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An architectonic macrolide library based on a C2-symmetric macrodiolide toward pharmaceutical compositions

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ABSTRACT

A stereodivergent approach to creation of a specific 14-membered macrolide library is described. We designed a new 14-membered macrolide template possessing 10 sterogenic centers, and established a new library of fully-synthesized 14-membered ring compounds. The designed macrodiolides were synthesized through a convergent approach using an Evans aldol reaction, Keck esterification, and Yamaguchi macrolactonization, or Mitsunobu macrolactonization, as key steps. Moreover, introduction of an aminosugar to a macrodiolide aglycone by Schmidt glycosylation also afforded a new macrodiolide. Comparison between the conformation analysis of the macrolides, which we designed, and NMR analysis of the synthetic macrolides, indicated our stereoisomer library has significant diversity.

1. Introduction

Macrolides are a large and attractive class of natural products due to their prevalence as numerous small molecules having significant and diverse biological and medicinal properties.[1] They have a specific structure, a macrocycle core, which bestows conformational flexibility in three dimensions; for macrocycles with more than 10 atoms in the ring, multiple low-energy conformations are often available. Hence, they have a more accessible surface area compared with ordinary small organic molecules. These characteristic structures allow them to interact with the surface of target proteins, as well as making them potentially useful compounds for modulating protein-protein interactions.[2–4]

For decades, efforts have been made to synthesize macrocycle chemical libraries.[5,6] An approach utilizing a diversity oriented synthesis (DOS) strategy, which was proposed by S. L. Schreiber,[7] increased use of non-natural macrocycles and stimulated attention on structural or stereochemical diversity in library design and drug development.[8] Macrolides are highly complex chiral molecules, and inversion of stereochemistry at certain carbon atoms usually changes the macrolide properties, in particular their biological activity or PK/PD properties. The investigation of the stereostructure-activity relationships (SSAR) of naturally or non-naturally occurring macrocycles has been undertaken.[9] G. Kragol et al. reported on the synthesis and evaluation of oleandomycin derivatives having different stereochemistry at C8 and/or C9 positions,[10] and J. E. Harvey et al. reported the synthesis of diastereomeric analogs of aigialomycin D.[11] Furthermore, a few research groups have published on the stereochemical diversity in library design and drug development.[12] H. Fuwa and M. Sasaki et al. described a stereoisomer library of 8, 9-dehydroneopeltolide using olefin metathesis,[13] D. P. Curran et al. also reported on the stereoisomer library of SCH725674 by fluorous mixture synthesis (FMS).[14] Moreover, L. A. Marcaurelle et al. completed the synthesis of 16 stereoisomers of the non-natural macrolactams, based on an aldol-based build/couple/pair (B/C/P) strategy.[15] As mentioned above, the total synthesis and diversity oriented synthesis of natural products and non-natural macrocycles with stereochemical complexity are

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0040-4020/

still very difficult and require considerable effort. Thus, we hypothesized that a means to systematically access the complete matrix of stereoisomers for a library of chiral, sp^3-rich compounds would be an important factors for the drug discovery process.

Among the macrolides, 14-membered ring compounds are considered to be the most important in medicinal chemistry, because a large number of 14-membered macrolides exist that have been shown to exhibit various useful bioactivity. Some 14-membered ring natural products are shown in Fig. 1,[16] such as erythromycin A, rustmicin, clonostachydiol, sekothrixide, migrastatin, and these compounds possess significant biological activity, which varies—or is influenced by—the specific structure of each compound. Consequently, a 14-membered ring macrolide library covering multiple, varied substituents promising diversity and complexity would be an attractive and important research tool. We have been interested in investigating relationships between 14-membered macrolides and biological activities and have previously reported the creation of EM 574,[17] which exhibits gastrointestinal motor-stimulating activity, and EM 900, which possesses *anti*-inflammatory and/or immunomodulatory properties without antibacterial activity.[18] Furthermore, to the best of our knowledge, the relationships between the stereochemistry and biological activities of 14-membered macrolides are still very unexplored field. Herein, we report the design and synthesis of a new macrolide template, and the creation of a new stereoisomer macrolide library. A new macrolide containing an aminosugar was also synthesized via Schmidt glycosylation. In addition, the most stable conformation was generated for each of the macrolides. The resulting conformations emphasized the stereochemical diversity of our macrolide library, as expected.

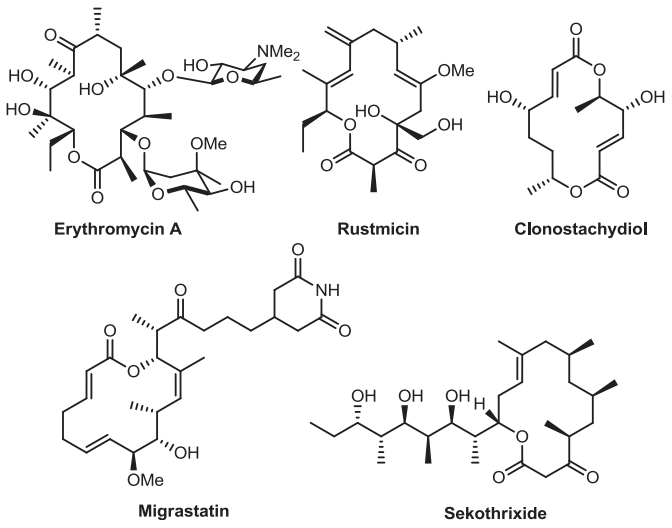

Fig. 1. The 14-membered macrolides.

2. Results and discussion

2.1. Strategy for construction of a stereoisomer library

Our approach was to focus on a 14-membered macrolide skeleton, the designed macrolide template being inspired by the natural product, erythromycin A, which shows various biological activities[1] and possesses five hydroxy groups, one carbonyl group and an ester group in its own lactone ring. Eight oxygen atoms exist in the macrolide skeleton. We anticipated that these oxygen atoms would play a role of hydrogen bond donor or acceptor, and would affect bioactivities. We envisioned that the 14-membered ring macrolide template would possess high fraction of sp^3-hybridized carbons[19] large surface area, numerous binding sites and drug-like physicochemical and pharmacokinetic properties. Furthermore, the characteristics of erythromycin A, plus the eight hydroxyl groups and two carbonyl groups, would be incorporated into the template. We designed a new macrolide template shown in Fig. 2. The template devised included a C2 symmetrical skeleton, 10 stereogenic centers and a macrodiolide backbone, having two ester groups in its own large ring. In addition, the template allows not only an easy synthetic route, but also derivation of a stereochemically diverse range of compounds. Macrolides possess some methyl, ethyl or other alkyl groups driven by propionates in the biosynthetic pathway, and these groups also affect the macrolide conformation. Consequently, we arranged six methyl groups and four hydroxy groups in the new macrolide ring. The template thereby acquires more flexibility and variable conformations via combinations of the stereochemistry of the methyl and hydroxy groups, and we expected that a macrolide so constructed would show significant bioactivity.

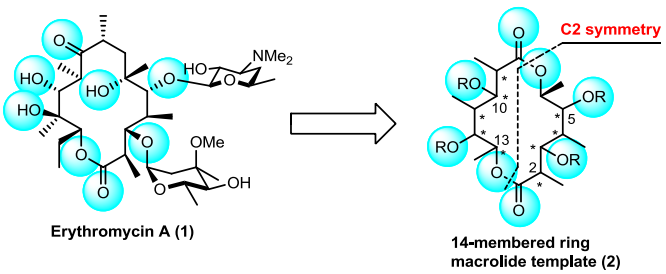

Fig. 2. Designed 14-membered macrolide template.

The synthetic plan of the new macrolide template is depicted in Scheme 1. To demonstrate the creation of a new macrolide stereoisomer library, we firstly planned to synthesize 32 stereoisomers, among the possible stereoisomers of template (2^{10}=1024). In order to prove our concept, we envisioned that the stereochemical diversity would be produced by two time-*syn*-Evans aldol reaction, Keck esterification, and Yamaguchi macrolactonization or Mitsunobu macrolactonization. Because of the C2 symmetical macrolide skeleton, the combination of various stereoisomer half units would also give 2-fold stereochemical diversity. Accordingly, four diastereomers of half units would lead to 32 stereoisomeric macrodiolide aglycones, and we could thus create the new divergent macrolide library based on our envisaged template.

The synthesis was started with the chiral lactic acid methyl ester **6**. Then, aldehyde **7** was prepared according to the reported procedure.[20] The first diversity was produced by the Evans aldol reaction[21] with (*R*) or (*S*)-chiral auxiliaries **8a**, **8b** afforded aldol products **9a**, **9b**[20] with high yield and diastereoselectivity. Subsequently, removal of chiral auxiliary and protection of the hydroxyl group gave the Weinreb amide **10a**, **10b** (**10a**; 76%, **10b**; 84% over two steps). Reduction of the Weinreb amide **10a**, **10b** afforded aldehydes **11a**, **11b**, in 98% and 94% yield, respectively. Then, a second diversity was produced by repeating the Evans aldol reaction, aldehydes **11a**, **11b** being subjected to the Evans aldol reaction to afford aldol products **12a**–**d** (Scheme 2) in 85–89% yield and high diastereoselectivity.[22]

In order to selectively remove key protecting groups at the late stage for glycosylation, we choose the BOM and TBS groups as the protecting groups. The protection of these aldol products with BOMCl and PMB deprotection of the resulting BOM ethers afforded the alcohols **13a**–**d** in 75–96% yield. The deprotection of aldol products **12a**–**d** using HF-pyridine afforded diols, which were conveniently transformed into carboxylic acids **14a**–**d** in 74–82% yield over two steps (Scheme 3). The esterification of possible

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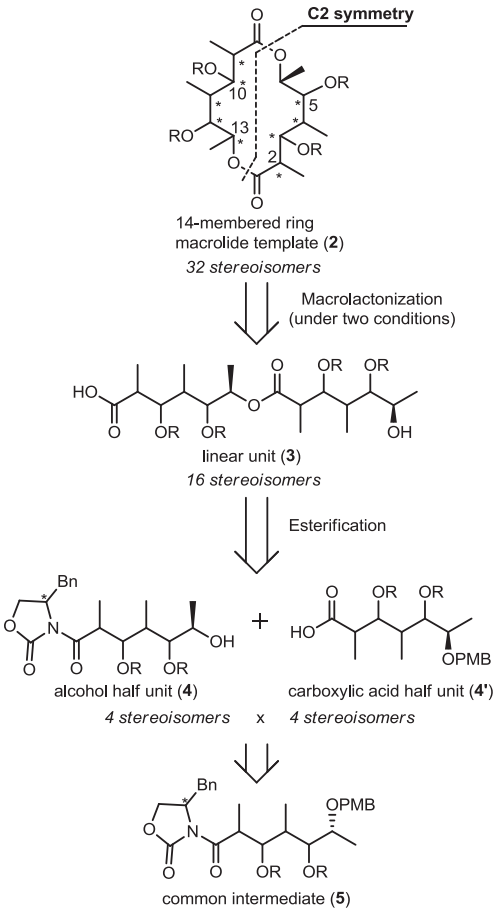
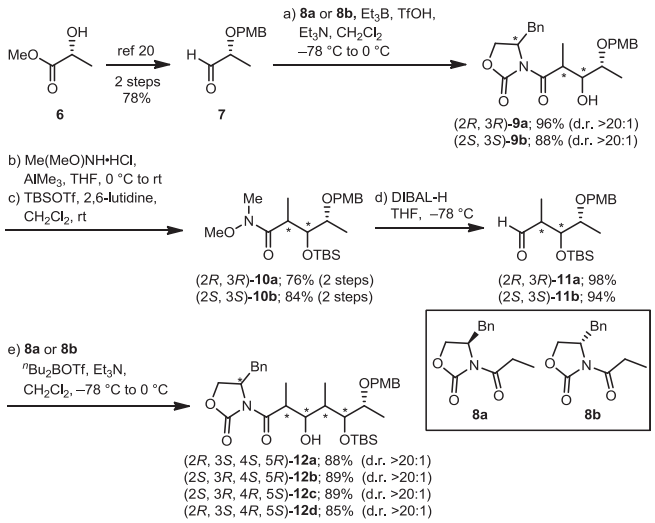


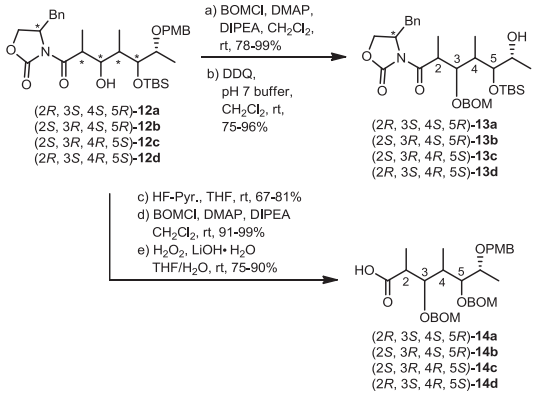
Scheme 1. Synthetic plan for construction of a stereoisomer library.



