molbank

MDPI

Communication

New Antimicrobial Accramycins from *Streptomyces* sp. MA37 Variant

Aziz Alabed [1], Kwaku Kyeremeh [2] and Hai Deng [1,*]

[1] Department of Chemistry, University of Aberdeen, Aberdeen AB24 3FX, UK; a.alabed.20@abdn.ac.uk
[2] Marine and Plant Research Laboratory of Ghana, Department of Chemistry, University of Ghana, Accra P.O. Box LG56, Ghana; kkyeremeh@ug.edu.gh
* Correspondence: h.deng@abdn.ac.uk

Abstract: In our continued desire to isolate more bioactive compounds from the *Streptomyces* sp. MA37 variant, ΔaccJ, three new accramycin derivatives have been successfully characterised. The structures of accramycin L-N (**1–3**) were established by high-resolution mass spectrometry and 1D and 2D nuclear magnetic resonance. The antimicrobial evaluation of accramycin L-N against *Staphylococcus aureus*, *Klebsiella pneumoniae*, and *Enterobacter cloacae* showed minimum inhibitory concentration (MIC) values ranging from 0.77 to 13.02 μg/mL. Accramycin L exhibited the most significant activity against *S. aureus*. In addition, accramycin L-N (**1–3**) displayed significant activity against *K. pneumoniae* at the MIC values of 0.81, 0.77, and 0.79 μg/mL, respectively.

Keywords: natural product; *Streptomyces* sp.; accramycin; polyketides; antimicrobial activity

1. Introduction

Naphthacemycins are aromatic polyketides derived from the type II polyketide biosynthetic pathways [1]. The backbone structure of this group of microbial natural products is composed of a partly reduced 1-phenyltetracene moiety (Figure 1) [2–15]. Due to their innate and potent antimicrobial activities, this group of polyketides has attracted the interest of medicinal chemists worldwide to study the structure–activity relationships of the different groups, especially the fasamycins [16–18].

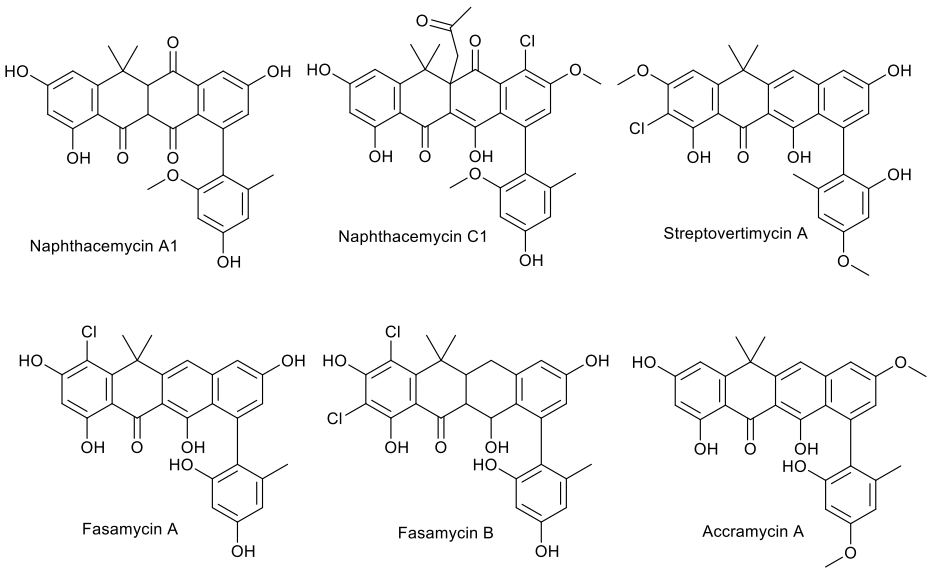

Figure 1. Structures of naphthacemycin derivatives.

check for updates

Citation: Alabed, A.; Kyeremeh, K.; Deng, H. New Antimicrobial Accramycins from *Streptomyces* sp. MA37 Variant. *Molbank* **2024**, *2024*, M1754. https://doi.org/10.3390/M1754

Received: 15 November 2023
Revised: 19 December 2023
Accepted: 19 December 2023
Published: 28 December 2023

The bacteria *Streptomyces* sp. MA37 is a talented natural product (NP) producer isolated from the rhizosphere soils of the Barkcloth tree belonging to the family Moraceae. The exact botanical name of this species is *Antiaris toxicaria* and it can be found growing at different spots in the University of Ghana Botanical Gardens. We have detailed in many previous publications that the strain MA37 produces a wealth of NPs, including fluorometabolites, bacterial alkaloids, and others [19,20]. Furthermore, the wild-type *Streptomyces* sp. MA37 also produces several type II PKS naphthacemycin derivatives which we have named the accramycins. Subsequently, we also discovered two accramycin A 1 derivatives, the structures of which contained chlorine atoms, in the extracts of the strain MA37 [21]. Due to the low yield of these chlorine containing accramycins, their exact molecular structures remained uncharacterized [21].

