine, which was purified over silica gel column using hexane-ethyl acetate mixture as eluent to give corresponding pure compound 9 (1.17 g, 2.69 mmoles) in 92% yield. IR (KBr): 2922, 1719, 1555, 1481, 1346, 1285, 1219, 1139 and 752 cm⁻¹; 1H NMR (CDCl3): δ 7.40 (2H, s), 3.70 (3H, s), 3.48 (2H, s), 1.06 (9H, s) and 0.35 (6H, s); LCMS: m/z 437, 439, 441 (1: 2: 1 ratio) (M++H), 379, 381, 383 (1: 2:1 ratio due to M++H - tBu), 319, 321, 323, 299, 267, 243, 207, and 73.

2-[3,5-Dibromo-4-(tert-butyl-dimethyl-silyloxy)-phenyl acetic acid methyl ester, 9: To a solution of compound 8 (947 mg, 2.92 mmoles) in dry dichloromethane (DCM, 50 mL) was added imidazole (399.9 mg, 5.88 mmoles) and the mixture stirred for 3 hr. After completion of the reaction, the solvent was evaporated under reduced pressure, water (15 mL) was added, and the mass extracted with ethyl acetate. The organic layer was concentrated under reduced pressure to give mesylated product, which was chromatographed over silica-gel column to give pure mesylated product (894 mg, 1.8 mmoles) in 82% yield. To a solution of mesylated compound (894 mg, 1.8 mmoles) in dry DMF (25 mL) was added sodium azide (NaN₃) (119 mg, 1.8 mmoles) and the mass refluxed under nitrogen. After 4 hr, the reaction mass was cooled to RT and water was added (15 mL). The mixture was extracted with ethylacetate. The organic layer was concentrated to give crude azide 11, which was purified over silica gel column to afford pure compound 11 (685 mg, 1.57 mmoles) in 86% yield. IR (KBr): 3492, 2932, 2861, 2102, 1729, 1553, 1475, 1361, 1252, 1163, 1067, 972, 825, 739 and 702 cm⁻¹; 1H NMR (CDCl3): δ 7.30 (2H, s), 3.49 (2H, t, J = 7.0 Hz), 2.78 (2H, t, J = 7.0 Hz), 0.10 (6H, s) and 0.92 (9H, s); LCMS: m/z 438 (M++H).
evaporated under reduced pressure, water was added. The organic layer was concentrated under reduced pressure to give crude phenolic compound 13, which upon silica gel column chromatography afforded pure compound 13 (62 mg, 0.15 mmoles) in 80% yield. m.p. 114.8-115.7°C; 1H NMR (CDCl3): δ 1.45 (9H, s), 2.70 (2H, t, J = 7.0 Hz), 3.30 (2H, quartet, J = 7.0, 6.2 Hz), 4.55 (1H, t, J = 6.2 Hz, NH), 5.95 (1H, brs, OH), and 7.24 (2H, s); FABMS: m/z 527, 525, 523 (M++1), 151.6, 137.5, 132.25 (2 carbons), 117.4 (2 carbons), 7.36 (2H, s), 4.00 (2H, t, J = 7.0, 6.2 Hz), 3.70 (3H, s, OMe), 3.50 (2H, t, J = 7.1, 6.2 Hz), 3.20 (2H, m), 2.98 (3H, s, N-Me), 2.80 (2H, m), and 2.06 (2H, m); LCMS: m/z 709 (M++), 216, 195, 154, 145, 130, 119, 109, 95, 81, 69 and 55.