Scheme 2. The synthesis of 4 type of stereisomers **12a**–**d** via the Evans aldol reaction.

combinations of alcohol units **13a**–**d** with carboxylic acid units **14a**–**d** produced linear units **15a**–**p** under Keck condition[23] (Table 1). As a result, Keck esterification afforded each of the linear units **15a**–**p** in 74–99% yield. Then, the removal of oxazolidinone by hydrolysis and PMB ether by DDQ afforded the corresponding *seco*-acids **16a**–**p** over two steps (Scheme 4).

The final diversity was produced by Yamaguchi and Mitsunobu macrolactonizations, leading to 32 stereoisomers. These *seco*-acids **16a**–**p** were cyclized under Yamaguchi condition[24] with the



Scheme 3. The preparation of alcohols **13a**–**d** and carboxylic acids **14a**–**d**.

retention of a stereocenter at C13 or Mitsunobu condition[25] with the inversion of a stereocenter at C13 (Scheme 4). Many macrolides syntheses have been performed, and the key macrolactonization step was often found to be problematic.[26] For the stereoisomeric macrolide library described in this paper, a variety of stereocenters are present. Thus, some compounds found in the library do not cyclize efficiently due, presumably, to steric repulsion. The structures of synthesized macrodiolide aglycones produced by Yamaguchi macrolactonization are shown in Table 2.

Yamaguchi macrolactonization of the *seco*-acid **16a** under room temperature proceeded smoothly, to afford macrodiolide aglycone **17a** in 70% yield. However, we found that other *seco*-acids could not be efficiently cyclized under Yamaguchi macrolactonization at room temperature, although heating would allow the conformation change to occur. By some modification, other *seco*-acids were cyclized by Yamaguchi macrolactonization at 80 °C. Therefore, we conducted Yamaguchi macrolactonization of other *seco*-acids under 80 °C conditions. In addition, partial epimerization at the C2 position occurred during Yamaguchi macrolactonization (2,4,6-trichlorobenzoyl chloride, DMAP, DIPEA, benzene, at 80 °C) of *seco*-acids **16b**, **16f**, **16g**, **16j**, **16l**, **16n**, and macrodiolide aglycones were obtained as diastereo mixtures, which could not be separated by flash column chromatography and preparative thin layer chromatography.

Conversely, Mitsunobu macrolactonization (DEAD, PPh_3, toluene) under room temperature proceeded, to afford macrodiolide aglycones **18a**–**p** in 10–86% yields (Table 3). These results indicated that the stereochemistry of *seco*-acids was an important factor, and macrolactonization of certain *seco*-acids **16f**, **16g**, **16l** was not efficient and very slowly cyclized under both conditions due to steric hindrance. Using this methodology, 16 *seco*-acids **16a**–**p** led to 32 macrodiolide aglycones **17a**–**p** and **18a**–**p**. Each of the stereoisomer macrodiolide aglycones shows ^1H and ^{13}C NMR spectra that are easily distinguishable from the other stereoisomers. These spectra data indicated that the conformation of synthesized macrodiolides were different and the library is of great worth with respect to stereodivergence.

2.2. Glycosylation of aglycone leading to a new macrolide

Macrolides with an amimosugar demonstrate more complexity and compound diversity. Therefore, such macrolides were expected to show various biological activities, as is the case with erythromycin A and other 14-membered macrolides. In order to examine the stereochemical diversity of these macrolides, we first performed conformational analysis to generate the most stable conformer for each one, using the CAMDAS (Conformational Analyzer with Molecular Dynamics and Sampling) program.[27] The procedure for the CAMDAS calculation was similar to that already described.[28]

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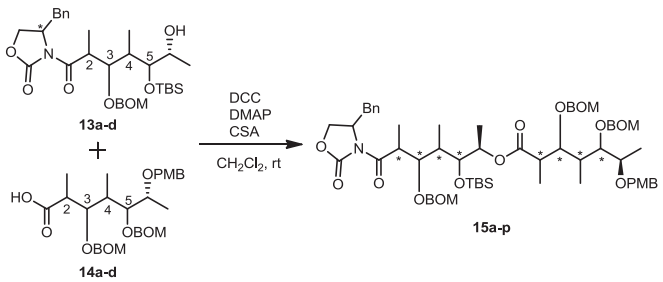
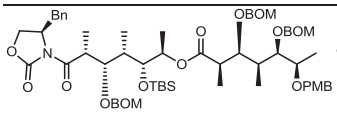
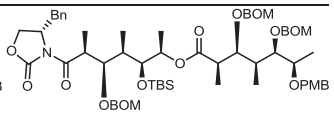
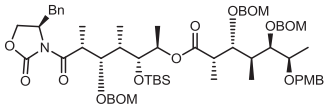
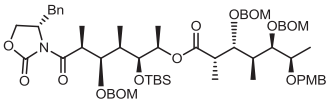
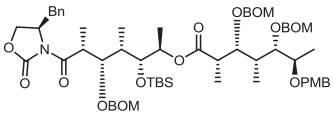
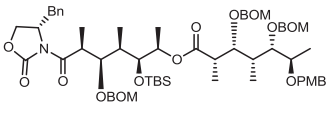
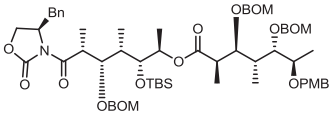
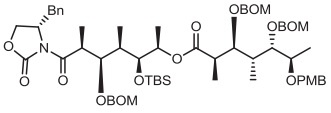
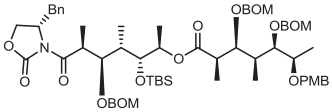
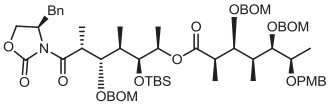
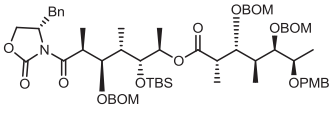
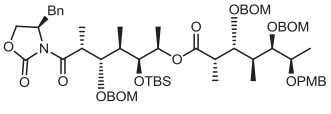
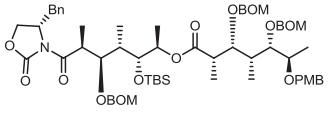
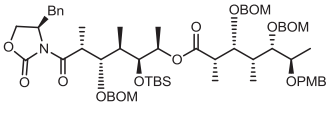
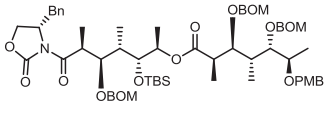
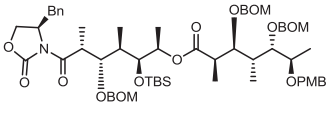
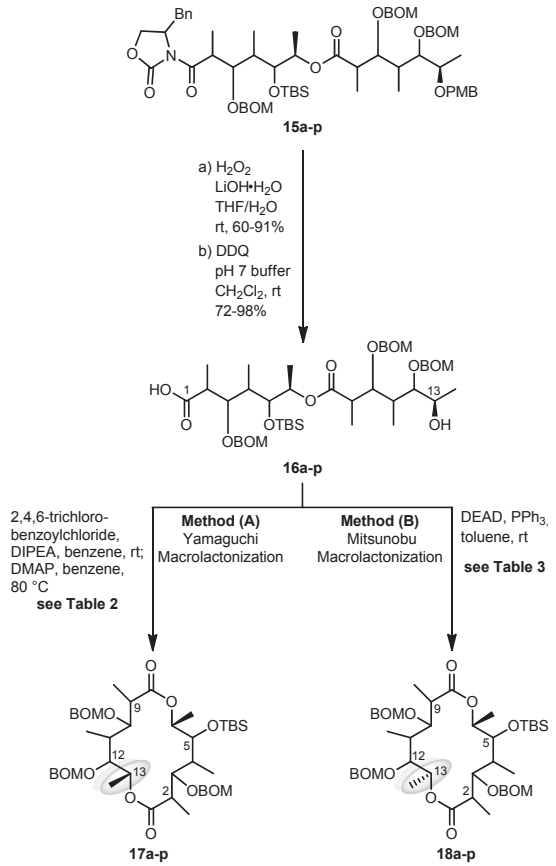
Table 1
The Keck esterification



Compound; % yield (Alcohols **13**-Carboxylic acids **14**)	
 **15a**; 83%[a] (**13a-14a**)[b]	 **15i**; 97%[a] (**13c-14a**)[b]
 **15b**; 82%[a] (**13a-14b**)[b]	 **15j**; 79%[a] (**13c-14b**)[b]
 **15c**; 74%[a] (**13a-14c**)[b]	 **15k**; 82%[a] (**13c-14c**)[b]
 **15d**; 93%[a] (**13a-14d**)[b]	 **15l**; 94%[a] (**13c-14d**)[b]
 **15e**; 93%[a] (**13b-14a**)[b]	 **15m**; 89%[a] (**13d-14a**)[b]
 **15f**; 75%[a] (**13b-14b**)[b]	 **15n**; 94%[a] (**13d-14b**)[b]
 **15g**; 77%[a] (**13b-14c**)[b]	 **15o**; 89%[a] (**13d-14c**)[b]
 **15h**; 74%[a] (**13b-14d**)[b]	 **15p**; 99%[a] (**13d-14d**)[b]

[a]Isolated yield. [b]The number of parenthesis indicates alcohols **13** and carboxylic acids **14**.



Scheme 4. The synthesis of Macrodiolide aglycones **17a**–**p** and **18a**–**p**. DDQ=2,3-dichloro-5,6-dicyano-*p*-benzoquinone, DEAD=diethyl azodicarboxylate, DMAP=4-dimethylaminopyridine, DIPEA=*N*, *N*-diisopropylethylamine.

The Merck Molecular Force Field (MMFF) was used to evaluate the potential energy surface of the molecule.[29] The CAMDAS calculation was performed in vacuo, and the electrostatic potential term was neglected in order to mimic the shield effects of solvent molecules on electrostatic interactions. The superimposition of the most stable conformers (provided in the Supplementary data) suggests that our macrolide library possesses a wide stereochemical diversity.