However, conservative genomics facilitated the identification of the biosynthetic gene cluster (*acc* BGC) of accramycin A 1 [22]. The deletion of one of the regulatory genes (*accJ*) within the *acc* BGC resulted in a variant, Δ*accJ*, which produced an array of accramycin derivatives, accramycins B-K and two known NPs, naphthacemycin B1 and fasamycin C, and two minor PKS compounds [22]. Accramycins showed high efficacy against multidrug-resistant Gram-positive pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecalis* (VRE) [22].

Herein, we report the isolation and structural elucidation of three previously uncharacterized chlorine containing accramycin derivatives, accramycins L-N (**1–3**), from the MA37 variant, Δ*accJ*. The compounds display potent antimicrobial activities against a panel of pathogens examined.

2. Results and Discussion

In our continuous efforts to further obtain bioactive accramycin-like metabolites, we subjected the Δ*accJ* mutant strain for culture fermentation in enriched media followed by extraction, and screening through chemical profiling by LC-MS. Manual dereplication using natural product databases (AntiBase [23] and Reaxys [24]) indicated the presence of accramycins-related molecular ion peaks which have not been reported previously. Hence, the crude extract was fractionated using vacuum liquid chromatography (VLC) to yield eight fractions (F1–F8). The extracts were then subjected to bioassay-guided purification, and F4 was identified to contain the accramycin metabolites. Further purification by reversed phase high-performance liquid chromatography (HPLC) afforded three new congeners, accramycins L (**1**), M (**2**), and N (**3**) (Figure 2).

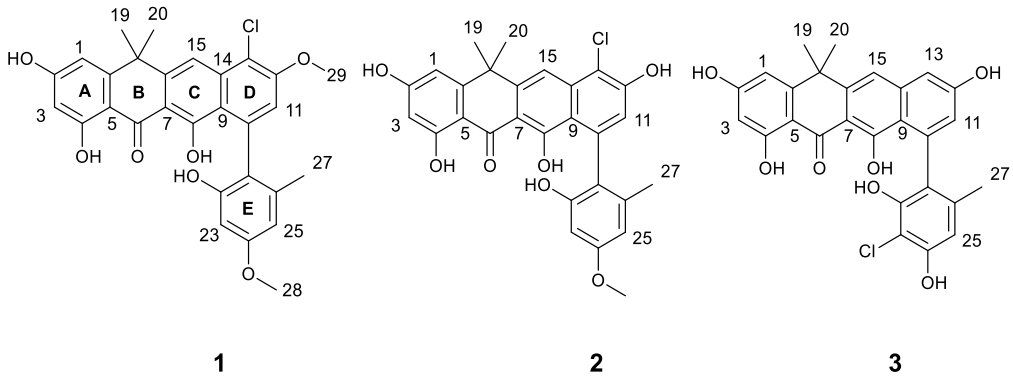

Figure 2. Structures of accramycins L-N (**1–3**).

Compound **1** (1.3 mg) was isolated as a yellowish compound. The molecular formula of $C_{29}H_{25}ClO_7$ with 17 degrees of unsaturation was confirmed by high-resolution ESI-MS that gave a protonated molecular ion at *m/z* 521.1354 (calculated for $C_{29}H_{26}ClO_7^+$, 521.1361 *m/z*, Δ = −1.45 ppm) and revealed a chlorinated isotopic pattern in the base peak chromatogram (Figure S1). The 1H, 13C, and HSQC data revealed the presence of 29 carbons, including 6 aromatic methine carbons, 3 methyl carbons, 2 methoxy carbons,

and 18 quaternary carbons (Table 1 and Figures S1–S7). The long-range correlations of HMBC spectrum revealed cross-peaks from H-1 (δ_H 6.69) to C-2 (δ_C 166.7), C-3 (δ_C 102.1), C-5 (δ_C 107.2), C-17 (δ_C 40.2), and C-18 (δ_C 155.7) and from H-3 (δ_H 6.22) to C-1 (δ_C 107.3), C-2 (δ_C 166.7), C-4 (δ_C 166.9), and C-5 (δ_C 107.2), suggesting 2, 4-dihydroxyl-substituted aromatic subunit in ring A. A dimethyl substituent assigned to C-19 and C-20 linked to C-16 and C-18 between ring A and C via C-17 was confirmed by the cross peaks from H_3-19 (δ_H 1.74) and H_3-20 (δ_H 1.76) to C-16 (δ_C 166.7), C-17, and C-18 (δ_C 155.7). In addition, a ketone moiety characterised by a downfield resonance at δ_C 191.6 was assigned to C-6 in ring B based on the HMBC correlations from H-1 and H-15 to the latter. C-8 was oxygenated due to the resonance signal at δ_C 160.5.

