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Total Synthesis and Structural Establishment/Revision of Antibiotics A54145

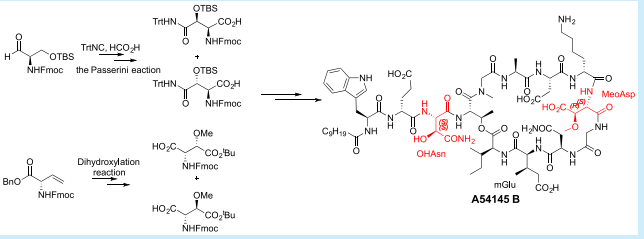
Delin Chen,[†,§] Hoi Yee Chow,[†,§] Kathy Hiu Laam Po,[‡] Wenjie Ma,[†] Emily Lok Yee Leung,[†] Zhenquan Sun,[†] Ming Liu,[†] Sheng Chen,[‡] and Xuechen Li*[,†]

[†]Department of Chemistry, State Key Laboratory of Synthetic Chemistry, The University of Hong Kong, Hong Kong, P. R. China

[‡]Department of Applied Biology and Chemical Technology, State Key Lab of Chiroscience, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong, P. R. China

Supporting Information

ABSTRACT: A54145 is a family of antibacterial cyclic lipodepsipeptides structurally resembling daptomycin. Since its discovery in 1990, only the ambiguous structures of the methoxy-aspartic acid (MeO-Asp) and the hydroxy-asparagine (HO-Asn) have been reported. We have developed efficient routes to obtain the fully protected L-MeO-Asp and L-HO-Asn building blocks compatible with Fmoc-SPPS, and a total synthesis of A54145 that enabled us to establish its structure, consisting of L-3*S*-HO-Asn and L-3*R*-MeO-Asp, revising the wrongly proposed structure of L-3*S*-MeO-Asp.



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Cyclic peptides represent an important class of antibiotics, most of which exert antibacterial effects through inhibiting nonprotein/enzyme targets,[1] such as vancomycin binding to lipid II,[1] polymyxin targeting lipopolysaccharide (LPS),[2] and daptomycin inserting into membranes.[3] The tendency to develop resistance to these antibiotics among bacteria is lower than those targeting bacterial enzymes or protein receptors.[1] According to the World Health Organization (WHO) in 2018,[4] antibiotic resistance became one of the biggest challenges to global health. Given the fact that bacteria have lower tendency to develop resistance to cyclic peptide antibiotics, development of an efficient chemical synthesis strategy of cyclic lipodepsipeptide antibiotic A54145 and analogues is worth investigating. The total synthesis will help the search of next-generation cyclic peptide antibiotics.

A54145 is a class of cyclic lipodepsipeptide isolated from *Streptomyces fradiae* whose structure exhibits remarkable similarities to daptomycin (Figure 1).[5] In addition to the nonproteinogenic 3-methyl-glutamic acid (3-mGlu), which is also present in daptomycin, A54145 contains two other nonproteinogenic amino acids: L-methoxy-aspartic acid (L-MeO-Asp) and L-hydroxy-asparagine (L-HO-Asn).

Daptomycin was approved by the FDA in 2003 for infections caused by Gram-positive pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococci* (VRE). However, daptomycin failed to treat community-acquired pneumonia (CAP) in clinical trials due to the inhibition by pulmonary surfactant.[6] Interestingly, A54145 antibacterial activities are much less affected by surfactant, despite the structural similarities with daptomycin, with only a 2-fold increase in its minimum inhibitory concentration (MIC) in the presence of surfactant. Nonetheless, A54145 is 2-fold less