We attempted to synthesize a new macrolide containing an aminosugar moiety via Schmidt glycosylation. The strategy of incorporating an aminosugar moiety is described in Scheme 5. We selected an aglycone **17a** in the synthesized library as the starting compound, because it resembled the conformation of Erythromycin A. At first, we tried to remove the TBS group by treatment with fluorine reagents. The treatment with HF-pyridine afforded the desired macrodiolide aglycone **19** in 65% yield, while treatment with TBAF failed to give the target product.[30] Schmidt glycosylation with trichloroacetimidate **20**[31] afforded the desired macrolide **21** in 48% yield under the reported condition.[20a,32] The selectivity of this reaction was highly β-selectivity together with no α-isomer, determined by ^{1}H NMR spectra ($J_{1,2}$=7.5 Hz). Then, the removal of BOM groups and acetyl group afforded a new macrolide **22** in 93% yield over two steps (Scheme 5).

We then determined the three-dimensional (3D) solution structure of **22** in MeOH-d_4 solution, by a combination method of NMR spectroscopy and conformational analysis.[18a,33] The structural constraints derived from NMR experiments are included in the Supplementary data. The resulting 3D solution structure of **22** is given in Fig. 3, together with one obtained as the most stable conformation in the conformational analysis. We could see that both structures were very similar. These results suggested that the

3D solution structure of the synthesized macrolide could be predicted as the most stable conformation obtained in the conformation analysis. In future, we expect our macrolide library to become a useful tool for drug discovery.

3. Conclusion

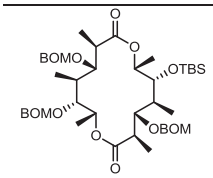
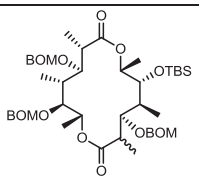
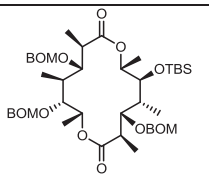
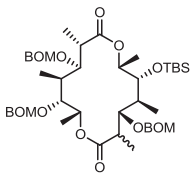
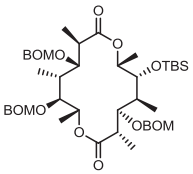
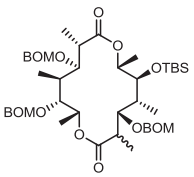
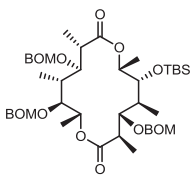
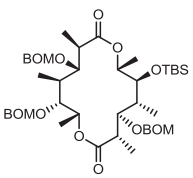
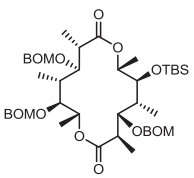
In conclusion, we have synthesized a stereoisomer library of 14-membered ring compounds using a custom-designed macrolide template. Four diastereomers of half units lead to 32 stereoisomer macrolides via Evans aldol reaction, Keck esterification and Yamaguchi macrolactonization or Mitsunobu macrolactonization. We also demonstrated the synthesis of a new macrolide with an aminosugar, the desosamine. Our ongoing efforts will synthesize non-natural macrolides and biologically active compounds based on a customized template, and biological screenings of the synthesized library are now underway.

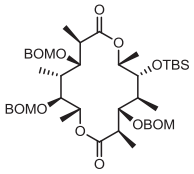
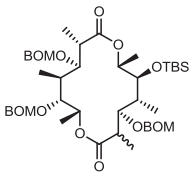
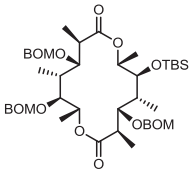
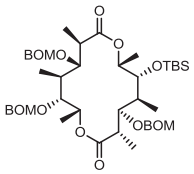
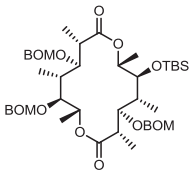
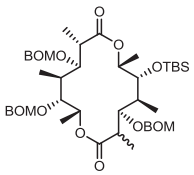
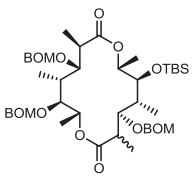
4. Experimental section

4.1. General

Unless otherwise stated, reactions were carried out under a nitrogen atmosphere. Dry dichloromethane (CH_2Cl_2), tetrahydrohuran (THF), benzene, toluene and hexane were purchased from Kanto Chemical Co., Inc. Pre-coated silica gel plates with a fluorescent indicator were used for analytical (Merck Millipore, TLC silica

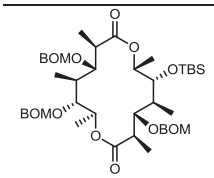
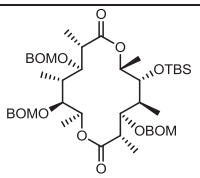
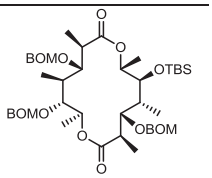
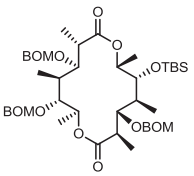
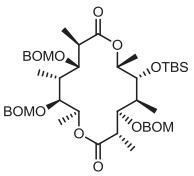
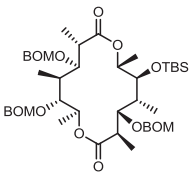
Table 2
Yamaguchi macrolactonization of *seco*-acids **16a**–**p**

Macrodiolide aglycone; % Yield; Stereochemistry		
		
17a; 70%[a, b]	**17g**; 34% (1:1)[c]	**17m**; 34%[b]
(2*R*, 3*S*, 4*S*, 5*R*, 6*R*, 9*R*, 10*S*, 11*S*, 12*R*, 13*R*)	(2*S*, 3*R*, 4*S*, 5*R*, 6*R*, 9*S*, 10*R*, 11*R*, 12*S*, 13*R*)	(2*R*, 3*S*, 4*R*, 5*S*, 6*R*, 9*R*, 10*S*, 11*S*, 12*R*, 13*R*)
		
17b; 85% (5:1)[c]	**17h**; 63%[b]	**17n**; 13% (2:1)[c]
(2*R*, 3*S*, 4*S*, 5*R*, 6*R*, 9*S*, 10*R*, 11*S*, 12*R*, 13*R*)	(2*S*, 3*R*, 4*S*, 5*R*, 6*R*, 9*R*, 10*S*, 11*R*, 12*S*, 13*R*)	(2*R*, 3*S*, 4*R*, 5*S*, 6*R*, 9*S*, 10*R*, 11*S*, 12*R*, 13*R*)
		
17c; 82%[b]	**17i**; 29%[b]	**17o**; 16%[b]
(2*R*, 3*S*, 4*S*, 5*R*, 6*R*, 9*S*, 10*R*, 11*R*, 12*S*, 13*R*)	(2*S*, 3*R*, 4*R*, 5*S*, 6*R*, 9*R*, 10*S*, 11*S*, 12*R*, 13*R*)	(2*R*, 3*S*, 4*R*, 5*S*, 6*R*, 9*S*, 10*R*, 11*R*, 12*S*, 13*R*)

		
17d; 73%[b]	**17j**; 12% (2:1)[c]	**17p**; 68%[b]
(2*R*, 3*S*, 4*S*, 5*R*, 6*R*, 9*R*, 10*S*, 11*R*, 12*S*, 13*R*)	(2*S*, 3*R*, 4*R*, 5*S*, 6*R*, 9*S*, 10*R*, 11*S*, 12*R*, 13*R*)	(2*R*, 3*S*, 4*R*, 5*S*, 6*R*, 9*R*, 10*S*, 11*R*, 12*S*, 13*R*)
		
17e; 47%[b]	**17k**; 48%[b]	
(2*S*, 3*R*, 4*S*, 5*R*, 6*R*, 9*R*, 10*S*, 11*S*, 12*R*, 13*R*)	(2*S*, 3*R*, 4*R*, 5*S*, 6*R*, 9*S*, 10*R*, 11*R*, 12*S*, 13*R*)	
		
17f; 23% (2:1)[c]	**17l**; 38% (1:1)[c]	
(2*S*, 3*R*, 4*S*, 5*R*, 6*R*, 9*S*, 10*R*, 11*S*, 12*R*, 13*R*)	(2*S*, 3*R*, 4*R*, 5*S*, 6*R*, 9*R*, 10*S*, 11*R*, 12*S*, 13*R*)	

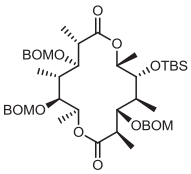
[a]*Seco*-acid **16a** was cyclized by Yamaguchi macrolactonization under room temperature, and afforded macrodiolide aglycone **17a** in 70% yield. [b]Isolated yield. [c]Epimerization occurred, and the diastereomer ratio was calculated by ^{1}H NMR spectra.

Table 3
Mitsunobu macrolactonization of *seco*-acids **16a**–**p**

Macrodiolide aglycone; % Yield[a]; Stereochemistry		
		
18a; 70%	**18g**; 27%	**18m**; 79%
(2*R*, 3*S*, 4*S*, 5*R*, 6*R*, 9*R*, 10*S*, 11*S*, 12*R*, 13*S*)	(2*R*, 3*S*, 4*S*, 5*R*, 6*R*, 9*S*, 10*R*, 11*S*, 12*R*, 13*S*)	(2*R*, 3*S*, 4*R*, 5*S*, 6*R*, 9*S*, 10*R*, 11*S*, 12*R*, 13*S*)
		
18b; 86%	**18h**; 27%	**18n**; 66%
(2*R*, 3*S*, 4*S*, 5*R*, 6*R*, 9*S*, 10*R*, 11*S*, 12*R*, 13*S*)	(2*S*, 3*R*, 4*R*, 5*S*, 6*R*, 9*S*, 10*R*, 11*R*, 12*S*, 13*S*)	(2*S*, 3*R*, 4*R*, 5*S*, 6*R*, 9*S*, 10*R*, 11*S*, 12*R*, 13*S*)

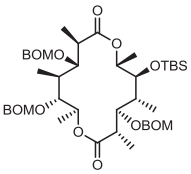
(*continued on next page*)

(continued)



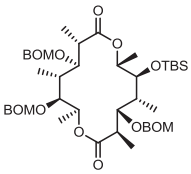
18c; 54%

(2*R*, 3*S*, 4*S*, 5*R*, 6*R*, 9*S*, 10*R*, 11*R*, 12*S*, 13*S*)



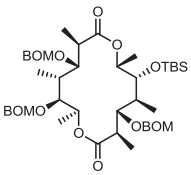
18i; 50%

(2*R*, 3*S*, 4*S*, 5*R*, 6*R*, 9*R*, 10*S*, 11*S*, 12*R*, 13*S*)



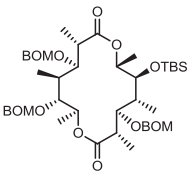
18o; 64%

(2*S*, 3*R*, 4*S*, 5*R*, 6*R*, 9*S*, 10*R*, 11*R*, 12*S*, 13*S*)



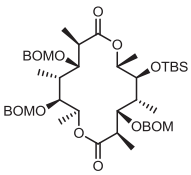
18d; 49%

(2*R*, 3*S*, 4*S*, 5*R*, 6*R*, 9*R*, 10*S*, 11*R*, 12*S*, 13*S*)



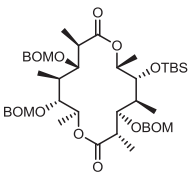
18j; 59%

(2*S*, 3*R*, 4*R*, 5*S*, 6*R*, 9*R*, 10*S*, 11*R*, 12*S*, 13*S*)



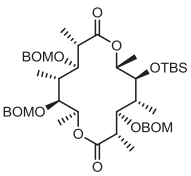
18p; 49%

(2*R*, 3*S*, 4*R*, 5*S*, 6*R*, 9*S*, 10*R*, 11*R*, 12*S*, 013*S*)



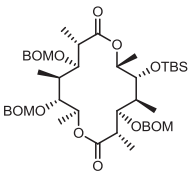
18e; 73%

(2*R*, 3*S*, 4*R*, 5*S*, 6*R*, 9*R*, 10*S*, 11*S*, 12*R*, 13*S*)



