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Total Synthesis and Anti-Hepatitis C Virus Activity of MA026

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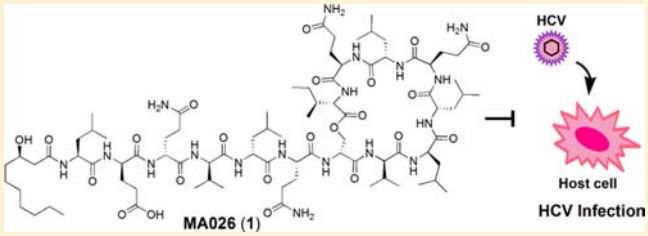
Supporting Information

ABSTRACT: The first total synthesis of MA026 and the identification of its candidate target protein for anti-hepatitis C virus activity are presented. MA026, a novel lipocyclodepsipeptide isolated from the fermentation broth of *Pseudomonas* sp. RtIB026, consists of a cyclodepsipeptide, a chain peptide, and an N-terminal (*R*)-3-hydroxydecanoic acid. The first subunit, side chain **2**, was prepared by coupling fatty acid moiety **4** with tripeptide **5**. The key macrocyclization of the decadepsipeptide at L-Leu[10]-D-Gln[11] provided the second subunit, cyclodepsipeptide **3**. Late-stage condensation of the two key subunits and final deprotection afforded MA026. This convergent, flexible, solution-phase synthesis will be invaluable in generating MA026 derivatives for future structure−activity relationship studies. An infectious hepatitis C virus (HCV) cell culture assay revealed that MA026 suppresses HCV infection into host hepatocytes by inhibiting the entry process in a dose-dependent manner. Phage display screening followed by surface plasmon resonance (SPR) binding analyses identified claudin-1, an HCV entry receptor, as a candidate target protein of MA026.



INTRODUCTION

MA026 (**1**) (Figure 1),[1] a novel lipocyclodepsipeptide, exhibits antiviral activity against hepatitis C virus (HCV). HCV, a member of the *Flaviviridae* family, is a major causative agent of chronic liver diseases such as liver cirrhosis and hepatocellular carcinoma[2] and is thought to affect more than 170 million individuals worldwide, resulting in approximately 280 000 deaths per year.[3] Unfortunately, antiviral treatments consisting of PEGylated interferon (IFN) in combination with ribavirin and newly approved protease inhibitors are limited by serious adverse effects. The emergence of drug-resistant viruses and the high cost of current treatment regimens has led to an urgent search for alternative approaches to prevent HCV infection.[4] The life cycle of HCV includes entry into the host cell (entry process), uncoating of the viral genome, translation of viral proteins, viral genome replication, and the assembly and release of viral particles.[5] The recent development of an HCV cell culture system facilitated the elucidation of the viral replication machinery.[6] Identification of anti-HCV compounds, such as MA026, may be important in establishing novel strategies to inhibit HCV infection.

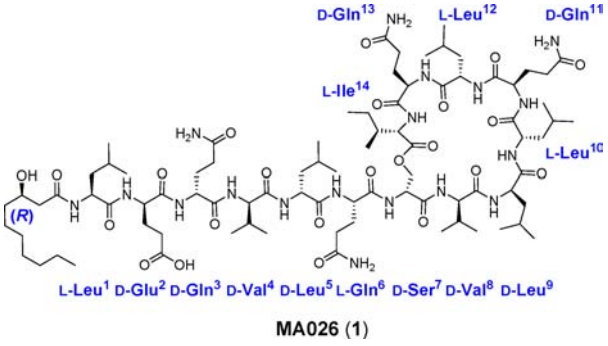


Figure 1. Chemical structure of MA026 (**1**).

MA026 (**1**) was isolated from the fermentation broth of *Pseudomonas* sp. RtIB026 found in the digestive tract of rainbow trout (*Oncorhynchus mykiss*).[1] Rainbow trout, an important aquaculture species, is known to be highly susceptible to infectious hematopoietic necrosis virus (IHNV).[7]IHNV, a member of the genus *Novirhabdovirus* in the *Rhabdoviridae* family, is a causative agent of infectious hematopoietic necrosis (IHN), which is one of the most serious infectious diseases of salmonids.[8] An outbreak of IHNV in rainbow trout aquaculture can cause extensive economic loss.[9] For this reason, surveys were conducted on farmed rainbow trout that identified individual fish resistant to IHNV infection. Our previous studies revealed that rainbow trout with

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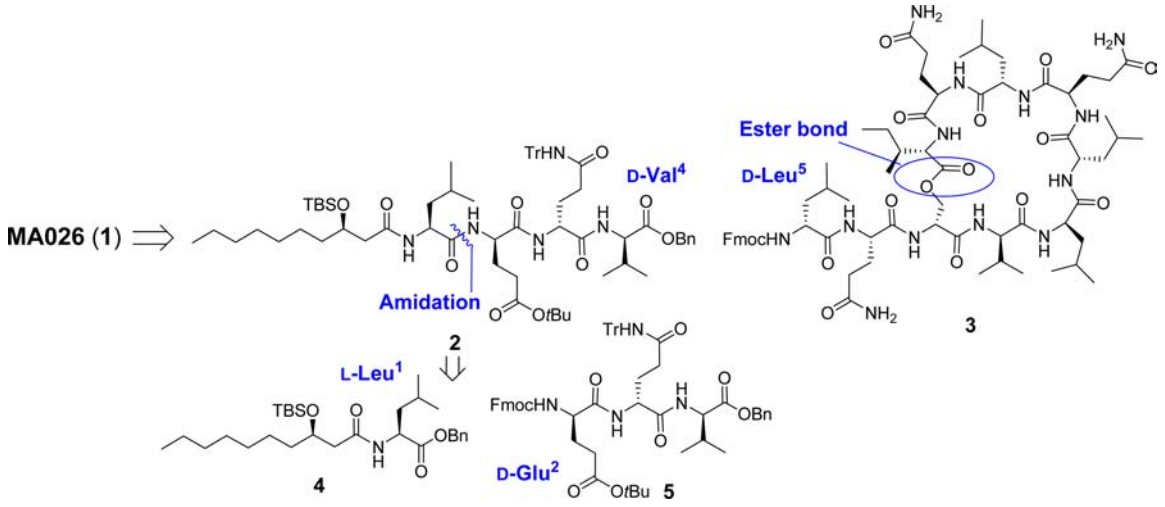
Scheme 1. Retrosynthetic Analysis of MA026 (1)



