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Studies on Catalytic Enantioselective Total Synthesis of Caprazamycin B: Construction of the Western Zone

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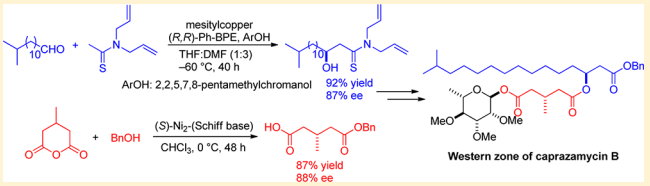
Supporting Information

ABSTRACT: We describe a simple and convenient synthesis of the western zone of caprazamycin B using two catalytic asymmetric reactions as key elements of our approach. Desymmetrization of 3-methylglutaric anhydride with the (*S*)-Ni$_2$-(Schiff base) complex as a catalyst furnished the chiral hemiester, and a thioamide-aldol reaction with mesitylcopper, (*R*,*R*)-Ph-BPE, and 2,2,5,7,8-pentamethylchromanol as a catalyst furnished the *β*-hydroxy thioamide in good yield and enantioselectivity. On further transformation, the thioamide functionality was converted to the corresponding *β*-hydroxy ester. Finally, a convergent synthesis of the western zone of caprazamycin B was achieved by connecting the hemiester, the *β*-hydroxy ester, and the 2,3,4-tri-*O*-methyl-L-rhamnose fragments.



INTRODUCTION

Globally, tuberculosis (TB) is one of the most common diseases responsible for human mortality, accounting for almost 2.5 million deaths annually. Although a number of drugs are available for treatment, the bacterium causing the disease continues to evolve and develop resistance against most modern day drugs, thereby necessitating the search for new anti-TB drugs with a different mode of action. Caprazamycin B, a novel lipo-nucleoside antibiotic (Figure 1),[1] was isolated from

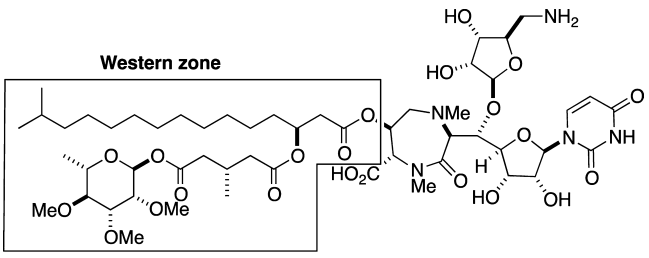


Figure 1. Structure of caprazamycin B.

the culture broth of the actinomycete strain *Streptomyces* sp. MK730-62F2 and shows excellent antimycobacterial activity in vitro against drug-susceptible and multidrug-resistant *Mycobacterium tuberculosis* (*M. tuberculosis*) strains. The MIC values of caprazamycin B were 3.13 μg/mL for *M. tuberculosis* H37Rv strains and 6.25−12.5 μg/mL for drug-susceptible *M. tuberculosis*. Moreover, caprazamycin B showed good efficacy in a murine TB model with no significant toxicity in mice that received single and repeated dose and also in genotoxicity and cyctotoxicity tests. Therefore, this molecule is considered as a promising candidate for an anti-TB drug.[1a]

The planar structure of caprazamycin B was assigned on the basis of 2D NMR experiments such as HMQC, HMBC, and NOESY, and its stereochemistry (including the absolute structure) was determined by NMR spectroscopy and X-ray crystallography of some of its degradation products.[1d] Caprazamycin B has a 5′-*β*-*O*-amino-ribosyl-glycyluridine and a *N*-methylated diazepanone moiety as characteristic structural motifs similar to liposidomycins.[2] However, unlike liposidomycins, caprazamycin B has a 2,3,4-tri-*O*-methyl-L-rhamnose moiety. Due to their structural similarity with liposidomycins, caprazamycin B may also possess the same mode of action and is also expected to be a translocase I inhibitor since MraY translocase is a common target for 6′-*N*-alkyl-5′-*β*-*O*-amino-ribosyl-C-glycyluridine class of antibiotics.[1e]

Although Matsuda et al. reported the first synthesis of caprazol (deacylated caprazamycin) and its derivatives,[3] the complete synthesis of caprazamycins remains challenging due to the complex nature of the molecules and their multiple stereogenic centers. Therefore, we attempted the first enantioselective total synthesis of caprazamycin B. Herein we report a catalytic asymmetric synthesis of the western zone of caprazamycin B.

RESULTS AND DISCUSSION

Our retrosynthetic strategy for synthesis of the western zone (Scheme 1) involves two key asymmetric transformations, namely, the thioamide-aldol reaction[4] and desymmetrization of 3-methylglutaric anhydride[5] previously developed by our group.

We first attempted to synthesize *β*-hydroxy carboxylic ester via a direct catalytic asymmetric aldol reaction of 12-methyltridecanal **1**[6] with thioamides **2a** and **2b** using a soft Lewis acid/hard Brønsted base cooperative catalyst system comprising of mesitylcopper (Mes-Cu), (*R*,*R*)-Ph-BPE and

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Scheme 1. Retrosynthetic Strategy of the Western Zone for the Synthesis of Caprazamycin B

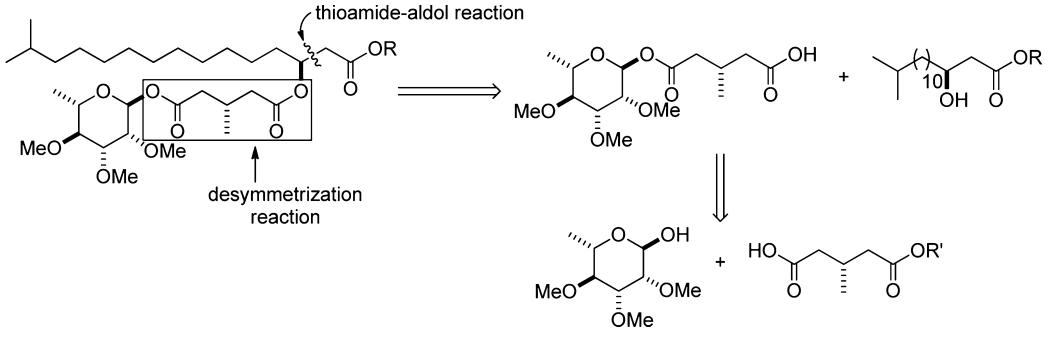
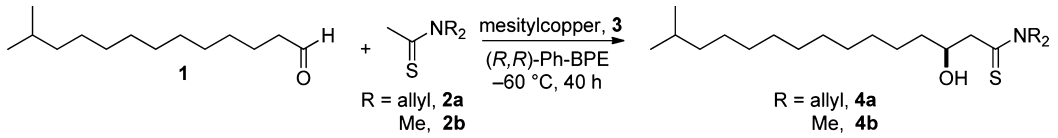
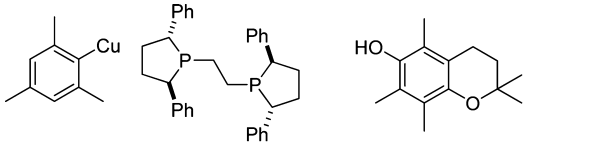


