ORIGINAL ARTICLE

Total synthesis of (\pm) -naphthacemycin A₉, possessing both antibacterial activity against methicillin-resistant *Staphylococcus aureus* and circumventing effect of β -lactam resistance

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The total synthesis of KB-3346-5A₉, named naphthacemycin A₉, has been accomplished by combining the Dötz reaction and Suzuki–Miyaura cross coupling as well as employing Friedel–Crafts reaction with dienone-phenol rearrangement as key steps. We also describe the preparation of the simplified tetarimycin A and naphthacemycin A analogs as a model study, which coincidentally reveal unique properties of naturally occurring naphthacene-5,6,11(12*H*)-trione framework. The synthesized compounds were evaluated for antibacterial activity against methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus* (VRE) to elucidate their structure-activity relationships (SARs), the results of which agreed with a previously reported preliminary SAR study of tetarimycin A.

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INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a typical drug-resistance organism and is a major cause of nosocomial infection.^{1,2} Currently, five anti-MRSA drugs are available: vancomycin;³ teicoplanin;⁴ arbekacin;⁵ linezolid;⁶ and daptomycin.⁷ However, owing to problems such as side effects and the emergence of highly drug-resistance strains, the development of new anti-MRSA drugs is a high priority.

Research in the field of infection control sciences at the Kitasato Institute is yielding success in the search for novel microbial secondary metabolites that exhibit selective anti-pathogenic activities and compounds that our group has designated 'anti-infective agents'. On the basis of our anti-infective agents concept, originally proposed by S. Ōmura,⁸ a screening system was established to identify microbial circumventors of imipenem resistance in MRSA, resulting in the isolation and structure determination of various natural products, including stemphones,9 cyslabdan^{10,11} and xanthoradones.^{12,13} More recently, through continuous screening for new microbial circumventors of β-lactam resistance in MRSA in our laboratory, a culture broth of Streptomyces sp. KB-3346-5 exhibited very potent activity. Activity-guided purification led to the discovery of 11 new compounds, KB-3346-5A1 to KB-3346-5A11, namely designated naphthacemycin A1 to A11 (1-11).14,15 These compounds have a characteristic skeleton composed of 7-phenylnaphthacene-5,6,11 (12H)-trione (Figure 1). The naphthacene framework of these novel

metabolites is related to tetarimycin A,16 whereas the naphthacene framework is related to fasamycins.^{17,18} Brady and co-workers also identified both tetarimycin A and fasamycins as antibiotics.¹⁶⁻¹⁸ The anti-MRSA activity of fasamycins was found to involve inhibition of FabF, an enzyme involved in type II fatty acid (FASII) biosynthesis, based on the results of FASII elongation assays and in silico docking studies using the crystal structure of Escherichia coli FabF.17,18 The antibacterial activity mechanisms of naphthacemycins A and tetarimycin A are thought to be the same as that of the fasamycins due to their related structures, but to date no studies have confirmed this hypothesis. Indeed, (-)-naphthacemycin A8 (8) and A9 (9) in particular exhibit both circumventing effect of β-lactam resistance (that is, imipenem) and anti-MRSA activity.¹⁵ The minimal inhibitory concentration (MIC) of imipenem against MRSA is 32 µg ml⁻¹ when used alone, but when used in combination with $0.5 \,\mu g \,m l^{-1}$ of 2, as a representative example, the MIC of imipenem changes to $0.125 \,\mu g \, m l^{-1}$, a 256-fold enhancement of activity. Interestingly, the circumventing effect of the naphthacemycins A extends only to imipenem against MRSA and not to aminoglycosides, glycopeptides, tetracyclines and quinolones.14,15

The naphthacemycins A are composed of naphthacene structure (A, B, C and D-rings) and the asymmetric E-ring moiety, and exhibit atropisomeric properties. However, the absolute configurations of the naphthacemycins A have yet to be determined. X-ray structure analysis revealed that (-)-naphthacemycin A₈ (8) and A₉ (9) have a distorted

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5,6-dicarbonyl moiety.¹⁵ Undoubtedly, their β -lactam-potentiating effect and scarcity in natural environment attract organic synthetic and medicinal chemists to embark on their synthesis. To date, the total synthesis of tetarimycin A has been reported only by Shia and co-workers, who employed a very efficient approach involving Hauser-Kraus annulation as a key step in constructing the naphthacene-5,6,11(12*H*)-trione framework.¹⁹ Our group is engaged in the total synthesis of bioactive natural products from microorganisms^{20,21} and was attracted to the fascinating biological profile of the naphthacemycins A. Here we report the total synthesis of (±)-naphthacemycin A₉ (**9**) and preparation of some artificial analogs. We also elucidated the structure-activity relationships (SARs) of these compounds based on analyses of their antibacterial activity.