resistance to IHNV infection live in symbiosis with *Pseudomonas* sp. RtIB026 in their digestive tracts.[1] Anti-IHNV bioassay-guided fractionation of organic extracts from the culture fluid of *Pseudomonas* sp. RtIB026 resulted in the isolation of a new lipocyclodepsipeptide, designated MA026, as a principal active constituent.

The structure of MA026 was established in 2002[1] by amino acid composition analyses and NMR analyses with chemical modifications. MA026 was found to consist of a cyclodepsipeptide composed of eight amino acids, a chain peptide composed of six amino acids, and an N-terminal (*R*)-3-hydroxydecanoic acid. In total, MA026 contains 14 amino acids, nine of which possess the D configuration, as shown by HPLC analyses using Marfey's reagent. The amino acid sequence was determined by MS/MS analyses and comparison of partial peptide segments obtained by degradation of the natural product with synthetic peptides. The cyclodepsipeptide comprises a 25-membered ring in which the carboxylic group of L-Ile[14] forms a lactone bond with the hydroxy group of D-Ser[7]. To date, a wide range of lipocyclodepsipeptides have been identified,[10] including xantholysin A, an analogue of MA026.[11] In terms of sequence, xantholysin A differs from MA026 by two amino acids, namely, Gln[10]-Leu[11] in xantholysin A versus L-Leu[10]-D-Gln[11] in MA026. However, absolute configurations at all stereogenic centers in xantholysin A have yet to be determined.

In common with a number of lipocyclodepsipeptides, MA026 possesses a complex structure and interesting biological activity. In particular, MA026 displays anti-HCV activity that could be used to develop a novel antiviral drug. However, in order to reveal the mechanism of this anti-HCV activity, it is essential to develop a flexible chemical synthesis of MA026 to facilitate chemical modification of its structure. Herein we describe the first total synthesis of MA026 (**1**). Using a HCV cell culture assay, we have clarified that MA026 inhibits the HCV entry process into a hepatocyte cell line. Moreover, phage display screening and surface plasmon resonance (SPR) binding analyses suggested that MA026 might interact with claudin-1 (CLDN1), a cellular entry receptor of HCV.

RESULTS AND DISCUSSION

Retrosynthetic Analysis. MA026 (**1**) was divided into two key segments to maximize the convergency of the synthesis: side chain **2** and cyclodepsipeptide **3** (Scheme 1). The cyclodepsipeptide contains a lactone bond composed of the carboxylic group of L-Ile[14] and the hydroxy group of D-Ser[7]. We envisaged a potential exchange of an ester bond with an amide bond by attack of a free N-terminal amine located proximal to the ester linkage.[12] To prevent such an exchange, it is necessary to maintain a sufficient distance between the ester bond and the N-terminus of the cyclodepsipeptide. Therefore, **3** should contain the cyclodepsipeptide plus an additional two amino acids, with the coupling site of **2** and **3** chosen to be D-Val[4]-D-Leu[5]. The side chain **2** was separated between L-Leu[1] and D-Glu[2] to give fatty acid moiety **4** and tripeptide **5**.

Key to the synthesis of cyclodepsipeptide **3** was the macrocyclization of a decapeptide (Scheme 2). Because it is more difficult to construct an ester bond than an amide bond,[13] we decided to disconnect the macrocycle at an amide bond and construct an ester bond in the early stage of the synthesis. The macrocyclization site was chosen at L-Leu[10]-D-Gln[11] considering the steric hindrance due to the isopropyl group of Val or the isobutyl group of Leu. The macrocyclization substrate, decadepsipeptide **6**, was to be prepared by the joining of hexadepsipeptide **7** with two dipeptides.

In the course of the construction of several peptide fragments, selective protection and deprotection of specific functional groups are critical. The Fmoc group was employed to protect the N-terminal amines of cyclodepsipeptide **3** and tripeptide **5**. The orthogonal Boc group was used to protect the N-terminal amines of other peptides. We also introduced a trityl (Tr) protecting group for the side-chain amides of D-Gln[3] and L-Gln[6] to maintain the solubility of the peptides in several organic solvents. In particular, the Tr group plays a significant role in affording solubility for peptides in aprotic solvents such as THF. During the preparation of Tr-protected Gln, an amine was protected with an Alloc group, as this protective group could be selectively removed using a palladium catalyst without affecting the Tr group.

Synthesis of Side Chain 2. We began our synthetic efforts by targeting fatty acid moiety **4** (Scheme 3). Protection of alcohol **8**[14] with a *tert*-butyldimethylsilyl (TBS) group afforded (*R*)-3-hydroxycarboximide **9** in 97% yield. The chiral auxiliary of **9** was hydrolyzed (58% yield), and the resulting carboxylic acid was then coupled with TsOH·L-Leu-OBn to provide fatty acid moiety **4** in 66% yield.