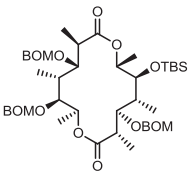
18k; 10%

(2*S*, 3*R*, 4*R*, 5*S*, 6*R*, 9*R*, 10*S*, 11*S*, 12*R*, 13*S*)



18f; 38%

(2*R*, 3*S*, 4*R*, 5*S*, 6*R*, 9*R*, 10*S*, 11*R*, 12*S*, 13*S*)

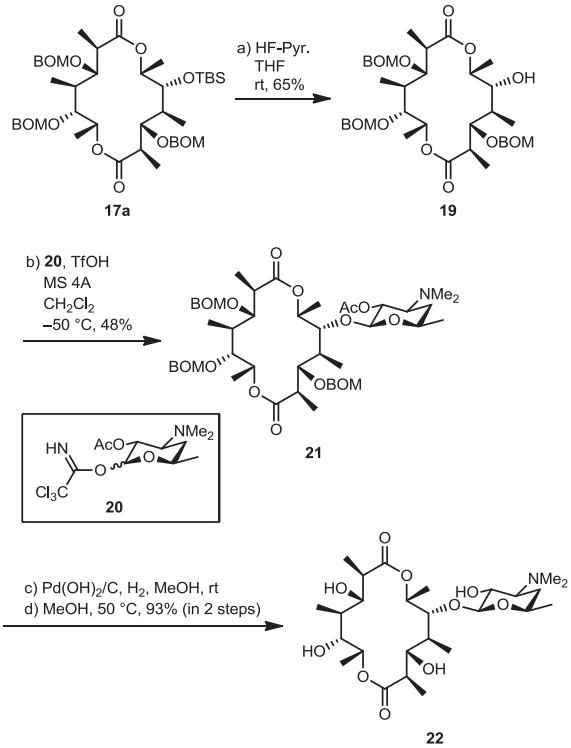


18l; 22%

(2*S*, 3*R*, 4*S*, 5*R*, 6*R*, 9*R*, 10*S*, 11*R*, 12*S*, 13*S*)

[a]Isolated yield.

gel 60 F_{254}) and preparative thin layer chromatography (Merck Millipore, PLC silica gel 60 F_{254}, 0.5 mm). Silica gel 60N, spherical neutral, for flash chromatography (Kanto Chemical Co., Inc., particle size 40–50 μm, Cat. No. 37563–84) was used for flash column chromatography. ^{1}H NMR spectra were recorded on 500 MHz spectrometers and ^{13}C NMR spectra were recorded on 125 MHz spectrometers on JEOL ECA-500 (500 MHz). The chemical shifts are expressed in parts per million downfield from internal solvent peaks $CDCl_3$ (7.26 ppm, ^{1}H NMR, 77.0 ppm, ^{13}C NMR), CD_3OD (3.31 ppm, ^{1}H NMR, 49.0 ppm, ^{13}C NMR) and coupling constant (*J* values) are given in Hertz. The coupling patterns are expressed by s (singlet), d (doublet), dd (double doublet), ddd (double double doublet), dt (double triplet), t (triplet), q (quartet), dq (double quartet), m (multiplet), br (broadened), complex m, app (appearance). The all infrared (IR) spectra were measured on a Horiba FT-710 spectrometer using a diamond horizontal ATR accessory. High- and low-resolution mass spectra were measured on JEOL JMS-700 MStation and JEOL JMS-T100LP. Optical rotations were measured with a Jasco P-1010 polarmeter.



Scheme 5. The synthesis of a new macrolide **22**.

*4.1.1. (R)-4-Benzyl-3-{(2′R,3′R,4′R)-3′-hydroxy-4′-[(4-methoxybenzyl)oxy]-2′-methylpentanoyl} oxazolidin-2-one (**9a**).* To a solution of Et_3B in hexane (1.04 M, 105 mL, 109 mmol) was added TfOH (9.7 mL, 111 mmol) under N_2 at 0 °C. After stirring for 1 h at 40 °C, to the solution mixture was added a solution of (*R*)-(−)-4-benzyl-3-propionyloxazolidin-2-one **8a** (22.8 g, 97.7 mmol) in CH_2Cl_2 (60 mL) and Et_3N (29.0 mL, 209 mmol) at 0 °C. Then, the mixture was cooled to −78 °C and to this mixture was slowly added a solution of aldehyde **7** (16.0 g, 82.4 mmol) in CH_2Cl_2 (65 mL). After stirring for 30 min, the mixture was warmed to 0 °C and stirred for 1 h. The reaction mixture was quenched with phosphate buffer solution in water (100 mL, pH=7.0) and MeOH/30% aq H_2O_2 solution in water (v/v, 2/1, 90 mL) at 0 °C. Resulted two layers were separated and the aqueous phase was extracted with $CHCl_3$ (50 mL×3). The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc=5/1, 3/1 to 2/1) to afford aldol product **9a** (33.9 g, 96%) as a colorless oil; $[\alpha]_D^{22}$ −48.6 (*c* 1.00, $CHCl_3$); IR (neat)/cm^{-1}; 3448, 1780, 1692, 1385, 1246, 1211, 1105, 1039, 754; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (m, 2H), 7.27 (d, *J*=6.3 Hz, 1H), 7.23 (d, *J*=8.6 Hz, 2H), 7.17 (d, *J*=8.0 Hz, 2H), 6.84 (d, *J*=8.6 Hz, 2H), 4.58 (d, *J*=11.5 Hz, 1H), 4.41 (m, 1H), 4.30 (d, *J*=11.5 Hz, 1H), 4.07 (dd, *J*=8.6, 1.7 Hz, 1H), 3.99 (dd, *J*=8.3, 8.3 Hz, 1H), 3.89 (dq, *J*=6.9, 6.9 Hz, 1H), 3.79 (m, 1H), 3.75 (s, 3H), 3.53 (m, 1H), 3.20 (dd, *J*=13.2, 2.9 Hz, 1H), 2.70 (dd, *J*=13.2, 9.7 Hz, 1H), 2.52 (d, *J*=6.9 Hz, 1H), 1.29 (d, *J*=6.9 Hz, 3H), 1.29 (d, *J*=6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3, 159.0, 152.7, 135.1, 130.1, 129.6 (C×2), 129.3 (C×2), 128.7 (C×2), 127.2, 113.6 (C×2), 74.9, 74.1, 69.9, 65.8, 55.1, 55.1, 40.2, 37.5, 15.2, 12.8; HRMS-ESI (*m*/*z*); $[M+Na]^+$ calcd for $C_{24}H_{29}NO_6Na$, 450.1893; found: 450.1902.

*4.1.2. (2R,3R,4R)-3-[(tert-Butyldimethylsilyl)oxy]-N-methoxy-4-[(4-methoxybenzyl)oxy]-N,2-dimethylpentamide (**10a**).* To a suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (11.7 g, 120 mmol) in THF (100 mL) was added $AlMe_3$ (1.06 M in hexane, 116 mL, 123 mmol) under N_2 at 0 °C. After stirring for 1 h, the reaction

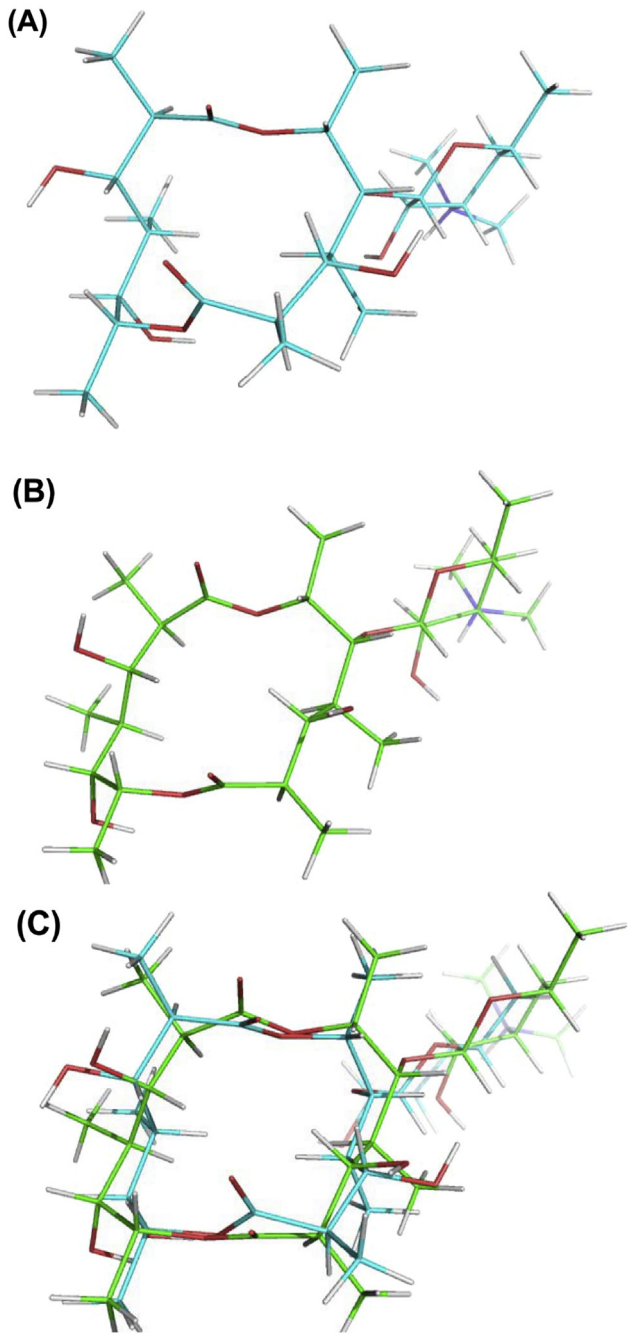


Fig. 3. The conformation of macrolide **22**. (**A**) The conformation determined by NMR analysis of synthesized macrolide **22** (Blue). (**B**) The most stable conformation of macrolide **22** calculated by CAMDAS (Green). (**C**) Superimposition of (A) and (B).

mixture was warmed to room temperature and stirred for 30 min. The mixture was then cooled to 0 °C and a solution of aldol product **9a** (20.5 g, 48.0 mmol) in THF (60 mL) was added. The reaction mixture was warmed to room temperature, and stirred for 13 h. The reaction was quenched with aq 1N HCl (80 mL) and resulted two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (40 mL×3). The combined organic layers were washed with water and brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was used in the next reaction without further purification.

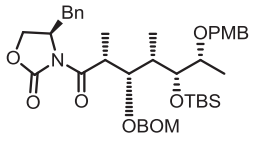
To a solution of crude mixture in CH_2Cl_2 (120 mL) was added 2,6-lutidine (18.0 mL, 155 mmol) under N_2. Then the mixture was cooled to 0 °C and TBSOTf (25.8 mL, 112 mmol) was added. After stirring for 4 h, the reaction mixture was quenched with aq 1N HCl (60 mL). Resulted two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (40 mL×3). The combined organic layers were washed with water and brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc=6/1, 4/1 to 3/1) to afford Weinreb amide **10a** (15.5 g, 76%) as a colorless oil; $[\alpha]_D^{24}$ +24.2 (*c* 1.00, $CHCl_3$); IR (neat)/cm^{-1}; 2935, 2362, 1658, 1514, 1466, 1383, 1252, 1095, 1043, 835, 777; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J*=8.0 Hz, 2H), 6.83 (d, *J*=7.5 Hz, 2H), 4.44 (d, *J*=11.5 Hz, 1H), 4.32 (d, *J*=11.5 Hz, 1H), 4.20 (dd, *J*=8.6, 4.6 Hz, 1H), 3.78 (s, 3H), 3.61 (s, 3H), 3.55 (m, 1H), 3.18 (app br s, 1H), 2.97 (s, 3H), 1.19 (d, *J*=6.3 Hz, 3H), 1.15 (d, *J*=6.9 Hz, 3H), 0.89 (s, 9H), 0.10 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.8, 158.9, 131.0, 129.3 (C×2), 113.4 (C×2), 76.95, 72.7, 70.7, 61.2, 55.2, 35.0, 32.2, 25.8 (C×3), 18.1, 15.6, 14.0, −4.5, −4.6; HRMS-ESI (*m*/*z*); $[M+Na]^+$ calcd for $C_{22}H_{39}NO_5SiNa$, 448.2495; found: 448.2494.