RESULTS AND DISCUSSION

Retrosynthetic analysis of (\pm) -naphthacemycin A₉

According to the retrosynthetic analysis of (\pm) -naphthacemycin A₉ (9) described in Scheme 1, 9 can be constructed by Brønsted acid-mediated intramolecular Friedel-Crafts cyclization to form B-ring from the precursor 12, followed by C-H oxidation to introduce the carbonyl function into the B-ring. Precursor 12 would be prepared by Suzuki-Miyaura coupling between the benzyl halide (as the equivalent of A-ring) and aryl-borane (13) in conjunction with the Dötz reaction.²²⁻²⁸ This reaction facilitates construction of the quinone moiety of the C-ring from an alkynyl-borane (14) and aryl chromium-carbene complex (15). The Dötz reaction between terminal alkynes and a chromium-carbene complex typically gives a single regioisomer; however, unsymmetrically substituted internal alkynes give mixtures of the two possible regioisomers.²⁹⁻³² On the other hand, incorporation of a boron unit into an unsymmetrically substituted internal alkyne is a rapid and efficient approach for the reliable and predictable synthesis of hydroquinone and quinone boronate esters, with excellent regioselectivity due to the Lewis acid/base interaction $[CO \rightarrow B(OR)_2]$ in the metallohexatriene intermediate, as shown in Scheme 1.33-35 The substrate of the Dötz reaction can be prepared by Suzuki-Miyaura coupling between the corresponding D and E-ring units (16 and 17).

Synthesis of the model naphthacene-5,6,11(12*H*)-trione framework (25)

Our synthesis commenced with the preparation of naphthacene compound **25** as a simpler model framework lacking the E-ring of the naphthacemycins A and two phenolic alcohols on A-ring (Scheme 2). Alkynylboronate ester 14^{36} underwent Dötz reaction with the *p*-methoxyphenylchromium–carbene complex (19), which was prepared by chromination of 4-bromoanisole (18; corresponding to 'D-ring' moiety). The crucial Dötz reaction in our synthetic strategy was then examined under various conditions by changing the solvents and/or temperature. The optimized conditions for Dötz reaction were



Scheme 1 Retrosynthetic analysis of (\pm) -naphthacemycin A₉ (9).



Scheme 2 Synthesis of model naphthacene-5,6,11(12*H*)-trione compound (25). A full color version of this figure is available at *The Journal of Antibiotics* journal online.

as follows: microwave irradiation at 130 °C for 5 min in 0.05 M Et₂O solution in sealed tube, followed by methylation of the generated hydroxyl group with MeI in the presence of Cs₂CO₃ to produce the desired naphthalylboronic ester (20) in 55% from 19 as the sole regioisomer. Regioselectivity of Dötz reaction and the structure of 20 was confirmed by the NOE observation of the precursor of 20 (Supplementary Information). Suzuki-Miyaura coupling reaction was realized between 20 and benzyl bromide (21; corresponding to 'A ring' moiety) by palladium catalyst to give the adduct in quantitative yield, with subsequent Friedel-Crafts cyclization under H2SO4/AcOH (1/4 v/v) acidic condition to yield the tetracyclic product (22) in 93% yield. Oxidation of the hydroquinone dimethyl ether moiety of 22 with cerium ammonium nitrate (CAN) afforded the quinone derivative (23) in 74% yield, along with the peroxidated product (24) in 18% yield. Although the efficiency of the reaction producing the desired benzylic alcohol (24) was low, the C-H oxidation of the benzylic position proceeded with CAN in the presence of H₂O while the hydroquinone moiety was oxidized. When compound (23) was subjected to the same optimized oxidation conditions in which 23 was synthesized from 22 over a three-cycle repetition, 24 was obtained from 23 in 73% yield. Finally, oxidation of the benzylic alcohol of 24 with MnO₂ yielded the preliminary model compound (25), the structure of which was confirmed by single-crystal X-ray diffraction analysis (CCDC1511863). From the ORTEP plot of 25, the benzoquinone moiety normally induces the planer conformation is slightly twisted, which could cause dipolar repulsion between 5,6-dicarbonyl moieties on B and C-rings. This observation resembles the threedimensional form of the crystalline tetarimycin A, as previously presented by Brady and co-workers.¹⁶

