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Total synthesis and NMR conformational study of signal peptidase II inhibitors, globomycin and SF-1902 A_5

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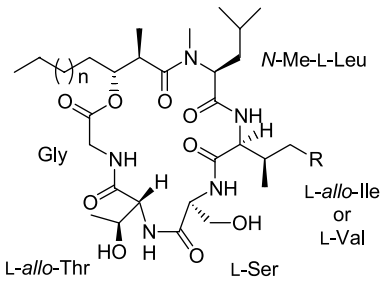
Abstract—A stereoselective total synthesis of an antibiotic, globomycin (**1a**), and its congener, SF-1902 A_5 (**1b**), was achieved. Two convergent macrocyclization routes via macrolactamization or macrolactonization to form **1a** are described. A conformational study by means of NMR spectroscopy was performed in several solvents. The ^{1}H NMR spectrum of **1a** indicated that the amide proton of only the L-*allo*-Thr residue was involved in the hydrogen bonding. The structure in solution phase was different from the X-ray structure. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

Globomycin (**1a**)[1] and its congeners, SF-1902 A_2–A_5 (**1b**–**f**),[2] first isolated from four different strains of actinomycetes (*Streptomyces halstedii* No. 13912 among others) in 1978, are 19-membered cyclic depsipeptides. The major component, **1a**, is the first natural product[1c,3] which contains both, an L-*allo*-Ile and L-*allo*-Thr, and has a biologically unique activity as an antibiotic against Gram-negative bacteria.[1,2] Globomycin (**1a**) has only been proven to be a specific inhibitor of signal peptidase II, a prolipoprotein-processing enzyme,[4] that processes the acylated precursor form of lipoprotein into apolipoprotein and a signal peptide in *Escherichia coli*.[6] A breakthrough in lipoprotein research was the finding that signal peptidase II is specifically inhibited by **1a**.[5,6] Inhibition of signal peptidase II by **1a** leads to the accumulation of the acylated form of lipoprotein in the cytoplasmic membrane and consequently to the death of the cell.[7a] Signal peptidase II represents an attractive target for developing a new class of antibiotics that function by a different mechanism from currently available drugs. Globomycin, which is known to inhibit the processing of lipoproteins, has been used routinely to demonstrate the acylation of newly identified lipoproteins.[8] It has been widely used for controlling the maturation of lipopeptides[7] and as an invaluable tool in studies of lipoprotein biosynthesis.[9] Structurally, **1a**–**f** commonly contain four natural amino acids, one *N*-Me amino acid and a β-hydroxy-α-methyl carboxylic acid which greatly contributes to the antibacterial activity.[2] The minor components, SF-1902 A_2–A_5 (**1b**–**f**), share four or five amino acids with **1a**, as shown in Figure 1.

The congeners, **1e** and **1f**, have an L-Val in place of an L-*allo*-Ile and the other congeners, **1b**–**1d**, have a shorter or longer alkyl side-chain in the fatty acid unit than **1a**. The relative and absolute stereochemistry of the 3-hydroxy-2-methylnonanoyl-*N*-Me-Leu moiety in **1a** remained ambiguous for a long time. However, we reported the absolute structure as determined by X-ray analysis and the first total synthesis of **1a** in a recent communication.[1d] Since then, we obtained more details on the structural conformation of **1a** in some solvents, which indicate a structure different from the X-ray structure. We present here the asymmetric total synthesis of **1a** and its congener **1b** based on the macrolactamization method, and an alternative convergent route via macrolactonization.



	R	n
1a	CH_3	3
1b	CH_3	5
1c	CH_3	4
1d	CH_3	1
1e	H	3
1f	H	5

Figure 1. Globomycin (**1a**) and its congeners.

Keywords: globomycin; macrolactamization; antibiotics; signal peptidase II; macrolactonization.

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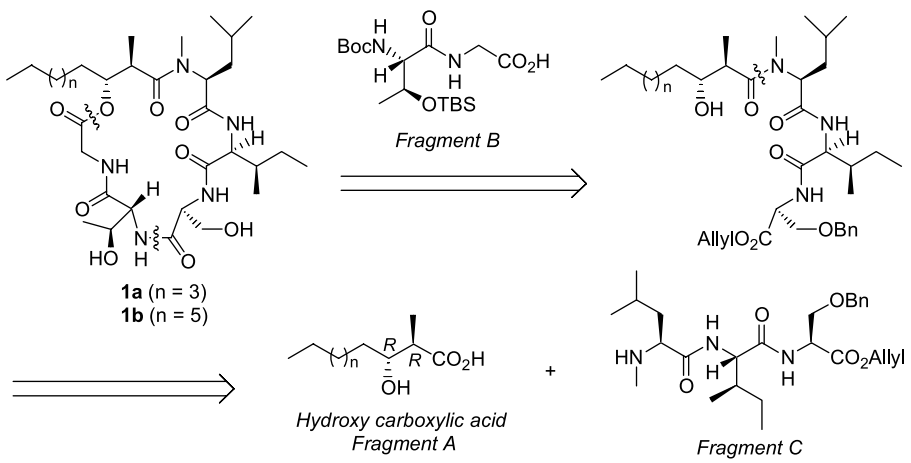


Scheme 1. Retro synthetic analysis.

2. Results and discussion

2.1. Synthetic plan

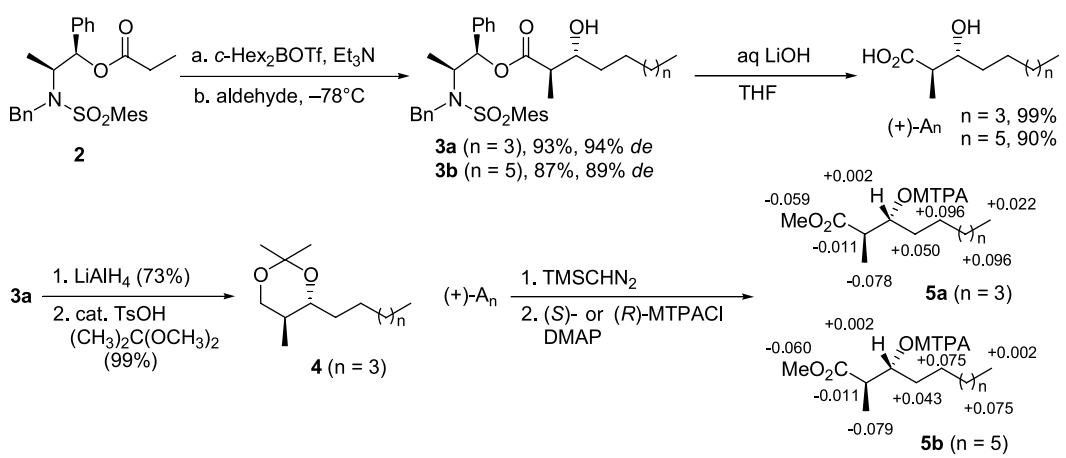
Our approach to the synthesis of **1** began by dividing the compound into three fragments as shown in Scheme 1: (i) (2*R*, 3*R*)-3-hydroxy-2-methylcarboxylic acid unit, Fragment A; (ii) L-*allo*-Thr-Gly unit, Fragment B; and (iii) *N*-Me-L-Leu-L-*allo*-Ile-L-Ser unit, Fragment C. These fragments were then combined to construct **1** with macrolactamization or macrolactonization as the key reaction. According to our strategy, the difficult *N*-acylation step between Fragment A and C was introduced early for both routes. In the route with macrolactamization, esterification to form the β-acyloxy acid moiety was carried out later to avoid a β-elimination reaction and a ring closure was attempted between the C terminus of Fragment C and the amine of Fragment B which was considered to be one of the less-hindered sites. On the other hand, the macrolactonization route has the great advantage that no epimerization occurs even under severe conditions because the C terminus is Gly.

2.2. Preparation of fragments

2.2.1. Fragment A. Of the three fragments, Fragment A is particularly important as it is the only non-amino acid containing part.

Thus, we choose the *anti*-selective boron-mediated asymmetric aldol reaction developed by Abiko and Masamune[10] for its preparation as shown in Scheme 2. The commercially available ester **2** was enolized with a dicyclohexylboron triflate in the presence of triethylamine, and then this was reacted with an aldehyde at −78°C to afford *anti*-aldol product **3** in high yield and with high selectivity (87–93%, 89–94% *de*).

Finally, hydroxy ester **3** was hydrolyzed with aqueous LiOH in THF to give (+)-A_n without epimerization in good yield (90–99%). The relative stereochemistry of (+)-A_n was confirmed from the ^{1}H NMR coupling constant[11] and NOESY experiment after the conversion to acetonide **4** (73%, 2 steps). Two large axial–axial coupling constants (J=11.0, 11.5 Hz) for the H_D proton and NOESY correlations among H_A, H_C and the axial methyl group in **4** were observed as shown in Figure 2. These results indicated that the relative stereochemistry of C(2)–C(3) in **4** was *anti*. Thereafter, the absolute configuration of C(3) in (+)-A_3 was established by the modified Mosher's method.[12] An acid (+)-A_3 was treated with $TMSCHN_2$[13] followed by esterification with (*R*)- or (*S*)-MTPA chloride to afford



Scheme 2. Synthesis of Fragment A.

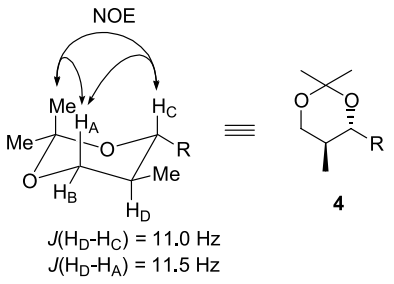
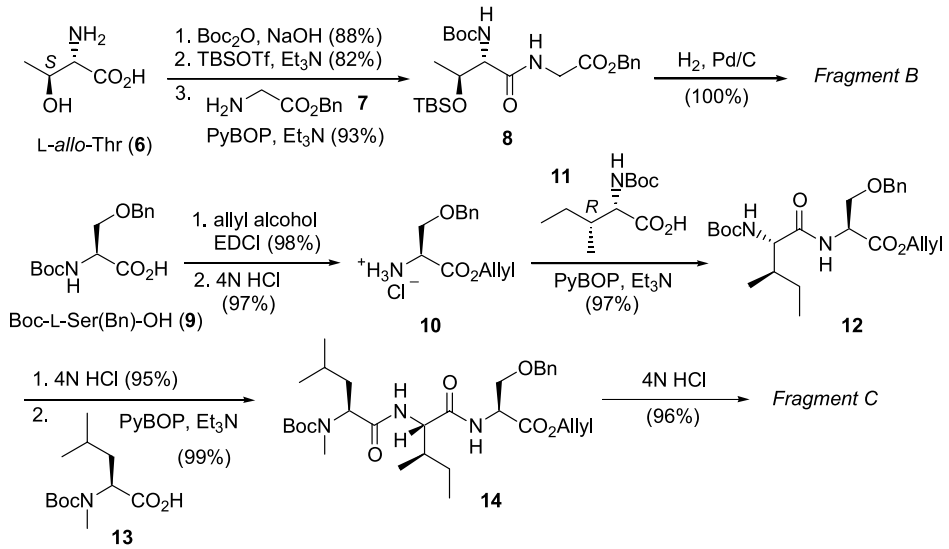


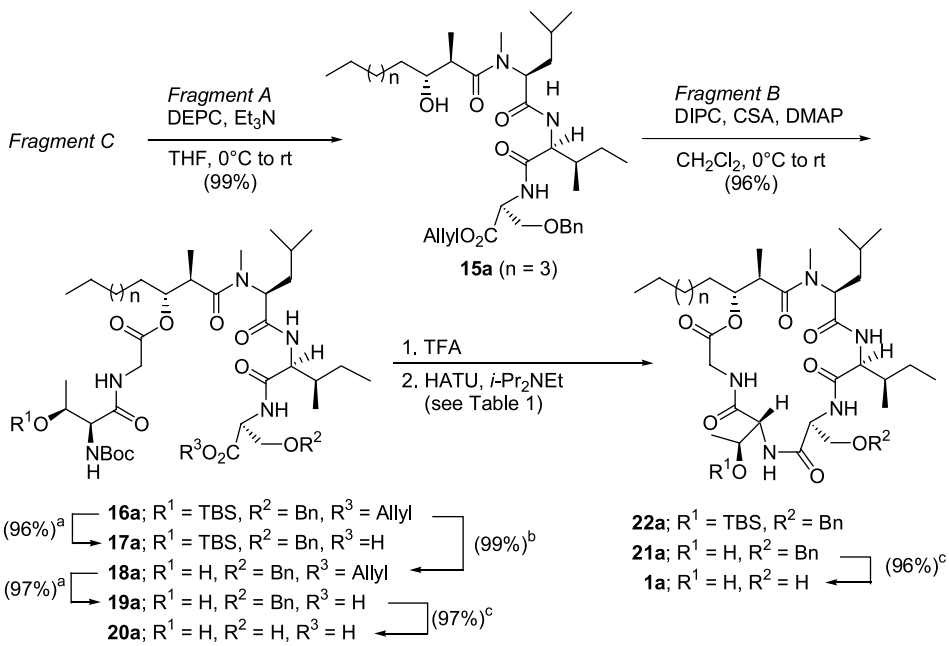
Figure 2. NOE experiment of acetonide **4**.