*4.1.3. (2R,3R,4R)-3-[(tert-Butyldimethylsilyl)oxy]-4-(4-methoxybenzyl)oxy-2-methylpentanal (**11a**).* To a solution of Weinreb amide **10a** (22.1 g, 51.9 mmol) in THF (100 mL) was added DIBAL-H (1.0 M in hexane, 110 mL, 110 mmol) under N_2 at −78 °C. After stirring for 1 h, the reaction was quenched with satd aq Rochelle's salt (150 mL) and stirred for 1 h at room temperature. Resulted two layers were separated and the aqueous phase was extracted with EtOAc (50 mL×3). The combined organic layers were washed with water and brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc=7/1 to 4/1) to afford aldehyde **11a** (18.6 g, 98%) as a colorless oil; $[\alpha]_D^{24}$ −26.4 (*c* 1.00, $CHCl_3$); IR (neat)/cm^{-1} 2954, 2931, 2885, 2854, 1720, 1512, 1250, 1088, 1034, 833, 771; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.72 (d, *J*=1.7 Hz, 1H), 7.21 (d, *J*=8.6 Hz, 2H), 6.87 (d, *J*=8.6 Hz, 2H), 4.46 (d, *J*=11.5 Hz, 1H), 4.34 (d, *J*=11.5 Hz, 1H), 3.98 (dd, *J*=5.7, 4.0 Hz, 1H), 3.80 (s, 3H), 3.55 (dq, *J*=6.3, 4.0 Hz, 1H), 2.55 (m, 1H), 1.18 (d, *J*=6.3 Hz, 3H), 1.05 (d, *J*=6.9 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.2, 159.1, 130.2, 129.3 (C×2), 113.6 (C×2), 75.2, 74.6, 70.3, 55.2, 48.9, 25.8 (C×3), 18.0, 14.6, 10.2, −4.5, −4.8; HRMS-ESI (*m*/*z*); $[M+Na]^+$ calcd for $C_{20}H_{34}O_4SiNa$, 389.2124; found: 389.2132.

*4.1.4. (R)-4-Benzyl-3-{(2′R,3′S,4′S,5′R,6′R)-5-[(tert-butyldimethylsilyl)oxy]-3-hydroxy-6-(4-methoxybenzyloxy)-2, 4-dimethylheptanoyl} oxazolidin-2-one (**12a**).* To a solution of (*R*)-(−)-4-benzyl-3-propionyloxazolidin-2-one **8a** (7.08 g, 30.4 mmol) in CH_2Cl_2 (55 mL) was added Et_3N (9.0 mL, 64.9 mmol) and $^nBu_2BOTf$ (1.0 M in CH_2Cl_2 solution, 40 mL, 40.0 mmol) under N_2 at 0 °C. After stirring for 40 min, the solution was cooled to −78 °C and a solution of aldehyde **11a** (8.77 g, 23.9 mmol) in CH_2Cl_2 (45 mL) was added. The reaction mixture was stirred at −78 °C for 1 h. Then the mixture was allowed to warm to 0 °C and stirred for 1 h. The reaction mixture was quenched with phosphate buffer solution in water (90 mL, pH=7.0) and MeOH/30% H_2O_2 solution in water (v/v, 2/1, 81 mL). After stirring for 1 h, resulted two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (40 mL×3). The combined organic layers were washed with water and brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc=8/1, 6/1 to 3/1) to afford aldol product **12a** (12.6 g, 88%) as a colorless oil; $[\alpha]_D^{26}$ −42.3 (*c* 1.00, $CHCl_3$); IR (neat)/cm^{-1}; 3564, 2939, 2893, 2854, 1774, 1697, 1381, 1242, 1211, 1026, 833, 741; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (m, 2H), 7.29−7.25 (complex m, 3H), 7.21 (d, *J*=7.5 Hz, 2H), 6.88 (d, *J*=8.6 Hz, 2H), 4.68 (m, 1H), 4.61 (d, *J*=11.5 Hz, 1H), 4.40 (d, *J*=11.5 Hz, 1H), 4.22 (m, 1H), 4.16 (d, *J*=5.2 Hz, 2H), 3.97 (dq, *J*=6.9, 6.9 Hz, 1H), 3.79 (s, 3H), 3.65 (dd, *J*=5.7, 5.2 Hz, 1H), 3.57 (m, 1H), 3.23 (dd, *J*=13.2, 3.3 Hz, 1H), 3.21 (d, *J*=3.9 Hz, 1H), 2.78 (dd, *J*=13.2, 9.2 Hz, 1H), 1.81 (m, 1H), 1.34 (d, *J*=6.9 Hz, 3H), 1.26 (d, *J*=6.3 Hz, 3H), 0.95 (d, *J*=6.9 Hz, 3H), 0.85 (s, 9H), 0.01 (s, 3H), −0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.7,

159.1, 152.6, 135.0, 130.3, 129.4 (C×2), 129.1 (C×2), 128.8 (C×2), 127.3, 113.7 (C×2), 77.5, 75.9, 71.8, 70.2, 65.8, 55.1, 54.9, 40.1, 37.9, 37.5, 25.8 (C×3), 18.1, 14.1, 13.4, 10.2, −4.3, −5.0; HRMS-ESI (*m*/*z*); $[M+Na]^+$ calcd for $C_{33}H_{49}NO_7SiNa$, 622.3176; found: 622.3181.

*4.1.5. (R)-4-Benzyl-3-{(2′R,3′S,4′S,5′R,6′R)-3′-[(benzyloxy)methoxy]-5′-[(tert-butyldimethylsilyl)oxy]-6′-[(4-methoxybenzyl)oxy]-2′,4′-dimethylheptanoyl} oxazolidin-2-one (**S1a**).*

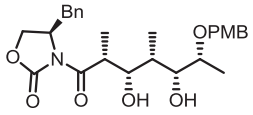


S1a

To a solution of Evans aldol product **12a** (3.06 g, 5.10 mmol) in CH_2Cl_2 (7.0 mL) was added DMAP (638 mg, 5.22 mmol) and DIPEA (22.0 mL, 129 mmol) under N_2 at room temperature. Then BOMCl (10.5 mL, 76.4 mmol) was added to the mixture at 0 °C. After stirring for 5 h at room temperature, the reaction was quenched with H_2O (20 mL) at 0 °C. The resulting mixture was diluted with CH_2Cl_2 (10 mL) and resulted two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (15 mL×3). The combined organic layers were washed with water and brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc=5/1 to 3/1) to afford **S1a** (3.42 g, 93%) as a colorless oil; $[\alpha]_D^{27}$ −33.7 (*c* 1.00, $CHCl_3$); IR (neat)/cm^{-1}; 3062, 2939, 2893, 2854, 1774, 1697, 1512, 1458, 1381, 1242, 1088, 1026, 833, 741; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36–7.23 (complex m, 10H), 7.11 (d, *J*=6.9 Hz, 2H), 6.84 (d, *J*=8.6 Hz, 2H), 4.82 (d, *J*=6.9 Hz, 1H), 4.81 (d, *J*=6.9 Hz, 1H), 4.69 (d, *J*=12.0 Hz, 1H), 4.58 (d, *J*=12.0 Hz, 1H), 4.54 (d, *J*=11.5 Hz, 1H), 4.47 (d, *J*=11.5 Hz, 1H), 4.35 (m, 1H), 4.12–4.05 (complex m, 2H), 4.01 (dd, *J*=9.2, 2.3 Hz, 1H), 3.93 (dd, *J*=8.0, 8.0 Hz, 1H), 3.88 (dd, *J*=5.2, 4.0 Hz, 1H), 3.78 (s, 3H), 3.55 (m, 1H), 3.23 (dd, *J*=13.2, 3.4 Hz, 1H), 2.70 (dd, *J*=13.2, 9.7 Hz, 1H), 2.02 (m, 1H), 1.28 (d, *J*=6.3 Hz, 3H), 1.16 (d, *J*=6.3 Hz, 3H), 0.96 (d, *J*=6.9 Hz, 3H), 0.86 (s, 9H), 0.03 (s, 3H), −0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4, 158.8, 153.0, 138.2, 135.3, 131.1, 129.4 (C×2), 129.0 (C×2), 128.8 (C×2), 128.2 (C×2), 127.4, 127.3 (C×2), 127.1, 113.5 (C×2), 96.7, 81.2, 77.4, 73.1, 70.2, 70.1, 65.8, 55.5, 55.2, 41.5, 37.7, 37.4, 25.9 (C×3), 18.2, 14.0, 12.5, 11.3, −4.4, −4.5; HRMS-ESI (*m*/*z*); $[M+Na]^+$ calcd for $C_{41}H_{57}NO_8SiNa$, 742.3751; found: 742.3744.

*4.1.6. (R)-4-Benzyl-3-{(2′R,3′S,4′S,5′R,6′R)-3′-(benzyloxy)methoxy-5′-[(tert-butyldimethylsilyl)oxy]-6′-hydroxy-2′,4′-dimethylheptanoyl} oxazolidin-2-one (**13a**).* To a solution of PMB ether **S1a** (3.26 g, 4.53 mmol) in CH_2Cl_2/pH 7.0 phosphate buffer solution in water (v/v, 4/3, 35 mL) was added DDQ (1.94 g, 8.55 mmol) at room temperature. The heterogeneous solution was stirred for 3 h. Then the reaction was quenched with satd aq $NaHCO_3$ (50 mL). Resulted two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (25 mL×3). The combined organic layers were washed with water and brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc=5/1 to 3/1) to afford alcohol **13a** (2.03 g, 75%) as a colorless oil; $[\alpha]_D^{25}$ −59.1 (*c* 1.00, $CHCl_3$); IR (neat)/cm^{-1}; 3548, 3510, 3062, 2931, 2893, 2854, 1782, 1689, 1381, 1211, 1026, 748; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.25 (complex m, 8H), 7.17 (d, *J*=6.9 Hz, 2H), 4.85 (s, 2H), 4.73 (d, *J*=12.0 Hz, 1H), 4.64 (d, *J*=12.0 Hz, 1H), 4.60 (m, 1H), 4.19–4.08 (complex m, 4H), 3.93 (dq, *J*=6.9, 2.9 Hz, 1H), 3.60 (dd, *J*=8.0, 2.9 Hz, 1H), 3.22 (dd, *J*=13.2, 2.3 Hz, 1H), 2.75 (dd, *J*=13.2, 9.7 Hz, 1H), 2.60 (br s, 1H), 1.88 (m, 1H), 1.31 (d, *J*=6.3 Hz, 3H), 1.16 (d, *J*=6.9 Hz, 3H), 0.99 (d, *J*=6.9 Hz, 3H), 0.91 (s, 9H), 0.08 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4, 152.8, 137.5, 135.0, 129.3 (C×2), 128.8 (C×2), 128.3 (C×2), 127.6, 127.2 (C×3), 96.5, 80.8, 76.1, 69.9, 68.6, 65.9, 55.2, 41.5, 39.3, 37.5, 26.0 (C×3), 19.6, 18.2, 14.3, 11.3, −3.8, −4.1; HRMS-ESI (*m*/*z*); $[M+Na]^+$ calcd for $C_{33}H_{49}NO_7Na$, 622.3176; found 622.3170.