Table 1. Optimization of the Thioamide-Aldol Reaction Conditions[a]



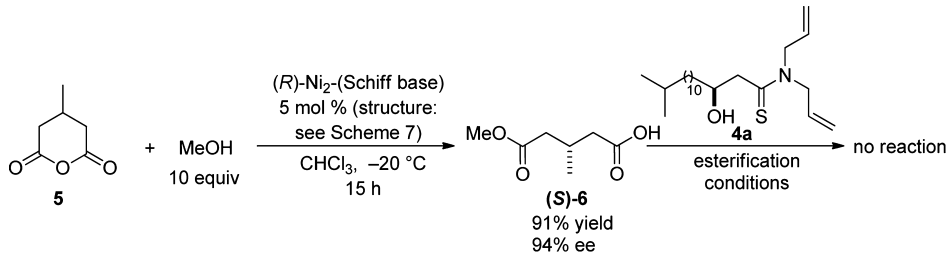
entry	thioamide (equiv)	catalyst (mol %)	solvent	product	yield (%)[b]	ee (%)
1	**2a** (1.2)	3	THF	**4a**	80	78
2	**2a** (1.2)	3	DMF	**4a**	48	84
3	**2a** (1.2)	5	DMF	**4a**	66	83
4	**2a** (2.0)	3	DMF	**4a**	65	80
5	**2a** (2.0)	5	DMF	**4a**	70	85
6	**2a** (2.0)	5	THF/DMF (1:1)	**4a**	>99	85
7[d]	**2a** (2.0)	5	THF/DMF (1:3)	**4a**	>99 (92)[c]	87
8	**2b** (4.0)	5	THF/DMF (1:3)	**4b**	71(69)[c]	93

[a]The reaction was performed using 0.20 mmol of **1**. [b]Yield based on ^{1}H NMR using 1,1,2,2-tetrachloroethane as the standard. [c]Isolated yield. [d]This reaction was also performed on a 1.0 g scale.



mesitylcopper (*R*,*R*)-Ph-BPE 2,2,5,7,8-pentamethylchromanol, **3**

Scheme 2. Desymmetrization of 3-Methylglutaric Anhydride with Methanol Followed by Esterification with Thioamide-Aldol Product 4a



2,2,5,7,8-pentamethylchromanol **3** (second generation catalyst).[4a] Chemoselective activation of thioamide by a soft−soft interaction between the copper and sulfur atoms formed the corresponding enolate even in the presence of aldehyde **1**, which then underwent aldol reaction to form the corresponding *β*-hydroxy thioamide derivative **4**.

A conventional aldol reaction using a chiral organocatalyst cannot be used in this case as the cross aldol reaction with acetaldehyde and another simple *α*-methylene aldehyde (12-methyltridecanal in this case) is seldom reported in the literature other than for enzyme-catalyzed reactions. Under the standard reaction conditions with THF as the solvent, diallylthioamide **2a**[7] gave **4a** in 80% yield and with good enantioselectivity (Table 1, entry 1), whereas with DMF as the solvent we obtained **4a** in good enantioselectivity and moderate yield (48% yield, 84% ee, Table 1, entry 2). Hence in the next step, the equivalents of thioamide and catalyst loading were increased to improve the chemical yield using DMF as the solvent (Table 1, entries 3 and 4), but the chemical yield improved to only 70% and the enantioselectivity changed little. Finally using a mixture of THF/DMF (1:3) as the solvent with 2 equiv of thioamide and 5 mol % catalyst loading, the reaction produced an almost quantitative yield of the thioamide-aldol product **4a** with good enantioselectivity (92% isolated yield and

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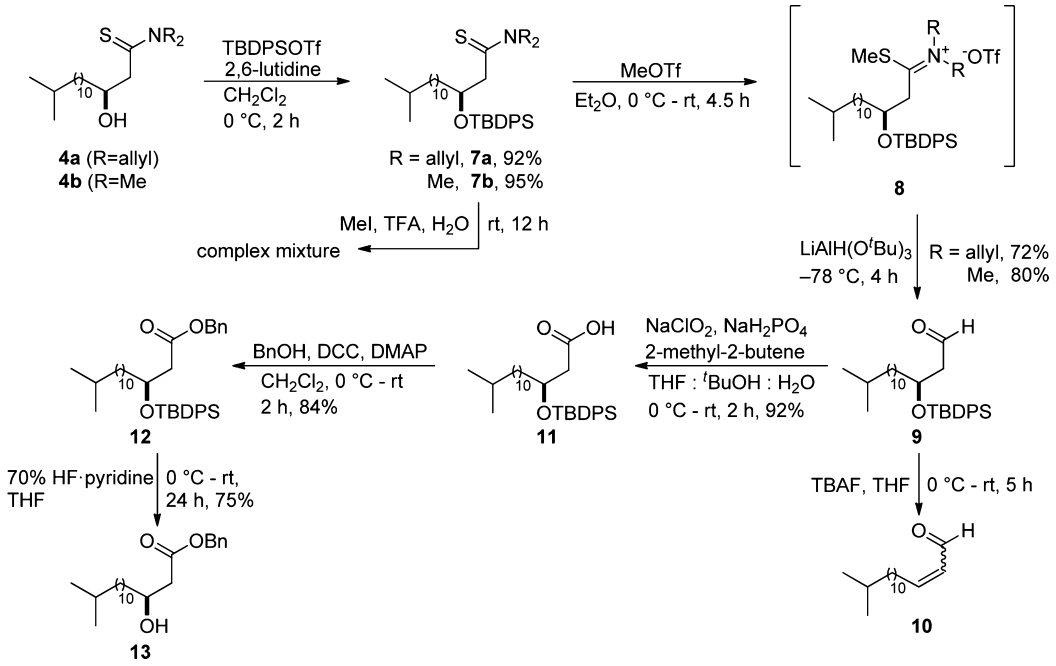
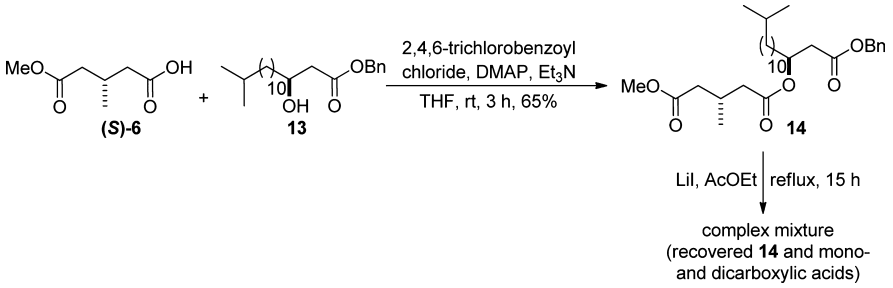
Scheme 3. Synthesis of β-Hydroxy Benzyl Ester 13



Scheme 4. Esterification of Chiral Hemiester (*S*)-6 with β-Hydroxy Benzyl Ester 13



87% ee, Table 1, entry 7). On the other hand, with dimethylthioamide **2b**, the thioamide-aldol product **4b** was obtained in modest yield (69%), but with better enantioselectivity (93% ee) under similar reaction conditions with 4 equiv of thioamide (Table 1, entry 8).

