EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201402430

Total Synthesis of (+)-Antimycin A_{3b} on Solid Supports

Yusuke Iijima,[a] Osamu Kimata,[a] Santida Decharin,[a] Hisashi Masui,[b] Yoichiro Hirose,[c] and Takashi Takahashi*[b]

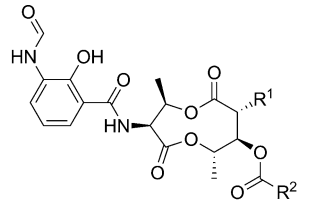
Keywords: Combinatorial chemistry / Solid-phase synthesis / Natural products / Antimycin / Lactones

A straightforward and convergent total synthesis of (+)-antimycin A_{3b} is reported. Four fragments were assembled on a solid support and the fully functionalized *seco* acid was cyclized in the solution phase. This synthetic route minimized the number of manipulations in the solution phase and is useful for a combinatorial library synthesis.

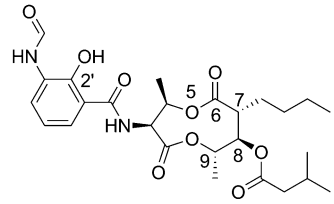
Introduction

Antimycin A was first isolated from *Streptomyces* in 1949 and since then more than 25 antimycins have been discovered (Figure 1).[1–12] Antimycins possess several attributes including antifungal,[1] insecticidal,[13] and nematocidal bioactivities.[10] These bioactivities originate from specific inhibition of the electron-transfer activity of ubiquinol-cytochrome c oxidoreductase in the cellular respiration system.[14] In 2001, Hockenbery and co-workers reported that antimycin A induced cell death of cancer cells.[15] Binding of antimycin A to Bcl-xL triggers apoptosis in cancer cells, however the 2′-methoxy derivative of antimycin A_{3b} is inactive as an inhibitor of cellular respiration but still binds to Bcl-xL. This discovery aroused our interest in elucidating the structure–activity relationship of antimycins in their binding with Bcl-xL.

Several groups have accomplished the total synthesis of antimycin A_{3b}.[16] Recently, Tsunoda and co-workers completed the total synthesis of 12 components of antimycins.[17] In all cases, a dilactone ring between the O-5 and C-6 position was constructed to avoid γ-lactone formation.[18] The 3-formamidosalicylate group was introduced after dilactone ring construction. The introduction of the C-8 *O*-acyl group was performed both before and after dilactone ring construction, although the presence of the C-8 *O*-acyl group lowered the cyclization yield. Wu and Yang reported dilactone ring formation of the *seco* acid with the C-8 *O*-acyl group in a good yield by using Shiina's method.[19]



Antimycin A_1–A_{20}



(+)-Antimycin A_{3b} (**1**)

R^1 = Et, *n*-butyl, *n*-hexyl, 4-methylhexyl, isopentyl, *n*-pentyl
R^2 = Me, *n*-propyl, isopropyl, *n*-butyl, *i*-butyl, *s*-butyl, isopentyl, 3-methylpentyl, Bn

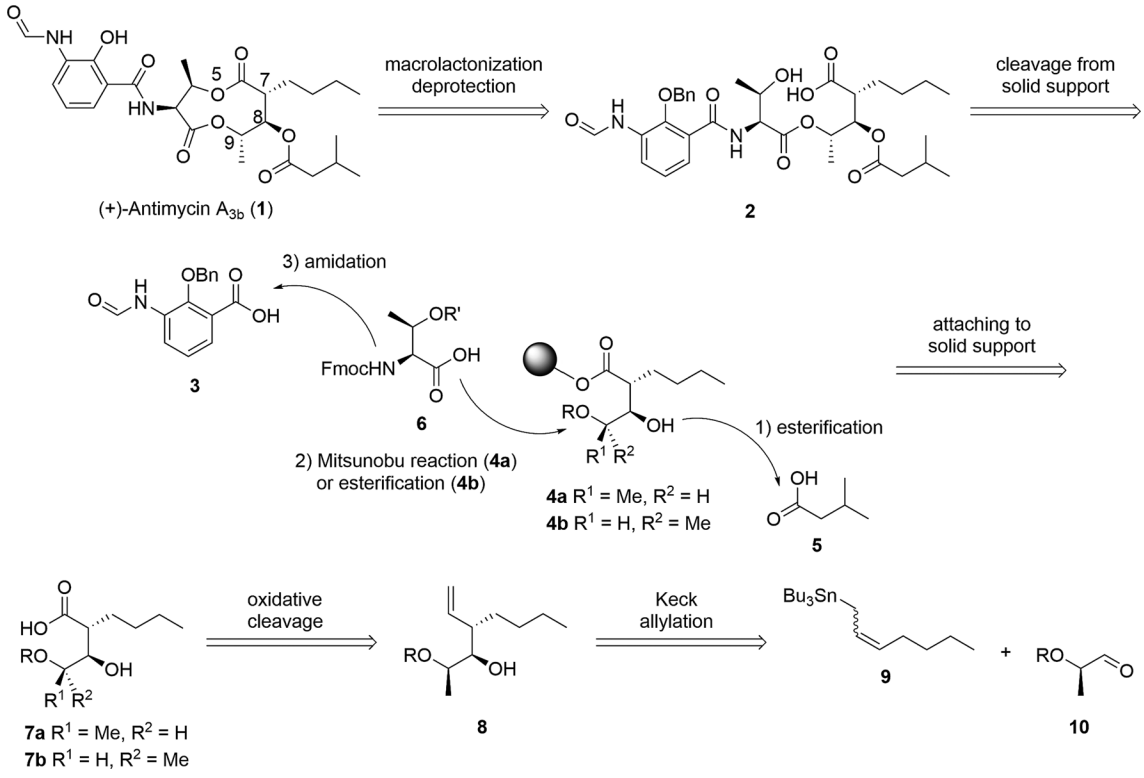
Figure 1. Structures of antimycin A_1–A_{20}.

