

Research Article

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Discovery and metabolic origin of 4,4'-dihydroxy-3,3',5,5'-tetrachlorobenzophenone from a *Burkholderia oklahomensis* clinical isolate

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Abstract: *Burkholderia oklahomensis* LMG 23618^T is a *B. pseudomallei*-like bacterium originally isolated in 1973 from a wound infection caused by a farming accident in Oklahoma. Metabolic profiling of an organic extract from cultures of *B. oklahomensis* LMG 23618^T using UHPLC-ESI-Q-ToF-MS led to identification of three known metabolites, betulinan A, yersiniabactin and ulbactin B, in addition to a novel polychlorinated compound. Mass-directed purification enabled isolation of the novel specialized metabolite, which was shown by X-ray crystallography and NMR spectroscopic analysis to be 4,4'-dihydroxy-3,3',5,5'-tetrachlorobenzophenone. Feeding experiments with stable isotope-labelled precursors established that the carbon skeleton of this unusual metabolite derives from two molecules of tyrosine. This led us to propose a plausible biosynthetic pathway via decarboxylative condensation of 3, 5-dichloro-4-hydroxybenzoic acid with its coenzyme A thioester derivative. The absolute configuration of ulbactin B was also established as 4'R, 3"S, 7"S, 8"R using X-ray crystallography and NMR spectroscopy.

Keywords: aromatic compounds; biosynthesis; chemistry of natural products; natural products; X-ray diffraction.

Introduction

Specialized metabolites produced by microbes are a rich source of novel molecular scaffolds with potent biological activities. Many clinically approved medicines are, or have origins in microbial specialized metabolites.¹ Traditionally, drug discovery programs have focused on Actinomycetes, but advances in genome sequencing and bioinformatics have revealed that underexplored bacterial taxa also harbour great potential for the production of novel specialized metabolites.^{2–4}

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The genus *Burkholderia* sensu lato encompasses ecologically diverse Gram-negative bacteria that inhabit a wide range of terrestrial and aquatic environments. These bacteria can be free-living or exist in association with a variety of hosts, including humans, animals, plants, and fungi.^{5,6} Their interactions with host organisms range from harmful, such as opportunistic infections caused by members of the *Burkholderia cepacia* complex (Bcc) in cystic fibrosis patients,⁷ to beneficial, promoting plant growth^{8,9} or acting as biopesticides by protecting crops from pathogens.^{10,11}

Burkholderia species are prolific producers of specialised metabolites, and genomic data suggest they harbour a vast untapped potential to assemble novel compounds with potential applications in medicine and agriculture.^{4,11–13} In our ongoing search for novel natural products from human pathogenic *Burkholderia* species,^{13–17} we have identified the novel specialised metabolite 4, 4'-dihydroxy-3, 3', 5, 5'-tetrachlorobenzophenone (**1**) from *B. oklahomensis* LMG 23618^T,¹⁸ along with known metabolites betulinan A (**2**), yersiniabactin (**3**), and ulbactin B (**4**) (Fig. 1). Incorporation experiments with stable isotope-labelled precursors demonstrate that the carbon skeleton of **1** derives from two molecules of tyrosine, leading us to propose a plausible biosynthetic pathway to this unusual metabolite.

Results and discussion

The specialized metabolite profile of an ethyl acetate extract from *B. oklahomensis* LMG 23618^T, cultured on Basal Salts Medium (BSM) supplemented with glycerol as the carbon source was analysed by UHPLC-ESI-Q-ToF-MS. Metabolites with molecular formulae corresponding to three known metabolites (**2**, **3**, and **4**) were identified in the extract, alongside a novel natural product with the molecular formula $C_{13}H_6Cl_4O_3$ (calculated $m/z = 350.9144$ for $[M + H]^+$; measured $m/z = 350.9149$). The mass spectrum of the novel metabolite exhibited the expected isotope distribution for a tetrachlorinated compound with signals of the expected intensity at $m/z = 350.9149$, 352.9121, 354.9091, and 356.9066, corresponding to the $[M + H]^+$ ions for the $^{35}Cl_4$, $^{35}Cl_3^{37}Cl$, $^{35}Cl_2^{37}Cl_2$ and $^{35}Cl^{37}Cl_3$ isotopes (Fig. S1). Mass-directed purification enabled the isolation of the compound, which was analysed using 1H , ^{13}C , COSY, HSQC, and HMBC NMR experiments (Figs. S2–S6). The 1H NMR spectrum had a single resonance at δ_H 7.67 ppm. In the ^{13}C NMR spectrum, four quaternary carbon signals were observed at δ_C 122.1, 128.8, 153.6, and