In the next step, we attempted the asymmetric desymmetrization of 3-methylglutaric anhydride developed by our group previously.[5] Treatment of 3-methylglutaric anhydride **5** with MeOH at −20 °C for 15 h in the presence of the homodinuclear (*R*)-Ni_2-(Schiff base) complex[8] (5 mol %) as a catalyst gave the corresponding chiral hemiester (*S*)-**6** in 91% yield and 94% ee. Reaction of hemiester (*S*)-**6** with thioamide-aldol product **4a** under a variety of esterification conditions such as $SOCl_2$/pyridine/DMAP, Yamaguchi esterification, PPh_3/NBS, and DCC/DMAP failed to give the expected ester (Scheme 2).

We next attempted to convert the thioamide functionality to a thioester (Scheme 3). Treatment of compound **4a** and **4b** with TBDPSOTf and 2,6-lutidine led to the corresponding TBDPS-protected thioamide-aldol adducts **7a** and **7b** in 92% and 95% yield, respectively. Then, conditions for a one-pot conversion of thioamide to thioester using MeI/TFA/H_2O[7] were applied to compound **7a**. However, silanol (TBDPSOH) was expelled from the molecule, and a mixture of *cis*- and *trans*-isomers of unsaturated thioesters was obtained. Hence, we decided to convert the thioamide functionality to a carboxylic ester to avoid the facile β-elimination.

Accordingly, **7a** and **7b** were subjected to a sequential one-pot conversion of thioamide to aldehyde **9** using MeOTf to activate the thioamide functionality by the formation of methylthioiminium salt **8**, which was then directly treated with $LiAlH(O^tBu)_3$ to give aldehyde **9**.[4b] Since **9** was also prone to β-elimination upon desilylation to give an enal **10**, the formyl group of **9** had to be transformed to an ester functionality before removal of the TBDPS group. Aldehyde **9** was converted to carboxylic acid **11** by Pinnick oxidation ($NaOCl_2$/NaH_2PO_4/2-methyl-2-butene) in 92% yield, which was followed by the DCC coupling with BnOH to afford benzyl ester **12** in 84% yield. Then, compound **12** was exposed to TBAF to cleave the silyl ether. However, the corresponding desilylated product was obtained in less than 50% along with the remaining starting material and other side products. Prolonged reaction time and addition of excess amount of TBAF did not show any beneficial effects. Hence, the deprotection was carried out with 70% HF·pyridine to give the desired β-hydroxy benzyl ester **13** in 75% yield. With the two chiral fragments in hand, the coupling of these compounds and the succeeding introduction of the rhamnose part were examined in the next stage.

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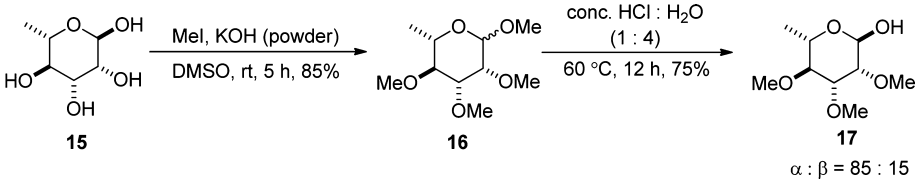
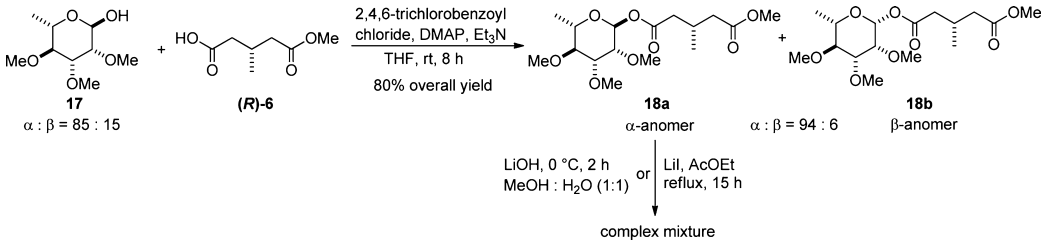
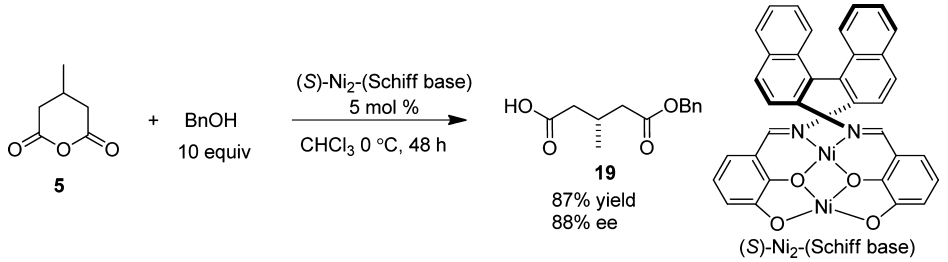
Scheme 5. Synthesis of 2,3,4-Tri-*O*-methyl-L-rhamnose 17



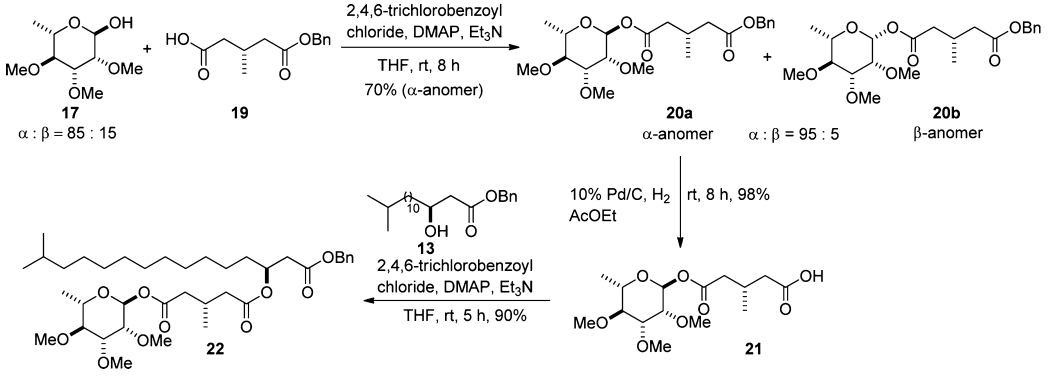
Scheme 6. Esterification of 2,3,4-Tri-*O*-methyl-L-rhamnose 17 Followed by Selective Deprotection of Methyl Ester