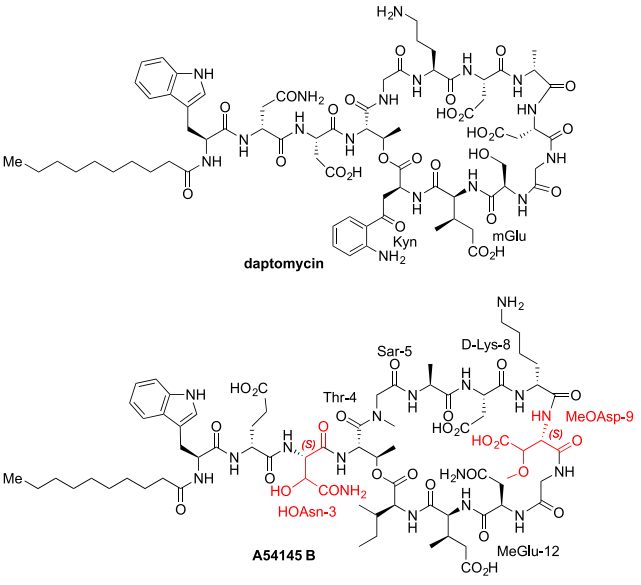

Figure 1. Structures of daptomycin and A54145B.

potent and more toxic than daptomycin.[7] It is conceivable that hybrid compounds of daptomycin and A54145 may exhibit optimal bactericidal activity in the presence of bovine surfactant, with the potential to treat CAP that is unresponsive to daptomycin. Toward this goal, Cubist scientists used bioengineering approaches to generate an array of daptomycin−A54145

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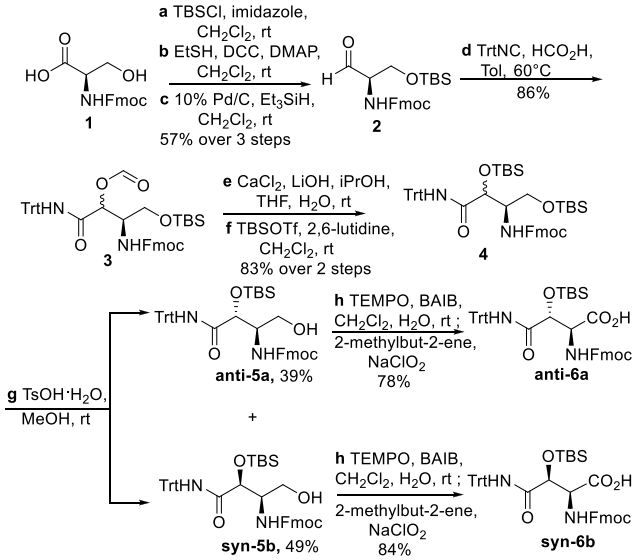
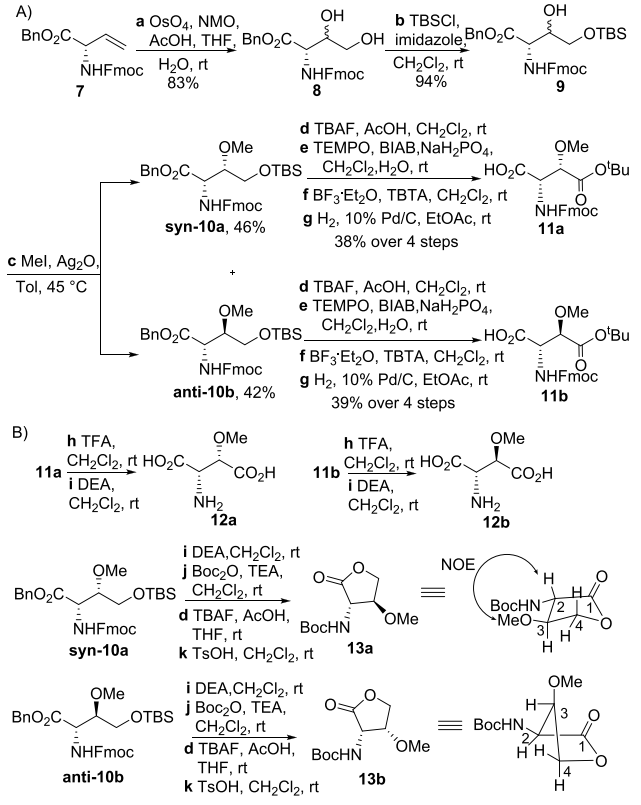
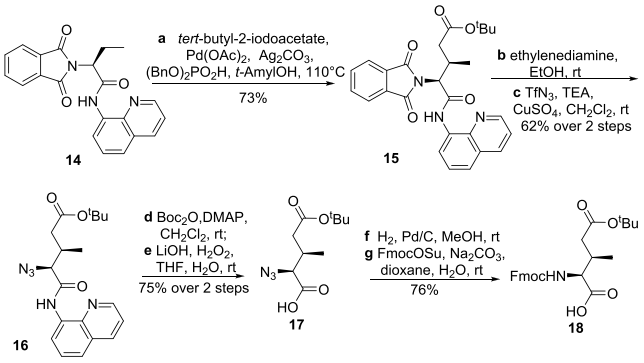
Scheme 1. Synthesis of HO-Asn Building Blocks