(*R*)- or (*S*)-MTPA ester ((*R*)- or (*S*)-**5a**), respectively. The $\Delta\delta$ ($\delta_{(S)\text{-MTPA ester}} - \delta_{(R)\text{-MTPA ester}}$) values of the C(4)$H_2$–C(11)$H_3$ group were positive and the same values of the C(2)H, C(3)′H_3 and OCH_3 group were negative, indicating that the configuration of C(3) in **5** was (*R*). Hence, the stereochemistry of fatty acid (+)-A_3 was (2*R*, 3*R*). The absolute configuration of (+)-A_5 was also confirmed in the same manner with (*R*)- and (*S*)-**5b**, and the same result was obtained.

2.2.2. Fragment B and C. The dipeptide unit, Fragment B, was prepared from commercially available L-*allo*-threonine (L-*allo*-Thr-OH) (**6**) and glycine benzyl ester (Gly-OBn) (**7**) as shown in Scheme 3. The protection of **6** with Boc_2O (88%) and then with TBSOTf (82%) gave *N*-Boc-L-*allo*-Thr(TBS)-OH. This acid was condensed with **7** to afford fully protected dipeptide **8** (93%). Compound **8** was hydrogenolyzed to give the dipeptide Fragment B (100%). L-Serine derivative (Boc-L-Ser(Bn)-OH) (**9**) was employed as the starting material for the synthesis of tripeptide Fragment C. The allylation of **9** followed by the deprotection of the Boc group with 4N HCl in EtOAc gave allyl ester



Scheme 3. Synthesis of Fragment B and C.



Scheme 4. Total synthesis of **1a** via macrolactamization. *Reagents and conditions*: (a) cat $Pd(PPh_3)_4$, morpholine (b) TBAF, AcOH (c) H_2, $Pd(OH)_2$.

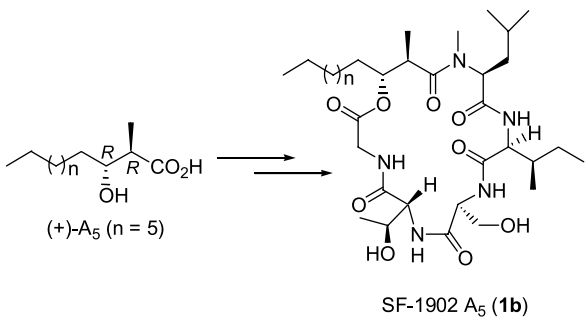
Table 1. Yield of macrolactamized product

Product	Yield (%) (2 steps)
22a	trace
21a	45
1a	39

10 as an HCl salt (95%, 2 steps). This salt was coupled with Boc-L-*allo*-isoleucine (Boc-L-*allo*-Ile-OH) (**11**) mediated by (benzotriazolyloxy) tris(pyrrolydino)phosphonium hexafluorophosphate (PyBOP)[14] to give dipeptide **12** (97%). The removal of the Boc group in **12** followed by the coupling with Boc-*N*-methyl-leucine (Boc-*N*-Me-L-Leu-OH) (**13**) produced tripeptide **14** (94%, 2 steps). The treatment of **14** with HCl in EtOAc and then with saturated $NaHCO_3$ aqueous solution afforded Fragment C as a free amine (96%).

2.3. Macrolactamization route

With the three Fragments A–C, the formation of a linear depsipeptide was attempted via two routes for macrolactamization. First, we tried coupling Fragment C and the ester synthesized from Fragment A and B. However, the reaction failed due to a β-elimination of the Fragment B unit from the depsipeptide. Successful synthesis of the target macrocyclic precursor was achieved by a coupling Fragment A and C followed by a esterification with Fragment B (Scheme 4).

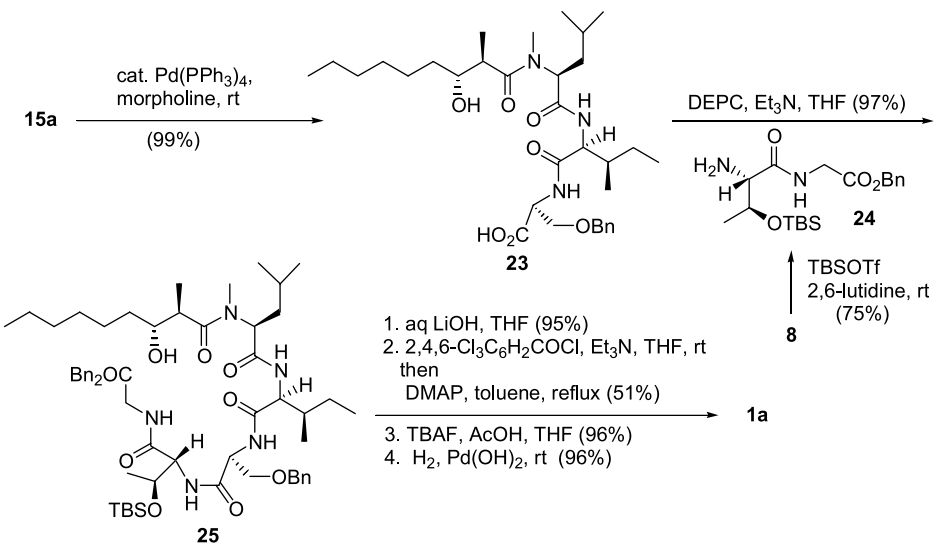


Scheme 5.

Tripeptide C was condensed with (+)-A_3 mediated by diethylcyanophosphate (DEPC)[15] and without protection of the hydroxyl group in (+)-A_3, to give the acylated tripeptide **15a** (99%). Esterification of **15a** was performed with diisopropylcarbodiimide (DIPC) and Fragment B under Keck's condition[16] to afford **16a** (96%). The treatment of the fully protected seco-acid **16a** with TBAF and AcOH provided **18a** (99%). The removal of the allyl group in **18a** with $Pd(PPh_3)_4$ and morpholine gave acid **19a** (99%). The macrocyclic precursor obtained by the deprotection of the Boc group was used for macrolactamization. As well other macrocyclic precursors were prepared from **17a** and debenzylated derivative **20a** and deprotected in the same manners as described above. The coupling reagent, *O*-(7-azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU)[17] gave the best result. A dilute solution of the intermediates was slowly added to the suspension of HATU and *N*,*N*-diisopropylethylamine to yield globomycin derivatives. In the case of the precursor derived from **17a**, the yield of macrolactam **22a** was very poor because of steric hindrance between TBS and the benzyl group during the cyclization step (Table 1). However, the derivatives in which the TBS group was removed gave cyclized products **21a** in moderate yield (45%, 2 steps). The benzyl group was not affected in the cyclization reaction (**1a**, 39% 2 steps from **20a**). *O*-Bn globomycin (**21a**) was treated with $Pd(OH)_2$ under H_2 atmosphere to produce **1a** (96%).

The congener **1b** was also obtained from (+)-A_5 as a starting material via the same synthetic route (Scheme 5).[18] All the physical properties (^1H, ^{13}C, IR, $[\alpha]_D$) of synthetic **1a** and **b** were identical to those of natural globomycin and SF-1902 A_5, respectively.[19]

Synthetic **1a** against *Escherichia coli* ATCC 11303 showed the same degree of antimicrobial activity (MIC=0.2 μg/mL) as that initially observed for natural **1a**. On the other hand, synthetic **1b** showed weaker activity than **1a** (MIC=0.4 μg/mL). However, the activity of the *O*-Bn derivative (**21a**) and the acyclic macrocyclization precursor were extremely diminished (MIC>50 μg/mL).[20] These



Scheme 6. Synthesis of **1a** via macrolactonization.

Table 2. Solvent effect on the ratio of rotamers

Structure	Solvent	Ratio of the rotamers[a]
1a	$CDCl_3$	5.9:1
1a	CD_3CN	4.4:1
1a	CD_3OD	2.8:1
1a	DMSO-d_6	1.9:1
		Single isomer[b]

[a] The ratio of the rotamers was determined by ^{1}H NMR analysis at the *N*-Me position (16 mM) at 27°C.
[b] ^{1}H NMR analysis at 100°C.

Table 3. Temperature coefficient values of NH proton

Residue	$-\Delta d/dT$ (ppb/K)
Gly	6.40
L-*allo*-Thr	1.07
L-Ser	4.90
L-*allo*-Ile	10.5

results suggest that the hydroxyl group in the Ser residue and the cyclic structure of **1** with an inner hydrophilic cavity were quite essential for the antimicrobial activity.[2b]

2.4. Macrolactonization route

In the total synthesis of **1a** via macrolactonization, the Gly at the C terminus did not cause any epimerization under severe conditions during the cyclization step. The common intermediate **15** was used as a starting material in the macrolactonization route (Scheme 6). The removal of the allyl group in **15** afforded hydroxy acid **23** ($Pd(PPh_3)_4$ and morpholine, 99%). Hydroxy acid **23** was then coupled with freshly prepared dipeptide **24**[21] synthesized from **8** with TBSOTf and 2,6-lutidine[22] to give linear peptide **25** (95%). After the treatment of **25** with aqueous LiOH to provide a hydroxy acid (95%), this seco-acid was used in the lactonization reaction by the Yamaguchi's method.[23] To the refluxed toluene solution of DMAP, was slowly added mixed-acid anhydride prepared with 2,4,6-$Cl_3C_6H_2COCl$ and triethylamine in THF, to give protected globomycin **22** (51%).[24] The removal of TBS and the benzyl group by conventional methods provided **1a**.

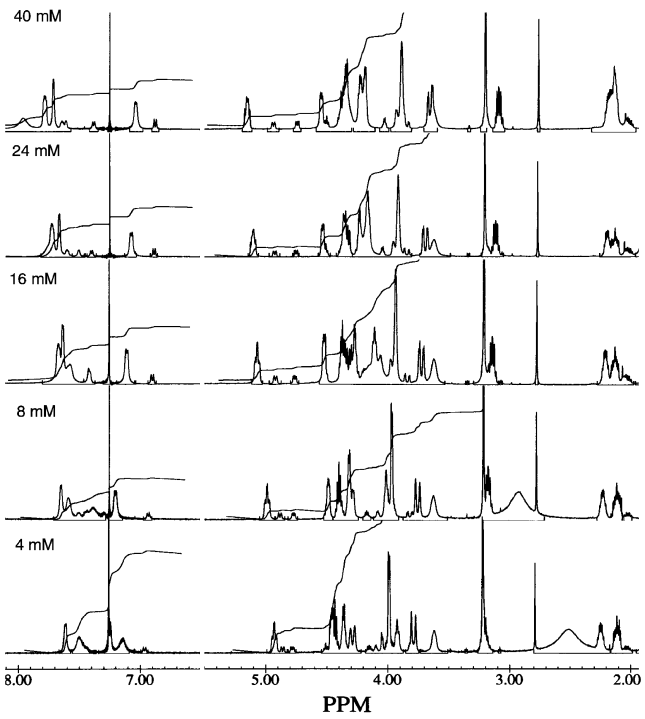


Figure 3. ^{1}H NMR spectra of **1a** at five different concentrations in $CDCl_3$.