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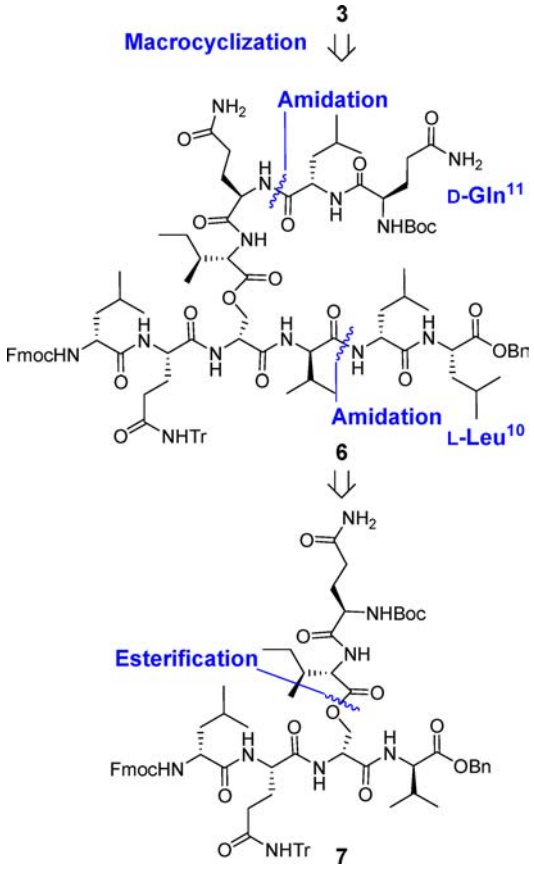
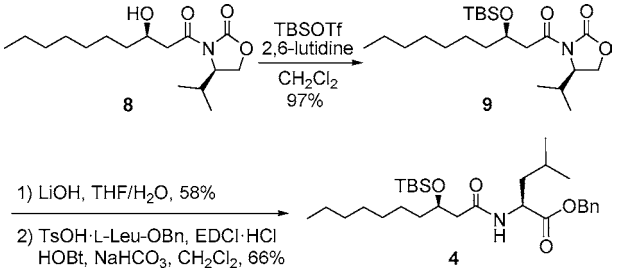
Scheme 2. Retrosynthetic Analysis of Cyclodepsipeptide 3

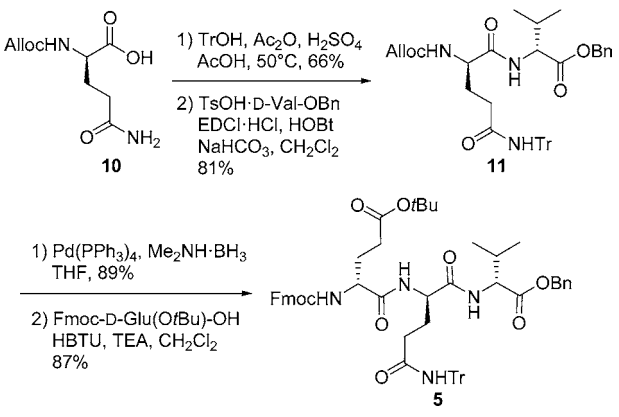


Scheme 3. Synthesis of Fatty Acid Moiety 4



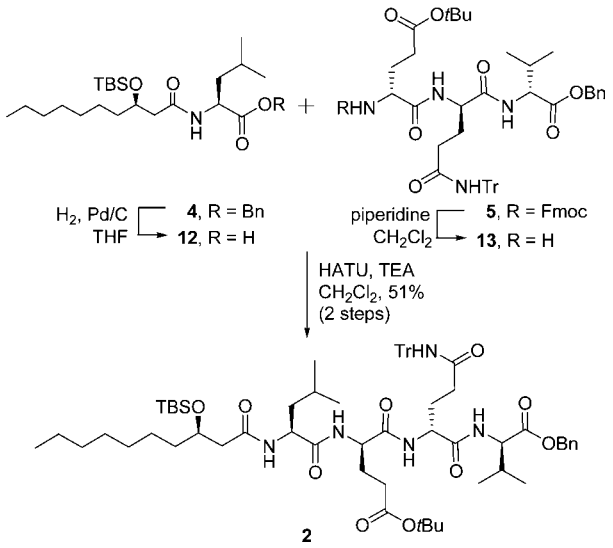
Tripeptide **5** was assembled as follows (Scheme 4). Alloc-D-Gln-OH (**10**) was treated with trityl alcohol and acetic anhydride under acidic conditions[15] to give the side-chain-protected residue in 66% yield. Subsequent condensation of this product with TsOH·D-Val-OBn provided dipeptide **11** in 81% yield. The Alloc group of **11** was then removed in the presence of a palladium catalyst and dimethylamine borane[16] (89% yield), and the resulting amine residue was coupled with Fmoc-D-Glu(O*t*Bu)-OH to afford **5** in 87% yield.

Scheme 4. Preparation of Tripeptide 5



With fatty acid moiety **4** and tripeptide **5** in hand, we tried to link them together to obtain side chain **2** (Scheme 5).

Scheme 5. Synthesis of Side Chain 2



Hydrogenolysis of the benzyl ester in **4** gave carboxylic acid **12**, and cleavage of the Fmoc group in **5** by treatment with piperidine provided amine **13**.[17] Condensation of **12** with **13** in the presence of 2-(1*H*-7-azabenzotriazol)-1-yl-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) and triethylamine (TEA) afforded side chain **2** in 51% yield over the two steps.