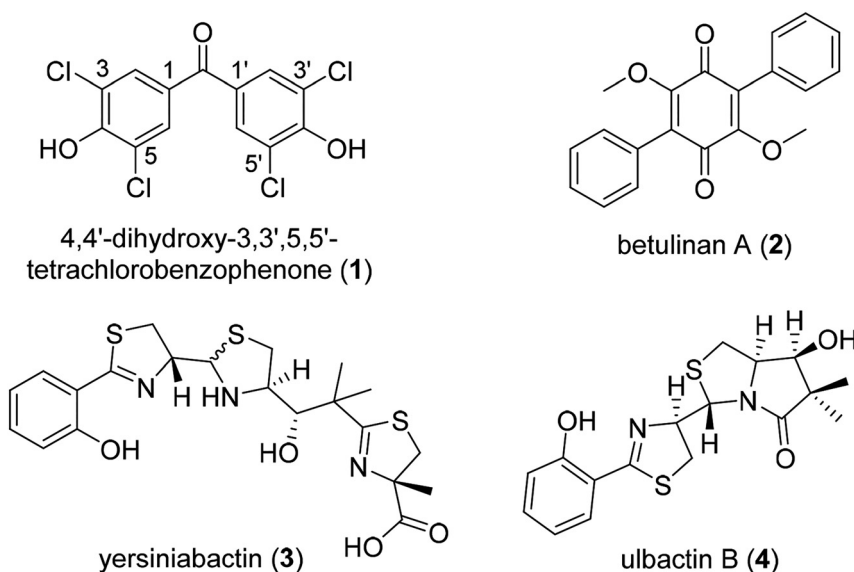


Fig. 1: Structures of 4,4'-dihydroxy-3,3',5,5'-tetrachlorobenzophenone (**1**), betulinan A (**2**), yersiniabactin (**3**), and ulbactin B (**4**) isolated from *B. oklahomensis* LMG 23618^T.

189.2 ppm, along with one sp^2 methine carbon at δ_C 130.1 ppm. The sole proton signal showed an HSQC correlation to the methine carbon and exhibited 2J and 3J HMBC correlations to the four quaternary carbons.

While the MS and NMR data were consistent with a symmetrical tetrachlorinated architecture, they did not allow unambiguous assignment of the structure. We therefore grew crystals for analysis by X-ray diffraction. Suitable single crystals were obtained by slow diffusion of hexane into an ethyl acetate solution of **1**. The resulting X-ray crystal structure showed that **1** is 4,4'-dihydroxy-3,3',5,5'-tetrachlorobenzophenone (Fig. 2). The symmetrical nature of this unusual tetrachlorinated metabolite explains the presence of only a single resonance in the 1H NMR spectrum and five distinct signals in the ^{13}C spectrum.

To elucidate the metabolic origin of **1**, feeding experiments were conducted using 1 mM uniformly ^{13}C -labelled tyrosine and acetic acid, each supplemented separately into the culture medium. *B. oklahomensis* LMG 23618^T was grown in BSM for three days, after which extracts were analysed by UHPLC-ESI-Q-ToF-MS. No incorporation of ^{13}C from acetic acid was detected. However, a high level of ^{13}C incorporation from tyrosine was observed for all carbons in **1** (Fig. 3a and b), confirming that its carbon skeleton derives from two molecules of tyrosine.