2.5. Spectroscopic analysis

The ^{1}H NMR spectrum indicates that **1a** exists as a mixture of two rotational isomers and that the proportion of each is dependent on the solvent (major/minor=5.9:1 in $CDCl_3$, 1.9:1 in DMSO-d_6, at 27°C). On the other hand, **1a** exists as a single isomer in DMSO-d_6 at 100°C (Table 2).

These results suggested that there is an equilibrium between the two isomers whose activation energies are not very high. Furthermore, the temperature-dependence of NH proton chemical shifts was measured in the range from 30 to 60°C increasing every 10°C ($CDCl_3$, 8 mM) in order to estimate the conformation of the major isomer. Temperature coefficients values ($-\Delta d/dT$) were evaluated from least-squares plots (Table 3).[25]

As a result, the NH proton only in the L-*allo*-Thr residue seemed to participate in the hydrogen bonding in contrast with the results of the X-ray structure.[1d] Consequently, the conformation in the solution phase is suspected to be different from the crystal X-ray structure. Further analyses on the conformation are being carried out based on molecular dynamics calculations. Interestingly, the chemical shifts of **1a** in the NMR spectra change with increasing concentrations only in $CDCl_3$ but those of *O*-benzyl derivative **21a** do not. Figure 3 shows the ^{1}H NMR spectra of **1a** at five different concentrations (4, 8, 16, 24, 40 mM). Large shifts ($\Delta\delta$ ppm) were observed for the C(3)H proton of the fatty acid moiety and the α proton of the L-Ser residue as well as for several amide NH protons. On the other hand, the protons of *N*-Me-Leu residue are shifted hardly. These results suggest the existence of intermolecular interactions such as a hydrogen bond among the OH group, the amide NH and the amide C=O group of **1a**. In particular, the primary hydroxyl group of the Ser residue was necessary. ^{1}H and ^{13}C NMR data in $CDCl_3$ for the major isomer of **1a** are summarized in Table 4, in which all of the protons and carbons were assigned based on DQF-COSY, HMQC and HMBC experiments.

The NOESY experiments indicated that these rotational isomers were derived from the rotation of the acyl *N*-methyl amide group. Since correlations among the *N*-methyl group, C(3)H and C(19)H were observed, the major isomer was ascribed to be in the *trans* form like in the conformation obtained by X-ray analysis while the minor isomer was considered to adopt a *cis* form as there was a correlation between C(3)H and C(19)H (Fig. 4).

3. Conclusion

We have completed the first total synthesis of globomycin as well as its congener, SF-1902 A_5, by a convergent

Table 4. ^{1}H and ^{13}C NMR data for the major isomer of **1a** in $CDCl_3$

	$^{1}H^{a}$	$^{13}C^{b}$		$^{1}H^{a}$	$^{13}C^{b}$
Fatty acid			*N*-Me-Leu		
C=O		176.9	C=O		173.2
2-CH	3.12–3.20 (m)	41.2	α-CH	3.63 (br s)	67.8
3-CH	5.08 (dt, 3.3, 8.8)	77.0	β-CH_2	1.57–1.71 (m) 2.11–2.17 (m)	38.2
3-CH_3	1.10 (d, 6.9)	15.0	γ-CH_2	1.49–1.56 (m)	25.3
4-CH_2	1.57–1.71 (m)	31.3	δ-CH_3	0.96 (d, 6.6)	21.9
5-CH_2	1.25–1.43 (m)	24.3	δ-CH_3		23.1
6-CH_2	1.25–1.43 (m)	29.1	*N*-Me	3.22 (s)	40.1
7-CH_2	1.25–1.43 (m)	31.6	*allo*-Ile		
8-CH_2	1.25–1.43 (m)	22.6	C=O		174.7
9-CH_3	0.88 (t, 7.0)	14.0	α-CH	4.53 (dd, 2.8, 7.4)	56.6
allo-Thr			β-CH	2.17–2.24 (m)	36.6
C=O		170.4	γ-CH_2	1.25–1.43 (m)	27.1
α-CH	4.24–4.28 (m)	59.1	γ-CH_3	0.91 (t, 7.3)	14.6
β-CH	4.38 (qu, 6.4)	66.9	δ-CH_3	0.93 (t, 7.3)	11.7
γ-CH	1.25 (d, 6.4)	18.9	Ser		
NH	7.12 (d, 7.3)		C=O		170.7
Gly			α-CH	4.12 (t, 6.5)	57.6
C=O		168.8	β-CH_2	3.94 (d, 4.5)	61.5
α-CH_2	3.73 (dd, 4.1, 17.3) 4.33 (dd, 8.0, 17.3)	40.5	NH	7.63 (d, 4.5)	
NH	7.68 (br t, 4.1)				

[a] 500 MHz; δ in ppm, J in Hz (16 mM).
[b] 100 MHz; δ in ppm (47 mM).

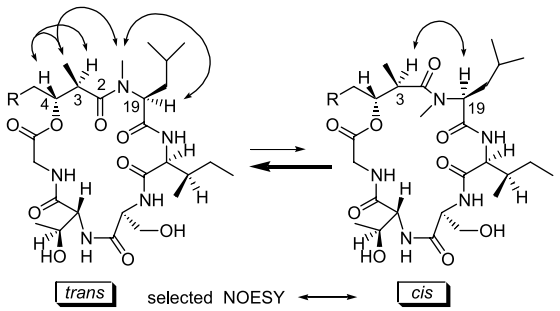


Figure 4. Selected NOESY correlations of **1a** in CD_2OD.

coupling of three fragments via two possible routes. A conformational study in solution was also performed. Further synthetic investigations examining the structure–activity relationship (SAR) and determining the exact conformation are currently underway.

4. Experimental

4.1. General procedure

All moisture-sensitive reactions were carried out under a N_2 atmosphere. Tetrahydrofuran (THF) was distilled from sodium-benzophenone ketyl. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride. Other anhydrous solvents were purchased from Aldrich or Kanto Kagaku. All reagents were commercially available and used as obtained unless otherwise stated. Analytical thin-layer chromatography (TLC) was performed using TLC plates precoated with Merck Silica gel 60 F_{254} (0.25 mm layer thickness). Preparative flash column chromatography was performed using Merck Silica gel 60 (230–400 mesh). NMR spectra were obtained on a JEOL ECP-500, JNM-GSX-400, Varian Inova-500, Mercury-400 or Brucker AVANCE 500 spectrometer. All ^{1}H NMR spectra are reported in ppm downfield from tetramethylsilane as an internal standard. All ^{13}C NMR spectra are reported in ppm relative to the central line for $CDCl_3$ (δ 77.0) or CD_3OD (δ 49.0). ^{13}C NMR spectra of **1a** and **1b** were obtained on a Brucker AVANCE 500 spectrometer with a CryoProbe. In the NMR spectral lists, chemical shifts which are assigned to the minor conformer are marked with an asterisk. Melting points (mp) measured with BÜCHI Schmelzpunktbestimmungs Apparat were uncorrected. Optical rotations measured on JASCO P-1030 are reported in g/100 mL. Infrared (IR) spectra are reported in wave number (cm^{-1}) measured on a JASCO FT-IR-350, FT-IR-8300 or FT-IR-8900 spectrometer. High-resolution mass spectra were obtained on a JEOL JMS-BU20, JMS-700 or JMS-700QQ spectrometer. Elemental analysis was performed on Yanaco MT-5 or MT-6. Preparative HPLC was performed using a GILSON liquid chromatography system equipped with a Model 305 and 306 pump, Model 119 UV detector, Model 811C dynamic mixture, Model 806 manometric module and Model 503 degasser. Two types of column (NOMURA CHEMICAL Develosil ODS-HG5; 10 mm×250 mm, 20 mm×250 mm) were used. Analytical HPLC was performed on a HITACHI D-6100 interface equipped with a HITACHI L-4000 UV detector, a HITACHI L-6200 intelligent pump and a HITACHI L-5025 column oven using a DAICEL CHIRALCEL OD (4.6 mm×250 mm) for **3a** or CHIRALCEL AD column (4.6 mm×250 mm) for **3b**.

4.2. Determination of the relative and absolute stereochemistry of (+)-A_3

4.2.1. Reduction of 3a. To a suspension of $LiAlH_4$ (101 mg, 2.66 mmol) in ether (3 mL) was added dropwise a solution of **3a** (157 mg, 0.264 mmol) in ether (2 mL) at 0°C. The reaction mixture was stirred at the same temperature for 3 h. After an addition of EtOAc (5 mL), the mixture was acidified with 5% aqueous HCl solution. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered and evaporated. The oil residue was

purified by column chromatography with a 3:1 mixture of hexane and EtOAc used as an eluent to give a diol (33.6 mg, 0.193 mmol, 73%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 0.890 (t, 3H, J=6.9 Hz), 0.892 (d, 3H, J=7.1 Hz), 1.25–1.35 (m, 7H), 1.41–1.51 (m, 2H), 1.54–1.61 (m, 1H), 1.66–1.76 (m, 1H), 2.74 (br s, 1H), 2.97 (br s, 1H), 3.51 (dt, 1H, J=3.2, 7.7 Hz), 3.62 (dd, 1H, J=7.2, 10.8 Hz), 3.77 (dd, 1H, J=3.6, 10.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 14.0, 14.1, 22.6, 25.2, 29.4, 31.9, 35.4, 39.9, 67.7, 77.4; IR ($CHCl_3$) cm^{-1}: 3623, 3502, 2959, 2930, 2873, 2858, 1467, 1247, 1025, 959; HRMS calcd for $C_{10}H_{23}O_2$ $(M+H)^+$ calcd 175.1712, found: 175.1698; $[\alpha]_D^{24}$=+29.5 (c 1.02, $CHCl_3$).

4.2.2. The acetonide of (2*S*, 3*R*)-2-methyl-1, 3-nonanediol (4). To a solution of the diol (11.0 mg, 63.1 μmol) in acetone (1.0 mL) were added *p*-toluenesulfonic acid (2.2 mg), dimethoxypropane (100 μL) and $MgSO_4$ (50 mg). After being stirred at room temperature for 27 h, the reaction mixture was filtered and evaporated. The residue was purified by column chromatography with a 6:1 mixture of hexane and EtOAc used as an eluent to give **4** (13.4 mg, 62.5 μmol, 99%) as a colorless volatile oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 0.74 (d, 3H, J=6.6 Hz), 0.88 (t, 3H, J=6.7 Hz), 1.22–1.52 (m, 9H), 1.38 (s, 3H), 1.42 (s, 3H), 1.55–1.70 (m, 2H), 3.42 (dt, 1H, J=2.2, 8.4 Hz), 3.48 (t, 1H, J=11.7 Hz), 3.68 (dd, 1H, J=5.1, 11.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 12.8, 14.1, 19.1, 22.6, 24.9, 29.3, 29.8, 31.9, 33.0, 34.1, 66.2, 75.0, 98.1; IR ($CHCl_3$) cm^{-1}: 2957, 2931, 2859, 1460, 1383, 1369, 1265, 1167, 1112, 1055; HRMS calcd for $C_{13}H_{27}O_2$ $(M+H)^+$ calcd 215.2011, found: 215.2015; $[\alpha]_D^{24}$=+41.9 (c 0.49, $CHCl_3$).