Scheme 2. Synthesis of MeO-Asp Building Blocks



Scheme 3. Synthesis of 3-mGlu Building Block



hybrid analogues. However, restricted by the inherent limitation of the biosynthetic method employed, structural variations were limited to several sites.[8] The structure of A54145 was elucidated in 1990, but the absolute configurations of the β carbon of L-HO-Asn and L-MeO-Asp were not established at the time.[5] These two amino acids have been proposed as L-3*S*-HO-Asn and L-3*S*-MeO-Asp in all the later literatures.[9−15] In order to establish the absolute configurations, we initiated the synthetic studies to prepare all four diastereomeric A54145B analogues with diastereomeric L-HO-Asn and L-MeO-Asp, with which we expected to establish the bona fide structure and to evaluate the relationship between the stereochemistry of the β carbon of HO-Asn and MeO-Asp and the antibacterial activity of A54145.

At the outset, we need to develop synthetic routes to access two diastereomeric building blocks of both L-HO-Asn and L-MeO-Asp, which are compatible with Fmoc-solid phase peptide synthesis (Fmoc-SPPS), the strategy that will be used to build the whole A54145 molecule.

L-HO-Asn is a nonproteinogenic amino acid found in many natural products.[16] L-HO-Asn building blocks with various protecting groups have been synthesized chemically by several enantioselective synthetic strategies.[15,17−20] However, the fully protected L-HO-Asn for Fmoc-SPPS, with Trt (trityl) and TBS (*tert*-butyldimethylsilyl) protecting the side-chain amide and hydroxy group, respectively, was only reported in 2017 by Inoue group through a 12-step synthesis.[20] As we had to get access to both diastereomers of L-HO-Asn with opposite configurations at the β carbon, we developed a strategy comprising eight steps only to gain two diastereomeric L-Fmoc-HO(TBS)-Asn(Trt)-OH **6a** and **6b** in gram-scale, based on the three-component coupling Passerini reaction,[21,22] with easy separation of the diastereomers in the penultimate step of the synthetic route.

The synthesis started with Fmoc-D-Ser-OH **1** as shown in Scheme 1. After TBS protection, thioesterification and the Fukuyama reduction,[23,24] the resultant aldehyde **2** was reacted with trityl isocyanide (TrtNC)[25] and formic acid in an atom-economical manner with excellent yield (86%). After switching the formyl protecting group on the hydroxy group with TBS, the primary TBS group on the resulting product **4** was removed selectively in the presence of the secondary TBS group. Through the extensive screening of the desilylation conditions including PTSA, PPTS, TBAF/AcOH, or CSA in different solvents and temperature, we found that using PTSA in MeOH at room temperature for 1 h was optimal and afforded the desired two diastereomers (88% in total), which could be easily separated by chromatography. The resultant primary alcohol **anti-5a** and **syn-5b** underwent a one-pot two-step oxidation to give rise to two Fmoc building blocks **anti-6a** and **syn-6b**. Both ^{1}H and ^{13}C NMR spectra of the compound **syn-6b** were identical to those published in the literature.[20] Hence, the absolute configuration of the two diastereomers was defined.