Synthesis of more functionalized model naphthacene compound (36) Turning our interest to the stability of the twisted form of naphthacene framework (25), the relief of which could lead the B and C-rings to assume a planer structure of keto-enol structure (Scheme 3), we attempted to synthesize the more complex model compound **36** by incorporating two hydroxy groups on A-ring of **25**.

According to the established model synthesis illustrated in Scheme 2, Suzuki-Miyaura coupling of the boronic ester (20) with the benzyl bromide derivative (26), which was prepared from commercially available 2,4-dihydroxybenzaldehyde in 82% yield for 3 steps (Supplementary Information), afforded the adduct (27) in 91% yield (Scheme 3). Subsequently, the two protective *p*-toluenesulfonyl (Ts) groups of 27 were replaced with methyl groups to yield the precursor for Friedel-Crafts cyclization (28) (68% for 2 steps), which has a higher electron density in the A-ring than that of bis-tosylate (27) and is thus a more suitable electron donor for the next cationic cyclization step. Indeed, tosyl substitution of the A-ring of 27 was completely suppressed during Friedel-Crafts cyclization. In addition, attempted Suzuki-Miyaura coupling of 20 with dimethoxybenzyl bromide under several conditions was also unsuccessful. Friedel-Crafts cyclization of 28 under acidic conditions identical to those used for the preparation of 22 as shown in Scheme 2 gave the cyclized compound (29) in 83% yield. Cyclized compound (29) contained an undesired spiro[4.5] frame and exhibited demethylation of the *p*-methoxy position of the A-ring. As compound 29 was selectively generated in our system, the formation of such a spirocyclic frame would be more preferable under Brønsted acid-mediated Friedel-Crafts cyclization, although Kende and co-worker reported an example of ring expansion in a spirocyclic frame via dienone-phenol rearrangements in several spirocyclic dienone derivatives in the presence of CF₃CO₂H in CH₂Cl₂.³⁷ Successful ring expansion was observed by using Lewis acid for dienone-phenol rearrangements with our substrate. We found that the spirocyclic frame is formed in the presence of a Brønsted acid, such as H₂SO₄ and AcOH, but not in the presence of Lewis acids. The dienone-phenol rearrangements of 29 proceed with TiCl₄ as the most appropriate Lewis acid in our experiments in CH2Cl2 solution,

Possible tautomerization between 1,3-diketo and keto-enol moieties on B,C-rings



Very unstable! and could not purified

Scheme 3 Incomplete synthesis of more complex model compound (36 and 39).

producing the desired naphthacene derivative (30), which was very rapidly oxidized under air atmosphere to the corresponding quinone methide (31) in 76% yield. For further oxidation of 31 to the target model compound (36), epoxidation of 31 with hydrogen peroxide under basic condition, followed by oxidation with AgO/HNO₃ to afford the epoxy-quinone (**32**) in 83% yield for 2 steps. For conversion of the B-ring epoxide of **32** to a ketone, direct one-pot imination of the quinone methide oxide moiety was carried out. After the addition of methylamine to the epoxide, the generated 1,2-hydroxylamine was immediately aromatized in the A-ring position via successive

β-elimination of the tertiary alcohol and tautomerization of the resulting quinone methide to afford the benzylic imine (**33**) in 88% yield. Subsequently, benzyl protection of the phenolic alcohol of **33** was then carried out, giving rise to **34**, which without purification was subjected to further hydrolysis to give **35** as a single keto-enol tautomeric isomer in 59% yield for 2 steps. Unfortunately, deprotection of the benzyl group of **35** under a variety of conventional conditions (hydrogenations with Pd/C or Pd(OH)₂; Burch reduction; BF₃•OEt₂ with EtSH; oxidative conditions such as RuO₂ with NaIO₄) did not provide the target molecule (**36**), even though the deprotection reaction proceeded, and only prompt decomposition or polymerization of the product was observed.