Table 1. Minimum inhibitory concentration (MIC) of compounds (**1–3**).

Compounds Name	MIC (μg/mL)		
	S. aureus **DSM 2569**	***K. pneumoniae*** **DSM 681**	***E. cloacae*** **DSM 30054**
Accramycin L (1)	0.81	0.81	13.02
Accramycin M (2)	6.16	0.77	11.54
Accramycin N (3)	12.68	0.79	12.68
Chloramphenicol	0.5	0.5	0.5

The HMBC cross-peaks from H-15 to C-7 (δ_C 110.2), C-9 (δ_C 116.3,), and C-13 (δ_C 119.5), from H-11 (δ_H 7.04) to C-9, C-10, and C-13, and from H3-29 (δ_H 4.0) to C-12 (δ_C 156.9) showed a complete connection of rings A-D indicating the presence of naphthacene moiety. The chlorine atom was assigned to C-13 (δ_C 119.5) as a result of a downfield shift in the sp [2] hydrogen-bearing carbon. The structure of **1** was elucidated by establishing the positions of the remaining protons signals on ring E, and its connection to ring D. This was revealed through a long-range HMBC cross peaks from H3-27 (δ_H 3.92) to C-21 (δ_C 125.1), C25 (δ_C 107.3, CH), and C-26 (δ_C 138.2); from H3-28 (δ_H 3.80) to C-24 (δ_C 160.7); and from H-23 (δ_H 6.34) to C-21, C-22, C-24, C-25, and H-25 (δ_H 6.39) to C-24. And it was further corroborated by NOESY correlations from H3-28 to H-25 (δ_H 6.39) and H3-27, from H3-27 to H-11 and H3-29, and from H3-29 to H-11 (δ_H 7.04), respectively (Figures S7 and S20), confirming **1** as a new accramycin L. Compound **1** was highly comparable to the aromatic polyketide, naphthacemycin B4 [5], but differed with the presence of an additional methoxy moiety, and the assignment of the methoxy groups at C-28 (δ_C 55.6) and C-29 (δ_C 57.0) (see Tables S2 and S3).

Compound **2** (1.2 mg) was determined by HRESI-MS to have a molecular formula of $C_{28}H_{24}ClO_7^+$ (observed mass at *m/z* 507.1205, calcd $[M + H]^+$ = 507.1205, Δ = 0.1 ppm), with 17 degrees of unsaturation and revealed a similar chlorine isotopic pattern as **1**. The analysis of 1D and 2D NMR spectra showed compound **2** to be similar to **1** except for the absence of one methoxy group signal in C-29 supported by HRESI-MS spectrum indicating a 14 Da mass difference between compound **2** and **1**. In addition, the de-methylation at C-29 of **2** was unequivocally established by Heteronuclear Single Quantum Correlation (HSQC) showing no proton-carbon correlation at δ_H 3.80 and δc 55.6 exhibited in **1**. Hence, the structure of **2**, trivially named accramycin M, was confirmed.

The molecular formula of $C_{27}H_{22}ClO_7$ for compound **3** was determined by the HRESI-MS at *m/z* 493.1052 (calculated for $C_{27}H_{22}ClO_7^+$, 493.1048) with 17 degrees of unsaturation and revealed a chlorinated isotopic pattern like **1** (Figure S14). But analysis of ^1H and ^{13}C NMR data (see Table 1 and Figures S15–S19) showed the replacement of the two methoxy group substituents (C-28 and C-29) observed in **1** by hydroxyl groups assigned to position C-12 (δ_C 153.0) and C-24 (δ_C 155.4) with upfield chemical shift relative to **1**, respectively.