Scheme 7. Desymmetrization of 3-Methylglutaric Anhydride 5 with Benzyl Alcohol



Scheme 8. Construction of the Western Zone of Caprazamycin B (22)



Applying the Yamaguchi's protocol (2,4,6-trichlorobenzoyl chloride, Et_3N, and DMAP) to chiral hemiester (*S*)-**6** and *β*-hydroxy benzyl ester **13** afforded the expected ester **14** in 65% yield. However, selective deprotection of the methyl ester in the next step using LiI in refluxing AcOEt was unsuccessful, and a complex mixture containing mono- and dicarboxylic acids along with the remaining starting material was obtained instead (Scheme 4).

Then, we decided to switch the order of the coupling reactions of the three components: coupling of the chiral hemiester and rhamnose subunits was carried out prior to the introduction of the *β*-hydroxy ester moiety. Toward this end, 2,3,4-tri-*O*-methyl-L-rhamnose **17** was synthesized from monohydrate of L-rhamnose **15** in two steps (Scheme 5).[9] The starting material **15** was treated with MeI and powdered KOH in DMSO to afford the corresponding 1,2,3,4-tetra-*O*-methyl-L-rhamnose **16**. Acidic hydrolysis of the glycosyl bond of this compound gave the corresponding 2,3,4-tri-*O*-methyl-L-rhamnose **17**.

Acylation of **17** with the carboxylate counterpart (*R*)-**6**, which was obtained using the (*S*)-Ni_2-(Schiff base) complex in the asymmetric desymmetrization of 3-methylglutaric anhydride, proceeded effectively to give a mixture of **18a** and **18b**. However, selective deprotection of methyl ester in the presence of the glycosyl ester linkage was very difficult (Scheme 6). This disappointing result led us to take advantage of chiral monobenzyl ester of 3-methylglutaric acid, which is expected to be deprotected by hydrogenolysis without affecting the glycosyl ester moiety.

As shown in Scheme 7, BnOH (10 equiv) was treated with 3-methylglutaric anhydride **5** at 0 °C for 48 h in the presence of the homodinuclear (*S*)-Ni_2-(Schiff base)[8] complex (5 mol %)

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as a catalyst. As the result, the corresponding chiral hemiester **19** was obtained in 87% yield and 88% ee. The enantioselectivity is only slightly lower than that observed in the case of methanolysis.

After successfully synthesizing the three key synthetic intermediates for synthesis of the western zone, we attempted to connect these intermediates. First, we performed a Yamaguchi esterification reaction between chiral glutaric acid monobenzyl ester **19** and 2,3,4-tri-*O*-methyl-L-rhamnose **17** in the presence of 2,4,6-trichlorobenzoyl chloride, Et_3N, and DMAP to give the corresponding diester with an α:β anomeric ratio of 95:5 (**20a** and **20b** in Scheme 8, respectively). After purification, the desired α-anomer **20a** was obtained in 70% isolated yield. The structure of **20a** was confirmed by NOE experiments (see Supporting Information). In the next step, hydrogenolysis of the benzyl ester of **20a** was achieved using 10% Pd/C under a hydrogen atmosphere to give the corresponding carboxylic acid **21** in 98% yield. Finally, we attempted the esterification reaction of carboxylic acid **21** with β-hydroxy benzyl ester **13** using the Yamaguchi esterification conditions to give the corresponding triester **22** in 90% yield as a single diastereomer (western zone of caprazamycin B) (Scheme 8).

CONCLUSION

We achieved a convergent synthesis of the western zone of caprazamycin B in a chiral fashion using a catalytic asymmetric desymmetrization reaction and a thioamide-aldol reaction as key steps with good yield and enantioselectivity. Further studies oriented toward the catalytic enantioselective total synthesis of caprazamycin B are underway.

EXPERIMENTAL SECTION

All the reactions were performed in oven-dried round-bottom flasks and test tubes with a Teflon-coated magnetic stirring bar unless otherwise noted. Air- and moisture-sensitive liquids were transferred via a gastight syringe and a stainless-steel needle. All workup and purification procedures were carried out with reagent-grade solvents under ambient atmosphere. Flash chromatography was performed using silica gel 60 (230−400 mesh). Infrared (IR) spectra were recorded on a Fourier transform infrared spectrophotometer. NMR was recorded on a 400 MHz spectrometer. For ^{1}H NMR (400 MHz), chemical shifts for proton are reported in parts per million downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CDCl_3$, δ 7.26 ppm). For ^{13}C NMR (100 MHz), chemical shifts were reported in the scale relative to NMR solvent ($CDCl_3$, δ 77.0 ppm) as an internal reference. NMR data are reported as follows: chemical shifts, multiplicity (s: singlet, d: doublet, dd: doublet of doublets, t: triplet, m: multiplet), coupling constant (Hz), and integration. Optical rotation was measured using a 2 mL cell with a 1.0 dm path length on a polarimeter. High-resolution mass spectra (ESI-Orbitrap) were measured on an ESIMS instrument equipped with an Orbitrap detector. HPLC analysis was conducted on a HPLC system equipped with chiral-stationary-phase columns (ϕ 0.46 cm × 25 cm).