4.2.3. The (*S*)-MTPA ester of methyl (2*R*, 3*R*)-3-hydroxy-2-methylnonanoate ((*S*)-5a). To a solution of (+)-A_3 (157 mg, 0.834 mmol) in CH_3OH (4 mL) was added dropwise trimethylsilyl diazomethane (2.0 M in hexane) at 0°C until the reaction mixture turned light yellow. The mixture was evaporated and the residue was purified by column chromatography with a 10:1 mixture of hexane and EtOAc used as an eluent to give an ester (165 mg, 0.816 mmol, 98%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 0.88 (t, 3H, J=6.8 Hz), 1.21 (d, 3H, J=7.3 Hz), 1.24–1.54 (m, 10H), 2.50–2.57 (m, 2H), 3.63–3.69 (m, 1H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 14.0, 14.3, 22.6, 25.5, 29.2, 31.8, 34.8, 45.2, 51.7, 73.4, 176.5; IR ($CHCl_3$) cm^{-1}: 3606, 2955, 2930, 2859, 1720, 1460, 1438, 1378, 1260, 1173; HRMS calcd for $C_{11}H_{23}O_3$ $(M+H)^+$ calcd 203.1647, found: 203.1644; $[\alpha]_D^{25}$=−6.9 (c 1.03, $CHCl_3$).

The ester (49.6 mg, 0.245 mmol) was dissolved in CH_2Cl_2 (1.5 mL). To this solution were added DMAP (60.2 mg, 0.493 mmol) and (*R*)-MTPACl (69 μL, 0.369 mmol) at room temperature. The mixture was stirred at the same temperature, and 5% aqueous HCl solution was added. The organic layer was separated and washed with a saturated K_2CO_3 aqueous solution and brine. The combined organic extracts were dried over Na_2SO_4, filtered and evaporated. The oil residue was purified by column chromatography with a 10:1 mixture of hexane and EtOAc used as an eluent to give (*S*)-**5a** (99.2 mg, 0.237 mmol, 97%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 0.88 (t, 3H, J=6.9 Hz), 1.09 (d, 3H, J=7.1 Hz), 1.24–1.30 (m, 8H), 1.63–1.68 (m, 2H), 2.84 (qu, 1H, J=7.1 Hz), 3.53 (d, 3H, J=1.1 Hz), 3.58 (s, 3H), 5.37 (q, 1H, J=6.1 Hz), 7.38–7.41 (m, 3H), 7.52–7.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 12.3, 14.0, 22.5, 24.6, 29.0, 30.3, 31.6, 42.4, 51.8, 55.4, 77.4, 84.5 (q, J=29 Hz), 123.3 (q, J=288 Hz), 127.4, 128.3, 129.6, 132.1, 165.9, 173.5; IR ($CHCl_3$) cm^{-1}: 2954, 2931, 2859, 1743, 1460, 1438, 1272, 1171, 1122, 1017; HRMS calcd for $C_{21}H_{30}F_3O_5$ $(M+H)^+$ calcd 419.2045, found: 419.2039; $[\alpha]_D^{25}$=−25.8 (c 1.02, $CHCl_3$).

For (*R*)-**5a**. By combining the ester (60.3 mg, 0.298 mmol), DMAP (55.5 mg, 0.454 mmol) and (*S*)-MTPACl (67 μL, 0.358 mmol), (*R*)-**5a** (124 mg, 0.295 mmol, 99%) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 0.86 (t, 3H, J=6.8 Hz), 1.08–1.27 (m, 8H), 1.17 (d, 3H, J=7.2 Hz), 1.58–1.63 (m, 2H), 2.85 (qu, 1H, J=7.2 Hz), 3.54 (d, 3H, J=1.1 Hz), 3.64 (s, 3H), 5.37 (q, 1H, J=6.1 Hz), 7.38–7.41 (m, 3H), 7.52–7.55 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 12.8, 14.0, 22.5, 24.1, 29.0, 30.3, 31.5, 42.6, 51.9, 55.4, 77.4, 84.5 (q, J=28 Hz), 123.3 (q, J=288 Hz), 127.4, 128.3, 129.5, 132.2, 166.0, 173.7; IR ($CHCl_3$) cm^{-1}: 2955, 2930, 2858, 1743, 1459, 1437, 1271, 1171, 1123, 1017; HRMS calcd for $C_{21}H_{29}F_3O_5Na$ $(M+Na)^+$ calcd 441.1865, found: 441.1871; $[\alpha]_D^{25}$=+25.1 (c 1.06, $CHCl_3$).

4.2.4. The (*S*)-MTPA ester of methyl (2*R*, 3*R*)-3-hydroxy-2-methylundecanoate ((*S*)-5b). From **3b** (452 mg, 2.09 mmol) and $TMSCHN_2$ was obtained a methyl ester (431 mg, 1.87 mmol, 90%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 0.88 (t, 3H, J=7.0 Hz), 1.21 (d, 3H, J=6.6 Hz), 1.27–1.53 (m, 14H), 2.49–2.57 (m, 2H), 3.63–3.68 (m, 1H), 3.71 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 14.1, 14.3, 22.7, 25.5, 29.2, 29.5, 29.6, 31.9, 34.8, 45.2, 51.7, 73.4, 176.5; IR ($CHCl_3$) cm^{-1}: 3459, 2952, 2927, 2855, 1740, 1461, 1437, 1377, 1263, 1172; HRMS calcd for $C_{13}H_{26}O_3Na$ $(M+Na)^+$ calcd 253.1780, found: 253.1770; $[\alpha]_D^{24}$=−2.5 (c 1.61, $CHCl_3$).

By combining the ester (56.0 mg, 0.243 mmol), DMAP (59 mg, 0.486 mmol) and (*R*)-MTPACl (68 μL, 0.365 mmol), (*S*)-**5b** (105 mg, 0.235 mmol, 97%) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 0.88 (t, 3H, J=7.0 Hz), 1.09 (d, 3H, J=7.3 Hz), 1.24–1.29 (m, 12H), 1.63–1.67 (m, 2H), 2.84 (qu, 1H, J=7.3 Hz), 3.53 (d, 3H, J=1.5 Hz), 3.58 (s, 3H), 5.37 (q, 1H, J=6.1 Hz), 7.38–7.41 (m, 3H), 7.52–7.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 12.3, 14.1, 22.6, 24.7, 29.2, 29.4, 30.3, 31.8, 42.4, 42.6, 51.8, 55.4, 77.4, 84.5 (q, J=28 Hz), 123.3 (q, J=288 Hz), 127.4, 128.4, 129.6, 132.1, 165.9, 173.5; IR ($CHCl_3$) cm^{-1}: 2954, 2928, 2856, 1743, 1460, 1438, 1271, 1172, 1122, 1017; HRMS calcd for $C_{23}H_{33}F_3O_5Na$ $(M+Na)^+$ calcd 469.2178, found: 469.2181; $[\alpha]_D^{26}$=−24.1 (c 1.17, $CHCl_3$).

For (*R*)-**5b**. By combining the ester (60.4 mg, 0.262 mmol), DMAP (64 mg, 0.524 mmol) and (*S*)-MTPACl (73 μL, 0.393 mmol), (*R*)-**5b** (116 mg, 0.260 mmol, 99%) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 0.88 (t, 3H, J=7.0 Hz), 1.10–1.29 (m, 12H), 1.17 (d, 3H, J=7.2 Hz), 1.54–1.63 (m, 2H), 2.85 (qu, 1H,

J=7.2 Hz), 3.53 (d, 3H, J=1.5 Hz), 3.64 (s, 3H), 5.37 (q, 1H, J=6.1 Hz), 7.38–7.41 (m, 3H), 7.52–7.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 12.8, 14.1, 22.6, 24.2, 29.1, 29.3, 30.3, 31.8, 42.6, 51.9, 55.4, 77.4, 84.6 (q, J=28 Hz), 123.3 (q, J=289 Hz), 127.4, 128.3, 129.6, 132.2, 166.0, 173.7; IR ($CHCl_3$) cm^{-1}: 2954, 2928, 2856, 1743, 1461, 1438, 1271, 1171, 1122, 1017; HRMS calcd for $C_{23}H_{33}F_3O_5Na$ $(M+Na)^+$ calcd 469.2178, found: 469.2167; $[\alpha]_D^{26}$=+26.9 (c 1.17, $CHCl_3$).

4.3. Macrolactamization route to obtain 1a

4.3.1. (2*R*, 3*R*)-3-[Boc-L-*allo*-Thr(TBS)-GlyO]-2-methylnonanoyl-*N*-methyl-L-Leu-L-*allo*-Ile-L-Ser(Bn)OH (17a). Compound **16a**[1d] (48.9 mg, 48.0 μmol) and morpholine (8.5 μL, 97.5 μmol) were dissolved in THF (4.0 mL). To this solution was added $Pd(PPh_3)_4$ (5.5 mg, 4.8 μmol), and the reaction mixture was stirred at room temperature for 2.5 days. The mixture was concentrated and purified by column chromatography with EtOAc and then a 10:1 mixture of CH_2Cl_2 and CH_3OH used as eluents to give **17a** (44.9 mg, 45.9 μmol, 96%) as a pale yellow amorphous foam. ^{1}H NMR (400 MHz, CD_3OD, major conformer) δ ppm: 0.06 (s, 3H), 0.09 (s, 3H), 0.85–0.95 (m, 12H), 0.88 (s, 9H), 0.96 (d, 3H, J=6.6 Hz), 1.10 (d, 3H, J=7.0 Hz), 1.13–1.18 (m, 4H), 1.28–1.45 (m, 10H), 1.45 (s, 9H), 1.56–1.66 (m, 3H), 1.73–1.81 (m, 1H), 1.91–1.97 (m, 1H), 3.06 (s, 3H), 3.23 (qu, 1H, J=6.8 Hz), 3.74 (d, 1H, J=17.7 Hz), 3.75 (dd, 1H, J=3.6, 9.7 Hz), 3.88 (dd, 1H, J=4.9, 9.7 Hz), 4.01 (d, 1H, J=17.7 Hz), 4.10–4.16 (br, 2H), 4.44–4.47 (m, 1H), 4.51 and 4.55 (AB type d's, each 1H, J=11.9 Hz), 4.63 (t, 1H, J=4.2 Hz), 5.08 (dt, 1H, J=3.8, 7.4 Hz), 5.19 (dd, 1H, J=5.4, 10.4 Hz), 7.24–7.33 (m, 5H); ^{13}C NMR (100 MHz, CD_3OD, both rotamers) δ ppm: −4.9, −4.5, 11.9, 12.8, 14.4, 14.8, 15.1, 18.8, 20.1, 22.2, 23.7, 26.1, 26.2, 26.3, 26.4, 27.4, 28.7, 30.3, 30.7, 31.2, 31.5, 32.9, 37.8, 38.5, 41.2, 42.2, 54.1, 55.8, 57.7, 57.8, 61.8, 69.9, 70.7, 74.2, 77.2, 80.8, 97.2, 128.7, 128.8, 129.4, 139.2, 157.7, 170.4, 172.8, 173.0, 173.1, 173.3, 173.5, 176.7; IR (KBr) cm^{-1}: 3326, 2959, 2932, 2860, 1725, 1663, 1520, 1253, 1200, 835; HRMS m/z M^+ calcd 978.6198, found: 978.6205. Anal. Calcd for $C_{50}H_{87}N_5O_{12}Si{\cdot}1/2H_2O$: C, 60.82; H, 8.98; N, 7.09. Found: C, 60.64; H, 8.88; N, 6.98; $[\alpha]_D^{23}$=−36.4 (c 0.99, $CHCl_3$).