The chlorine atom in **3** was assigned to C-23 (δ_C 113.5) instead of C-13 (δ_C 119.5) in **1** and **2** because meta-coupling was observed in ring D of **3** between aromatic protons H-11

and H-13, and a presence of a proton singlet H-25 (δ_H 6.41) which suggested a displacement of the chlorine atom position (Figure S20). This was further supported by the HMBC correlation from H-13 to C-15 (δ_C 112.2) and C-9 (δ_C 116.3), from H-11 to C-9 and C-13, and from H-25 to C-23, respectively (Figure S20). All the information obtained therefore pointed to accramycin N **3** as a new accramycin congener previously detected in extracts at low concentrations and recently isolated from the strain MA37 [19,20]. Compound **3** was highly comparable to the aromatic polyketide, naphthacemycin B3 [5], but differed with the absence of a methoxy signal at C-22 (see Table S4).

Bioactivities of Fractions and Compound **1–3**

Following bioassay-guided purification of the fractions from strain MA37, the preliminary evaluation of fractions (F4–F7) against 3 pathogenic microorganisms (*Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*) was performed. The acetone fraction (F4) and acetone/methanol fractions (F5) displayed moderate zones of inhibition against *Staphylococcus aureus*, but no activity was recorded against the two Gram-negative bacteria, *Escherichia coli*, and *Pseudomonas aeruginosa* at the highest concentration (50 µg/mL) tested (Table S1). The inactivity observed against the two Gram-negative bacteria was consistent with the bioactivity reported on other previously isolated accrymacin-type compounds from the strain MA37 [21,22].

As a result of the preliminary zones of inhibitions observed, we further expanded our testing by evaluating the antimicrobial potential of the pure compounds **1–3**, isolated from the acetone fraction against a panel of clinically isolated pathogenic bacteria, including one Gram-positive bacterium, *S. aureus* DSM 2569, and two Gram-negative bacteria, *K. pneumoniae* DSM 681 and *E. cloacae* DSM 30,054 (Table 1). Compound **1** showed the most significant antimicrobial activity against *S. aureus* DSM 2569 with the MIC at 0.81 µg/mL. This bioactivity was comparable to the positive control chloramphenicol with the MICs at 0.5 µg/mL (Table 1), and also consistent with the previous findings that depicted naphthacene-derived compounds, including fasamycins, nephthacemycins, formicamycins, and accramycins, to possess considerable antimicrobial bioactivity [2–15]. The presence of methoxy groups in C-28 and C-29 of **1** was likely responsible for the significant activity displayed in **1** which exhibited 6-fold and 12-fold inhibitions over **2** and **3**, respectively. In turn, **2** showed considerable mild activity against *S. aureus* DSM 2569 with 2-fold inhibition over **3** due to the presence of one O-methyl group in C-28. The presence of an electronegative chlorine atom or its positional change in structure **3** did not assert any form of bioactivity, as was the case with previously reported accramycins [21]. In addition, all three compounds (**1–3**) showed remarkable activity (MIC = 0.77–0.81 µg/mL) against *K. pneumoniae* DSM 681 but exhibited weak activities against the growth of *E. cloacae* DSM 30,054 (Table 1). To the best of our knowledge, this is the first recorded activity of the naphthacemycine-typed compounds to have exhibited considerable activity against the aforementioned Gram-negative bacteria. However, further studies at the molecular level will be required to elucidate the structure–activity relationship of compound **1–3** with respect to the observed bioactivity against *K. pneumoniae* DSM 681.

3. Materials and Methods

3.1. General Experimental Procedures

Mass spectra were measured in the positive ion mode electrospray ionisation using an MS system (Bruker MAXIS II equipped with a quadrupole time-of-flight mass analyser) coupled to an HPLC (Agilent 1290 Infinity equipped with a diode array detector) equipped with a Phenomenex analytical C18 column (2.5 µm, 100 Å, 4.6 × 150 mm), and eluted with a starting mobile phase of 5% ACE: 95% H_2O (containing 0.1% formic acid) followed by a gradient of up to 100% ACN: 0% H_2O that including 0.1% formic acid) for 15 min at a flow rate of 1 mL/min. The raw data files were analysed using compact Data Analyst (Bruker software, version 5.1) to provide accurate and high-resolution mass-per-charge molecular ions. The NMR spectra were recorded on a Bruker AVANCE III HD 400 MHz (Ascend® 9.4

Tesla). Trimethylsilane (TMS) was used as an internal standard. Deuterated solvents were obtained from Goss Scientific (Crewe, UK).

3.2. Bacterial Cultivation

The producing strain, *Streptomyces* sp. MA37 was isolated from the soil sample that was collected from Legon, Ghana. The deletion of the accJ gene, which encodes for multiple antibiotic resistance regulator (MarR) in accramycin biosynthesis, was described previously [22].