(*S*)-*N*,*N*-Diallyl-3-hydroxy-14-methylpentadecanethioamide (4a). To a flame-dried test tube equipped with a magnetic stirring bar and a 3-way glass stopcock were added (*R*,*R*)-Ph-BPE/mesitylcopper/2,2,5,7,8-pentamethylchromanol (**3**) solution (0.1 M/THF, 100 μL, 0.010 mmol, 5 mol %), dry DMF and THF (3:1) (2 mL), diallylthioamide (**2a**) (64 μL, 0.40 mmol), and aldehyde **1** (51.2 μL, 0.2 mmol) under Ar at −60 °C. After 40 h of stirring at that temperature, 0.1 M AcOH (100 μL), saturated aq NH_4Cl, and bipyridine (3.0 mg) were added to the reaction mixture (for the dissociation of product from copper complex). The reaction mixture was then stirred at room temperature for 15 min. The aqueous layer was then extracted with AcOEt. The combined organic layers were washed with brine and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (eluent *n*-hexane/AcOEt) to give compound **4a** (67.6 mg, 92%) as a pale yellow oil. Enantiomeric excess was determined by chiral HPLC analysis. IR (neat) ν 3406, 2924, 2853, 1642, 1490, 1409 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.86−5.66 (m, 2H), 5.23−5.06 (m, 4H), 4.65−4.49 (m, 2H), 4.20−4.03 (m, 4H), 2.70 (dd, J = 16.0 Hz, 1.2 Hz, 1H), 2.56 (dd, J = 16.0 Hz, 9.6 Hz, 1H), 1.53−1.18 (m, 19H), 1.10−1.05 (m, 1H), 0.79 (d, J = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 202.9, 130.5, 130.4, 118.6, 117.8, 69.9, 55.6, 52.8, 47.9, 39.0, 36.6, 29.9, 29.6, 29.5, 27.9, 27.3, 25.6, 22.6; $[\alpha]^{23}_D$ +46.8 (*c* 0.21, $CHCl_3$, 87% ee sample); HRMS (ESI-Orbitrap) calcd for $C_{22}H_{41}NNaOS$ *m*/*z* 390.2801 $[M + Na]^+$, found 390.2802; HPLC (Daicel CHIRALCEL OD-H, ϕ 0.46 cm × 25 cm, detection 254 nm, *n*-hexane/^{i}PrOH = 19/1, flow rate = 0.5 mL/min) t_R = 9.3 min (minor), t_R = 11.0 min (major). [Note: The above procedure was used for entries 1−6 in Table 1 with the corresponding thioamide equivalents and solvents shown in the table.]

(*S*)-3-Hydroxy-*N*,*N*,14-trimethylpentadecanethioamide (4b). To a flame-dried test tube equipped with a magnetic stirring bar and a 3-way glass stopcock were added (*R*,*R*)-Ph-BPE/mesitylcopper/2,2,5,7,8-pentamethylchromanol solution (0.1 M/THF, 100 μL, 0.010 mmol, 5 mol %), dry DMF and THF (3:1) (2 mL), dimethylthioamide (**2b**) (82.4 mg, 0.80 mmol), and aldehyde **1** (51.2 μL, 0.2 mmol) under Ar at −60 °C. After 40 h of stirring at that temperature, 0.1 M AcOH (100 μL), saturated aq NH_4Cl, and bipyridine (3.0 mg) were added to the reaction mixture (for the dissociation of product from copper complex). The reaction mixture was then stirred at room temperature for 15 min. The aqueous layer was then extracted with AcOEt. The combined organic layers were washed with brine and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (eluent *n*-hexane/AcOEt) to give compound **4b** (43.5 mg, 69%) as a colorless oil. Enantiomeric excess was determined by chiral HPLC analysis. IR (neat) ν 3433, 2924, 2853, 1643, 1522 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.26 (d, J = 2.0 Hz, 1H), 4.17−4.15 (m, 1H), 3.50 (s, 3H), 3.31 (s, 3H), 2.72 (dd, J = 16 Hz, 0.8 Hz, 1H), 2.59 (dd, J = 16 Hz, 5.6 Hz, 1H), 1.63−1.26 (m, 19H), 1.15−1.12 (m, 2H), 0.86 (d, J = 6.2 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 201.6, 69.4, 48.3, 44.3, 41.6, 39.0, 36.5, 29.9, 29.7, 29.64, 29.59, 27.9, 27.4, 26.7, 22.6; $[\alpha]^{23}_D$ +81.0 (*c* 0.43, $CHCl_3$, 93% ee sample); HRMS (ESI-Orbitrap) calcd for $C_{18}H_{37}NNaOS$ *m*/*z* 338.2488 $[M + Na]^+$, found 338.2494; HPLC (Daicel CHIRALCEL OD-H, ϕ 0.46 cm × 25 cm, detection 254 nm, *n*-hexane/^{i}PrOH = 19/1, flow rate = 1.0 mL/min) t_R = 8.1 min (minor), t_R = 11.6 min (major).

(*S*)-5-Methoxy-3-methyl-5-oxopentanoic Acid ((*S*)-6). To an oven-dried glass test tube equipped with a magnetic stirring bar was charged 3-methylglutaric anhydride **5** (25.6 mg, 0.20 mmol), (*R*)-Ni_2-(Schiff base) (6.8 mg, 0.01 mmol, 5 mol %), and $CHCl_3$ (0.4 mL, 0.5 M). The reaction mixture was then cooled to −20 °C, followed by the addition of MeOH (81 μL, 2.0 mmol, 10 equiv). The reaction mixture was then stirred for 15 h. CH_2Cl_2 (2 mL) was added to the reaction mixture and then extracted with saturated $NaHCO_3$. The aqueous layer was then washed with CH_2Cl_2 and acidified to pH = 1.0 using 1 N HCl. The compound was then extracted with ethyl acetate, dried over Na_2SO_4, and evaporated under reduced pressure to to give compound **6** (29.1 mg, 91%, 94% ee) as a colorless oil. Data has already been reported.[5]

(*S*)-*N*,*N*-Diallyl-3-((*tert*-butyldiphenylsilyl)oxy)-14-methylpentadecanethioamide (7a). To a stirred solution of **4a** (73.4 mg, 0.20 mmol) in CH_2Cl_2 (3 mL) were added 2,6-lutidine (46 μL, 0.40 mmol) and TBDPSOTf (93 μL, 0.30 mmol) at 0 °C, and stirring was continued for another 2 h. Saturated aq NH_4Cl was then added, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (eluent *n*-hexane/AcOEt) to give compound **7a** (111 mg, 92%) as a colorless oil. IR

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(neat) ν 2925, 2854, 1643, 1486, 1464, 1427 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.69−7.67 (m, 4H), 7.44−7.34 (m, 6H), 5.95−5.86 (m, 1H), 5.74−5.67 (m, 1H), 5.24−5.20 (m, 3H), 5.17 (dd, J = 2.8 Hz, 1.2 Hz, 1H) 4.85 (dd, J = 14.4 Hz, 5.7 Hz, 1H), 4.50 (dd, J = 13.0 Hz, 5.7 Hz, 1H), 4.43−4.31 (m, 2H), 3.91−3.86 (m, 1H), 3.02 (dd, J = 13.5 Hz, 7.8 Hz, 1H), 2.88 (dd, J = 13.5 Hz, 5.3 Hz, 1H), 1.55−1.45 (m, 1H), 1.44−1.36 (m, 2H), 1.25−1.04 (m, 16H), 1.02−0.94 (m, 11H), 0.86 (d, J = 6.4 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 203.0, 136.0, 135.8, 134.5, 133.6, 131.5, 131.4, 129.6, 129.5, 127.53, 127.48, 119.1, 117.6, 74.8, 56.2, 53.0, 50.0, 39.0, 36.9, 29.9, 29.7, 29.6, 29.5, 29.4, 29.3, 28.0, 27.4, 27.1, 24.8, 22.7, 19.4; $[\alpha]^{23}_D$ +21.5 (c 0.34, $CHCl_3$, 87% ee sample); HRMS (ESI-Orbitrap) calcd for $C_{38}H_{59}NNaOSSi$ m/z 628.3979 $[M + Na]^+$, found 628.3979.