4.3.2. (2*R*, 3*R*)-3-(Boc-L-*allo*-Thr-GlyO)-2-methyl-nonanoyl-*N*-methyl-L-Leu-L-*allo*-Ile-L-SerOH (20a). Compound **19a**[1d] (48.9 mg, 56.6 μmol) was dissolved in CH_3OH (1.5 mL). To this solution, $Pd(OH)_2$ (20 wt%, 20.2 mg) was added and the resulting mixture was stirred at room temperature for 2.5 h under H_2 atmosphere. $Pd(OH)_2$ was removed by filtration and the filtrate was evaporated to give **20a** (42.5 mg, 54.9 μmol, 97%) as colorless needles (mp 104–106°C). ^{1}H NMR (400 MHz, CD_3OD, major conformer) δ ppm: 0.87–0.93 (m, 12H), 0.98 (d, 3H, J=6.6 Hz), 1.11 (d, 3H, J=6.8 Hz), 1.18–1.45 (m, 11H), 1.20 (d, 3H, J=6.2 Hz), 1.45 (s, 9H), 1.52–1.66 (m, 3H), 1.75–1.82 (m, 1H), 1.90–2.00 (m, 1H), 3.07 (s, 3H), 3.24 (qu, 1H, J=6.9 Hz), 3.82 (dd, 1H, J=3.9, 11.2 Hz), 3.89 (d, 1H, J=17.7 Hz), 3.89–4.03 (m, 3H), 4.08 (br d, 1H, J=5.3 Hz), 4.44–4.50 (m, 2H), 5.10 (dt, 1H, J=3.6, 7.4 Hz), 5.20 (dd, 1H, J=5.4, 10.3 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ ppm: 12.0, 12.8, 14.4, 14.8, 19.4, 22.1, 23.64, 23.66, 26.1, 26.2, 27.4, 28.7, 30.3, 31.3, 31.6, 32.7, 32.9, 37.8, 38.6, 41.2, 42.2, 55.9, 56.1, 57.7, 61.3, 62.9, 68.9, 77.3, 80.8, 170.7, 173.1, 173.5, 176.8; IR (KBr) cm^{-1}: 3328, 2961, 2934, 2875, 1726, 1659, 1525, 1369, 1201, 1170; HRMS m/z $(M+K)^+$ calcd 812.4423, found: 812.4436. Anal. Calcd for $C_{37}H_{67}N_5O_{12}{\cdot}H_2O$: C, 56.11; H, 8.78; N, 8.84. Found: C, 56.34; H, 8.65; N, 8.59; $[\alpha]_D^{25}$=−55.3 (c 0.52, CH_3OH).

Globomycin (1a)[1d] *from* **20a**. To a solution of **20a** (42.5 mg, 54.9 μmol) in CH_2Cl_2 (1.5 mL), was added TFA (0.3 mL) at room temperature. After being stirred at the same temperature, the solvents were removed in vacuo. The residue was dissolved in CH_2Cl_2 and reconcentrated repeatedly to remove excess TFA. The crude product was dried under reduced pressure to afford a TFA salt (43.8 mg) and used for macrocyclization without further purification. This salt (15.6 mg, 19.6 μmol) was dissolved in THF (10 mL) and the solution was slowly added to a suspension of HATU (75.5 mg, 0.199 mmol) and DIEA (52 μL, 0.298 mmol) in THF (10 mL) for over 3.5 h at 0°C with a syringe pump under highly diluted conditions. The reaction mixture was stirred at the same temperature for an additional 2 h, warmed to room temperature and stirred for 16 h. This mixture was evaporated, diluted with 3:1 mixture of CH_3OH and EtOAc and filtered. The filtrate was concentrated, dissolved in EtOAc and washed with 1% aqueous HCl solution, saturated $NaHCO_3$ aqueous solution and then brine. The organic layer was dried over Na_2SO_4, filtered and evaporated. The residue was purified by preparative HPLC (column: Develosil ODS-HG5 (10 mm×250 mm); wavelength: 210 nm; flow rate: 5.0 mL/min) with a 70:30 mixture of CH_3OH and 1% aqueous triethylammonium acetate used as an eluent to give **1a** (5.0 mg, 7.6 μmol, 39% (2 steps)) as a colorless solid.

4.4. Total synthesis of SF-1902 A_5 (1b)

4.4.1. *anti*-Selective asymmetric aldol reaction. *Major isomer* **3b**. To a stirred solution of (1*R*, 2*S*)-**2** (575 mg, 1.20 mmol) in CH_2Cl_2 (14 mL) was added Et_3N (0.40 mL, 2.88 mmol). The solution was cooled to −78°C and to this was transferred via cannula a solution of c-Hex_2BOTf (1.0 M in hexane, 2.52 mL, 2.52 mmol), which was precooled to −78°C. The resulting solution was stirred at −78°C for 1.5 h to complete enolization. A solution of nonylaldehyde (0.41 mL, 2.40 mmol) in CH_2Cl_2 (3 mL) was added dropwise to the enolate solution and the reaction mixture was stirred at −78°C for 3 h and at 0°C for 2 h. The reaction was quenched by the addition of pH 7 buffer solution (5.7 mL) followed by CH_3OH (10 mL) and 30% H_2O_2 (1 mL). The mixture was stirred overnight vigorously at room temperature. The resulting solution was extracted with ether (70 mL×3). The organic extracts were combined, dried over $MgSO_4$, and concentrated in vacuo. The resulting crude product was partially purified by silica gel flash column chromatography (n-hexane/AcOEt=10:1) to afford a mixture of aldol products (694 mg, 1.12 mmol, 93%). The ratio of the diastereomers (94.3:5.7) was determined by HPLC analysis (DAICEL CHIRALCEL AD 0.46 cm×25 cm, n-hexane/i-PrOH=90:10, 1.0 mL/min, 40°C). Purification of the diastereomers by silica gel flash column chromatography (n-hexane/AcOEt=10:1) gave compound **3b** as a viscous oil (650 mg, 1.05 mmol, 87%). ^{1}H NMR

(400 MHz, $CDCl_3$, major isomer) δ ppm: 0.88 (t, 3H, J=6.9 Hz), 1.13 (d, 3H, J=7.3 Hz), 1.18 (d, 3H, J=6.8 Hz), 1.26–1.47 (m, 14H), 2.28 (s, 3H), 2.42–2.53 (m, 2H, 1H D_2O exchangeable), 2.48 (s, 6H), 3.59–3.65 (m, 1H), 4.10 (dq, 1H, J=4.5, 6.9 Hz), 4.54 and 4.76 (AB type d's, each 1H, J=16.5 Hz), 5.83 (d, 1H, J=4.4 Hz), 6.86–6.88 (m, 2H), 6.86 (s, 2H), 7.16–7.30 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 13.5, 14.11, 14.13, 20.9, 22.7, 22.9, 25.4, 29.3, 29.57, 29.61, 31.6, 31.9, 34.5, 45.5, 48.3, 56.7, 73.2, 78.2, 126.0, 127.2, 127.7, 128.0, 128.3, 128.4, 132.1, 133.4, 138.2, 138.4, 140.3, 142.6, 174.6; IR ($CHCl_3$) cm^{-1}: 3619, 3544, 2928, 2856, 1728, 1605, 1456, 1322, 1153, 1012; HRMS calcd for $C_{37}H_{51}O_5NSNa$ $(M+Na)^+$ 644.3386, found: 644.3378; $[\alpha]_D^{24}$=+20.4 (c 1.55, $CHCl_3$).

4.4.2. (2*R*, 3*R*)-3-Hydroxy-2-methylundecanoic acid (A_5). A solution of **3b** (117 mg, 0.188 mmol) and $LiOH\cdot H_2O$ (47.0 mg, 0.94 mmol) in THF–CH_3OH–H_2O (1:1:1, 2.7 mL) was stirred at room temperature overnight. $LiOH\cdot H_2O$ (47.0 mg, 0.94 mmol) in H_2O (0.5 mL) was added, and the resulting mixture was stirred for 1 day. The mixture was poured into water (5 mL) and extracted with CH_2Cl_2 to recover the chiral auxiliary. The aqueous layer was acidified with 10% aqueous $KHSO_4$ solution and extracted with CH_2Cl_2. The extracts were washed with brine and dried with $MgSO_4$. Filtration and concentration gave (+)-A_5 as a colorless oil (36.7 mg, 0.170 mmol, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 0.88 (t, 3H, J=6.8 Hz), 1.20–1.61 (m, 18H), 2.56 (qu, 1H, J=7.1 Hz), 3.68–3.72 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 14.1, 14.2, 22.7, 25.5, 29.3, 30.0, 31.9, 34.6, 45.2, 73.3, 180.8; IR ($CHCl_3$) cm^{-1}: 3615, 3511, 2928, 2857, 1740, 1704, 1464, 1397, 1380, 1289; HRMS calcd for $C_{12}H_{25}O_3$ $(M+H)^+$ calcd 217.1804, found: 217.1806; $[\alpha]_D^{23}$=+3.6 (c 1.13, $CHCl_3$).

4.4.3. (2*R*, 3*R*)-3-Hydroxy-2-methyl-undecanoyl-*N*-methyl-L-Leu-L-*allo*-Ile-L-Ser(Bn)OAllyl (15b). Fragment A_5 (192 mg, 0.888 mmol) and Fragment C[1d] (352 mg, 0.740 mmol) were dissolved in THF (3.0 mL) and then Et_3N (0.52 mL, 3.7 mmol) was added. To the solution was added DEPC (0.3 mL, 1.85 mmol) at 0°C. The reaction mixture was stirred at 0°C for 2 h and at room temperature for an additional 1 day. After saturated $NaHCO_3$ aqueous solution was added, the organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered and evaporated. The oil residue was purified by column chromatography with a 4:1 mixture of hexane and EtOAc used as an eluent to give **15b** (497 mg, 0.296 mmol, 99%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, two rotamers (major/minor=2.4:1)) δ ppm: 0.80–0.97 (m, 15H), 1.06–1.22 (m, 2H), 1.22–1.47 (m, 16H), 1.58–1.70 (m, 1H), 1.78–1.85 (m, 2/3H), 1.93–2.01 (m, 4/3H), 2.69–2.77 (m, 2/3H), 2.80* (s, 1H), 2.84–2.93* (m, 1/3H), 2.95 (s, 2H), 3.62 (br, 1H), 3.68 (dd, 1H, J=3.0, 9.6 Hz), 3.68–3.77 (m, 2H), 3.91–3.95 (m, 1H), 4.56 and 4.47 (AB type d's, each 1H, J=12.3 Hz), 4.43–4.68 (m, 11/3H), 4.74–4.78 (m, 4/3H), 5.09 (dd, 2/3H, J=5.6, 10.0 Hz), 5.22–5.33 (m, 7/3H), 5.81–5.92 (m, 1H), 6.64 (d, 2/3H, J=8.2 Hz), 6.79–6.84 (m, 1H), 7.24–7.37 (m, 5H), 7.63* (d, 1/3H, J=9.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, both rotamers) δ ppm: 11.7, 14.1, 14.2, 14.4, 14.8, 14.9, 21.7, 21.8, 22.6, 23.2, 23.4, 24.3, 24.5, 24.7, 26.0, 26.3, 26.4, 29.27, 29.33, 29.49, 29.55, 29.66, 29.71, 31.1, 31.6, 31.8, 31.9, 34.4, 35.6, 35.8, 36.8, 37.5, 37.7, 40.9, 41.3, 52.60, 52.62, 56.1, 56.6, 59.2, 66.2, 66.2, 69.5, 73.4, 73.6, 74.5, 75.7, 77.2, 118.76, 118.85, 127.7, 127.91, 127.92, 128.2, 128.5, 128.6, 131.3, 131.4, 136.8, 137.3, 169.3, 169.6, 170.71, 170.74, 170.8, 171.5, 176.8, 178.1; IR ($CHCl_3$) cm^{-1}: 3431, 2961, 2930, 2858, 1746, 1672, 1622, 1502, 1464, 1273, 1103, 1048; HRMS calcd for $C_{38}H_{64}O_7N_3$ $(M+H)^+$ 674.4744, found: 674.4724; $[\alpha]_D^{24}$=−59.4 (c 1.46, $CHCl_3$).