Synthesis of Cyclodepsipeptide 3. The synthesis of the other key subunit, cyclodepsipeptide **3**, started with the construction of hexadepsipeptide **7**, an intermediate leading to the macrocyclization substrate, decadepsipeptide **6** (Scheme 6). To assemble **7** efficiently, three dipeptides were prepared as follows. Alloc-L-Gln-OH (**14**)[18] was treated with benzyl bromide and 1,8-diazabicycloundec-7-ene (DBU) to give the benzyl ester in 92% yield. Subsequent side-chain protection with a Tr group (86% yield) and removal of the Alloc group were performed by the same procedure as described earlier to give amine residue **15** in 94% yield. Condensation of **15** with Fmoc-D-Leu (93% yield) followed by hydrogenolysis of the benzyl ester afforded the corresponding dipeptide carboxylic acid **16** in 98% yield. Boc-D-Ser[19] and D-Val-OBn were coupled (92% yield), and cleavage of the carbamate linkage under acidic conditions furnished the corresponding dipeptide amine **17** in quantitative yield. Condensation of Boc-D-Gln with L-Ile-OBn (95% yield) and subsequent benzyl ester hydrogenolysis provided the corresponding dipeptide carboxylic acid **18** in 92% yield. Coupling of **16** with **17** in the presence of *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU) and TEA afforded tetrapeptide **19** in 90% yield. The key esterification of the hindered alcohol of **19** with dipeptide carboxylic acid **18** was problematic. A wide range of procedures were examined, including the use of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

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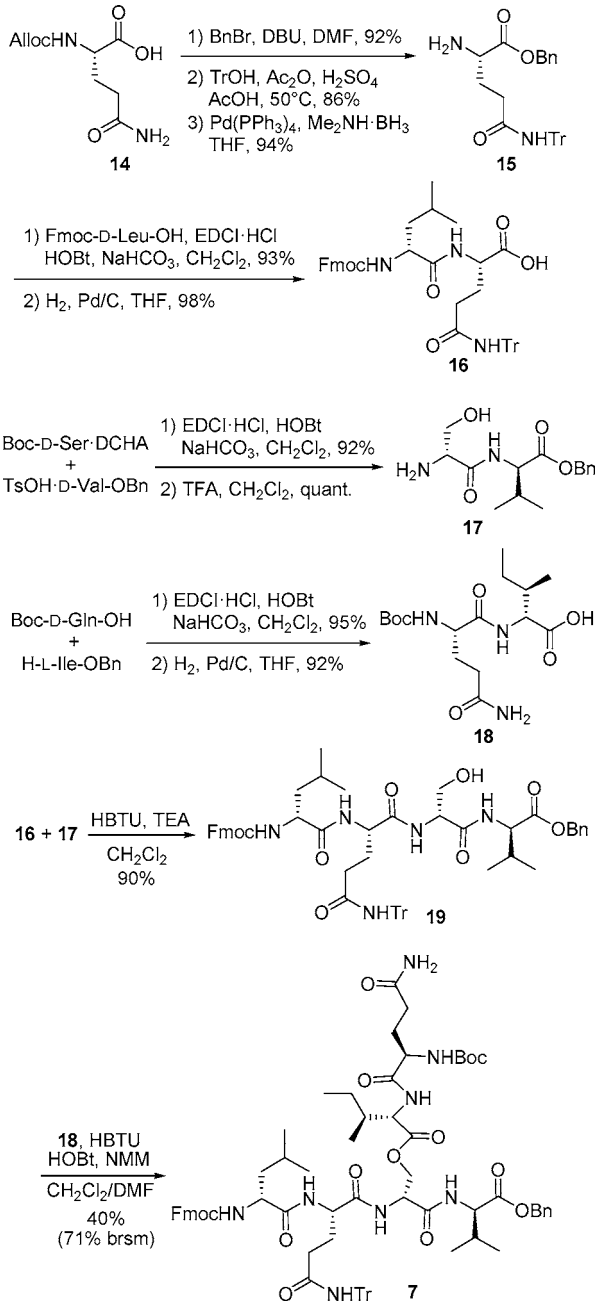
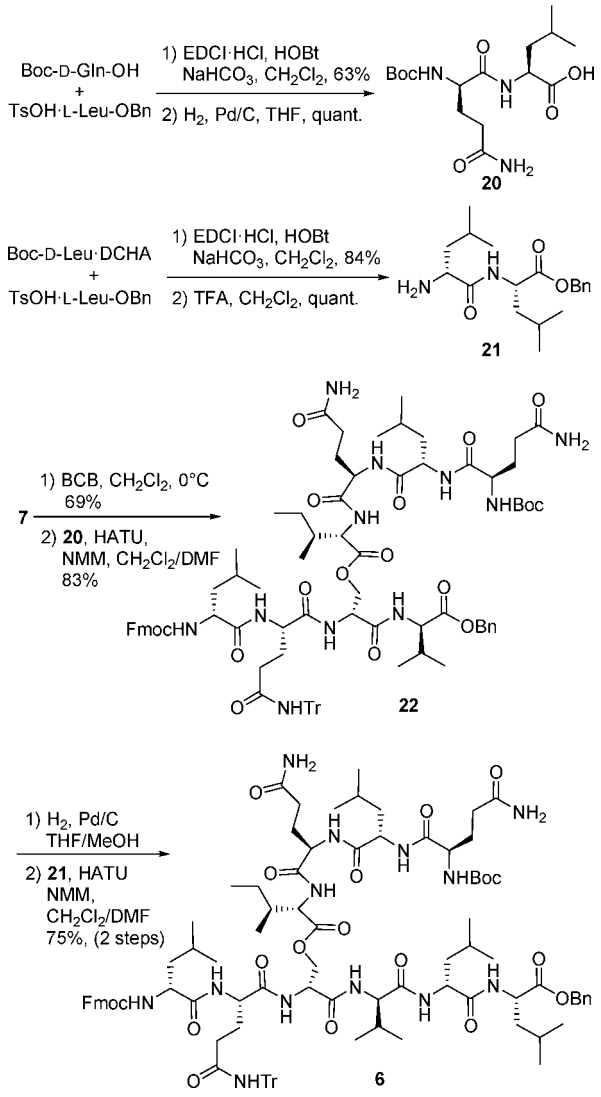
Scheme 6. Construction of Hexadepsipeptide 7