Alternatively, we examined the preparation of 39 as a similar model compound in order to confirm the stability of the 1,3-dicarbonyl moiety on the B- and C-rings in relation to the oxygen substituted A-ring (Scheme 3). To introduce a carbonyl function on the B-ring, the quinone methide moiety of 31 was temporarily reduced to phenol using NaBH₄ in MeOH, then the generated phenolic hydroxyl group of the air sensitive product was immediately protected with an acetyl group to afford 37 in 95% yield for 2 steps. Subsequently, C-H oxidation of benzyl position of 37 was carried out under modified CAN oxidation condition in the presence of H₂O while the oxidation of hydroquinone moiety proceeded. Further oxidation of the benzyl alcohol was examined without purification of 38; however, the desired product (39) was not obtained under any of the oxidation conditions examined (for example, MnO₂, Dess-Martin[O], Parikh-Doering[O], DEAD-ZnBr₂,³⁸ TPAP-NMO, PCC and PDC), even though the oxidation reaction proceeded.

With respect to synthesis of originally designed model compound (36 or 39), it was confirmed that the 5,6-dione portion in the naphthacene-5,6,11(12H)-trione framework is very unstable. Interestingly, the 5,6-dione is stable and conserved in naturally occurring naphthacemycins A and tetarimycin A. We therefore hypothesized that the relatively bulky functions at the C7 position of the naphthacene-5,6,11(12H)-trione framework (methyl for tetarimycin A and aryl for the naphthacemycins A) contribute to the stability of the whole structure (Figure 2). In case of the model compounds, the dipole interaction between the C5 and C6 carbonyls is relieved by keto-enol isomerization of the C5 carbonyl in conjunction with the C4 phenol alcohol. In contrast to the model compounds, C7 substitution of the natural products creates a steric interaction with the C6 carbonyl, which guides the twisted conformation of the benzoquinone moiety, eliminating the repulsion associated with the C5, C6-dicarbonyl in the natural products. On the basis of these observations and the characteristics of the naturally occurring naphthacene-5,6,11(12H)-trione framework, we conclude that



Figure 2 Plausible reason for the stability of the naturally occurring naphthacene-5,6,11(12*H*)-trione compounds.

our scheme for the synthesis of model compounds having a C7 substitution is applicable to the production of such natural products, as evidenced by our total synthesis of (\pm) -naphthacemycin A₉ (9).

Total synthesis of (\pm) -naphthacemycin A₉ (9)

We next approached the total synthesis of racemic naphthacemycin A_{9} (9), which differs only in having an aryl function at the C7 position in the planar structure of model compound of 36. Therefore, to access 9, 2,4-dimethoxy-6-methylphenyl boronic acid, prepared from a corresponding bromobenzene (40), was subjected to Suzuki-Miyaura coupling with 2-bromo-5-methoxyphenyl iodide $(41)^{39}$ to furnish the biphenyl product (42) in 76% for 2 steps (Scheme 4). Chromination of 42 gave the corresponding chromium-carbene complex (43) in 77% yield. Dötz reaction of 43 with an alkynylboronic ester $(14)^{36}$ was then performed under microwave irradiation. We initially expected that the Dötz reaction of 43 would afford the desired phenylboronic ester (45) as the sole product in a predictable manner. However, the yield of 45 was unsatisfactory (14%) and was accompanied by the production of an undesired cyclobutenone derivatives (44) in 40% yield. This was probably due to steric interaction between the methoxy group and the aryl function (E-ring) connecting to D-ring, resulting in a twisted bond forming between the phenyl ring (D-ring) and the vinyl moiety. As a result, formation of the cyclobutenone proceeded via 'path a' preferentially to the desired quinone formation via 'path b', as illustrated in Scheme 4. Nevertheless, the vinyl ketene intermediate of Dötz reaction tended to become the cyclopentenone via [2+2] cvclization.