4.4.4. (2*R*, 3*R*)-3-[Boc-L-*allo*-Thr(TBS)-GlyO]-2-methyl-undecanoyl-*N*-methyl-L-Leu-L-*allo*-Ile-L-Ser(Bn)OAllyl (16b). To a solution of **15b** (244 mg, 0.361 mmol) and Fragment B[1d] ((212 mg, 0.542 mmol) in CH_2Cl_2 (1.5 mL), were added DMAP (44 mg, 0.36 mmol), CSA (42 mg, 0.18 mmol) followed by DIC (113 μL, 0.722 mmol) at room temperature. The reaction mixture was stirred at the same temperature. Moreover, Fragment B and other reagents were sometimes added in order to finish the reaction. The mixture was concentrated and diluted with hexane and EtOAc. The mixture was filtered and washed with 10% aqueous citric acid, saturated $NaHCO_3$, aqueous solution and brine. The organic layer was dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography with a gradient elution system, a 3:1–1:1 mixture of hexane and EtOAc used as eluents to give **16b** (310 mg, 0.296 mmol, 82%) as a colorless amorphous foam. ^{1}H NMR (400 MHz, $CDCl_3$, two rotamers (major/minor=9:1), major conformer) δ ppm: 0.02 (s, 3H), 0.05 (s, 3H), 0.78–0.90 (m, 25H), 0.92 (d, 3H, J=6.6 Hz), 1.08 (d, 3H, J=6.9 Hz), 1.15 (d, 3H, J=6.3 Hz), 1.18–1.28 (m, 8H), 1.36–1.43 (m, 3H), 1.42 (s, 9H), 1.55–1.62 (m, 3H), 1.68–1.76 (m, 1H), 1.92–1.98 (m, 1H), 2.97 (s, 3H), 3.06 (t, 1H, J=6.9 Hz), 3.64 (dd, 1H, J=3.3, 9.4 Hz), 3.76 (dd, 1H, J=4.2, 18.4 Hz), 3.89 (dd, 1H, J=3.0, 9.4 Hz), 4.06–4.16 (m, 3H), 4.39–4.41 (m, 1H), 4.43 and 4.53 (AB type d's, each 1H, J=12.0 Hz), 4.59–4.62 (m, 2H), 4.72 (dt, 1H, J=3.1, 8.2 Hz), 5.05 (d, 1H, J=7.6 Hz), 5.08–5.13 (m, 2H), 5.20 (dd, 1H, J=1.4, 8.5 Hz), 5.28 (dd, 1H, J=1.4, 16.9 Hz), 5.78–5.89 (m, 1H), 6.61 (d, 1H, J=8.2 Hz), 6.66–6.68 (m, 2H), 7.23–7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: −5.0, −4.7, 11.7, 12.2, 14.1, 14.2, 17.9, 19.5, 21.8, 22.6, 23.2, 24.8, 25.1, 25.5, 25.7, 26.3, 28.3, 29.2, 29.3, 29.4, 29.5, 29.9, 30.5, 31.8, 31.9, 35.8, 37.2, 39.9, 41.1, 52.6, 54.3, 56.2, 66.2, 68.7, 69.5, 73.3, 76.4, 77.5, 118.7, 127.7, 127.9, 128.4, 131.5, 137.3, 169.0, 169.6, 170.3, 170.8, 174.4; IR ($CHCl_3$) cm^{-1}: 3431, 2959, 2930, 2859, 1743, 1677, 1499, 1369, 1256, 1162, 1106; HRMS calcd for $C_{55}H_{95}O_{12}N_5SiNa$ $(M+Na)^+$ 1068.6644, found: 1068.6702. Anal. Calcd for $C_{55}H_{95}O_{12}N_5Si\cdot 1/2H_2O$: C, 62.59; H, 9.17; N, 6.64. Found: C, 62.41; H, 8.98; N, 6.80. $[\alpha]_D^{25}$=−52.1 (c 1.08, $CHCl_3$).

4.4.5. (2*R*, 3*R*)-3-(Boc-L-*allo*-Thr-GlyO)-2-methyl-undecanoyl-*N*-methyl-L-Leu-L-*allo*-Ile-L-Ser(Bn)OAllyl (18b). To a solution of **16b** (301 mg, 0.288 mmol) in THF (1.5 mL) was added a mixture of AcOH (82 μL, 1.43 mmol) and TBAF (1.0 M THF solution, 1.44 mL, 1.44 mmol) at 0°C. The solution was stirred at the same temperature and at room temperature for an additional 22 h. This reaction mixture was diluted with EtOAc and washed with a saturated $NaHCO_3$ aqueous solution. The resulting

organic layer was dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography with a 1:1 mixture of hexane and EtOAc used as an eluent to give **18b** (225 mg, 0.216 mmol, 94%) as a colorless amorphous foam. ^{1}H NMR (400 MHz, $CDCl_3$, major conformer) δ ppm: 0.82–0.98 (m, 16H), 0.95 (d, 3H, J=6.6 Hz), 1.11 (d, 3H, J=7.1 Hz), 1.21–1.32 (m, 11H), 1.27 (d, 3H, J=6.2 Hz), 1.41–1.49 (m, 1H), 1.45 (s, 9H), 1.58–1.66 (m, 3H), 1.73–1.81 (m, 1H), 1.94–1.99 (m, 1H), 3.00 (s, 3H), 3.07 (t, 1H, J=6.9 Hz), 3.67 (dd, 1H, J=3.1, 9.5 Hz), 3.74 (br d, 1H, J=5.9 Hz), 3.92 (dd, 1H, J=3.1, 9.5 Hz), 3.95 (br s, 1H), 4.03 (br d, 1H, J=4.9 Hz), 4.08 (br s, 1H), 4.42–4.46 (m, 1H), 4.46 and 4.56 (AB type d's, each 1H, J=12.2 Hz), 4.62–4.64 (m, 2H), 4.75 (dt, 1H, J=3.1, 8.1 Hz), 5.06 (dd, 1H, J=5.9, 9.7 Hz), 5.12–5.17 (m, 1H), 5.23 (dd, 1H, J=1.4, 8.4 Hz), 5.30 (dd, 1H, J=1.4, 17.6 Hz), 5.48 (d, 1H, J=7.7 Hz), 5.81–5.91 (m, 1H), 6.67 (d, 1H, J=8.1 Hz), 6.73 (d, 1H, J=8.3 Hz), 6.92 (br, 1H), 7.26–7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 11.7, 12.6, 14.1, 14.3, 19.8, 20.2, 21.9, 22.6, 23.2, 24.9, 25.1, 26.3, 28.3, 29.2, 29.4, 29.5, 30.3, 31.6, 31.8, 35.9, 37.3, 40.0, 41.3, 52.7, 54.9, 56.3, 66.2, 69.2, 69.5, 73.3, 76.6, 77.5, 118.8, 127.7, 127.9, 128.5, 131.5, 137.4, 169.2, 169.6, 170.75, 170.84, 171.5, 174.5; IR ($CHCl_3$) cm^{-1}: 3433, 2961, 2930, 2873, 1744, 1674, 1498, 1369, 1254, 1161; HRMS calcd for $C_{49}H_{81}O_{12}N_5Na$ $(M+Na)^+$ 954.5799, found: 954.5791; $[\alpha]_D^{25}=-69.6$ (c 1.43, $CHCl_3$).

4.4.6. (2*R*, 3*R*)-3-(Boc-L-*allo*-Thr-GlyO)-2-methyl-undecanoyl-*N*-methyl-L-Leu-L-*allo*-Ile-L-Ser(Bn)OH (19b). Compound **18b** (217 mg, 0.233 mmol) and morpholine (46 μL, 0.52 mmol) were dissolved in THF (1.0 mL). To this solution, was added $Pd(PPh_3)_4$ (cat.), and the reaction mixture was stirred at room temperature for 3 days. The mixture was concentrated and purified by column chromatography with EtOAc and then 10:1 mixture of CH_2Cl_2 and CH_3OH used as an eluents to give **19b** (193 mg, 0.216 mmol, 93%) as a slightly yellow amorphous foam. ^{1}H NMR (400 MHz, CD_3OD, major conformer) δ ppm: 0.85–0.96 (m, 14H), 0.96 (d, 3H, J=6.6 Hz), 1.10 (d, 3H, J=6.8 Hz), 1.20 (d, 3H, J=6.4 Hz), 1.10–1.49 (m, 14H), 1.45 (s, 9H), 1.58–1.63 (m, 2H), 1.74–1.81 (m, 1H), 1.89–1.99 (m, 1H), 3.06 (s, 3H), 3.23 (qu, 1H, J=6.8 Hz), 3.75 (dd, 1H, J=3.6, 9.6 Hz), 3.85–3.96 (m, 1H), 3.88 and 3.96 (AB type d's, each 1H, J=14.6 Hz), 3.98–4.03 (m, 1H), 4.08 (d, 1H, J=6.0 Hz), 4.44–4.74 (m, 1H), 4.51 and 4.56 (AB type d's, each 1H, J=11.9 Hz), 4.62–4.65 (m, 1H), 5.01 (dt, 1H, J=3.9, 7.3 Hz), 5.19 (dd, 1H, J=5.4, 10.4 Hz), 7.24–7.36 (m, 5H); ^{13}C NMR (100 MHz, CD_3OD) δ ppm: 11.9, 12.8, 14.4, 14.8, 19.4, 22.1, 23.6, 23.7, 26.1, 26.2, 27.38, 27.45, 28.7, 30.4, 30.59, 30.60, 31.3, 31.6, 33.0, 37.8, 38.5, 41.2, 42.2, 54.1, 55.8, 57.7, 57.8, 61.3, 68.9, 70.7, 74.2, 77.3, 80.8, 128.7, 128.8, 129.4, 139.2, 170.7, 173.0, 173.1, 173.5, 173.6, 176.7; IR ($CHCl_3$) cm^{-1}: 3411, 2962, 2930, 2859, 1726, 1666, 1500, 1394, 1370, 1252, 1162; HRMS calcd for $C_{46}H_{77}O_{12}N_5Na$ $(M+Na)^+$ 914.5466, found: 914.5413. Anal. Calcd for $C_{46}H_{77}O_{12}N_5\cdot 1/2H_2O$: C, 61.31; H, 8.72; N, 7.77. Found: C, 61.31; H, 8.64; N, 7.75. $[\alpha]_D^{24}=-46.7$ (c 1.16, CH_3OH).