Scheme 7. Synthesis of Decadepsipeptide 6



(EDCI), reactive mixed-anhydride activations, Yamaguchi esterification,[20] the Mukaiyama reagent,[21] and the Shiina reagent.[22] An esterification with EDCI, 1-hydroxybenzotriazole (HOBt) and *N*-methylmorpholine (NMM) resulted in low conversion, while the other protocols yielded no detectable product. Finally, esterification of **19** with **18** was successfully achieved in the presence of HBTU, HOBt, and NMM to afford hexadepsipeptide **7** in 40% yield (71% brsm).

With hexadepsipeptide **7** assembled, we turned our attention to the synthesis of decadepsipepide **6** (Scheme 7). Two dipeptides **20** and **21**, components of **6**, were prepared as described below. Condensation of Boc-D-Gln with L-Leu-OBn (63% yield) followed by benzyl ester hydrogenolysis gave the corresponding dipeptide carboxylic acid **20** in quantitative yield. Boc-D-Leu and L-Leu-OBn were coupled (84% yield), and removal of the Boc group under acidic conditions provided the corresponding dipeptide amine **21** in quantitative yield. The next step was the incorporation of these dipeptides into hexadepsipeptide **7**. Selective removal of the Boc group of **7** without affecting the Tr group was accomplished by treatment with *B*-bromocatecholborane (BCB)[23] in CH_2Cl_2 in 69% yield, and the resulting hexadepsipeptide amine was coupled with **20** in the presence of HATU and NMM to afford octadepsipeptide **22** in 83% yield. Next, benzyl ester hydrogenolysis of **22** was performed. However, an unexpected cleavage of the Fmoc group was observed when this reaction was conducted in methanol (MeOH). In the case of another benzyl ester hydrogenolysis that provided dipeptide carboxylic acid **16** (Scheme 6), the Bn group was removed without the cleavage of the Fmoc group in tetrahydrofuran (THF). Octadepsipeptide **22** was difficult to dissolve in a moderately polar aprotic solvent such as THF, while the dipeptide described above dissolved with ease. This problem was resolved by introducing a 3:1 mixture of THF and MeOH as the solvent and adjusting the reaction time to allow complete benzyl ester hydrogenolysis.[24] Removal of the Bn group of **22** in 3:1 THF/MeOH provided the corresponding carboxylic acid. Subsequent coupling with **21** afforded decadepsipeptide **6** in 75% yield over the two steps.