Given that L-tyrosine is known to be degraded to *p*-hydroxybenzoic acid (pHBA),^{19,20} we propose **1** is biosynthesised as follows (Fig. 4). Ammonia is eliminated from L-tyrosine by tyrosine ammonia lyase (TAL) yielding *p*-coumaric acid (pCA), which is subsequently converted to the corresponding coenzyme (CoA) thioester by feruloyl-CoA synthetase (Fcs). The activated intermediate undergoes hydration and retro-Aldol cleavage between the α and β carbons, catalysed by enoyl-CoA hydratase (Ech), resulting in *p*-hydroxybenzaldehyde (pHBAL) and acetyl-CoA. Oxidation of pHBAL by vanillin dehydrogenase (Vdh) yields pHBA, which is dichlorinated at both *meta* carbons by an FADH₂-dependent halogenase (FDH). One molecule of *m, m*-dichloro-*p*-hydroxybenzoic acid (*mmDpHBA*) is converted to the corresponding CoA thioester by an acyl-CoA synthetase (ACS), enabling it to acylate the *ipso* position of the phenol in a second molecule of *mmDpHBA*. Decarboxylation of the resulting intermediate restores aromaticity resulting in the formation of **1**. It is currently unclear what type of enzyme might catalyse the final acylation-decarboxylation sequence.

Yersiniabactin (**3**) and ulbactin B (**4**) are structurally related metabolites identified in the extract of *B. oklahomensis*. Yersiniabactin is a siderophore previously reported to be produced by several pathogenic bacteria, including *Yersinia pestis*, *Y. pseudotuberculosis*, *Y. enterocolitica*, *E. coli*, and *Salmonella enterica*.^{21–24} Like other siderophores, yersiniabactin plays a crucial role in bacterial pathogenicity by facilitating iron acquisition.²⁵ The structurally related siderophore pyochelin has been identified in other pathogenic *Burkholderia* species.²⁶ To our knowledge this is the first report of yersiniabactin production in *Burkholderia*.

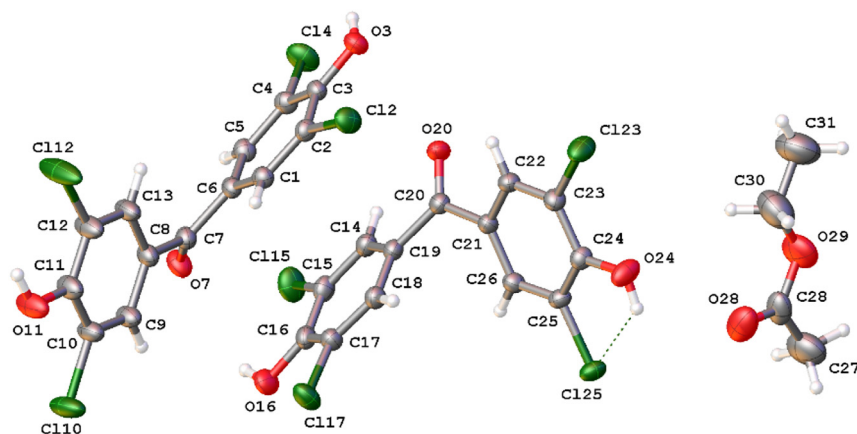


Fig. 2: Asymmetric unit of 4,4'-dihydroxy-3,3',5,5'-tetrachlorobenzophenone (**1**) crystals with atom labelling and thermal ellipsoids drawn at 50 % probability level. The molecule of ethyl acetate was refined at 50 % occupancy.

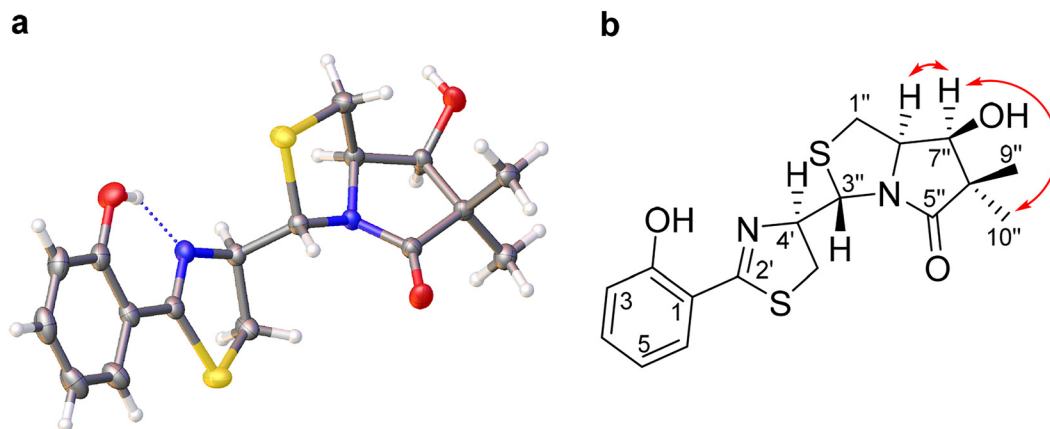


Fig. 5: (a) Solid-state molecular structure of ulbactin B (**4**) with absolute stereochemistry assigned as 4''R, 3''S, 7''S, 8''R based on single-crystal X-ray diffraction analysis. (b) Key NOESY correlations supporting the stereochemical assignment.