Compound 14: To a mixture of compound 13 (68 mg, 0.17 mmoles) and compound 6 (56 mg, 0.26 mmoles) in dry acetone (20 mL), was added K2CO3 (35 mg, 0.26 mmoles) and refluxed for 12 hr. After completion of the reaction, acetone was evaporated under reduced pressure, water (10 mL) was added, and the mass extracted with ethyl acetate. The organic layer was concentrated under vacuum to give corresponding ether 14, which upon column chromatography over silica gel with hexane and ethyl acetate as eluent afforded pure compound 14 (77 mg, 0.15 mmoles) in 86% yield as a viscous liquid. IR (neat): 3346.3, 2976.3, 2880.9, 1694.2, 1545.2, 1457.0, 1394.0, 1366.0, 1253.7, 1217.2, 1167.5, 1038.4, and 772 cm−1; 1H NMR (CDCl3): δ 0.93 (3H, t, J = 7.2 Hz), 2.97 (3H, s, N-Me), 3.32 (2H, quartet, J = 7.2, 6.7 Hz), 3.52 (2H, dd, J = 7.1, 6.2 Hz), 3.70 (3H, s, OMe), 4.00 (2H, t, J = 6.4, 5.6 Hz), 4.60 (1H, br t, NH), 7.30 (2H, s); 13C NMR (CDCl3): δ 156.4, 154.8, 151.6, 137.5, 132.25 (2 carbons), 117.4 (2 carbons), 79.0, 70.08, 52.0, 46.0, 45.5, 41.0, 34.5, 29.0, and 28.0 (3 carbons); FABMS: m/z 527, 525, 523 (M’+1), 511, 469, 130, 116, 102, 71, and 57.

Compound 15: Compound 14 (100 mg, 0.19 mmoles) was taken in 10 mL of dichloromethane (DCM): trifluroacetic acid (TFA), (1:1) mixture at RT and stirred for 0.5 hr. The reaction was quenched with disopropylethylamine (2.5 mL), water added (10 mL), and the mass extracted with dichloromethane. The organic layer was concentrated under reduced pressure to get free amine 15, which was purified over silica-gel column using chloroform and methanol as eluent to afford pure amine 15 (76 mg, 0.18 mmoles) in 94% yield. IR (neat): 3418, 2924, 2362, 1683, 1457, 1397, 1218, and 772 cm−1; 1H NMR (CDCl3): δ 7.36 (2H, s), 4.00 (2H, t, J = 6.4, 5.6 Hz), 3.70 (3H, s, OMe), 3.50 (2H, t, J = 7.1, 6.2 Hz), 3.20 (2H, m), 2.98 (3H, s, N-Me), 2.80 (2H, m), and 2.06 (2H, m); FABMS: m/z 427, 425, 423 (1:2:1) (M’+), 216, 195, 154, 145, 130, 119, 109, 95, 81, 69 and 55.

Compound 18: To a solution of compound 17 (58 mg, 0.2 mmoles) in dry dimethyl formamide (DMF, 10 mL), N-hydroxybenzotriazole (HOBT) (56 mg, 0.4 mmoles) was added and the reaction mixture stirred for 15 min at RT. The reaction mixture was then cooled to 0°C, and 1-[3-(dimethylamino) propyl] 3-ethyl carbodiimide (EDCI) (80 mg, 0.4 mmoles) was added and the stirring continued for 30 min at 0°C. To this stirred mass was then added compound 15 (88 mg, 0.2 mmoles). The reaction mass was stirred at RT for 1 hr. After completion of the reaction, water was added (10 mL), and the mass extracted with diethyl ether. The organic layer was concentrated under reduced pressure to give crude product 18, which was then purified over silica gel column using hexane and ethyl acetate mixture as eluent to afford corresponding pure compound 18 (126 mg, 0.18 mmoles) in 89% yield. Colourless crystalline compound; m.p. 186-88°C; IR (KBr): 3352.1, 3013.8, 2949.7, 2877.8, 1676.3, 1615.4, 1454.3, 1396.0, 1217.0, 1036.8, 970.0, 903.6, and 764.6 cm−1; 1H NMR (methanol-d4): δ 7.37 (2H, s), 7.01 (2H, d, J = 8.018 Hz), 6.64 (2H, d, J = 8.82 Hz), 5.32 (1H, t, J = 3.0 Hz), 3.93 (2H, t, J = 6.41, 5.61 Hz), 3.77 (2H, d, J = 4.0 Hz), 3.63 (3H, s), 3.47 to 3.54 (4H, m), 3.39 (2H, dd, J = 6.41, 7.21 Hz), 2.91 (3H, s), 2.69 (2H, dd, J = 7.21, 6.41 Hz), 2.03 (2H, quintet), and 1.50 to 1.80 (6H, m); 13C NMR (methanol-d4): δ 165.0, 158.5, 156.4, 154.5, 152.2, 138.6, 133.90 (2 carbons), 131.0 (2 carbons), 128.0, 118.4 (2 carbons), 115.8 (2 carbons), 102.0, 72.0, 62.94, 52.5, 48.2, 41.8, 34.4, 30.3, 29.2, 26.02, and 20.0; LCMS: m/z 709 (M’+ Na), 708, 707, 685, 684, 683, 602, 601, 600, and 543.