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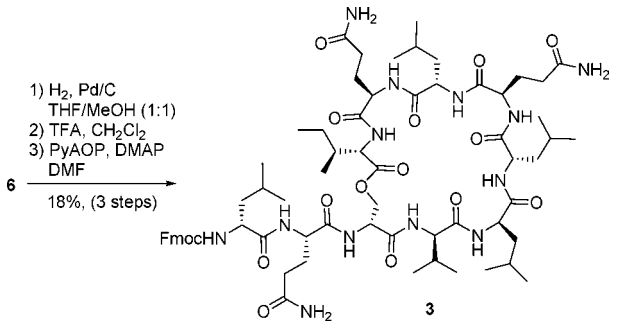
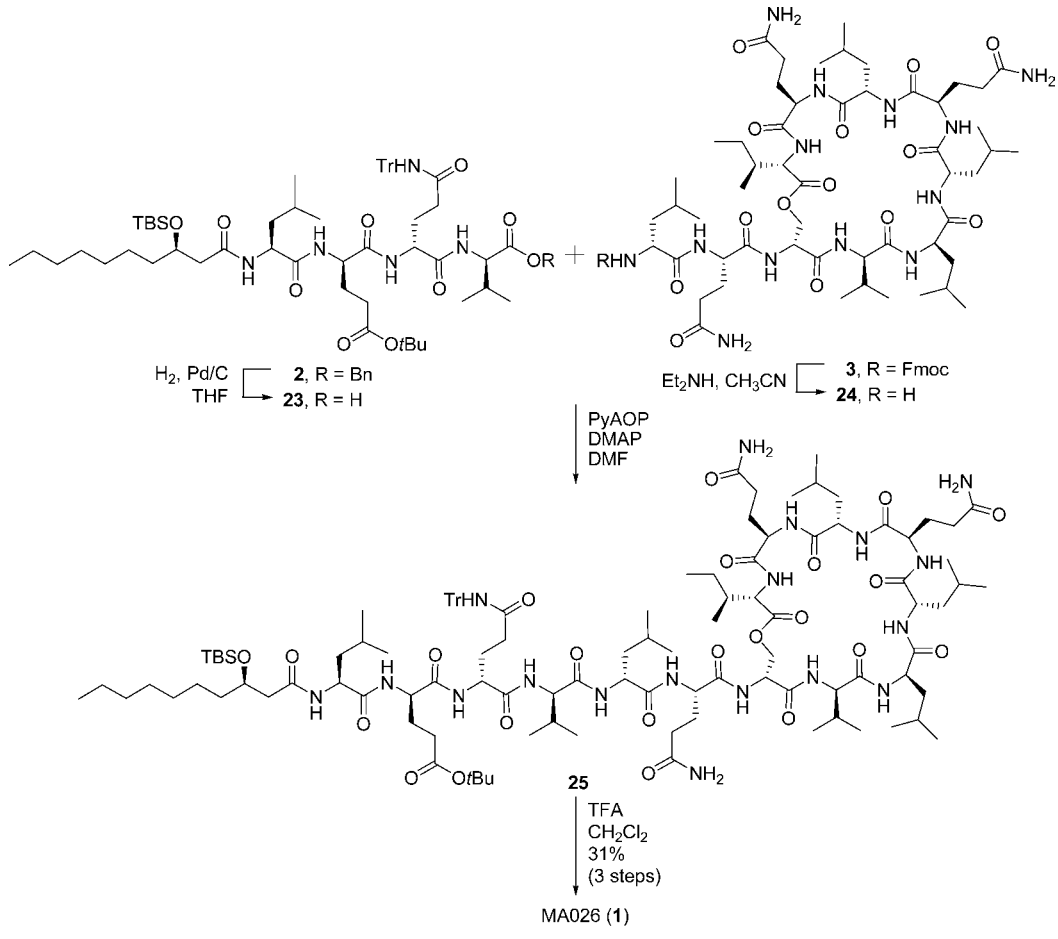
Having successfully obtained the macrocyclization substrate decadepsipeptide **6**, we next examined the cleavage of the Boc, Bn, and Tr groups and the subsequent intramolecular macrocyclization (Scheme 8). First, the Boc and Tr groups of **6** were removed under acidic conditions to provide the corresponding decadepsipeptide amine. The resulting product was next subjected to benzyl ester hydrogenolysis. However, it proved difficult to remove the benzyl ester selectively without affecting the Fmoc group because the decadepsipeptide amine dissolved in polar protic solvents such as MeOH or mixed solvents of THF/MeOH containing MeOH at a higher rate. Therefore, the deprotection sequence was changed. Benzyl ester hydrogenolysis of **6** proceeded in 1:1 THF/MeOH to provide the corresponding decadepsipeptide carboxylic acid, and then the Boc and Tr groups were removed with trifluoroacetic acid (TFA) in CH_2Cl_2 to afford the macrocyclization precursor.[25] At the stage of macrocyclization, reactions were performed under high-dilution conditions by slow addition of the substrate using a syringe pump in order to prevent the intermolecular reaction. We conducted the macrocyclization reaction with several coupling reagents,[26] including HATU, (benzotriazol-1-yloxy)tris(dimethylamino)-phosphonium hexafluorophosphate (BOP), (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBop), and (7-azabenzotriazol-1-yloxy)-tripyrrolidinophosphonium hexafluorophosphate (PyAOP). The protocol using PyAOP and 4-dimethylaminopyridine (DMAP) in DMF was found to promote the closure of the 25-membered ring to afford cyclodepsipeptide **3** in 18% yield over the three steps.

Scheme 8. Synthesis of Cyclodepsipeptide 3



Total Synthesis of MA026. With the two required key segments (side chain **2** and cyclodepsipeptide **3**) in hand, we sought to link them together to accomplish the synthesis of MA026 (**1**) (Scheme 9). Removal of the N-terminal Fmoc group of **3** proceeded with diethylamine in DMF to provide the corresponding cyclodepsipeptide amine **24**. An alternative deprotection with piperidine resulted in the formation of several side products that were difficult to separate from **24**. Benzyl ester hydrogenolysis of **2** and subsequent coupling with amine **24** in the presence of PyAOP and DMAP furnished **25**. Although the deprotection of **2** and **3** gave corresponding

Scheme 9. Synthesis of MA026 (1)



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carboxylic acid **23** and amine **24** in quantitative yield, their coupling did not proceed completely. Finally, a single-step cleavage of the Tr, *t*Bu, and TBS groups in **25** was achieved with TFA. The crude material was purified by reversed-phase HPLC to furnish pure **1** in 31% yield over the three steps. Analysis of synthetic **1** by ^{1}H and ^{13}C NMR spectroscopy, along with other spectroscopic data, showed it to be identical to the natural product.

Anti-HCV Activity of MA026 (1). MA026 shows antiviral activity against both IHNV and HCV. Given the fact that IHNV and HCV share a common entry process,[27,28] we reasoned that MA026 might inhibit the HCV entry process, which consists of attachment, internalization, and endocytosis. On the basis of this prediction, we studied the anti-HCV activity of MA026 by measuring the HCV infectivity to determine whether MA026 inhibits the HCV entry process. Moreover, we compared the anti-HCV activity of synthetic **1** with that of the natural product (Figure 2).[29] Infectious HCV