Fermentation, Extraction, Metabolite Screening: Seed cultures of the ΔaccJ mutant strain were prepared by inoculating 0.05 mL of the glycerol stocks in 100 mL YEME (yeast extract 3 g, tryptone 5 g, malt extract 3 g, glucose 10 g, sucrose 103 g, in 1 L H_2O), and incubating for three days in a closed shaker system at 28 °C and 180 rpm. The 3-day seed culture (100 mL) was then used to inoculate sixteen 1000 mL Erlenmeyer flasks containing 250 mL of ISP2 media (glucose 4 g, yeast extract 4 g, malt extract 10 g, agar 20 g, in 1 L H_2O) and incubated for ten days at the same temperature and shaking conditions (at 28 °C, 180 rpm).

3.3. Extraction and Isolation of Metabolites

After the incubation, Diaion® HP-20 (3 g/50 mL) was added to each culture flask under sterile conditions and shaken for 12 h. Subsequently, the HP-20 resin was filtered and extracted with 100% methanol (5 × 400 mL) followed by dichloromethane (DCM) (2 × 400 mL). The combined organic extracts were dried under reduced pressure to yield 4000 mg of crude extract.

The combined extract was fractionated using vacuum liquid chromatography on normal phase Silica gel using a stepwise gradient of increasing polarity: 100% hexane, 1:1 hexane/DCM, 100% DCM, 100% acetone, 1:1ACE/MeOH, 100% MeOH, and 100% MeOH/0.05% TFA to obtain a total of eight fractions. The fractions were then concentrated using a rotary evaporator and nitrogen drier. The eight VLC fractions were weighed and yielded F1 (20 mg), F2 (25 mg), F3 (35 mg), F4 (750 mg), F5 (1000 mg), F6 (600 mg), and F7 (1200 mg). It was not possible to work on the first three fractions because of the low yields for these samples.

The fractions (F4–F7) were then subjected to HPLC-UV and mass spectrometric dereplication and disc diffusion assays to target isolation of accramycin-like compounds. Out of the eight fractions, only F4 showed bioactivity and the characteristic accramycin UV chromophores (226, 250, 286, 355, and 420 nm) [21,22]. Hence, fraction F4 was further subjected to purification on semi-preparative RP-HPLC (Sunfire column C18, 5 µm, 10 × 250 mm) using a linear gradient of H_2O/MeOH 100–0% over 45 min to 100% MeOH at a flow rate of 2.5 mL/min, yielding three new accramycin congeners, **1** (3.1 mg, t_R 42.3 min), **2** (1.3 mg, t_R 38.2 min) and **3** (1.3 mg, t_R 33.3 min).

Accramycin L (**1**): Yield 3.1 mg; yellowish powder; IR: 614, 1023, 1114, 1446, 2049, 1348, 2532, 2832, 2946, 3312; UV (MeOH) λmax: 225, 250, 290, 360, 420 nm; 1H, 13C NMR data (see Table S1 and Figures S1–S7); HRESIMS (*m/z*): 521.1357 $[M + H]^+$, calcd for $C_{29}H_{26}ClO_7$, 521.1361, Δ = −0.8 ppm.

Accramycin M (**2**): Yield 1.3 mg; yellowish powder; IR: 651, 1022, 1123, 1450, 2829, 2944, 3327; UV (MeOH) λmax: 250, 280, 300, 355, 430 nm; 1H, 13C NMR data (see Table 1 and Figures S8–S13); HRESIMS (*m/z*): 493.1052 $[M + H]^+$, calcd for $C_{27}H_{22}ClO_7$, 493.1048, Δ = 0.7 ppm.

Accramycin N (**3**): Yield 1.3 mg; yellowish powder; IR: 582, 1011, 1114, 1410, 2044, 2353, 2516, 2824, 2927, 3267; UV (MeOH) λmax: 250, 290, 300, 355, 420 nm; 1H, 13C NMR data (see Table 1 and Figures S14–S19); HRESIMS (*m/z*): 493.1052 $[M + H]^+$, calcd for $C_{27}H_{22}ClO_7$, 493.1048, Δ = 0.7 ppm.