4.4.7. *O*Bn-SF-1902 A_5 (21b). To a solution of **19b** (112 mg, 126 μmol) in CH_2Cl_2 (1.0 mL) was added TFA (0.5 mL) at room temperature. After being stirred at the same temperature, the solvents were removed in vacuo. The residue was dissolved in CH_2Cl_2 and reconcentrated repeatedly to remove excess TFA. The crude products were dried under reduced pressure to afford a TFA salt (113 mg) and which was used for macrocyclization without further purification. This salt (52.1 mg, 58.0 μmol) was dissolved in THF (29 mL) and the solution was slowly added to a suspension of TBTU (185 mg, 0.575 mmol) and DIEA (200 μL) in THF (29 mL) for over 9 h at room temperature with a syringe pump under highly diluted condition. After being stirred at the same temperature for an additional 3 days, the mixture was evaporated, diluted with a 3:1 mixture of CH_3OH and EtOAc and filtered. The filtrate was concentrated, dissolved in EtOAc and washed with 1% aqueous HCl solution, saturated $NaHCO_3$ aqueous solution and then brine. The organic layer was dried over Na_2SO_4, filtered and evaporated. The residue was purified by preparative HPLC (column: Develosil ODS-HG5 (10 mm× 250 mm); wavelength: 210 nm; flow rate: 4.0 mL/min) with an 86:14 mixture of CH_3OH and 1% aqueous ammonium acetate used as an eluent to give **21b** (17.6 mg, 22.7 μmol, 39% (2 steps)) as a pale yellow solid (mp 57–59°C). ^{1}H NMR (400 MHz, $CDCl_3$, two rotamers (major/minor= 3.5:1)) δ ppm: 0.86–0.96 (m, 15H), 1.10 (d, 12/5H, J= 6.9 Hz), 1.16 (d, 3/5H, J=6.9 Hz), 1.26–1.54 (m, 20H), 1.55–1.67 (m, 1H), 1.70–1.77 (m, 1H), 2.01–2.07 (m, 1H), 2.08–2.18 (m, 1H), 2.79 (s, 3/5H), 3.09–3.14 (m, 1H), 3.17 (s, 12/5H), 3.62 (dd, 4/5H, J=3.5, 17.1 Hz), 3.68–3.77 (br, 4/5H), 3.79–4.00 (m, 12/5H), 4.02* (t, 1/5H, J=6.0 Hz), 4.08–4.17 (m, 1H), 4.19–4.23 (m, 4/5H), 4.27–4.29 (m, 4/5H), 4.31–4.47 (m, 2H), 4.53 and 4.57 (AB type d's, each 1H, J=11.9 Hz), 4.77* (dd, 1/5H, J=3.5, 9.3 Hz), 4.84* (br d, 1/5H, J=10.6 Hz), 5.10–5.14 (m, 4/5H), 6.82–6.89 (m, 11/5H), 7.18* (br d, 1/5H, J=8.4 Hz), 7.30–7.38 (m, 5H), 7.63 (br d, 4/5H, J=5.1 Hz), 7.91 (br, 4/5H); ^{13}C NMR (100 MHz, $CDCl_3$, both rotamers) δ ppm: 11.77, 11.81, 14.1, 14.7, 14.8, 15.1, 19.8, 19.9, 21.8, 22.5, 22.6, 23.08, 23.14, 24.2, 24.8, 25.2, 26.3, 26.9, 27.1, 28.8, 29.2, 29.4, 29.49, 29.54, 29.7, 31.3, 31.8, 31.9, 36.9, 37.5, 38.1, 38.4, 39.5, 40.5, 40.8, 41.3, 55.4, 55.7, 56.2, 56.9, 57.4, 58.0, 59.3, 67.7, 68.0, 73.4, 73.9, 76.6, 78.2, 127.9, 128.2, 128.5, 128.65, 128.72, 136.6, 137.1, 169.1, 169.3, 169.8, 170.1, 170.9, 171.0, 171.5, 172.4, 172.8, 173.9, 174.3, 176.7; IR ($CHCl_3$) cm^{-1}: 3691, 3421, 3342, 2961, 2929, 1666, 1543, 1502, 1468, 1101; HRMS m/z $(M+Na)^+$ calcd 796.4836, found: 796.4838; $[\alpha]_D^{24}=+6.9$ (c 1.65, $CHCl_3$).

4.4.8. SF-1902 A_5 (1b). Compound **21b** (17.8 mg, 0.0230 mmol) was dissolved in CH_3OH (0.5 mL). To this solution, $Pd(OH)_2$ (cat.) was added and the resulting mixture was stirred at room temperature for 5.5 h under H_2 atmosphere. $Pd(OH)_2$ was removed by filtration and the filtrate was evaporated. The residue was purified by column chromatography with a 10:1 mixture of CH_2Cl_2 and CH_3OH used as an eluent to give **1b** (14.2 mg, 0.0208 mmol, 90%) as colorless needles (mp 100–102°C). ^{1}H NMR (500 MHz, $CDCl_3$, 16 mM, two rotamers (major/minor=5.7:1)) δ ppm: 0.82–1.05 (m, 17H), 1.09 (d, 18/7H, J=6.8 Hz), 1.15* (d, 3/7H, J=6.8 Hz), 1.13–1.42 (m, 15H), 1.48–1.58 (m, 6/7H), 1.61–1.71 (m, 3H), 1.91 (br, 15/7H), 2.00–2.07* (m, 2/7H), 2.11–2.16 (m, 6/7H), 2.17–2.21 (m, 6/7H), 2.74* (s, 3/7H), 3.01–3.17 (m, 1H), 3.21 (s, 18/7H), 3.63 (br, 6/7H), 3.70 (dd, 6/7H, J=3.4, 17.1 Hz), 3.85* (dd, 1/7H,

J=3.9, 18.6 Hz), 3.92 (br, 12/7H), 3.96* (br, 2/7H), 4.05* (d, 1/7H, J=4.9 Hz), 4.17 (br, 8/7H), 4.23–4.28 (m, 1H), 4.32–4.41 (m, 12/7H), 4.50–4.54 (m, 1H), 4.76* (dd, 1/7H, J=4.4, 9.3 Hz), 4.92* (d, 1/7H, J=9.8 Hz), 5.09–5.11 (m, 6/7H), 6.91* (d, 1/7H, J=9.8 Hz), 7.08 (d, 6/7H, J=6.8 Hz), 7.40* (d, 1/7H, J=7.8 Hz), 7.46* (br, 1/7H), 7.58–7.65* (m, 1/7H), 7.65 (br, 6/7H), 7.71 (br, 6/7H), 7.67 (br, 6/7H); ^{13}C NMR (125 MHz, $CDCl_3$, 18 mM, both rotamers) δ ppm: 11.7, 12.3, 14.1, 14.6, 14.9, 15.0, 18.8, 19.0, 21.9, 22.6, 22.7, 22.9, 23.1, 24.3, 24.8, 25.2, 25.9, 26.9, 27.1, 29.2, 29.36, 29.43, 29.5, 29.6, 29.7, 31.3, 31.6, 31.8, 36.6, 37.3, 38.1, 38.4, 39.2, 40.2, 40.5, 41.1, 56.2, 56.6, 57.6, 57.8, 57.9, 59.06, 59.15, 60.7, 61.4, 66.8, 67.1, 67.8, 78.0, 168.9, 170.3, 170.7, 170.9, 171.1, 173.2, 173.5, 174.6, 174.7, 176.9; IR ($CHCl_3$) cm^{-1}: 3675, 3339, 2962, 2930, 2858, 1736, 1663, 1545, 1467, 1378, 1247, 1190; HRMS calcd for $C_{34}H_{61}O_9N_5Na$ $(M+Na)^+$ 706.4367, found: 706.4382. Anal. Calcd for $C_{34}H_{61}N_5O_9{\cdot}4/5H_2O$: C, 58.48; H, 9.04; N, 10.03. Found: C, 58.37; H, 8.85; N, 9.91. $[\alpha]_D^{25}$=−7.5 (c 1.10, $CHCl_3$); $[\alpha]_D^{25}$=+20.8 (c 1.04, CH_3OH).

4.5. Yamaguchi macrolactonization route

4.5.1. L-*allo*-Thr(TBS)-GlyOBn (24). To a solution of **8**[1d] (303 mg, 0.630 mmol) in CH_2Cl_2 (4.0 mL) were added TBSOTf (290 μL, 1.26 mmol) and 2,6-lutidine (220 μL, 1.89 mmol). After being stirred at room temperature for 1 h, saturated NH_4Cl aqueous solution was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography with a 30:1 mixture of CH_2Cl_2 and CH_3OH used as an eluent to give **24** (181 mg, 0.474 mmol, 75%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 0.06 (s, 6H), 0.87 (s, 9H), 1.03 (d, 3H, J=6.1 Hz), 3.51 (d, 1H, J=4.2 Hz), 4.01 (dd, 1H, J=5.5, 18.3 Hz), 4.11 (dd, 1H, J=5.9, 18.3 Hz), 4.29 (dq, 1H, J=4.2, 6.1 Hz), 5.15 and 5.16 (AB type d's, each 1H, J=12.1 Hz), 7.29–7.37 (m, 5H), 7.77 (br t, 1H, J=5.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: −5.0, −4.7, 17.1, 18.0, 25.8, 40.8, 60.7, 67.1, 68.9, 128.4, 128.5, 128.6, 135.2, 169.7, 173.2; IR ($CHCl_3$) cm^{-1}: 3376, 2956, 2931, 2858, 1747, 1670, 1515, 1385, 1358, 1258; HRMS m/z $(M+H)^+$ calcd 381.2209, found: 381.2205; $[\alpha]_D^{24}$=−10.7 (c 1.23, $CHCl_3$).

4.5.2. (2*R*, 3*R*)-3-Hydroxy-2-methyl-nonanoyl-L-*N*-methyl-Leu-L-*allo*-Ile-L-Ser(Bn)OH (23). Compound **15a** (162 mg, 0.252 mmol) and morpholine (44 μL, 0.505 mmol) were dissolved in THF (4.0 mL). To this solution was added $Pd(PPh_3)_4$ (15.2 mg, 0.013 mmol), and the reaction mixture was stirred at room temperature for 2.5 days. The mixture was concentrated and purified by column chromatography with EtOAc and then a 10:1 mixture of CH_2Cl_2 and CH_3OH used as eluents to give **23** (151 mg, 0.249 mmol, 99%) as a slightly yellow amorphous foam. ^{1}H NMR (400 MHz, CD_3OD, both rotamers) δ ppm: 0.86–0.98 (m, 15H), 1.05* (d, 1H, J=6.6 Hz), 1.10 (d, 2H, J=6.8 Hz), 1.12–1.23 (m, 1H), 1.31–1.66 (m, 13H), 1.73–1.88 (m, 1H), 1.90–1.99 (m, 1H), 2.75* (s, 1H), 2.90 (qu, 2/3H, J=6.9 Hz), 3.01 (s, 2H), 3.04* (dq, 1/3H, J=2.7, 6.5 Hz), 3.64–3.71 (m, 1H), 3.75 (dd, 1H, J=3.6, 9.8 Hz), 3.86* and 3.88 (dd, 1H, J=5.1, 9.8 Hz), 4.40* and 4.48 (dd, 1H, J=6.2, 8.4 Hz), 4.52, 4.54 and 4.57* (AB type d's, total 2H, J=12.1 Hz), 4.62–4.68 (m, 1H), 4.83–4.87* (m, 1/3H), 5.21 (dd, 2/3H, J=5.3, 10.2 Hz), 7.24–7.33 (m, 5H); ^{13}C NMR (100 MHz, CD_3OD, both rotamers) δ ppm: 14.4, 14.8, 15.22, 15.28, 22.2, 22.5, 23.7, 25.5, 25.9, 26.7, 27.4, 29.9, 30.5, 31.8, 33.0, 35.5, 37.7, 38.0, 38.3, 38.6, 42.5, 43.3, 54.1, 55.9, 57.6, 57.7, 58.8, 58.9, 60.0, 70.7, 74.2, 74.8, 76.2, 128.7, 128.8, 129.4, 139.2, 172.5, 172.6, 172.8, 173.1, 173.2, 173.5, 173.9, 179.2, 179.3; IR (KBr) cm^{-1}: 3309, 2959, 2932, 2873, 1736, 1651, 1532, 1456, 1207, 1116; HRMS m/z $(M+K)^+$ calcd 644.3677, found: 644.3671. Anal. Calcd for $C_{33}H_{55}N_3O_7{\cdot}1/2H_2O$: C, 64.46; H, 9.18; N, 6.83. Found: C, 64.55; H, 8.95; N, 6.79; $[\alpha]_D^{24}$=−51.2 (c 1.09, CH_3OH).