Synthetic routes to access MeO-Asp have been reported by several groups,[15,26,27] with the Fmoc-SPPS compatible L-Fmoc-*threo*-MeO-Asp(O*t*Bu)-OH building block reported by the Taylor group through five steps[15] in late 2018. As shown in Scheme 2, our 7-step synthesis to obtain both diastereomeric L-Fmoc-MeO-Asp(O*t*Bu)-OH building blocks **11a** and **11b** started with the dihydroxylation of the commercially available alkene **7** with OsO_4/NMO/AcOH in THF/water (3:1) at room

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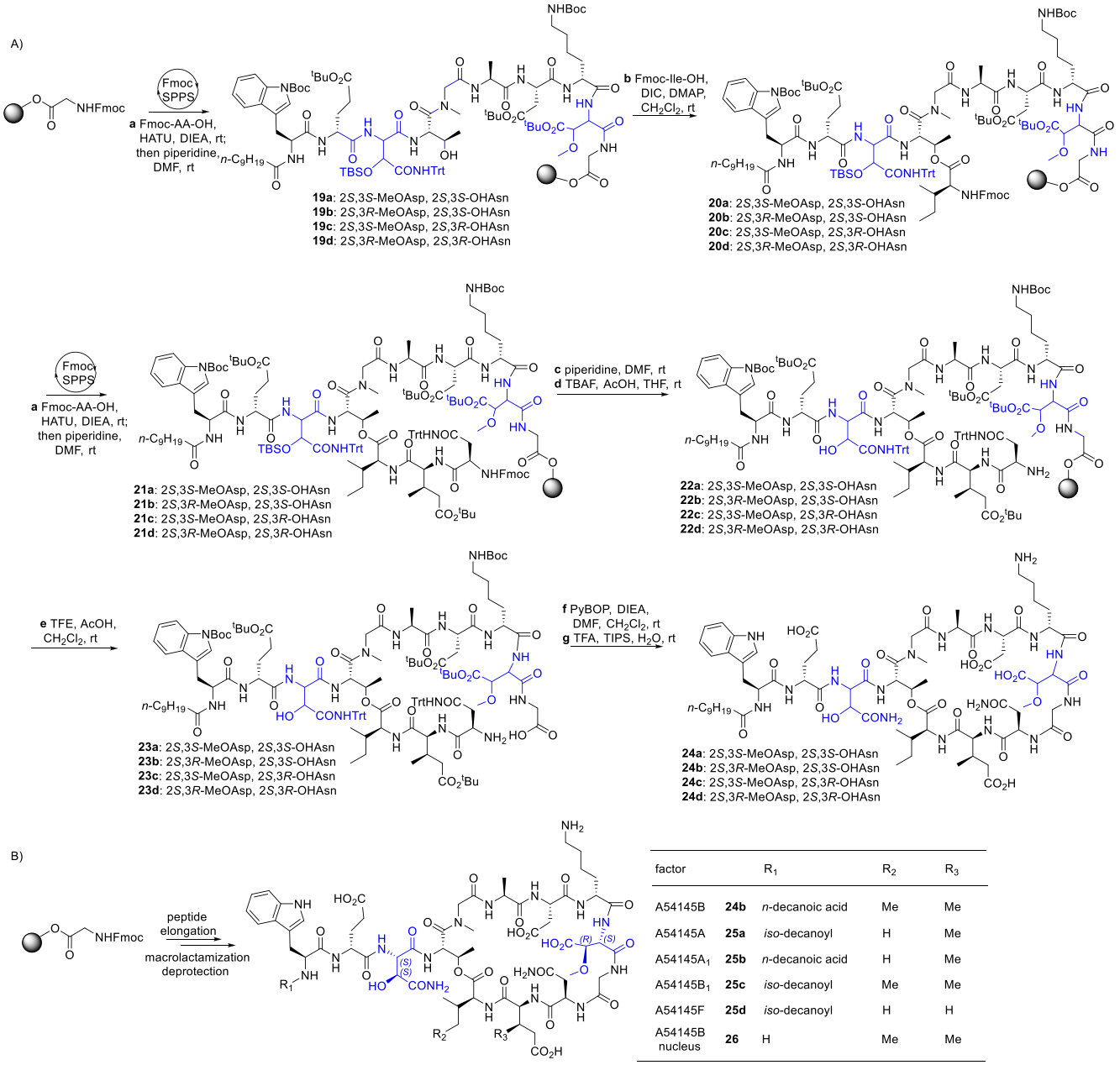
Scheme 4. Syntheses of A54145 and Analogues