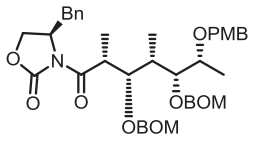
*4.1.7. (R)-4-Benzyl-3-{(2′R,3′S,4′S,5′R,6′R)-3′,5′-dihydroxy-6′-[(4-methoxybenzyl)oxy]-2′,4′-dimethylheptanoyl} oxazolidin-2-one (**S2a**).*



S2a

To a solution of 70% HF·Pyr (4.00 mL) in THF (15 mL) was added a solution of aldol product **12a** (2.10 g, 3.50 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 36 h. The reaction was diluted with CH_2Cl_2 (15 mL) and quenched by the addition of cold satd aq $NaHCO_3$ (40 mL). Then the mixture was poured into water (20 mL) and resulted two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (20 mL×3). The combined organic layers were washed with water and brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc=5/1 to 3/1) to afford a diol **S2a** (1.30 g, 81%) as a colorless oil; $[\alpha]_D^{26}$ −60.5 (*c* 1.00, $CHCl_3$); IR (neat)/cm^{-1}; 3533, 3062, 2978, 2939, 2877, 1774, 1689, 1381, 1242, 1211, 1034, 748; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33 (dd, *J*=7.5, 6.9 Hz, 2H), 7.29 (d, *J*=6.9 Hz, 1H), 7.26 (d, *J*=8.6 Hz, 2H), 7.21 (d, *J*=6.9 Hz, 2H), 6.89 (d, *J*=8.6 Hz, 2H), 4.68 (m, 1H), 4.61 (d, *J*=10.9 Hz, 1H), 4.35 (d, *J*=10.9 Hz, 1H), 4.23–4.16 (complex m, 2H), 4.09 (dd, *J*=5.2, 4.2 Hz, 1H), 3.98 (dq, *J*=6.9, 6.9 Hz, 1H), 3.81 (s, 3H), 3.60 (app d, *J*=8.0 Hz, 1H), 3.50 (m, 1H), 3.24 (dd, *J*=13.8, 3.4 Hz, 1H), 2.77 (dd, *J*=13.8, 9.7 Hz, 1H), 1.70 (m, 1H), 1.33 (d, *J*=6.9 Hz, 3H), 1.15 (d, *J*=6.3 Hz, 3H), 0.94 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.9, 159.3, 152.7, 135.0, 130.1, 129.4 (C×2), 129.4 (C×2), 129.0 (C×2), 127.4, 113.9 (C×2), 77.9, 76.8, 75.0, 70.8, 66.0, 55.3, 55.0, 40.3, 37.7, 35.9, 15.1, 13.4, 6.9; HRMS-ESI (*m*/*z*); $[M+Na]^+$ calcd for $C_{27}H_{35}NO_7Na$, 508.2311; found: 508.2298.

*4.1.8. (R)-4-Benzyl-3-{(2′R,3′S,4′S,5′R,6′R)-3′,5′-bis[(benzyloxy)methoxy]-6′-[(4-methoxybenzyl)oxy]-2′,4′-dimethylheptanoyl} oxazolidin-2-one (**S3a**).*



S3a

To a solution of diol **S2a** (1.21 g, 2.49 mmol) in CH_2Cl_2 (12 mL) was added DMAP (632 mg, 5.17 mmol) and DIPEA (17 mL, 100 mmol) under N_2 at room temperature. BOMCl (7.0 mL, 51.0 mmol) was then added at 0 °C. After stirring for 6 h at room temperature, the reaction was quenched with H_2O (20 mL) at 0 °C. Then, the resulting mixture was diluted with CH_2Cl_2 (10 mL) and resulted two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (15 mL×3). The combined organic layers were washed with water and brine, dried over Na_2SO_4 and concentrated in vacuo. The residue

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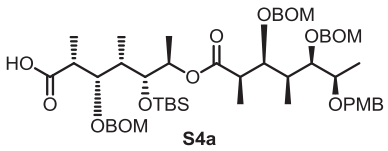
was purified by flash column chromatography on silica gel (hexanes/EtOAc=5/1 to 3/1) to afford a BOM ether **S3a** (1.79 g, 99%) as a colorless oil; $[\alpha]_D^{23}$ −42.6 (*c* 1.00, $CHCl_3$); IR (neat)/cm^{-1}; 3024, 2978, 2939, 2885, 1774, 1697, 1381, 1211, 1026, 741; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36–7.23 (complex m, 15H), 7.07 (d, *J*=6.9 Hz, 2H), 6.83 (d, *J*=8.6 Hz, 2H), 4.90 (d, *J*=7.5 Hz, 1H), 4.88 (d, *J*=7.5 Hz, 1H), 4.88 (d, *J*=6.9 Hz, 1H), 4.85 (d, *J*=6.9 Hz, 1H), 4.69 (d, *J*=12.0 Hz, 1H), 4.66 (d, *J*=11.5 Hz, 1H), 4.64 (d, *J*=12.0 Hz, 1H), 4.60 (d, *J*=11.5 Hz, 1H), 4.56 (d, *J*=11.5 Hz, 1H), 4.47 (d, *J*=11.3 Hz, 1H), 4.20–4.11 (complex m, 2H), 4.06 (dd, *J*=5.2, 5.2 Hz, 1H), 3.91 (dd, *J*=8.9, 2.0 Hz, 1H), 3.80–3.75 (complex m, 4H), 3.73–3.68 (complex m, 2H), 3.19 (dd, *J*=13.4, 3.2 Hz, 1H), 2.66 (dd, *J*=13.2, 9.8 Hz, 1H), 2.05 (m, 1H), 1.28 (d, *J*=6.9 Hz, 3H), 1.19 (d, *J*=6.3 Hz, 3H), 1.08 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3, 158.9, 153.1, 138.2, 138.1, 135.3, 131.1, 129.3 (C×2), 129.1 (C×2), 128.7 (C×2), 128.3 (C×2), 128.2 (C×2), 127.7 (C×2), 127.5 (C×2), 127.5 (C×2), 127.1, 113.5 (C×2), 97.4, 96.4, 82.5, 80.7, 76.2, 70.8, 70.4, 70.3, 65.8, 55.4, 55.2, 41.0, 37.8, 37.4, 15.9, 12.4, 10.8; HRMS-ESI (*m*/*z*); $[M+Na]^+$ calcd for $C_{43}H_{51}NO_9Na$, 748.3462; found 748.3453.

*4.1.9. (2R,3S,4S,5R,6R)-3,5-Bis[(benzyloxy)methoxy]-6-(4-methoxybenzyl)oxy-2,4-dimethylheptanoic acid (**14a**).* To a solution of 30% H_2O_2 solution in water (25 mL) in H_2O (15 mL) was added $LiOH·H_2O$ (489 mg, 11.7 mmol) at 0 °C. After stirring for 15 min, a solution of BOM ether **S3a** (1.71 g, 2.36 mmol) in THF (25 mL) was added at 0 °C. Then the mixture was allowed to warm to room temperature and stirred for 4 h. The reaction was quenched with satd aq $NaHCO_3$ (25 mL). Resulted two layers were separated and the aqueous phase was extracted with $CHCl_3$ (25 mL×3). The combined organic layers were washed with water and brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc=4/1 to 3/1) to afford carboxylic acid **14a** (1.00 g, 75%) as a colorless oil; $[\alpha]_D^{25}$ +3.1 (*c* 1.00, $CHCl_3$); IR (neat)/cm^{-1}; 3224–3170 (br), 3062, 2978, 2939, 2885, 1705, 1512, 1458, 1250, 1026, 748; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33–7.25 (complex m, 10H), 7.22 (d, *J*=8.6 Hz, 2H), 6.84 (d, *J*=8.6 Hz, 2H), 4.94 (d, *J*=6.9 Hz, 1H), 4.84 (d, *J*=6.9 Hz, 1H), 4.77 (d, *J*=6.9 Hz, 1H), 4.73 (d, *J*=6.9 Hz, 1H), 4.70 (d, *J*=12.6 Hz, 1H), 4.61 (d, *J*=12.6 Hz, 1H), 4.60 (d, *J*=12.0 Hz, 1H), 4.57 (d, *J*=12.0 Hz, 1H), 4.52 (d, *J*=11.5 Hz, 1H), 4.40 (d, *J*=11.5 Hz, 1H), 4.08 (dd, *J*=7.5, 3.4 Hz, 1H), 3.78 (s, 3H), 3.69 (dq, *J*=6.3, 6.3 Hz, 1H), 3.50 (dd, *J*=6.3, 4.0 Hz, 1H), 2.94 (dq, *J*=6.9, 3.4 Hz, 1H), 1.96 (m, 1H), 1.16 (d, *J*=6.9 Hz, 3H), 1.15 (d, *J*=6.3 Hz, 3H), 1.04 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.0, 159.0, 137.9, 137.8, 130.5, 129.3 (C×2), 128.3 (C×4), 127.7 (C×2), 127.7 (C×2), 127.5 (C×2), 113.7 (C×2), 96.3, 96.2, 81.6 (C×2), 76.8, 71.0, 70.2, 70.1, 55.2, 41.8, 37.2, 15.9, 10.6, 10.4; HRMS-ESI (*m*/*z*); $[M+Na]^+$ calcd for $C_{33}H_{42}O_8Na$, 589.2777; found 589.2782.

*4.1.10. (2′R,3′R,4′S,5′S,6′R)-7-[(R)-4″-Benzyl-2″-oxazolidin-3″-yl]-5′-[(benzyloxy)methoxy]-3′-[(tert-butyldimethylsilyl)oxy]-4′,6′-dimethyl-7′-oxoheptan-2′-yl (2R,3S,4S,5R,6R)-3,5-bis[(benzyloxy)methoxy]-6-[(4-methoxybenzyl)oxy]-2,4-dimethylheptanoate (**15a**).* To a solution of alcohol **13a** (335 mg, 558 μmol) and carboxylic acid **14a** (355 mg, 626 μmol) in CH_2Cl_2 (2.5 mL) was added DMAP (45.2 mg, 370 μmol) and CSA (38.7 mg, 167 μmol) under N_2. The mixture was cooled to 0 °C and added DCC (310 mg, 1.50 mmol). After stirring for 21 h at room temperature, the reaction was quenched with H_2O (5.0 mL). Resulted two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (10 mL×3). The combined organic layers were washed with water and brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc=6/1 to 4/1) to afford a **15a** (532 mg, 83%) as a colorless oil; $[\alpha]_D^{24}$ −21.3 (*c* 1.00, $CHCl_3$); IR (neat)/cm^{-1}; 2954, 2885, 1782, 1712, 1373, 1234, 1026, 748; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35–7.21 (complex m, 20H), 7.08 (d, *J*=6.9 Hz, 2H), 6.81 (d, *J*=8.6 Hz, 2H), 5.00 (m, 1H), 4.87 (d, *J*=6.9 Hz, 1H), 4.82 (d, *J*=6.9 Hz, 1H), 4.80 (s, 2H), 4.79 (s, 2H), 4.69–4.64 (complex m, 4H), 4.57 (d, *J*=12.6 Hz, 1H), 4.57 (d, *J*=12.6 Hz, 1H), 4.49 (d, *J*=11.5 Hz, 1H), 4.43 (d, *J*=11.5 Hz, 1H), 4.39 (m, 1H), 4.18 (dd, *J*=5.2, 5.2 Hz, 1H), 4.05–3.93 (complex m, 4H), 3.83 (dd, *J*=4.6, 4.0 Hz, 1H), 3.77 (s, 3H), 3.72 (dq, *J*=6.3, 6.3 Hz, 1H), 3.57 (dd, *J*=5.2, 5.2 Hz, 1H), 3.18 (dd, *J*=13.2, 2.9 Hz, 1H), 2.94 (m, 1H), 2.66 (dd, *J*=13.8, 9.7 Hz, 1H), 2.01 (m, 1H), 1.96 (m, 1H), 1.27 (d, *J*=6.9 Hz, 3H), 1.25 (d, *J*=7.5 Hz, 3H), 1.17–1.14 (complex m, 6H), 1.07 (d, *J*=6.9 Hz, 3H), 0.97 (d, *J*=6.9 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 174.3, 159.0, 153.0, 138.2, 138.0, 138.0, 135.3, 130.8, 129.4 (C×2), 129.3 (C×2), 128.8 (C×2), 128.3 (C×2), 128.3 (C×2), 128.2 (C×2), 127.7 (C×2), 127.6 (C×2), 127.5, 127.4, 127.4, 127.3 (C×2), 127.2, 113.6 (C×2), 96.5, 96.3, 96.1, 81.5, 80.9, 80.9, 76.9, 73.0, 73.0, 70.9, 70.2, 70.0 (C×2), 65.9, 55.5, 55.2, 42.7, 41.4, 38.6, 37.4 (C×2), 25.9 (C×3), 18.3, 15.9, 15.5, 12.5, 12.0, 11.1, 10.7, −4.1, −4.2; HRMS-ESI (*m*/*z*); $[M+Na]^+$ calcd for $C_{66}H_{89}NO_{14}SiNa$, 1170.5950; found 1170.5949.