4.5.3. (2*R*, 3*R*)-3-Hydroxy-2-methyl-nonanoyl-L-*N*-methyl-Leu-L-*allo*-Ile-L-Ser(OBn)-L-*allo*-Thr(TBS)-GlyOBn (25). Compound **23** (59.8 mg, 98.7 μmol) and compound **24** (40.1 mg, 105 μmol) were dissolved in THF (1.5 mL) and then Et_3N (41 μL, 294 μmol) was added. To this solution was added DEPC (32 μL, 196 μmol) at 0°C. The reaction mixture was stirred at 0°C for 2 h and at room temperature for an additional 16 h. After saturated $NaHCO_3$ aqueous solution was added, the organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered and evaporated. The oil residue was purified by column chromatography with a gradient elution system, a 5:1–3:1 mixture of hexane and EtOAc used as eluents to give **25** (92.4 mg, 95.4 μmol, 97%) as a colorless solid (mp 166–169°C). ^{1}H NMR (400 MHz, $CDCl_3$, major isomer) δ ppm: 0.02 (s, 3H), 0.06 (s, 3H), 0.79–0.96 (m, 15H), 0.84 (s, 9H), 1.15 (d, 3H, J=6.4 Hz), 1.22 (d, 3H, J=7.1 Hz), 1.27–1.47 (m, 13H), 1.53–1.60 (m, 1H), 1.78–1.85 (m, 1H), 1.90–2.05 (m, 1H), 2.71–2.74 (m, 1H), 2.93 (s, 3H), 3.56 (dd, 1H, J=7.6, 9.2 Hz), 3.61–3.63 (m, 1H), 3.77 (dd, 1H, J=5.1, 18.2 Hz), 3.84 (dd, 1H, J=4.5, 9.2 Hz), 3.98 (dd, 1H, J=5.7, 18.2 Hz), 4.22–4.30 (m, 1H), 4.42 (dd, 1H, J=4.4, 7.7 Hz), 4.49–4.58 (m, 5H), 5.07 (dd, 1H, J=5.5, 10.1 Hz), 5.14 (s, 2H), 6.84–4.92 (m, 4H), 7.24–7.39 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$, both rotamers) δ ppm: −5.0, −4.7, 11.6, 14.1, 14.3, 14.6, 14.7, 14.8, 16.0, 17.9, 19.5, 19.6, 21.69, 21.74, 22.6, 23.2, 23.4, 24.6, 24.7, 25.7, 25.9, 26.5, 29.2, 29.3, 29.6, 31.2, 31.8, 34.3, 35.7, 36.8, 37.0, 37.4, 41.0, 41.1, 41.7, 52.8, 52.9, 54.9, 56.7, 59.18, 59.24, 65.2, 67.0, 67.1, 68.4, 68.6, 69.3, 73.6, 74.5, 75.5, 127.8, 128.1, 128.4, 128.5, 128.6, 135.3, 137.1, 169.2, 169.4, 169.6, 169.7, 171.2, 171.4, 178.3; IR (KBr) cm^{-1}: 3281, 2959, 2931, 2859, 1757, 1640, 1547, 1257, 1123, 834; HRMS $C_{52}H_{55}N_5O_{10}K$ $(M+K)^+$ calcd 1006.5703, found: 1006.5692. Anal. Calcd for $C_{52}H_{85}N_5O_{10}{\cdot}1/2H_2O$: C, 63.90; H, 8.87; N, 7.17. Found: C, 63.86; H, 8.62; N, 7.13; $[\alpha]_D^{24}$=−43.7 (c 1.04, $CHCl_3$).

4.5.4. *O*′TBS-*O*Bn-globomycin (22a). A solution of **25** (30.4 mg, 31.4 μmol) and $LiOH{\cdot}H_2O$ (9.2 mg, 220 μmol) in THF–CH_3OH–H_2O (3:1:1, 1.0 mL) was stirred at 0°C for 2 h. The mixture was acidified with 10% aqueous $KHSO_4$ solution and extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and evaporated. The oil residue was purified by column chromatography with a gradient elution system, a 20:1–10:1 mixture of CH_2Cl_2 and CH_3OH used as eluents to give

the seco-acid (21.6 mg, 29.7 μmol, 95%) as a colorless solid (mp 205–207°C). ^{1}H NMR (400 MHz, $CDCl_3$, both rotamers) δ ppm: 0.04 (s, 3H), 0.08 (s, 3H), 0.84–0.98 (m, 15H), 0.87 (s, 9H), 1.05* (d, 1H, *J*=6.5 Hz), 1.09 (d, 2H, *J*=6.7 Hz), 1.17 (d, 3H, *J*=6.3 Hz), 1.31–1.66 (m, 14H), 1.75–1.83 (m, 1H), 1.84–1.95 (m, 1H), 2.73* (s, 1H), 2.90 (qu, 2/3H, *J*=6.9 Hz), 3.01 (s, 2H), 3.04–3.08* (m, 1/3H), 3.61–3.78 (m, 4H), 3.84 and 3.85* (d, 1H, *J*=17.8 Hz), 4.15–4.22 (m, 1H), 4.34–4.37* (m, 1/3H), 4.42–4.53 (m, 5/3H), 4.54 and 4.55* (s, 2H), 4.68–4.75 (m, 1H), 5.20 (dd, 2/3H, *J*=5.1, 10.4 Hz), 7.24–7.34 (m, 5H); ^{13}C NMR (100 MHz, CD_3OD, both rotamers) δ ppm: −4.8, −4.4, 12.0, 14.37, 14.42, 14.9, 15.2, 15.4, 18.8, 20.3, 22.1, 22.6, 23.7, 25.5, 25.8, 26.0, 26.3, 26.7, 27.4, 27.5, 29.9, 30.5, 31.8, 33.0, 33.1, 35.5, 37.7, 38.2, 38.5, 41.8, 42.5, 43.3, 54.4, 55.8, 55.9, 57.8, 57.9, 60.6, 69.9, 70.9, 71.0, 74.4, 74.8, 76.2, 128.8, 128.92, 128.95, 129.5, 139.1, 171.8, 172.2, 173.6, 179.4; IR (KBr) cm^{-1}: 3295, 2959, 2931, 2859, 1736, 1642, 1541, 1455, 1120, 834; HRMS calcd for $C_{45}H_{80}N_5O_{10}Si$ $(M+H)^+$ calcd 878.5674, found: 878.5682. Anal. Calcd for $C_{45}H_{79}N_5O_{10}Si\cdot 1/2H_2O$: C, 60.92; H, 9.09; N, 7.89. Found: C, 61.04; H, 8.58; N, 7.90; $[\alpha]_D^{25}=-43.2$ (*c* 0.50, CH_3OH).

A solution of the seco-acid (29.7 mg, 33.8 μmol) in THF (0.7 mL) was treated with 2,4,6-trichlorobenzoyl chloride (6.9 μL, 44.1 μmol) and Et_3N (14 μL, 100 μmol), and stirred at room temperature for 14.5 h. This mixed anhydride solution was diluted with toluene (16.1 mL) and introduced over 5 h via a syringe pump into a refluxed solution of DMAP (84.1 mg, 688 μmol) in toluene (17.0 mL). This mixture was refluxed for an additional 3 h. The cooled reaction mixture was evaporated, diluted with EtOAc, filtered and washed with 5% HCl aqueous solution, saturated $NaHCO_3$ aqueous solution and then brine. The organic layer was dried over Na_2SO_4, filtered and evaporated. The residue was purified by preparative HPLC (column: Develosil ODS-HG5 (10 mm×250 mm); wavelength: 220 nm; flow rate: 4.0 mL/min) with a 94:6 mixture of CH_3OH and 1% aqueous triethylammonium acetate used as an eluent to give **22a** (14.8 mg, 17.2 μmol, 51%) as a colorless solid (mp 70–72°C). ^{1}H NMR (500 MHz, $CDCl_3$, two rotamers (major/minor=7:3)) δ ppm: 0.059 (s, 21/10H), 0.065* (s, 9/10H), 0.070 (s, 21/10H), 0.08* (s, 9/10H), 0.84–0.99 (m, 21H), 0.845 (s, 63/10H), 0.855* (s, 9/10H), 1.07–1.17 (m, 6H), 1.19–1.40 (m, 11H), 1.41–1.56 (m, 3H), 1.63–1.75 (m, 27/10H), 1.90–1.94 (m, 1H), 2.00–2.02* (m, 3/10H), 2.11–2.14* (m, 3/10H), 2.19–2.24 (m, 7/10H), 2.78* (s, 9/10H), 3.02 (dq, 7/10H, *J*=6.9, 9.6 Hz), 3.13–3.16* (m, 3/10H), 3.16 (s, 21/10H), 3.55 (dd, 7/10H, *J*=3.7, 17.2 Hz), 3.71 (br s, 7/10H), 3.78 (dd, 7/10H, *J*=6.3, 10.2 Hz), 3.85 (dd, 7/10H, *J*=4.8, 10.2 Hz), 3.89* (dd, 3/10H, *J*=5.5, 10.4 Hz), 3.93–3.98 (m, 1H), 4.20–4.23 (m, 7/10H), 4.30 (q, 3/10H, *J*=4.6 Hz), 4.39 (dd, 7/10H, *J*=8.9, 17.2 Hz), 4.43–4.49* (m, 18/10H), 4.51 and 4.61 (AB type d's, each 7/10H, *J*=11.8 Hz), 4.55* (dd, 3/10H, *J*=4.6, 7.9 Hz), 4.61–4.65 (m, 14/10H), 4.77* (dd, 3/10H, *J*=3.9, 9.4 Hz), 4.83* (d, 3/10H, *J*=10.9 Hz), 5.26–5.31 (m, 7/10H), 6.40 (d, 7/10H, *J*=7.7 Hz), 6.45 (d, 7/10H, *J*=2.7 Hz), 6.69–6.73 (m, 6/10H), 6.89* (d, 3/10H, *J*=9.4 Hz), 7.05* (t, 3/10H, *J*=5.5 Hz), 7.26–7.40 (m, 5H), 7.72 (dd, 7/10H, *J*=3.6, 8.7 Hz), 8.22 (br s, 7/10H); ^{13}C NMR (100 MHz, $CDCl_3$, both rotamers) δ ppm: −4.8, −4.7, −4.6, 11.9, 14.17, 14.19, 15.06, 15.15, 15.3, 18.1, 18.4, 19.0, 21.7, 22.6, 22.7, 23.2, 23.3, 24.1, 25.0, 25.3, 25.8, 26.5, 27.0, 27.1, 27.2, 29.07, 29.15, 29.3, 29.4, 29.8, 31.6, 31.7, 31.8, 37.5, 37.6, 38.2, 38.5, 39.6, 40.1, 40.5, 42.1, 56.1, 56.2, 56.3, 56.7, 59.1, 59.3, 59.4, 66.6, 67.0, 67.9, 73.4, 73.8, 76.2, 76.5, 77.2, 78.2, 127.9, 128.0, 128.2, 128.3, 128.4, 128.6, 136.5, 136.6, 168.5, 169.0, 169.1, 169.3, 169.5, 169.7, 171.4, 172.6, 172.8, 174.0, 174.3, 177.0; IR (KBr) cm^{-1}: 3330, 2957, 2928, 2857, 1740, 1656, 1542, 1256, 1118, 834; HRMS calcd for $C_{45}H_{78}N_5O_9Si$ $(M+H)^+$ calcd 860.5569, found: 860.5590. Anal. Calcd for $C_{45}H_{77}N_5O_9Si\cdot 2H_2O$: C, 60.31; H, 9.11; N, 7.81. Found: C, 60.49; H, 8.77; N, 7.67; $[\alpha]_D^{26}=+11.9$ (*c* 1.01, CH_3OH).

4.6. *O*Bn-Globomycin (21a)[1d] from 22a

To a solution of **22a** (9.4 mg, 10.9 μmol) in THF (0.5 mL), was added a mixture of AcOH (40 μL, 0.70 mmol) and TBAF (1.0 M THF solution, 0.5 mL, 0.5 mmol) at 0°C. The solution was stirred at the same temperature for 1 h and at room temperature for additional 26 h. This reaction mixture was diluted with EtOAc and washed with a saturated $NaHCO_3$ aqueous solution. This organic layer was dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography with a gradient elution system, a 30:1–20:1 mixture of CH_2Cl_2 and MeOH used as eluents to give **21a** (7.8 mg, 10.4 μmol, 96%) as a colorless solid.

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18. In the macrocyclization step, 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU)[17] was used as the coupling reagent (40% yield, 2 steps).
19. Natural **1a**: $[\alpha]_D^{23}=+24.1$ (*c* 0.50, CH_3OH), synthetic **1a**: $[\alpha]_D^{25}=+23.8$ (*c* 0.50, CH_3OH). Natural **1b**: $[\alpha]_D^{25}=+21.3$ (*c* 1.15, CH_3OH), synthetic **1b**: $[\alpha]_D^{25}=+20.8$ (*c* 1.04, CH_3OH).
20. Acetylation of **1a** in L-Ser and L-*allo*-Thr residue diminished the activity.[2]
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