X-ray diffraction. This enabled its absolute configuration to be assigned as 4''R, 3''S, 7''S, 8''R. This stereochemistry is supported by NOESY correlations between H-10'' and H-7'', as well as between H-7'' and H-8'' (Fig. 5).

Conclusions

This study reports the discovery and metabolic origin of the novel polychlorinated metabolite 4,4'-dihydroxy-3,3',5,5'-tetrachlorobenzophenone from the clinical isolate *B. oklahomensis* LMG 23618^T, along with three known metabolites betulinan A, yersiniabactin, and ulbactin B. Stable isotope feeding experiments revealed that the carbon framework of this unusual benzophenone is derived from two molecules of tyrosine, leading us to propose a plausible biosynthetic pathway involving decarboxylative condensation of halogenated 4-hydroxybenzoic acid derivatives. The absolute stereochemistry of ulbactin B was also determined for the first time using X-ray crystallography.

B. oklahomensis is closely related to *B. pseudomallei*, the causative agent of melioidosis, which a recent outbreak in northern Australia has shown leads to mortality in 20 % of those infected. *B. oklahomensis* has been reported to be much less virulent than *B. pseudomallei*.²⁸ However, our finding that it produces yersiniabactin, a siderophore that has been shown to play an important role in the virulence of other bacteria, such as the plague pathogen *Y. pestis*,²⁹ warrants further investigation. Interestingly, *B. pseudomallei* does not rely on yersiniabactin for iron acquisition, instead employing pyochelin and malleobactin, which appear not to play a critical role in virulence.³⁰

Materials and methods

General Experimental Procedures: UHPLC-ESI-Q-ToF-MS analyses were performed using a Dionex UltiMate 3000 UHPLC system coupled to a Bruker MaXis IMPACT mass spectrometer via a Zorbax Eclipse Plus C18 column (100 × 2.1 mm, 1.8 μm). The mobile phases consist of water and acetonitrile, both containing 0.1 % formic acid. Chromatographic separation was achieved using a gradient elution from 5 % to 100 % acetonitrile over 30 min at a flow rate of 0.2 mL/min. The mass spectrometer was operated in positive ion mode with a scan range of *m/z* 50–3000. A 1 mM sodium formate solution was used for calibration, introduced via a 20 μL loop injection at the start of each run. NMR spectra were recorded on a Bruker 600 MHz spectrometer using DMSO-*d*₆ as the solvent. ¹H and ¹³C NMR chemical shifts were referenced to the DMSO-*d*₆ solvent signals at δ_H 2.50 and δ_C 39.51, respectively. Single crystal X-ray diffraction data were collected on either a Rigaku Xcalibur Gemini diffractometer equipped with a

Ruby CCD area detector or a Rigaku Oxford Diffraction SuperNova diffractometer with a dual source (Cu at zero) system and an AtlasS2 CCD area detector.

Production and Purification of Specialized Metabolites from *B. oklahomensis*: *B. oklahomensis* LMG 23618^T (strain BCC1605 in the Cardiff University Collection⁷) was cultured on 1 L of solid Basal Salts Medium (BSM) supplemented with glycerol as the carbon source³¹ for 3 days at 30 °C. After incubation, the agar was chopped into small blocks and extracted twice with EtOAc. The combined EtOAc extracts were dried using a rotary evaporator, then resuspended on 1 mL MeOH and pre-adsorbed onto C18-bonded silica. The dried mixture was packed into a stainless steel HPLC guard cartridge (10 × 30 mm) and connected to a semi-preparative reverse-phase C18 Betasil column (21.2 × 150 mm). Purification was carried out using initial isocratic elution with 5 % acetonitrile for 5 min, followed by a linear gradient from 5 % to 100 % acetonitrile over 45 min, and a final isocratic hold at 100 % acetonitrile for 10 min. The flow rate was maintained at 9 mL/min. Fractions were collected every minute for a total of 60 min. Ulbactin B was eluted in fraction 36, 4,4'-dihydroxy-3,3',5,5'-tetrachlorobenzophenone was obtained pure in fractions 46, and betulinan A was eluted in fraction 47. The structure of the known compounds were confirmed by comparing the molecular formulae obtained via HR-MS and ¹H NMR, and where necessary, 2D NMR, with published data.