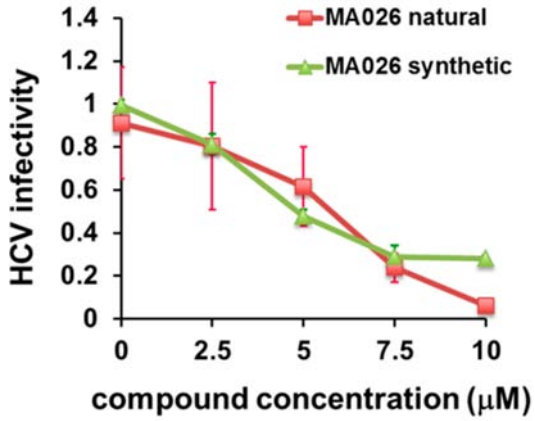

Figure 2. Evaluation of the anti-HCV activity of synthetic and natural **1**. The normalized infectivity was calculated as the HCV infectivity divided by the cell viability.

particles were pretreated with compounds for 1 h and infected into Huh-7.5.1 cells for 4 h. After residual virus and the test compound were washed out, cells were further cultured with growth medium in the absence of the compound for 72 h. The infectivity of HCV in the medium was quantified, and half-maximal inhibitory concentration (IC_{50}) values of the compounds were determined. In this assay, cells were exposed to the test compound only before and during HCV infection. Therefore, this pretreatment procedure could evaluate the potency of the test compound to inhibit the HCV entry process into the host cells. As shown in Figure 2, both synthetic **1** and the authentic natural product suppressed HCV infection into the host cells in a dose-dependent manner (IC_{50} = 4.39 and 4.68 μM, respectively). Moreover, incubation in the presence of these compounds did not induce significant cytotoxicity within the concentration range used in these tests (Figure S1 in the Supporting Information). Thus, our data suggest that MA026 inhibits HCV infection by blocking the entry process. **Phage display screening and SPR binding analyses suggested claudin-1 as a candidate target for the anti-HCV activity of MA026.**

To identify MA026 binding proteins, we applied a chemical biology approach and performed phage display screening.[30] Previously, we used phage display analyses to elucidate a novel mechanism of HCV replication by identifying the target protein of cyclosporin A.[31] Here we employed the same strategy to identify the target of MA026. MA026 was first immobilized on photoaffinity resin containing a photoactive diazirine group that we previously developed (Scheme S1 in the Supporting Information).[32,33] The mixture of photoafiinity resin and MA026 was irradiated with UV light. The highly reactive carbene induced by UV irradiation reacted with MA026, resulting in the production of immobilized MA026 in a nonspecific manner. Having prepared the MA026-immobilized resin, we then performed phage display screening using a random phage library displaying random peptides composed of 15 amino acids.[34] The phage display screening method is a powerful tool for identifying binding proteins of specific ligands. In this method, the phage library displaying peptides on phage particles (Input) was incubated with either MA026-immobilized resin or control resin (Bind) (Figure 3A and Figure S2A in the Supporting Information). Unbound phage particles were removed by washing (Selection). Phage particles bound to the MA026-immobilized resin were then eluted (Elute) and amplified in *Escherichia coli* (Amplify). The recovered phage clones (Input) were subsequently subjected to the next round of biopanning. Upon iteration of the biopanning cycles, the recovery rate of eluted phage clones compared with Input increased (Figure S2B). The relative enrichment of phage particles bound to MA026-immobilized resin was the highest upon the elution from the fourth round of biopanning (Figure 3B). Therefore, we randomly picked 27 single phage clones from the fourth-round elution. The sequence of peptides displayed on the phage particles, which were responsible for interaction with MA026, were determined from the DNA sequences of the corresponding phage vectors (Table S1 in the Supporting Information). Multiple sequence alignment analyses using CLUSTALW[35] indicated that peptides 1, 3, 10, 19, and 24 shared homology (Figure S3). Among them, we found the peptide sequence VFDSLL, a partially homologous sequence. We then searched the protein database using BLAST[36] to find proteins that showed similarities to the VFDSLL sequence. A single protein that includes the VFDSLL sequence, claudin-1 (CLDN1), was identified in the NCBI database. CLDN1 is highly expressed in the liver and plays an important role during the post cell binding process of HCV entry.[37]

On the basis of this knowledge and the result of phage display screenings followed by CLUSTALW and BLAST analyses, we proposed a hypothesis that MA026 might interact with CLDN1 and thereby suppress HCV infection. To confirm the interaction between CLDN1 and MA026, we performed SPR binding analyses using recombinant CLDN1 protein with an N-terminal glutathione S-transferase tag (CLDN1-GST). CLDN1-GST, or GST itself as a negative control, was first immobilized on a sensor chip of the SPR biosensor (Biacore 3000), and MA026 samples at different concentrations were then injected over the immobilized proteins.[38] The SPR data (Figure 3C) were subsequently analyzed to determine the dissociation constant (K_D). Our results showed a specific dose-dependent binding response of MA026 with CLDN1-GST (K_D = 2.5 × 10^{-6} M). By contrast, the response with GST itself was significantly weaker (K_D = 4.0 × 10^{-5} M). These results indicate a specific interaction between MA026 and recombinant CLDN1 protein.