*4.1.11. (2R,3S,4S,5R,6R)-3-[(Benzyloxy)methoxy]-6-({(2′R,3′S,4′S,5′R,6′R)-3′,5′-bis[(benzyloxy)methoxy]-6′-[(4-methoxybenzyl)oxy]-2′,4′-dimethylheptanoyl}oxy)-5-[(tert-butyldimethylsilyl)oxy]-2,4-dimethylheptanoic acid (**S4a**).*



S4a

To a solution of 30% H_2O_2 solution in water (6.0 mL) in H_2O (4.0 mL) was added $LiOH·H_2O$ (78.8 mg, 1.88 mmol) at 0 °C. After stirring for 15 min, a solution of linear unit ester **15a** (421 mg, 367 μmol) in THF (10 mL) was added at 0 °C. Then the mixture was allowed to warm to room temperature and stirred for 9 h. The reaction was quenched with satd aq $NaHCO_3$ (30 mL). Resulted two layers were separated and the aqueous phase was extracted with $CHCl_3$ (20 mL×3). The combined organic layers were washed with water and brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc=5/1 to 3/1) to afford carboxylic acid **S4a** (264 mg, 73%) as a colorless oil; $[\alpha]_D^{24}$ −11.7 (*c* 1.00, $CHCl_3$); IR (neat)/cm^{-1}; 3224–3155 (br), 3062, 3032, 2939, 2885, 2862, 1728, 1458, 1250, 1149, 1026, 833, 741; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.24 (complex m, 17H), 6.84 (d, *J*=8.6 Hz, 2H), 5.03 (dq, *J*=6.3, 2.3 Hz, 1H), 4.90 (d, *J*=7.5 Hz, 1H), 4.83–4.78 (complex m, 4H), 4.76 (d, *J*=12.6 Hz, 1H), 4.75 (d, *J*=6.9 Hz, 1H), 4.70–4.66 (complex m, 3H), 4.59 (d, *J*=12.6 Hz, 1H), 4.56 (d, *J*=12.6 Hz, 1H), 4.54 (d, *J*=11.5 Hz, 1H), 4.43 (d, *J*=11.5 Hz, 1H), 4.06 (dd, *J*=6.9, 4.6 Hz, 1H), 3.80–3.76 (complex m, 4H), 3.74–3.68 (complex m, 2H), 3.54 (dd, *J*=5.2, 5.2 Hz, 1H), 2.86 (dq, *J*=6.9, 4.6 Hz, 1H), 2.71 (dq, *J*=7.5, 7.5 Hz, 1H), 1.93 (m, 1H), 1.88 (m, 1H), 1.20 (d, *J*=6.9 Hz, 6H), 1.15 (d, *J*=6.3 Hz, 3H), 1.13 (d, *J*=6.3 Hz, 3H), 1.09 (d, *J*=6.9 Hz, 3H), 1.00 (d, *J*=6.9 Hz, 3H), 0.91 (s, 9H), 0.08 (s, 3H), −0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.2, 174.3, 159.0, 137.9, 137.5, 137.3, 130.4, 129.6 (C×2), 128.4 (C×2). 128.3 (C×2), 128.3 (C×2), 128.2 (C×2), 127.7 (C×2), 127.7, 127.6, 127.5, 127.4 (C×2), 113.6 (C×2), 96.7, 96.5, 95.2, 82.7, 81.5, 80.6, 75.9, 74.3, 71.0, 70.6, 70.2, 69.9, 69.6, 55.2, 43.9, 42.3, 38.9, 37.3, 26.0 (C×3), 18.3, 17.0, 15.8, 13.7, 11.6, 10.7, 10.7, −3.5, −3.8; HRMS-ESI (*m*/*z*); $[M+Na]^+$ calcd for $C_{56}H_{80}O_{13}SiNa$, 1011.5266; found 1011.5259.

*4.1.12. (2R,3S,4S,5R,6R)-3-[(Benzyloxy)methoxy]-6-({(2′R,3′S,4′S,5′R,6′R)-3′,5′-bis[(benzyloxy)methoxy]-6′-hydroxy-2′,4′-dimethylheptanoyl}oxy)-5-[(tert-butyldimethylsilyl)oxy]-2,4-dimethylheptanoic acid (**16a**).* A solution of PMB ether **S4a** (193 mg,

195 μmol) in CH_2Cl_2 (5.5 mL) and pH 7.0 phosphate buffer solution in water (5.0 mL) at room temperature was added to DDQ (130 mg, 573 μmol). The heterogeneous solution was stirred for 3 h. Then the reaction was quenched with satd aq $NaHCO_3$ (30 mL). Resulted two layers were separated and the aqueous phase was extracted with $CHCl_3$ (15 mL×3). The combined organic layers were washed with water and brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc=5/1 to 3/1) to afford *seco*-acid **16a** (134 mg, 79%) as a colorless oil; $[\alpha]_D^{25}$ −29.2 (*c* 1.00, $CHCl_3$); IR (neat)/cm^{-1}; 3448, 3293, 3170 (br), 3062, 3032, 2939, 2893, 1728, 1458, 1381, 1026, 833, 741; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36−7.25 (complex m, 15H), 5.04 (dq, *J*=6.3, 1.7 Hz, 1H), 4.86 (d, *J*=6.9 Hz, 1H), 4.84 (d, *J*=6.9 Hz, 1H), 4.81 (d, *J*=6.9 Hz, 1H), 4.80 (d, *J*=6.9 Hz, 1H), 4.79 (d, *J*=6.9 Hz, 1H), 4.75 (d, *J*=6.9 Hz, 1H), 4.72 (d, *J*=12.0 Hz, 1H), 4.71 (d, *J*=12.0 Hz, 1H), 4.68 (d, *J*=12.0 Hz, 1H), 4.65 (d, *J*=12.0 Hz, 1H), 4.58 (d, *J*=12.0 Hz, 1H), 4.58 (d, *J*=12.0 Hz, 1H), 4.06 (m, 1H), 4.00 (dd, *J*=5.7, 4.6 Hz, 1H), 3.78 (m, 1H), 3.71 (dd, *J*=8.0, 1.7 Hz, 1H), 3.43 (dd, *J*=6.9, 4.0 Hz, 1H), 2.76−2.69 (complex m, 2H), 1.86 (m, 1H), 1.82 (m, 1H), 1.24 (d, *J*=6.9 Hz, 3H), 1.20 (d, *J*=6.9 Hz, 3H), 1.14 (d, *J*=6.3 Hz, 3H), 1.13 (d, *J*=6.3 Hz, 3H), 1.06 (d, *J*=7.5 Hz, 3H), 0.99 (d, *J*=6.9 Hz, 3H), 0.91 (s, 9H), 0.08 (s, 3H), −0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.1, 174.8, 137.5, 137.4, 137.2, 128.4 (C×2), 128.4 (C×4), 127.8 (C×2), 128.8, 127.8 (C×2), 127.7, 127.6, 127.4 (C×2), 96.6, 96.4, 96.0, 85.8, 81.5, 79.9, 74.1, 71.5, 70.4, 70.1, 69.9, 67.8, 43.6, 43.2, 38.8, 38.8, 26.0 (C×3), 19.3, 18.3, 16.7, 13.6, 13.0, 10.6, 10.3, −3.7, −3.9; HRMS-ESI (*m*/*z*); $[M+Na]^+$ calcd for $C_{48}H_{72}O_{12}SiNa$, 891.4691; found 891.4690.

*4.1.13. (3R,4S,5S,6R,7R,10R,11S,12S,13R,14R)-4,11,13-Tris[(benzyloxy) methoxy]-6-[(tert-butyldimethylsilyl)oxy]-3,5,7,10,12,14-hexamethyl-1,8-dioxacyclotetradecane-2,9-dione (**17a**).* To a solution of *seco*-acid **16a** (30.3 mg, 34.9 μmol) and DIPEA (120 μL, 706 μmol) in benzene (5.0 mL) was added 2,4,6-trichlorobenzoyl chloride (90.0 μL, 576 μmol) dropwise under N_2 at 0 °C. Then, the reaction mixture was allowed to warm to room temperature and stirred for 1.5 h. The mixture was diluted with benzene (2.0 mL) and added dropwise over a period of 2 h to a refluxing solution of DMAP (63.9 mg, 523 μmol) in benzene (4.5 mL). Then, the mixture was stirred for 3 h at 80 °C and quenched with satd aq NH_4Cl (3.0 mL) at 0 °C. Resulted two layers were separated and the aqueous phase was extracted with EtOAc (10 mL×3). The combined organic layers were washed with water and brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc=8/1 to 6/1) to afford a macrodiolide aglycone **17a** (19.8 mg, 67%) as a colorless oil; $[\alpha]_D^{24}$ −25.6 (*c* 1.00, $CHCl_3$); IR (neat)/cm^{-1}; 2939, 2893, 2862, 1728, 1458, 1373, 1165, 1095, 1026, 741; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35−7.25 (complex m, 15H), 5.20 (q, *J*=6.3 Hz, 1H), 5.09 (q, *J*=6.3 Hz, 1H), 4.84−4.67 (complex m, 9H), 4.65 (d, *J*=12.0 Hz, 1H), 4.58 (d, *J*=12.6 Hz, 1H), 4.53 (d, *J*=12.0 Hz, 1H), 3.86 (d, *J*=9.2 Hz, 1H), 3.75 (d, *J*=9.7 Hz, 1H), 3.67 (d, *J*=9.2 Hz, 2H), 2.87−2.75 (complex m, 2H), 1.80 (m, 1H), 1.67 (m, 1H), 1.22−1.18 (complex m, 9H), 1.11 (d, *J*=6.3 Hz, 3H), 1.06 (d, *J*=7.5 Hz, 3H), 1.01 (d, *J*=6.9 Hz, 3H), 0.91 (s, 9H), 0.06 (s, 3H), −0.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 174.2, 138.0, 137.6, 137.5, 128.4 (C×2), 128.3 (C×2), 128.3 (C×2), 127.6, 126.6, 127.5 (C×5), 127.3 (C×2), 96.8, 96.6, 96.4, 81.6, 81.1, 80.8, 74.4, 70.6, 70.4, 70.2, 70.0, 69.8, 44.6, 44.3, 40.1, 38.8, 26.0 (C×3), 18.4, 17.1, 17.0, 14.5, 14.3, 10.7, 9.7, −3.4, −3.9; HRMS-ESI (*m*/*z*); $[M+Na]^+$ calcd for $C_{48}H_{70}O_{11}SiNa$, 873.4585; found 873.4589.