Moser and co-workers provided evidence that the chromium-free vinyl ketene is slowly converted to an equilibrium mixture of vinyl ketene and cyclobutenone at room temperature (Scheme 4).⁴⁰ In addition, in the approach for synthesizing annulated hydroquinones, the 4-aryl groups of respective cyclobutenones can be converted to quinone products via selective electrocyclic ring opening of the cyclobutenone to the corresponding conjugated ketene, followed by ring closure to provide the hydroquinone, as reported by Moore and Perri (Scheme 4).⁴¹

Encouraged by these reports, we carried out thermal rearrangement of the cyclobutenone product (44), and after optimization of the reaction condition, this approach was turned out to be successful, in that 44 could be converted under microwave irradiation at 160-180 °C in toluene to yield the half methyl-ether quinone, which was immediately methylated to furnish 45 in 42% (69% based on recovered 44) (Scheme 4). Again Suzuki-Miyaura coupling of 45 with 26 performed to furnish the corresponding product (47) in 75% yield over a 4-cycle repetition, which was necessary due to the low reactivity of 45. After performing the same replacement process (63% for 2 steps) that was done for model compound 28, acid-mediated Friedel-Crafts cyclization was carried out to afford the corresponding spirocyclic-dienone (48) as an inseparable diastereomixture (d.r. = 1:1)in 83% yield. Oxidation with CAN under optimized conditions let to conversion of 48 into the spirocyclic-quinone in 76% yield, which was followed by dienone-phenol rearrangement using TiCl4 to give the naphthacene product in 44% yield (83% based on recovered SM). CAN oxidation to the quinone after the dienone-phenol rearrangement reaction was not successful. However, acetylation of the generated phenol followed by oxidation of the benzyl position using CAN gave the desired the benzyl alcohol (49) as an inseparable diastereomixture (d.r. = 1:1). The crucial oxidation of the benzyl alcohol of 49 to a ketone, which is characterized by a troublesome dipole interaction on the B and C-rings,



Examples for equilibrium isomerization between vinyl ketenes and cyclobutenones



Scheme 4 Completion for synthesis of (\pm) -naphthacemycin A₉ (9).

was not successful under conditions (for example, PCC at room temoperature, Swern[O], MnO_2 , Dess-Martin[O] and Jones[O]) other than PCC at 80 °C (59% yield). After deacetylation under basic condition to afford methyl-naphthacemycin A₉ (50) (63% yield), the final chemoselective demethylation was examined. At first,

we attempted the chemoselective demethylation reaction using it by boron trihalides to take advantage of the coordination of the B-ring carbonyl function, but the reaction did not work. Fortunately, the reaction proceeded well with CeCl₃·7H₂O-NaI in MeCN under reflux,⁴² furnishing the target (\pm)-9 in 64% yield.

Using HPLC analysis of (\pm) -9 and natural (-)-9 with a chiral column, we next confirmed the atropisomer of compound (Figure 3). The chirality of **9** was clearly observed, and both the (-) and (+)-antipodes of synthetic (\pm) -9 were separated without racemization and individually characterized. Synthetic (-)-9 was identical to naturally occurring (-)-9^{14,15} in all respects (¹H NMR, ¹³C NMR, HRMS) with the chiroptical property, and also synthetic (+)-9 was identical as antipode of natural (-)-9 {syn-(-)-9, $[\alpha]_D^{23}$ -46.0 (c 0.05, MeOH); syn-(+)-9, $[\alpha]_D^{27}$ +43.6 (c 0.05, MeOH); nat-(-)-9, $[\alpha]_D^{23}$ -44.1 (c 0.2, MeOH)¹⁵}.

Figure 3 HPLC analysis of natural and synthetic **9**. HPLC condition: DAICEL CHIRALPAK IE 100×250 mm, UV detection at 277 nm, 50% *i*-PrOH/hexane mobile phase, flow rate 3.0 ml min⁻¹.