3.4. Bioassay Screening of Fractions F4–F7

Bioassay screening of the fractions (F4–F7) was performed by Kirby–Bauer (K-B) disk antimicrobial susceptibility test following the prescribed guidelines of the Clinical & Laboratory Standards Institute [25]. The test pathogens consisted of *Escherichia coli* (ATCC 25922), *Staphylococcus aureus* (ATCC 25923), and *Pseudomonas aeruginosa* (ATCC 27853). The turbidity and density of which were standardized to 0.5 McFarland. The standardized bacterial suspension was then streaked uniformly onto the surface of the Mueller–Hilton agar using a sterile swab. Subsequently, sterile paper discs (6 mm) containing the test extracts (2 mg/mL DMSO) were placed on the agar surface. The positive and negative controls consisted of chloramphenicol (30 μg/mL) and DMSO, respectively. The plates were then incubated at 37 °C for 24 h, and the zones of inhibition were measured.

3.5. Minimum Inhibitory Concentrations

Minimum inhibitory concentrations (MIC) of compounds, **1–3**, were determined against a range of Gram-positive bacteria, *Staphylococcus aureus* (DSM 2569) and *Enterococcus faecalis* (DSM 17050), and Gram-negative bacteria, *Enterobacter cloacae* (DSM 30054), *Pseudomonas aeruginosa* (DSM 1117), *Acinetobacter baumannii* (DSM 30008), and *Klebsiella pneumonia* (DSM 681). The pathogenic strains were provided by the DSMZ-GERMAN collection of microorganisms and cells.

4. Conclusions

As part of our continuous research into the chemistry of the mutant strain of MA37 isolated from Accra, Ghana, we confirmed this streptomyces species to be remarkable in the production of the novel secondary metabolites accramycins A-K. Herein, we have detailed the further discovery of three new analogues, accramycins L-N (**1–3**) from the acetone fractions of the strain. The structures of compounds **1–3** were elucidated by HRESIMS, 1D, and 2D NMR spectroscopy and also in comparison to similar data obtained previously for the accramycins A-K. The preliminary evaluation of fraction (F4–F7) against three pathogenic microorganisms, *E. coli*, *S. aureus*, and *P. aeruginosa*, led to acetone fraction (F4) and acetone/methanol fractions (F5) displaying a moderate zone of inhibition against *Staphylococcus aureus* (Table S1). Further screening showed accramycin L (**1**) significantly inhibited the clinically isolated *S. aureus* DSM 2569. Meanwhile, all the compounds (**1–3**) were potent against *K. pneumoniae* DSM 681. This discovery is an important step in sourcing a new antimicrobial natural product for drug development. However, the selective inhibition of the Gram-negative *K. pneumoniae* as against the Gram-negative *E. cloacae* by the compounds **1–3** remains to be explained.

Supplementary Materials: The following supporting information can be downloaded online. Figures S1 and S2: HRESIMS and 1H-NMR spectra of Accramycin L 1 (CD3OD, 400 MHz); Figures S3 and S4: 13C NMR and 1H-1H COSY NMR spectra of Accramycin L 1 (CD3OD, 400 MHz); Figures S5 and S6: HSQC NMR and HMBC NMR spectra of Accramycin L 1 (CD3OD, 400 MHz); Figure S7: 1H-1H-NOESY spectra of Accramycin L 1 (CD3OD, 400 MHz); Figures S8 and S9: HRESIMS and 1H-NMR spectra of Accramycin M 2 (CD3OD, 400 MHz); Figures S10 and S11: 1H-1H COSY NMR and HSQC NMR spectra of Accramycin M 2 (CD3OD, 400 MHz); Figures S12 and S13: HMBC NMR spectra and 1H-1H-NOESY spectra of Accramycin M 2 (CD3OD, 400 MHz); Figures S14 and S15: HRESIMS and 1H-NMR spectra of Accramycin N 3 (CD3OD, 400 MHz); Figures S16 and S17: 1H-1H COSY and HSQC NMR spectra of Accramycin N 3 (CD3OD, 400 MHz); Figures S18 and S19: HMBC and 1H-1H-NOESY spectra of Accramycin N 3 (CD3OD, 400 MHz); Figure S20: HMBC and NOESY correlations observed in Accramycins L-N (1-3); Table S1: Minimum inhibitory concentration (MIC) of compounds (μg/mL) of Accramycin L-M 1-3; Table S2: 1H and 13C NMR data of Accramycin L-M (1-3) (400 MHz, CD3OD); Table S3: 1H and 13C NMR data of Accramycin L and naphthamycin B4; Table S4: 1H and 13C NMR data of Accramycin N and naphthamycin B4.

Author Contributions: Conceptualization, H.D. and K.K.; methodology: H.D.; investigation: A.A.; resources, A.A., K.K. and H.D.; writing—original draft preparation A.A.; writing—review and editing, K.K. and H.D. funding acquisition, H.D. and K.K. All authors have read and agreed to the published version of the manuscript.