factor		R_1	R_2	R_3
A54145B	**24b**	*n*-decanoic acid	Me	Me
A54145A	**25a**	*iso*-decanoyl	H	Me
$A54145A_1$	**25b**	*n*-decanoic acid	H	Me
$A54145B_1$	**25c**	*iso*-decanoyl	Me	Me
A54145F	**25d**	*iso*-decanoyl	H	H
A54145B nucleus	**26**	H	Me	Me

Table 1. Minimal Inhibitory Concentrations (in μg/mL) of A54145 Analogues

bacterial strain	MRSA86	MRSA88	SA ATCC29213
Daptomycin	0.5	0.5	0.5
24a	⩾32[a]	⩾32[a]	⩾32[a]
24b	1	0.5	0.5
24c	⩾32[a]	⩾32[a]	⩾32[a]
24d	⩾32[a]	⩾32[a]	⩾32[a]
25a	16	8	8
25b	8	8	8
25c	2	2	2
25d	⩾32[a]	16	16

[a]The highest concentration tested was 16 μg/mL.

temperature overnight to afford compound **8** as a pair of epimers in 3:2 ratio. Dihydroxylation with higher stereoselectivity using Sharpless asymmetric dihydroxylation could allow us to get a single diastereomer in the first step of the synthetic route once we define the stereocenters of L-MeO-Asp in A54145. The primary alcohol of diol **8** was selectively protected with TBS group, followed by methylation of the secondary hydroxy group with Ag_2O and MeI to yield the corresponding methyl ether epimers **10a** and **10b** that could be easily separated by chromatography. Both of the resulting epimers were transformed to the desired carboxylic acid **11a** and **11b** by a four-step sequence involving: (1) removal of the TBS protect group via TBAF/AcOH; (2) oxidation of the resulting hydroxy group to the corresponding carboxylic acid by treating with TEMPO/BAIB/NaH_2PO_4 in DCM/THF/H_2O; (3) esterification of the carboxylic acid using *tert*-butyl trichloroacetimindate (TBTA) under the catalysis of $BF_3{\cdot}Et_2O$; (4) removal of the benzyl group by catalytic hydrogenation. In order to confirm the absolute stereochemistry at the 3-OMe position, compounds **11a** and

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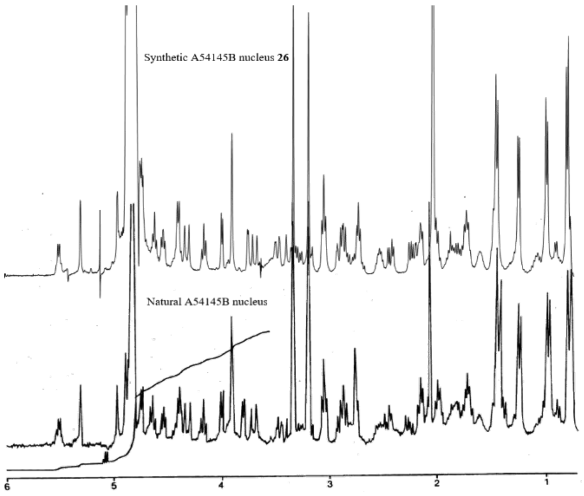