Evaluation of antibacterial activity

The antibacterial activity (vide ante) of synthetic naphthacemvcin Ao and the related model compounds along with some derivatives (51, 52, 53 and 54; see the Supplementary Information for preparation method) from (-)-9 was examined in vitro against 13 Gram-positive bacteria using standard serial-dilution techniques.⁴³ As summarized in Table 1, naphthacemycin A9 not only showed potent anti-MRSA and anti-VRE, the compound also exhibited activity against macrolideand linezolid-resistant S. aureus activities, with MIC values for each tested bacteria in the µg ml⁻¹ range. Previously, Shia et al.¹⁹ reported the preliminary SARs for tetarimycin A, which is identical to the naphthacene moiety of 9 (that is, the A,B,C,D-ring of 9), and its related analogs.¹⁹ They reveled that alkylation of a hydroxyl group in the A-ring so that it cannot form a hydrogen bond with a carbonyl of the B-ring abolishes the antibiotic activity. Our preliminary SAR studies agreed with the results of Shia et al.¹⁹ with respect to the complete elimination of the activity for 25, 35, 53 and 54. In contrast, the acylation of the hydroxyl group(s) on the A-ring of the naphthacene moiety had no effect on antibacterial activity. In addition, a comparison of (\pm) -9, (-)-9 (natural type) and (+)-9 (antipode of the natural type) indicated that atropisomeric chirality dose not contribute to the antibacterial activity. Importantly, this new class of antibiotics exhibited anti-MRSA activity almost equal to its anti-VMC activity; thus, we hypothesize that these antibiotic compounds act in disrupting a unique target enzyme, such as FASII,^{17,18} which has been identified as an alternative target in drug-resistance bacteria.

Table 1 MICs of naphthacemycin A₉ (9) and related compounds against different bacterial strains⁴³

Strains/compounds	MICs (μg ml ⁻¹)										
	VCM	Synthetic (±)-9	Synthetic (–)-9	Synthetic (+)- 9	25	35	50	51	52	53	54
S. aureus FDA209P ^a	1	4	4	4	>64	>64	32	2	2	>64	>64
S. aureus Smith ^a	2	2	2	2	>64	>64	32	2	1	>64	>64
MRSA KUB853 ^b	1	2	2	2	>64	>64	4	2	1	>64	>64
MRSA KUB854 ^b	1	2	1	1	>64	>64	4	1	1	>64	>64
MRSA 70 ^b	0.5	2	2	1	>64	>64	8	1	1	>64	>64
MRSA 92-1191 ^b	1	2	2	2	>64	>64	32	1	1	>64	>64
S. aureus KUB857 ^c	1	2	2	2	>64	>64	32	1	1	>64	>64
S. aureus KUB858 ^d	1	1	2	2	>64	>64	8	1	1	>64	>64
VISA Mu50	8	2	4	1	>64	>64	>32	4	2	>64	>64
S. aureus KUB860 ^e	2	4	4	4	>64	>64	>32	2	4	>64	>64
E. faecalis ATCC29212f	4	4	4	4	>64	>64	>32	2	2	>64	>64
E. faecalis NCTC12201g	>128	8	4	4	>64	>64	>32	2	2	>64	>64
E. faecium NCTC12204h	>128	4	4	8	>64	>64	>32	4	2	>64	>64

Abbreviations: MRSA, methicillin-resistant S. aureus; MSSA, methicillin-susceptible Staphylococcus aureus; VCM, Vancomycin; VISA, VCM-intermediate S. aureus.

aMSSA: FDA209P and Smith.

^bMRSA: MRSA KUB853, KUB854, MRSA 70, and MRSA 92–1191: MRSA strains isolated from clinical patients.

^cMacrolide-resistant S. aureus KUB857: inducible resistant strain; encoded by erm gene.

^dMacrolide-resistant S. aureus KUB858: constitutively resistant strain; encoded by erm gene.

^eLinezolid-resistant S. aureus KUB860.

^fEnterococcus faecalis ATCC29212: susceptible strain.

^gVCM-resistant *E. faecalis* NCTC12201: encoded by *vanA* gene.

hVCM-resistant E. faecium NCTC12204: encoded by vanA gene

CONCLUSION

We have achieved the total synthesis of (\pm) -naphthacemycin A₉ (9). The synthesis scheme featured the Dötz reaction expanding to Suzuki–Miyaura coupling to produce a highly substituted hydroquinone, Friedel–Crafts cyclization, and dienone-phenol rearrangement. The longest linear sequence involved 16 steps to 9 from commercially available 40. This synthetic process provides viable routes for the synthesis of naphthacemycins and new potential analogs thereof. Our results also revealed how twisting of the benzoquinone moiety relaxes the dipole interaction between two neighboring parallel carbonyls set on the originally planer naphthaceme framework, thus stabilizing the structures of the naphthacemycins. Further studies to elucidate the mechanism of the circumventing effect of imipenem resistance of the naphthacemycins are now in progress.

MATERIALS AND METHODS

Details of experimental procedures, characterization data and NMR spectra for all new compounds can be found in the Supplementary Information.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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