Funding: H.D. and K.K. thank the financial supports of Leverhulme Trust–Royal Society Africa award (AA090088) and the jointly funded UK Medical Research Council (MRC) and the UK Foreign, Commonwealth & Development Office (FCDO) under the MRC/FCDO Concordat agreement (MR/S00520X/1).

Data Availability Statement: Data are contained within the article and Supplementary Materials.

Acknowledgments: H.D. and A.A. thank Federica Casolari for the critical comments and suggestions during the manuscript preparation.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Maglangit, F.; Deng, H. Cell Factory for Phenylnaphthacenoid Polyketide Production. *SynBio* **2023**, *1*, 89–102. [CrossRef]
2. Feng, Z.; Kallifidas, D.; Brady, S.F. Functional Analysis of Environmental DNA-Derived Type II Polyketide Synthases Reveals Structurally Diverse Secondary Metabolites. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 12629–12634. [CrossRef] [PubMed]
3. Feng, Z.; Chakraborty, D.; Dewell, S.B.; Reddy, B.V.B.; Brady, S.F. Environmental DNA-Encoded Antibiotics Fasamycins A and B Inhibit FabF in Type II Fatty Acid Biosynthesis. *J. Am. Chem. Soc.* **2012**, *134*, 2981–2987. [CrossRef] [PubMed]
4. Fukumoto, A.; Kim, Y.-P.; Iwatsuki, M.; Hirose, T.; Sunazuka, T.; Hanaki, H.; Ōmura, S.; Shiomi, K. Naphthacemycins, Novel Circumventors of β-Lactam Resistance in MRSA, Produced by *Streptomyces* sp. KB-3346-5. II. Structure Elucidation. *J. Antibiot.* **2017**, *70*, 568–573. [CrossRef]
5. Fukumoto, A.; Kim, Y.-P.; Matsumoto, A.; Takahashi, Y.; Suzuki, M.; Onodera, H.; Tomoda, H.; Matsui, H.; Hanaki, H.; Iwatsuki, M.; et al. Naphthacemycins, Novel Circumventors of β-Lactam Resistance in MRSA, Produced by *Streptomyces* sp. KB-3346-5. I. The Taxonomy of the Producing Strain, and the Fermentation, Isolation and Antibacterial Activities. *J. Antibiot.* **2017**, *70*, 562–567. [CrossRef]
6. Qin, Z.; Munnoch, J.T.; Devine, R.; Holmes, N.A.; Seipke, R.F.; Wilkinson, K.A.; Wilkinson, B.; Hutchings, M.I. Formicamycins, Antibacterial Polyketides Produced by Streptomyces Formicae Isolated from African Tetraponera Plant-Ants. *Chem. Sci.* **2017**, *8*, 3218–3227. [CrossRef]
7. Qin, Z.; Devine, R.; Hutchings, M.I.; Wilkinson, B. A Role for Antibiotic Biosynthesis Monooxygenase Domain Proteins in Fidelity Control during Aromatic Polyketide Biosynthesis. *Nat. Commun.* **2019**, *10*, 3611. [CrossRef]
8. Shen, W.; Lu, X.; Zhu, J.; Mu, Y.; Xu, Y.; Gao, J.; Zhang, X.; Zheng, Z. Discovery of Naphthacemycins as a Novel Class of PARP1 Inhibitors. *Bioorg. Med. Chem. Lett.* **2019**, *29*, 1904–1908. [CrossRef]
9. Yuan, J.; Wang, L.; Ren, J.; Huang, J.-P.; Yu, M.; Tang, J.; Yan, Y.; Yang, J.; Huang, S.-X. Antibacterial Pentacyclic Polyketides from a Soil-Derived *Streptomyces*. *J. Nat. Prod.* **2020**, *83*, 1919–1924. [CrossRef]
10. Huo, C.; Zheng, Z.; Xu, Y.; Ding, Y.; Zheng, H.; Mu, Y.; Niu, Y.; Gao, J.; Lu, X. Naphthacemycins from a *Streptomyces* sp. as Protein-Tyrosine Phosphatase Inhibitors. *J. Nat. Prod.* **2020**, *83*, 1394–1399. [CrossRef]
11. Yang, L.; Li, X.; Wu, P.; Xue, J.; Xu, L.; Li, H.; Wei, X. Streptovertimycins A–H, New Fasamycin-Type Antibiotics Produced by a Soil-Derived Streptomyces Morookaense Strain. *J. Antibiot.* **2020**, *73*, 283–289. [CrossRef] [PubMed]
12. Gao, Y.-H.; Nie, Q.-Y.; Hu, Y.; Lu, X.; Xiang, W.; Wang, X.; Tang, G.-L. Discovery of Glycosylated Naphthacemycins and Elucidation of the Glycosylation. *Biochem. Biophys. Res. Commun.* **2022**, *622*, 122–128. [CrossRef] [PubMed]
13. Devine, R.; McDonald, H.P.; Qin, Z.; Arnold, C.J.; Noble, K.; Chandra, G.; Wilkinson, B.; Hutchings, M.I. Re-Wiring the Regulation of the Formicamycin Biosynthetic Gene Cluster to Enable the Development of Promising Antibacterial Compounds. *Cell Chem. Biol.* **2021**, *28*, 515–523.e5. [CrossRef] [PubMed]
14. McDonald, H.P.; Alford, A.; Devine, R.; Hems, E.S.; Nepogodiev, S.A.; Arnold, C.J.; Rejzek, M.; Stanley-Smith, A.; Holmes, N.A.; Hutchings, M.I.; et al. Heterologous Expression of the Formicamycin Biosynthetic Gene Cluster Unveils Glycosylated Fasamycin Congeners. *J. Nat. Prod.* **2023**, *86*, 1677–1689. [CrossRef] [PubMed]
15. Li, X.; Wu, P.; Wang, W.; Xue, J.; Li, H.; Tan, H.; Wei, X. Anti-MRSA Dimeric and Brominated Phenyltetracenoids Produced by *Streptomyces Morookaense* SC1169. *J. Nat. Prod.* **2023**, *86*, 2571–2579. [CrossRef] [PubMed]
16. Li, J.; Renata, H. Concise chemoenzymatic synthesis of fasamycin A. *J. Org. Chem.* **2021**, *86*, 11206–11211. [CrossRef]
17. Jiang, D.; Xin, K.; Yang, B.; Chen, Y.; He, H.; Gao, S. Total synthesis of three families of natural antibiotics: Anthrabenzoxocinones, fasamycins/naphthacemycins, and benastatins. *CCS Chem.* **2020**, *2*, 800–812. [CrossRef]
18. Huang, J.K.; Yang Lauderdale, T.L.; Lin, C.C.; Shia, K.S. Total Synthesis of Tetarimycin A, (±)-Naphthacemycin A9, and (±)-Fasamycin A: Structure-Activity Relationship Studies against Drug-Resistant Bacteria. *J. Org. Chem.* **2018**, *83*, 6508–6523. [CrossRef]