(*S*)-3-((*tert*-Butyldiphenylsilyl)oxy)-*N*,*N*,14-trimethylpentadecanethioamide (7b). To a stirred solution of **4b** (0.20 mmol) in CH_2Cl_2 (3 mL) were added 2,6-lutidine (46 μL, 0.40 mmol) and TBDPSOTf (93 μL, 0.30 mmol) at 0 °C, and stirring was continued for another 2 h. Saturated aq NH_4Cl was then added, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (eluent *n*-hexane/AcOEt) to give compound **7b** (105 mg, 95%) as a colorless oil. IR (neat) ν 2926, 2854, 1515, 1465, 1427, 1391 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.70−7.67 (m, 4H), 7.42−7.34 (m, 6H), 4.47−4.41 (m, 1H), 3.43 (s, 3H), 3.22 (s, 3H), 3.13 (dd, J = 13.0 Hz, 8.0 Hz, 1H), 2.90 (dd, J = 13.0 Hz, 5.0 Hz, 1H), 1.55−1.48 (m, 1H), 1.46−1.40 (m, 2H), 1.29−1.07 (m, 16H), 1.02−0.94 (m, 11H), 0.86 (d, J = 6.4 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 201.7, 136.0, 135.8, 134.5, 133.5, 129.7, 129.5, 127.6, 127.5, 76.6, 50.1, 44.7, 42.3, 39.0, 37.2, 29.9, 29.7, 29.6, 29.5, 29.4, 27.9, 27.4, 27.0, 24.8, 22.7, 19.4; $[\alpha]^{23}_D$ +37.8 (c 0.06, $CHCl_3$, 93% ee sample); HRMS (ESI-Orbitrap) calcd for $C_{34}H_{55}NNaOSSi$ m/z 576.3666 $[M + Na]^+$, found 576.3665.

(*S*)-3-((*tert*-Butyldiphenylsilyl)oxy)-14-methylpentadecanal (9). To a stirred solution of **7a** (60.6 mg, 0.10 mmol) in ether (1.0 mL) was added MeOTf (22 μL, 0.20 mmol) at 0 °C. [Note: Compound **7b** (55.4 mg, 0.10 mmol) also gave the same aldehyde **9** (79 mg, 80%).] After stirring at room temperature for 4.5 h, the reaction mixture was cooled to −78 °C. To the mixture was added $LiAlH(O^tBu)_3$ (200 μL, 1.0 M in THF, 0.20 mmol), and the resulting solution was stirred for 4 h. The reaction was quenched with silica gel (1.4 g) at −78 °C and diluted with CH_2Cl_2 (5 mL). The resulting mixture was then stirred at −30 °C for 15 h and filtered through a short pad of silica gel with CH_2Cl_2 as eluent. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (eluent *n*-hexane/AcOEt = 99/1 → 50/1) to give compound **9** (71.1 mg, 72%) as a colorless oil. IR (neat) ν 2926, 2855, 1727, 1465, 1427 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.71 (t, J = 2.6 Hz, 1H), 7.68−7.64 (m, 4H), 7.45−7.36 (m, 6H), 4.22−4.16 (m, 1H), 2.49−2.47 (m, 2H), 1.57−1.45 (m, 3H), 1.23−1.06 (m, 18H), 1.04 (s, 9H), 0.86 (d, J = 6.7 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 202.4, 135.9, 135.8, 133.9, 129.8, 129.7, 127.7, 127.6, 69.3, 50.2, 39.0, 37.3, 29.9, 29.7, 29.6, 29.5, 29.4, 29.3, 28.0, 27.4, 26.9, 24.9, 22.7, 19.3; $[\alpha]^{23}_D$ +11.5 (c 0.82, $CHCl_3$, 87% ee sample); HRMS (ESI-Orbitrap) calcd for $C_{32}H_{50}NaO_2Si$ m/z 517.3472 $[M + Na]^+$, found 517.3478.

(*S*)-3-((*tert*-Butyldiphenylsilyl)oxy)-14-methylpentadecanoic Acid (11). To a stirred solution of aldehyde **9** (98.8 mg, 0.20 mmol), NaH_2PO_4 (72 mg, 0.60 mmol), and 2-methyl-2-butene (170 μL, 1.60 mmol) in THF/^{t}BuOH/H_2O (1:3:5) (4.5 mL) was added $NaClO_2$ (54.3 mg, 0.60 mmol) at 0 °C, and stirring was continued for 2 h at room temperature. The reaction mixture was then quenched with 1 N HCl and extracted with AcOEt. The combined extracts were washed with brine and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (eluent *n*-hexane/AcOEt = 9/1) to give compound **11** (94.0 mg, 92%) as a colorless oil. IR (neat) ν 3418, 2926, 2855, 1711, 1428 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.69−7.64 (m, 4H), 7.45−7.34 (m, 6H), 4.15−4.09 (m, 1H), 2.59 (d, J = 5.7 Hz, 2H), 1.53−1.43 (m, 3H), 1.25−1.06 (m, 18H), 1.04 (s, 9H), 0.86 (d, J = 6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 176.6, 135.89, 135.86, 133.7, 133.5, 129.72, 129.70, 127.6, 127.5, 70.3, 41.4, 39.1, 36.7, 29.9, 29.7, 29.6, 29.5, 29.4, 29.3, 28.0, 27.4, 26.9, 24.8, 22.7, 19.3; $[\alpha]^{23}_D$ +14.6 (c 0.55, $CHCl_3$, 87% ee sample); HRMS (ESI-Orbitrap) calcd for $C_{32}H_{50}NaO_3Si$ m/z 533.3421 $[M + Na]^+$, found 533.3412.