Figure 2. Comparison of NMR spectra of synthetic A54145B nucleus (400 MHz) and the natural A54145B nucleus (270 MHz).[33]

11b were, respectively, treated with TFA to remove the *t*Bu group followed by deprotecting the Fmoc group using diethylamine (DEA) in DCM to yield the dicarboxylic acid **12a** and **12b**. Their ^{1}H NMR spectra were compared to the same compounds with known stereochemistry reported in the literature[26,27] (see Supporting Information). We also transformed epimers **10a** and **10b** to the five-membered ring lactones **13a** and **13b** through four-step reaction to determine the stereochemistry by 2D-NOESY NMR. The proton at C-2 position and proton of MeO group of compound **13a** showed NOE correlation (Scheme 2 and Supporting Information). Results from the two NMR studies are consistent with each other, and the evidence obtained provide additional confirmation of the absolute configurations of compounds **11a** and **11b** shown in Scheme 2.

The reported synthesis of (2*S*,3*R*)-3-mGlu building block **18** is lengthy (14 steps from L-glutamic acid) and labor-intensive;[28] therefore, we developed an improved synthetic route that consists of 10 steps for the synthesis of **18** based on C−H activation strategy.[29,30] As depicted in Scheme 3, stereoselective alkylation of the known compound **14**[31] with *tert*-butyl-2-iodoacetate successfully proceeded to provide the desired product **15** in 73% yield utilizing the Chen's condition for C−H activation: $Pd(OAc)_2$, Ag_2CO_3, and $(BnO)_2PO_2H$ at 110 °C in *t*-AmylOH.[32] Deprotection of *N*-phthalimide of **15** with ethylenediamine followed by conversion of the released free amine into an azido group through treatment with TfN_3 yielded **16**. After activation of the amide group of **16** with the Boc group, the free carboxylic acid **17** was obtained in 75% yield under $LiOH/H_2O_2$ conditions. Reduction of the azido group into amine via hydrogenation, followed by protection with FmocOSu, furnished **18** in 76% yield over two steps.

With all these building blocks in hand, we continued with the total synthesis of A54145. Due to the small steric hindrance and the absence of epimerization during fragment coupling, we envisaged that the amide bond between Gly and D-Asn could be selected for the macrolactamization step, and the requisite linear peptide precursor was readily assembled via the standard Fmoc-SPPS on 2-chlorotrityl chloride resins. After the resin-Gly-MeO-Asp(O*t*Bu)-D-Lys(Boc)-Asp(O*t*Bu)-Ala-Sar-Thr-HO(TBS)-Asn(Trt)-D-Glu(O*t*Bu)-Trp(Boc)-C_9H_{19} **19a−d** was assembled with the cycles of 20% piperidine/DMF-promoted *Nα*-Fmoc group deprotection (20 min, rt) and HATU-mediated amine coupling (1 h, rt), the on-resin esterification was achieved by reacting the freshly prepared symmetric anhydride of Fmoc-Ile-OH by DIC with the threonine−OH catalyzed by DMAP for 48 h. Then the resultant resin-linked peptide was subsequently coupled with Fmoc-3-mGlu(O*t*Bu)-OH **18** and Fmoc-D-Asn(Trt)-OH under standard SPPS conditions to afford the whole linear sequence. After deprotecting the N-terminal Fmoc group and TBS group of the linear peptide, the side-chain protected linear peptide was released from the trityl resin with AcOH/TFE/DCM (1:1:8, v/v/v) to give the acyclic precursor **22a−d**. The macrocyclization proceeded smoothly in DCM/DMF(3:1) with PyBOP as the coupling reagent to afford the cyclic peptide. Then global deprotection of the side chain protecting groups (*t*Bu, Trt, Boc) via TFA/TIPS/H_2O (95:2.5:2.5, v/v/v) afforded all four possible diastereomeric A54145B analogues **24a−d** (as shown in Scheme 4) in around 3% yield in average after semipreparative reverse-phase HPLC purification (calculated based on the resin loading).