*4.1.14. (3R,4S,5S,6R,7R,10R,11S,12S,13R,14S)-4,11,13-Tris[(benzyloxy) methoxy]-6-[(tert-butyldimethylsilyl)oxy]-3,5,7,10,12,14-hexamethyl-1,8-dioxacyclotetradecane-2,9-dione (**18a**).* To a solution of PPh_3 (92.3 mg, 352 μmol) and *seco*-acid **16a** (79.6 mg, 91.6 μmol) in toluene (18 mL) was added DEAD (40% in toluene, 0.24 ml, 48.0 μmol) under N_2 at 0 °C. The reaction mixture was stirred for 30 min at 0 °C. After warming to room temperature, the reaction mixture was stirred for 21 h. Silica gel (15 cc) was added to the reaction mixture, which was then concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc=9/1 to 6/1) to afford macrodiolide aglycone **18a** (54.3 mg, 70%) as a colorless oil; $[\alpha]_D^{26}$ −2.5 (*c* 0.50, $CHCl_3$); IR (neat)/cm^{-1}; 2939, 2885, 2862, 1728, 1458, 1373, 1250, 1026, 841, 733; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36−7.26 (complex m, 15H), 5.10 (m, 1H), 4.94 (m, 1H), 4.87–4.76 (complex m, 6H), 4.70−4.67 (complex m, 3H), 4.62 (d, *J*=12.0 Hz, 1H), 4.59 (d, *J*=12.6 Hz, 2H), 3.97 (d, *J*=9.2 Hz, 1H), 3.94 (dd, *J*=8.0, 3.4 Hz, 1H), 3.77 (dd, *J*=9.2, 2.3 Hz, 1H), 3.65 (dd, *J*=8.6, 2.9 Hz, 1H), 2.85−2.75 (complex m, 2H), 1.91 (m, 1H), 1.87 (m, 1H), 1.30 (d, *J*=5.7 Hz, 3H), 1.28 (d, *J*=6.9 Hz, 3H), 1.23 (d, *J*=6.9 Hz, 3H), 1.11 (d, *J*=6.3 Hz, 3H), 1.04 (d, *J*=7.5 Hz, 3H), 1.02 (d, *J*=7.5 Hz, 3H), 0.91 (s, 9H), 0.06 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3, 173.1, 137.9, 137.7, 137.5, 128.4 (C×4), 128.3 (C×2), 127.6 (C×3), 127.6 (C×3), 127.5, 127.5 (C×2), 96.9, 96.2, 95.7, 82.5, 81.3, 81.2, 74.1, 72.5, 71.2, 70.4, 70.1 (C×2), 46.1, 45.9, 39.7, 38.6, 26.0 (C×3), 18.3, 18.0, 15.5, 14.9, 14.6, 10.9, 9.4, −3.7, −4.0; HRMS-ESI (*m*/*z*); $[M+Na]^+$ calcd for $C_{48}H_{70}O_{11}SiNa$, 873.4585; found 873.4576.

*4.1.15. (3R,4S,5S,6R,7R,10R,11S,12S,13R,14R)-3,6,11-Tris[(benzyloxy) methoxy]-13-hydroxy-3,5,7,10,12,14-hexamethyl-1,8-dioxacyclotetradecane-2,9-dione (**19**).* To a plastic centrifuge tube in THF (1.2 mL) solution of substrate **17a** (35.4 mg, 41.6 μmol) was added 70% HF·Pyr. (200 μL) under N_2 at 0 °C. The reaction mixture was stirred for 28 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (5.0 mL) and quenched by the addition to cold satd aq $NaHCO_3$ (15 mL). The mixture was then poured into water (5 mL) and resulted two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (10 mL×3). The combined organic layers were washed with water and brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc=4/1 to 2/1) to afford macrodiolide **19** (20.0 mg, 65%) as a colorless oil; $[\alpha]_D^{25}$ −49.6 (*c* 1.00, $CHCl_3$); IR (neat)/cm^{-1}; 3410, 3379, 3062, 3032, 2970, 2939, 2885, 1728, 1450, 1373, 1165, 1088, 1018, 733; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37−7.24 (complex m, 15H), 5.23−5.15 (complex m, 2H), 4.84 (d, *J*=6.9 Hz, 1H), 4.83−4.74 (complex m, 6H), 4.71−4.65 (complex m, 3H), 4.53 (d, *J*=11.5 Hz, 2H), 3.73 (d, *J*=10.3 Hz, 1H), 3.71 (d, *J*=10.3 Hz, 1H), 3.66 (d, *J*=9.7 Hz, 1H), 3.51 (m, 1H), 2.81 (m, 1H), 2.75 (m, 1H), 1.62 (m, 1H), 1.44 (m, 1H), 1.19 (d, *J*=6.9 Hz, 3H), 1.17 (d, *J*=6.9 Hz, 3H), 1.16 (d, *J*=6.3 Hz, 3H), 1.13 (d, *J*=6.3 Hz, 3H), 1.09 (d, *J*=6.9 Hz, 3H), 1.08 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.9, 174.2, 137.9, 137.5, 137.3, 128.5 (C×2), 128.3 (C×4), 127.8, 127.8 (C×2), 127.6, 127.5, 127.5 (C×2), 127.5 (C×2), 96.9, 96.8, 96.7, 81.3, 81.0, 80.9, 74.4, 70.7, 70.5, 70.2, 70.1, 70.0, 44.4 (C×2), 40.2, 39.4, 17.3, 16.8, 14.8, 14.7, 9.9, 9.6; HRMS-ESI (*m*/*z*); $[M+Na]^+$ calcd for $C_{42}H_{56}O_{11}Na$, 759.3720; found 759.3720.

*4.1.16. Protected macrodiolide (**21**).* To a mixture of trichloroacetimidate **20** (35.3 mg, 97.6 μmol), macrodiolide aglycone **19** (29.5 mg, 40.0 μmol) and molecular sieves 4 Å powder (228 mg) were dissolved in CH_2Cl_2 (2.0 mL) and stirred under N_2 at room temperature. After stirring for 1 h, the mixture was cooled to −50 °C and then TfOH (13.0 μmL, 147 μmol) was added. The resulting mixture was stirred for 26 h at −50 °C. The reaction was quenched with $NaHCO_3$ (150 mg) at 0 °C. After filtration through a pad of Celite with $CHCl_3$/MeOH (v/v, 10/1, 10 mL×3), the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc/MeOH=20/1 to 15/1) to afford macrodiolide **21** (18.0 mg, 48%) as a yellow oil; $[\alpha]_D^{24}$ −36.0 (*c* 0.20, $CHCl_3$); IR (neat)/cm^{-1}; 3062, 2978, 2939, 2885, 1728, 1458, 1373, 1165, 1018, 748; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36−7.24

(complex m, 15H), 5.19 (q, J=6.3 Hz, 2H), 4.88–4.82 (complex m, 3H), 4.79–4.70 (complex m, 6H), 4.68 (d, J=12.0 Hz, 1H), 4.63 (d, J=12.0 Hz, 1H), 4.54 (d, J=12.6 Hz, 1H), 4.52 (d, J=12.0 Hz, 1H), 4.31 (d, J=7.5 Hz, 1H), 3.74 (d, J=9.7 Hz, 1H), 3.70 (d, J=10.3 Hz, 1H), 3.67 (dd, J=9.7, 6.3 Hz, 2H), 3.20 (m, 1H), 2.85–2.72 (complex m, 3H), 2.38 (br s, 6H), 2.11 (s, 3H), 1.73–1.64 (complex m, 2H), 1.36–1.24 (complex m, 2H), 1.22 (d, J=6.3 Hz, 3H) 1.20–1.16 (complex m, 9H), 1.08–1.04 (complex m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 174.4, 169.8, 137.9, 137.6, 137.6, 128.5 (C×2), 128.4 (C×2), 128.3 (C×2), 127.7, 127.6, 127.5, 127.5 (C×2), 127.5 (C×2), 127.3 (C×2), 101.9, 97.0, 96.9, 96.5, 81.6, 81.3, 80.9, 79.8, 70.4 (C×2), 70.4, 70.1, 70.0, 69.8, 68.6, 63.4, 44.2, 44.1, 40.5 (C×2), 39.7, 39.2, 30.6, 21.3, 20.9, 17.3, 17.1, 14.7 (C×2), 9.4, 9.3; HRMS-ESI (m/z); $[M+H]^+$ calcd for $C_{52}H_{74}NO_{14}$, 936.5109; found 936.5100.

*4.1.17. Macrodiolide (**22**).* To a solution of macrolide **21** (15.4 mg, 16.5 μmol) in MeOH (1.0 mL) was added Pearlman's catalyst 20% on carbon (wetted with ca. 50% water, 8.0 mg, 5.70 μmol) at 0 °C. The mixture was purged with H_2 under 1 atm at room temperature. After stirring for 22 h, the mixture was filtered through a pad of Celite with $CHCl_3$/MeOH (v/v, 10/1, 10 mL×3) and the filtrate was concentrated in vacuo. The resulting crude product was used for subsequent reaction without further purification.

The crude product was dissolved in MeOH (1.5 mL). This mixture was heated to 50 °C and stirred for 4.5 h. The mixture was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel ($CHCl_3$/MeOH=8/1, 5/1 to 3/1) to afford macrodiolide **22** (8.2 mg, 93%) as a colorless oil; $[\alpha]_D^{23}$ −4.4 (c 0.21, MeOH); IR (neat)/cm^{-1}; 3417, 2978, 2939, 2877, 1728, 1705, 1458, 1373, 1265, 1165, 1026, 756; ^{1}H NMR (500 MHz, CD_3OD) δ 5.08 (q, J=6.3 Hz, 1H), 5.05 (m, 1H), 4.32 (d, J=7.5 Hz, 1H), 3.81 (dd, J=6.9, 2.9 Hz, 1H), 3.57 (m, 1H), 3.55 (d, J=10.3 Hz, 1H), 3.52 (d, J=10.3 Hz, 1H), 3.43 (d, J=9.7 Hz, 1H), 3.35 (dd, J=10.3, 7.5 Hz, 1H), 2.74–2.66 (complex m, 2H), 2.61 (dq, J=9.7, 6.9 Hz, 1H), 2.38 (s, 6H), 1.78 (ddd, J=12.9, 4.0, 1.7 Hz, 1H), 1.71 (dq, J=6.9, 6.9 Hz, 1H),1.63 (m, 1H), 1.31–1.27 (complex m, 7H), 1.22 (d, J=5.7 Hz, 3H), 1.17 (d, J=6.9 Hz, 3H), 1.17 (d, J=6.9 Hz, 3H), 1.09 (d, J=7.5 Hz, 3H), 1.00 (d, J=6.9 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 177.0, 177.0, 106.0, 82.3, 76.0, 75.5, 73.6, 73.3, 71.9, 71.5, 70.3, 65.8, 45.4, 45.1, 40.9 (C×2), 40.7, 40.2, 32.1, 21.4, 17.6, 17.3, 15.3, 14.9, 9.4, 8.7; HRMS-ESI (m/z); $[M+Na]^+$ calcd for $C_{26}H_{47}NO_{10}Na$, 556.3098; found 556.3095.

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Supplementary data

Supplementary data (Full details of experimental procedures and spectra data for new compounds, together with) related to this article can be found at http://dx.doi.org/10.1016/j.tet.2015.01.030.

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