(*S*)-Benzyl 3-((*tert*-Butyldiphenylsilyl)oxy)-14-methylpentadecanoate (12). To a stirred solution of carboxylic acid **11** (102 mg, 0.20 mmol) in CH_2Cl_2 (5 mL) were added BnOH (31 μL, 0.30 mmol), DCC (82.4 mg, 0.40 mmol), and DMAP (2.4 mg, 0.02 mmol) at 0 °C. Stirring was continued for 2 h at room temperature followed by filtration of the reaction mixture through a Celite pad. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (eluent *n*-hexane/AcOEt = 50/1 → 20/1) to give compound **12** (101 mg, 84%) as a colorless oil. IR (neat) ν 2925, 2854, 1738, 1589 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.68−7.64 (m, 4H), 7.42−7.30 (m, 9H), 7.26−7.24 (m, 2H), 5.01 (d, J = 12.4 Hz, 1H), 4.95 (d, J = 12.4 Hz, 1H), 4.22−4.16 (m, 1H), 2.57−2.43 (m, 2H), 1.55−1.39 (m, 3H), 1.24−1.01 (m, 27H), 0.86 (d, J = 6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 171.4, 135.91, 135.87, 135.8, 134.1, 134.0, 129.5, 128.4, 128.2, 128.1, 127.4, 70.4, 66.1, 42.1, 39.1, 37.0, 29.9, 29.7, 29.6, 29.5, 29.4, 29.3, 28.0, 27.4, 26.9, 24.7, 22.7, 19.3; $[\alpha]^{23}_D$ +9.5 (c 0.07, $CHCl_3$, 87% ee sample); HRMS (ESI-Orbitrap) calcd for $C_{39}H_{56}NaO_3Si$ m/z 623. 3891 $[M + Na]^+$, found 623.3896.

(*S*)-Benzyl 3-Hydroxy-14-methylpentadecanoate (13). To a stirred solution of TBDPS ether **12** (120 mg, 0.20 mmol) in THF (4 mL) at room temperature was added 70% HF·pyridine (2.0 mL) (reaction was carried out in a plastic container). The reaction mixture was stirred at room temperature for 24 h, quenched with $NaHCO_3$, and extracted with AcOEt. The combined organic extracts were concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (eluent *n*-hexane/AcOEt = 20/1 → 10/1) to give compound **13** (54.5 mg, 75%) as a white solid. Mp 35−37 °C; IR (neat) ν 3450, 2925, 2853, 1734, 1465 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.40−7.31 (m, 5H), 5.15 (s, 2H), 4.06−3.99 (m, 1H), 2.85 (d, J = 3.9 Hz, 1H), 2.56 (dd, J = 16.3 Hz, 3.2 Hz, 1H), 2.46 (dd, J = 16.3 Hz, 8.6 Hz, 1H), 1.55−1.12 (m, 21H), 0.86 (d, J = 6.4 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 172.9, 135,6, 128.6, 128.4, 128.3, 68.0, 66.5, 41.3, 39.0, 36.5, 29.9, 29.7, 29.64, 29.58, 29.54, 29.50, 27.5, 27.4, 25.4, 22.7; $[\alpha]^{23}_D$ +14.5 (c 0.08, $CHCl_3$, 87% ee sample); HRMS (ESI-Orbitrap) calcd for $C_{23}H_{38}NaO_3$ m/z 385.2713 $[M + Na]^+$, found 385.2713.

(3*R*,4*R*,5*S*,6*S*)-3,4,5-Trimethoxy-6-methyltetrahydro-2*H*-pyran-2-ol (17). A solution of **16**[9] (44.0 mg, 0.20 mmol) in conc HCl/H_2O (1:4, 5 mL) was heated at 60 °C for 12 h. The reaction was then quenched with saturated $NaHCO_3$ and extracted with AcOEt. The combined organic extracts were concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (eluent *n*-hexane/AcOEt = 10/1 → 5/1) to give compound **17** (30.9 mg, 75%) as a colorless oil. Compound **17** is already reported.[9]

(*R*)-5-(Benzyloxy)-3-methyl-5-oxopentanoic Acid (19). To an oven-dried glass test tube equipped with a magnetic stirring bar were charged 3-methylglutaric anhydride **5** (25.6 mg, 0.20 mmol), (*S*)-Ni_2-(Schiff base) (6.8 mg, 0.01 mmol, 5 mol %) and $CHCl_3$ (0.4 mL. 0.5 M). The reaction mixture was then cooled to 0 °C, followed by the addition of BnOH (207 μL, 2.0 mmol, 10 equiv). The reaction mixture was then stirred for 48 h. CH_2Cl_2 (2 mL) was added to the reaction mixture and then extracted with saturated $NaHCO_3$. The aqueous layer collected was then washed with CH_2Cl_2 and then acidified to pH = 1.0 using 1 N HCl. The compound was then extracted with AcOEt, dried over Na_2SO_4, and evaporated under reduced presuure to to give compound **19** (41.0 mg, 87%, 88% ee) as a colorless oil. IR (neat) ν 3034, 1734, 1708, 1455 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.39−7.29 (m, 5H), 5.12 (s, 2H), 2.56−2.41 (m, 2H), 2.38−2.25 (m, 2H), 1.04 (d, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 178.3, 172.1, 135.8, 128.5, 128.2, 66.3, 40.7, 40.4, 27.2, 19.8; $[\alpha]^{23}_D$ −3.6 (c 0.43, $CHCl_3$, 88% ee sample); HRMS (ESI-Orbitrap) calcd for $C_{13}H_{15}O_4$ m/z 235.0965. $[M - H]^-$, found 235.0972; HPLC (Daicel CHIRALCEL AD-H, ϕ 0.46

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cm × 25 cm, detection 220 nm, *n*-hexane/^{i}PrOH = 19/1, flow rate = 1.0 mL/min) t_R = 12.3 min (minor), t_R = 14.3 min (major).

(*S*)-1-Benzyl 5-((2*S*,3*R*,4*R*,5*S*,6*S*)-3,4,5-Trimethoxy-6-methyltetrahydro-2*H*-pyran-2-yl) 3-Methylpentanedioate (20a). To a solution of 2,3,4-tri-*O*-methyl-L-rhamnose **17** (47.4 mg, 0.20 mmol), 3-methylglutaric acid monobenzyl ester **19** (53.5 mg, 0.26 mmol, 88% ee), and 2,4,6-trichlorobenzoyl chloride (41 μL, 0.26 mmol) in THF (3 mL) was added Et_3N (56 μL, 0.40 mmol) dropwise, and the solution was stirred for about 2 min followed by the addition of DMAP (6.1 mg, 0.05 mmol). The reaction mixture was stirred for 5 h and quenched with water followed by extraction with AcOEt. The organic phase was then washed with saturated aq $NaHCO_3$, dried over Na_2SO_4, and evaporated to give a crude material containing a mixture of α/β-anomers (α/β = 95/5). The residue was purified by silica gel column chromatography (eluent *n*-hexane/AcOEt = 10/1 → 5/1) to afford compound **20a** (61.6 mg, 70%). IR (neat) ν 2934, 2830, 1734, 1736, 1456 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.34−7.30 (m, 5H), 6.15 (d, *J* = 1.6 Hz, 1H), 5.10 (s, 2H), 3.64−3.59 (m, 1H), 3.58−3.52 (m, 4H), 3.50 (s, 3H), 3.47 (s, 3H), 3.41 (dd, *J* = 9.4 Hz, 3.2 Hz, 1H), 3.15 (t, *J* = 9.4 Hz, 1H), 2.52−2.38 (m, 3H), 2.33−2.22 (m, 2H), 1.26 (d, *J* = 6.2 Hz, 3H), 1.02 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 171.9, 170.6, 135.8, 128.6, 128.3, 128.2, 90.8, 81.5, 80.7, 76.2, 70.4, 66.3, 61.1, 59.0, 57.8, 40.6, 27.3, 19.8, 17.8; $[\alpha]^{23}_D$ −42.5 (*c* 0.55, $CHCl_3$); HRMS (ESI-Orbitrap) $C_{22}H_{32}NaO_8$ *m*/*z* 447.1989 [M + Na]$^+$, found 447.1989.