The antimicrobial activities of all four possible diastereomeric A54145B analogues synthesized were assessed by determining their MICs against Gram-positive bacteria strains including SA ATCC29213 and MRSA clinical isolated strains. Our data indicated that **24a**, **24c**, and **24d** showed low antibacterial activities, while compound **24b** has MICs in agreement with the reported A54145B[7] (Table 1). This suggested that **24b** is the synthetic version of A54145B, consisting of L-3*S*-HO-Asn and L-3*R*-MeO-Asp.

Based on the established structure of A54145B, we synthesized other factors of A54145 **25a−d** (Scheme 4). Their MICs are also in good agreement with the reported studies that none of which showed better antibacterial activities than A54145B, the most potent factor of A54145.[7] A54145B being the most effective among all factors reflected that Ile, 3-mGlu, and the *n*-decanoyl tail are important for high antibacterial activities. The MIC results of **24a−d** showed that the absolute configuration of the *β* carbon of both L-HO-Asn and L-MeO-Asp also take important roles in the antibacterial activities. This work therefore will provide a potential direction for analogue designs for medicinal chemistry studies.

As A54145B nucleus (A54145B without the lipid tail) has a high-quality ^{1}H NMR spectrum published in the literature,[33] while the literature reported ^{1}H NMR spectrum of A54145B has severe line broadening,[34] we prepared the A54145B nucleus **26** for NMR comparison. The ^{1}H NMR spectrum of the synthetic A54145B nucleus **26** matched with the one reported in the patent by Eli Lily[33] (Figure 2). The optical rotation of the synthetic A54145B **24b** was in close agreement with reported value[34] (see Supporting Information). Thus, we are confident to conclude that compound **24b** has the same structure as A54145B, comprising L-3*S*-HO-Asn and L-3*R*-MeO-Asp.

In summary, A54145 is a class of antibacterial cyclic lipodepsipeptides with potentials for drug development. We have developed efficient synthetic routes to obtain diastereomeric building blocks compatible with Fmoc-SPPS of both L-HO-Asn and L-MeO-Asp, with eight steps and seven steps, respectively. We also reported a 10-step synthesis of L-Fmoc-3*R*-mGlu(*t*Bu)-OH via the C−H activation strategy. Furthermore, we have established the first total synthesis of A54145 to obtain all four possible A54145B diastereomers. After correlating the structure to antibacterial activities, and comparing the NMR of the synthetic compound to the literature, the bona fide structure of A54145B was established to contain L-3*S*-HO-Asn and L-3*R*-

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MeO-Asp, correcting the structure of A54145 with L-3S-MeO-Asp provided in all literature. Our study also showed that the absolute configuration at the β carbon of L-HO-Asn and L-MeO-Asp are critical for the A54145B activities.

The chemical synthesis of A54145, together with the total synthesis of daptomycin,[28] will enable generations of a library of hybrid compounds of daptomycin and A54145. The high flexibility in structural modifications of total synthesis, in contrast to bioengineering approaches, will help the search of analogues with better performance compared to both of the parent antibiotics in the presence of bovine surfactant, thereby expanding the antibiotic spectrum of daptomycin or enhancing the potency of A54145 while reducing the toxicity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01972.

Experimental procedures, characterization data of the synthetic compounds, and 1D and 2D NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: xuechenl@hku.hk.

ORCID

Xuechen Li: 0000-0001-5465-7727

Author Contributions

[§]These authors contributed equally.

Notes

The authors declare no competing financial interest.

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