Purpuramine K as THP ether, 19: A mixture of compound 18 (50 mg, 0.07 mmoles) and N-bromo succinimide (NBS, 13 mg, 0.07 mmoles) in dry tetrahydrofuran (THF, 20 mL) was stirred at RT for 0.5 hr. After completion of the reaction, the reaction mass was quenched with saturated sodium thiosulfate solution. The solvent was removed under reduced pressure, and the mass extracted with ethyl acetate. The organic layer was concentrated under vacuum to give corresponding crude monobromo compound, which was purified over silica gel column to get pure monobromo compound (50 mg, 0.06 mmoles) in 90% yield. To a cooled (0°C) solution of the above monobromo compound (20 mg, 0.02 mmoles) methyl
iodide (MeI, 0.02 mL, 0.10 mmoles) in dry acetone (15 mL), K₂CO₃ (21 mg, 0.15 mmoles) was added. The reaction mixture was refluxed for 12 hr. After completion of the reaction, the solvent was evaporated under reduced pressure and then water was added (10 mL). The mass was extracted with ethyl acetate. The organic layer was concentrated under vacuum to give crude compound 19, which was further purified over silica gel column to afford pure compound 19 (20.4 mg, 0.02 mmoles) in 96% yield. Colourless solid; m.p. 162.4-164.3°C; IR (KBr): 2948.7, 2853.2, 1679.5, 1512.1, 1457.2, 1396.0, 1254.5, 1216.1, 1037.7, 968.5, and 770.8 cm⁻¹; ¹H NMR (CDCl₃): δ 7.34 (2H, s), 7.28 (1H, d, J = 2.2 Hz), 6.96 (1H, br t, NH), 6.83 (1H, d, J = 8.3 Hz), 6.81 (1H, d, J = 2.2 Hz), 5.38 (1H, t, J = 3.02), 4.02 (2H, t, J = 6.04 Hz), 3.93 (1H, dd, J = 7.55, 2.26 Hz), 3.87 (1H, s), 3.78 (2H, s), 3.71 (3H, s), 3.4 to 3.70 (6H, m), 2.98 (3H, s), 2.75 (2H, ddd, J = 3.02, 7.55, 10.57 Hz), 2.10 (2H, m), and 1.73 to 1.82 (6H, m); FABMS: m/z 804, 802, 800, 798, (M⁺+ Na), 722, 614, 500, 393, 330, 294, 237, 128, and 74.

**Conclusion**

To conclude, the first total synthesis of purpuramine K with commercially available simple starting materials using lucid chemical transformations has been achieved. The ¹H and ¹³C NMR spectral data of the THP protected purpuramine K 19 are in full agreement with the corresponding signals obtained for purpuramine K. This constitutes the first reported total synthesis of purpuramine K, and provides a reliable and versatile method for the synthesis of related compounds, which may act as potent anti-bacterial agents. Further activity studies of purpuramine K, and synthesis of its analogues are under progress.

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**References**