(*S*)-1-Methyl 5-((2*S*,3*R*,4*R*,5*S*,6*S*)-3,4,5-Trimethoxy-6-methyltetrahydro-2*H*-pyran-2-yl) 3-Methylpentanedioate (18a). Same procedure to synthesize **20a** as above was employed using 3-methylglutaric acid monomethyl ester (*R*)-**6** to give a crude mixture of α/β-anomers (α/β = 94/6). The residue was purified by silica gel column chromatography (eluent *n*-hexane/AcOEt = 10/1 → 5/1) to afford compound **18a** (55.7 mg, 80% yield). Separation of the diastereomers was not attempted. A colorless oil. IR (neat) ν 2933, 1739, 1587, 1123 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.17 (d, *J* = 1.8 Hz, 1H), 3.68−3.60 (m, 4H), 3.58−3.56 (m, 4H), 3.53 (s, 3H), 3.51 (s, 3H), 3.47−3.43 (m, 1H), 3.18 (t, *J* = 9.4 Hz, 1H), 2.52−2.37 (m, 3H), 2.32−2.24 (m, 2H), 1.30 (d, *J* = 6.2 Hz, 3H), 1.05 (d, *J* = 5.7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.6, 170.5, 90.7, 81.4, 80.7, 76.2, 70.4, 61.0, 59.0, 57.8, 51.5, 40.6, 40.4, 27.3, 19.8, 17.7 (NMR data for the major α-anomer is shown); $[\alpha]^{23}_D$ −44.6 (*c* 0.41, $CHCl_3$); HRMS (ESI-Orbitrap) $C_{16}H_{28}NaO_8$ *m*/*z* 371.1674 [M + Na]$^+$, found 371.1676.

(*S*)-3-Methyl-5-oxo-5-(((2*S*,3*R*,4*R*,5*S*,6*S*)-3,4,5-trimethoxy-6-methyltetrahydro-2*H*-pyran-2-yl)oxy)pentanoic Acid (21). To a suspension of 10% Pd/C in AcOEt (4 mL) was added compound **20a** (88.0 mg, 0.20 mmol). The reaction mixture was stirred under H_2 atmosphere for 8 h followed by the filtration of the catalyst over Celite pad with AcOEt. The filtrate was concentrated under reduced pressure to give compound **21** (65.6 mg, 98%) as a colorless oil in pure form without column chromatography. IR (neat) ν 3435, 2936, 1735, 1644, 1455, 1386 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.18 (d, *J* = 2.0 Hz, 1H), 3.66−3.61 (m, 1H), 3.58−3.56 (m, 4H), 3.53 (s, 3H), 3.51 (s, 3H), 3.46 (dd, *J* = 9.4 Hz, 3.4 Hz, 1H), 3.19 (t, *J* = 9.6 Hz, 1H), 2.53−2.42 (m, 3H), 2.35−2.28 (m, 2H), 1.30 (d, *J* = 6.2 Hz, 3H), 1.08 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 177.7, 170.5, 90.7, 81.5, 80.6, 76.2, 70.3, 61.0, 58.9, 57.8, 40.5, 40.2, 27.0, 19.7, 17.7; $[\alpha]^{23}_D$ −49.3 (*c* 0.24, $CHCl_3$); HRMS (ESI-Orbitrap) $C_{15}H_{26}NaO_8$ *m*/*z* 357.1520 [M + Na]$^+$, found 357.1519.

(*S*)-1-((*S*)-1-(Benzyloxy)-14-methyl-1-oxopentadecan-3-yl) 5-((2*S*,3*R*,4*R*,5*S*,6*S*)-3,4,5-Trimethoxy-6-methyltetrahydro-2*H*-pyran-2-yl) 3-Methylpentanedioate (22). To a solution of compound **21** (87.0 mg, 0.26 mmol), β-hydroxy benzyl ester **13** (72.5 mg, 0.20 mmol, 87% ee) and 2,4,6-trichlorobenzoyl chloride (41 μL, 0.26 mmol) in THF (8 mL), Et_3N (56 μL, 0.40 mmol) was added dropwise and the solution was stirred for about 2 min followed by the addition of DMAP (6.1 mg, 0.05 mmol). The reaction mixture was stirred for 5 h and quenched with water followed by extraction with AcOEt. The organic phase was then washed with saturated aq $NaHCO_3$, dried over Na_2SO_4, and evaporated to give a crude material. No peaks for minor diastereomers could be observed by NMR analysis. The residue was purified by silica gel column chromatography (eluent *n*-hexane/AcOEt = 10/1 → 5/1) to give compound **22** (122 mg, 90%, a single diastereomer) as a colorless oil. IR (neat) ν 2926, 2854, 1740, 1457, 1384 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.39−7.30 (m, 5H), 6.17 (d, *J* = 1.8 Hz, 1H), 5.28−5.21 (m, 1H), 5.11 (s, 2H), 3.68−3.61 (m, 1H), 3.57−3.56 (m, 4H), 3.53 (s, 3H), 3.50 (s, 3H), 3.45 (dd, *J* = 9.4 Hz, 3.4 Hz, 1H), 3.17 (t, *J* = 9.4 Hz, 1H), 2.67−2.56 (m, 2H), 2.45−2.38 (m, 2H), 2.30−2.16 (m, 3H), 1.61−1.46 (m, 3H), 1.30−1.24 (m, 19H), 1.15−1.12 (m, 2H), 1.00 (d, *J* = 6.4 Hz, 3H), 0.86 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ171.4, 170.5, 170.2, 135.7, 128.5, 128.34, 128.30, 90.7, 81.5, 80.7, 76.2, 70.7, 70.4, 66.5, 61.0, 59.0, 57.8, 40.7, 40.6, 39.1, 39.0, 34.0, 29.9, 29.7, 29.6, 29.5, 29.4. 29.3, 27.9, 27.4, 27.3, 25.1, 22.6, 19.6, 17.8; $[\alpha]^{23}_D$ −25.5 (*c* 0.94, $CHCl_3$); HRMS (ESI-Orbitrap) $C_{38}H_{62}NaO_{10}$ *m*/*z* 701.4235 [M + Na]$^+$, found 701.4233.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra for all new compounds, NOE data for **20a**, and HPLC data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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