19. Ma, L.; Bartholome, A.; Tong, M.H.; Qin, Z.; Yu, Y.; Shepherd, T.; Kyeremeh, K.; Deng, H.; O'Hagan, D. Identification of a Fluorometabolite from *Streptomyces* sp. MA37: (2R3S4S)-5-Fluoro-2,3,4-Trihydroxypentanoic Acid. *Chem. Sci.* **2015**, *6*, 1414–1419. [CrossRef]
20. Huang, S.; Tabudravu, J.; Elsayed, S.S.; Travert, J.; Peace, D.; Tong, M.H.; Kyeremeh, K.; Kelly, S.M.; Trembleau, L.; Ebel, R.; et al. Discovery of a Single Monooxygenase That Catalyzes Carbamate Formation and Ring Contraction in the Biosynthesis of the Legonmycins. *Angew. Chem. Int. Ed.* **2015**, *54*, 12697–12701. [CrossRef]
21. Maglangit, F.; Fang, Q.; Soldatou, S.; Ebel, R.; Kyeremeh, K.; Deng, H. Accramycin A, a New Aromatic Polyketide, from the Soil Bacterium, *Streptomyces* sp. MA37. *Molecules* **2019**, *24*, 3384. [CrossRef] [PubMed]
22. Maglangit, F.; Zhang, Y.; Kyeremeh, K.; Deng, H. Discovery of New Antibacterial Accramycins from a Genetic Variant of the Soil Bacterium, *Streptomyces* sp. MA37. *Biomolecules* **2020**, *10*, 1464. [CrossRef] [PubMed]
23. Laatsch, H. AntiBase: The Natural Compound Identifier. Available online: https://sciencesolutions.wiley.com/solutions/technique/screening/wiley-identifier-of-natural-products/ (accessed on 4 November 2023).
24. Reaxys. Available online: https://www.reaxys.com/#/search/quick (accessed on 10 January 2021).
25. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing*, 30th ed.; Clinical and Laboratory Standards Institute (CLSI): Wayne, PA, USA, 2020.