The process of HCV entry into human hepatocytes requires the interaction of HCV glycoproteins E1 and E2 with host

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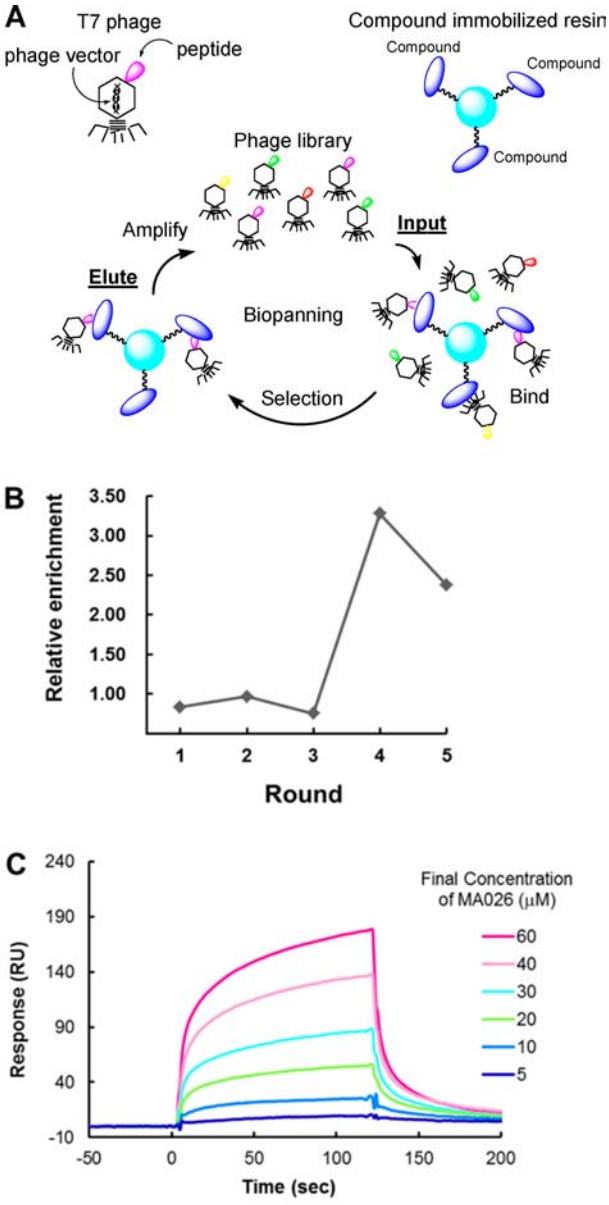

Figure 3. Phage display screenings and SPR analyses. (A) Procedure of phage display screening. (B) Relative enrichment of phage particles bound to MA026-immobilized resin. Relative enrichment was determined as the ratio of phage titer of elution from MA026-imobilized resin to phage titer of elution from control resin. (C) SPR analysis of binding between CLDN1-GST and MA026. Response units (RU) were calculated by subtracting the background response measured on the control flow cell from the response with the MA026 flow cell.

receptors, including tetraspanin CD81 and the high density lipoprotein receptor scavenger receptor class B type I (SR-BI).[39] It was reported that these two receptors are not sufficient for HCV entry and that more host proteins are involved.[40] CLDN1 is a transmembrane protein and belongs to a family of tight junction proteins that act as a barrier in cellular permeability.[41] It has been proposed that during the course of HCV entry, CLDN1 interacts with CD81 and influences the cell entry process, including endocytosis.[42] Although direct binding between HCV particles and CLDN1 has not been conclusively demonstrated, it has been shown that monoclonal anti-CLDN1 antibodies prevent HCV infection.[43] The peptide sequence VFDSLL, which is likely to interact with MA026, is conserved in the first extracellular loop (EL1) of CLDN1, and this loop is required for HCV entry.[37] The SPR analysis showed an interaction between MA026 and CLDN1-GST, and this result supports our hypothesis that MA026 might interact with CLDN1 and thereby prevent CLDN1 from interacting with CD81 and the HCV particle.

CONCLUSIONS

The first total synthesis of MA026 was achieved in the solution phase with two key segments: side chain **2** and cyclodepsipeptide **3**. The construction of side chain **2** was accomplished with good efficiency by coupling of fatty acid moiety **4** with tripeptide **5**. In the preparation of macrocyclization substrate decadepsipeptide **6**, an appropriate choice of solvent was required to avoid the cleavage of the N-terminal Fmoc group through hydrogenolysis reactions. The key macrocyclization of the decadepsipeptide at L-Leu[10]-D-Gln[11] was accomplished with PyAOP to afford **3**. This convergent modular synthetic route will be useful for the synthesis of a series of MA026 derivatives that will facilitate structure−activity relationship studies. Moreover, xantholysin A, an analogue of MA026, could be synthesized via this route once the stereochemistry is determined.

The anti-HCV activities of synthetic **1** and the authentic natural product were assessed and found to be similar. In this assay, the cells were exposed to the test compound only before and during HCV infection and then subsequently cultured in the absence of the test compound until sampling. Our results suggest that MA026 might inhibit the early step of HCV infection, including the cell entry process, rather than the following steps such as RNA replication and viral assembly and release. Phage display screenings were performed using MA026-immobilized resin and a random phage library. As the biopanning cycle was repeated, the ratio of phage clones bound to MA026 increased. We randomly picked 27 single phage clones and determined the peptide sequences displayed on the phage particles. From the results of multiple sequence alignment analyses using CLUSTALW, we found VFDSLL, a partially homologous peptide sequence. A BLAST search identified CLDN1 as a protein bearing the VFDSLL sequence. This protein plays an important role in the HCV entry process. The specific interaction between MA026 and recombinant CLDN1 protein was then confirmed by SPR analyses. Because the VFDSLL sequence is conserved in EL1 of CLDN1, we speculate that MA026 might interact with EL1 of CLDN1 and thereby interrupt HCV entry into the host cell.

Further investigations to develop an improved synthetic route that provides more efficient access to analogues and to reveal the detailed mechanism of the anti-HCV activity of MA026 are currently underway and will be disclosed in due course.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analytical data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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