4,4'-dihydroxy-3,3',5,5'-tetrachlorobenzophenone (**1**): (1.3 mg); ¹H NMR (600 MHz, DMSO-*d*₆): δ_H 7.67; ¹³C NMR (150 MHz, DMSO-*d*₆): δ_C 122.1 (C3, C5, C3', C5'), 128.8 (C1, C1'), 130.1 (C2, C6, C2', C6'), 153.6 (C4, C4'), 189.2 (C=O); HRESIMS *m/z* 350.9147 [M + H]⁺ (calcd for C₁₃H₆Cl₄O₃, 350.9144).

X-ray data collection and structure refinement: Single crystals of [C₁₃H₆Cl₄O₃]₂ [ethyl acetate]_{0.5} (**1**) and C₁₇H₂₀N₂O₃S₂ (**4**) were obtained by slow diffusion of hexane into ethyl acetate solutions of the respective compounds. A suitable crystal of compound **1** was selected, mounted on a Mitegen loop using Fromblin oil, and analysed using an Xcalibur Gemini diffractometer equipped with a Ruby CCD area detector. For ulbactin B (**4**), a suitable crystal was mounted on a glass fibre with Fromblin oil and placed on a Rigaku Oxford Diffraction SuperNova diffractometer with a dual source (Cu at zero) and an AtlasS2 CCD area detector.

Crystals were kept at 150(2) K during data collection. The structures were solved using Olex2,³² with the ShelXT³³ structure solution program via Direct Methods and refined using ShelXL³⁴ with Least Squares minimisation.

Crystal Data for [C₁₃H₆Cl₄O₃]₂[ethyl acetate]_{0.5} (*M* = 748.01 g/mol) (CCDC 1995977): monoclinic, space group P2₁/n (no. 14), *a* = 8.055 20(7) Å, *b* = 35.3030(3) Å, *c* = 11.551 29(7) Å, β = 92.0406(7)°, *V* = 3282.79(4) Å³, *Z* = 4, *T* = 150(2) K, μ(CuKα) = 6.650 mm⁻¹, *D*_{calc} = 1.513 g/cm³, 66 701 reflections measured (8.058° ≤ 2θ ≤ 156.496°), 7000 unique (*R*_{int} = 0.0496, *R*_{sigma} = 0.0200) which were used in all calculations. The final *R*₁ was 0.0447 (*I* > 2σ(*I*)) and *wR*₂ was 0.1495 (all data).

Crystal Data for C₁₇H₂₀N₂O₃S₂ (*M* = 364.47 g/mol) (CCDC 1995978): monoclinic, space group P2₁ (no. 4), *a* = 6.501 89(5) Å, *b* = 9.742 07(6) Å, *c* = 13.674 78(10) Å, β = 92.0045(7)°, *V* = 865.656(11) Å³, *Z* = 2, *T* = 150(2) K, μ(CuKα) = 2.943 mm⁻¹, *D*_{calc} = 1.398 g/cm³, 39 269 reflections measured (11.154° ≤ 2θ ≤ 147.16°), 3472 unique (*R*_{int} = 0.0724, *R*_{sigma} = 0.0240) which were used in all calculations. The final *R*₁ was 0.0261 (*I* > 2σ(*I*)) and *wR*₂ was 0.0697 (all data).

The molecule crystallised in the chiral space group P2(1) and the Flack parameter refined to −0.001(9) (Shelx 2018) and Hoofit parameter −0.015(5) (Olex2).^{35,36}

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Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

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Conflict of interest: G.L.C. is a co-founder, shareholder and consultant of Erebagen Ltd. All other authors state no conflict of interest.

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Data availability: All raw data are available from the corresponding authors upon written request.

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