As a part of our studies on solid-support combinatorial library synthesis of antimycins, here, we report the total synthesis of (+)-antimycin A_{3b} on solid supports. We set the side chain of the C-7 position, the C-8 *O*-acyl group, and the aromatic ring as diversity points for the combinatorial library synthesis. Our prerequisite was that all diversities should be introduced prior to cleavage from the solid support to minimize the number of treatments in solution phase. The strategy included performing a macrolactonization in the solution phase after cleavage from the solid support because the formation of the nine-membered dilactone is not reliable by on-resin cyclization or cyclization release. Therefore, it is desirable to introduce the C-8 *O*-acyl group and the *N*-acyl group before cleavage from the solid support. Since macrolactonization should be performed on the fully functionalized *seco* acid, this synthetic route is very straightforward.

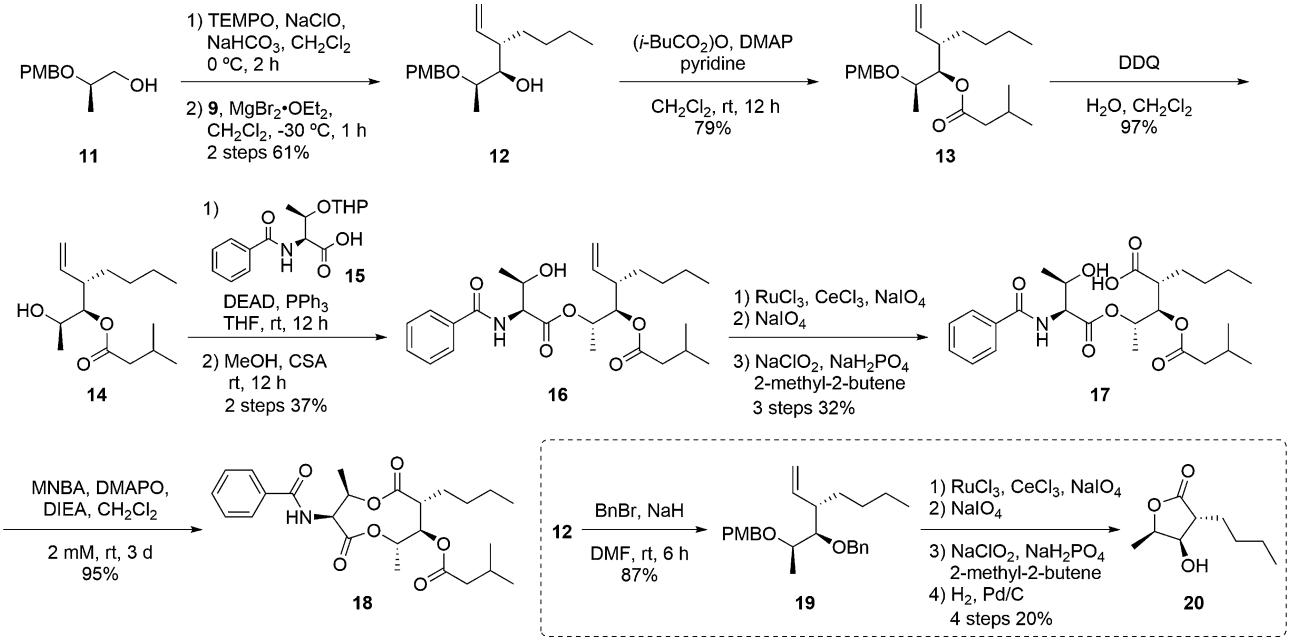
[a] Department of Applied Chemistry, Tokyo Institute of Technology,
2-12-1 Ookayama, Meguro, Tokyo 152-8552, Japan
[b] Yokohama College of Pharmacy,
601 Matano-cho, Totsuka-ku, Yokohama 245-0066, Japan
E-mail: ttak@hamayaku.ac.jp
http://www.hamayaku.jp/lab/la_26.html
[c] PRISM BioLab Co., Ltd.,
4259-3, Nagatsuda-cho, Midori-ku, Yokohama,
Kanagawa 226-8510, Japan
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201402430.

Results and Discussion

Our retrosynthetic route is shown in Scheme 1. (+)-Antimycin A_{3b} (**1**) can be synthesized by cleavage of the *seco* acid **2** from the solid support, followed by macrolactonization and deprotection of the phenolic hydroxy group. The *seco* acid **2** can be synthesized by assembling four fragments on the solid support. The consecutive stereogenic centers of the hydroxy acid **7** could be constructed by utilizing Keck's allylation to a protected D-lactaldehyde with chelation control.[20] This reaction would give a C-9 epimer that could be corrected by exploiting Mitsunobu inversion with either threonine coupling or at the protection step. The resultant alkene would be used as a protected carboxylic acid moiety



Scheme 1. Strategy for the total synthesis of (+)-antimycin A_{3b} on solid supports.

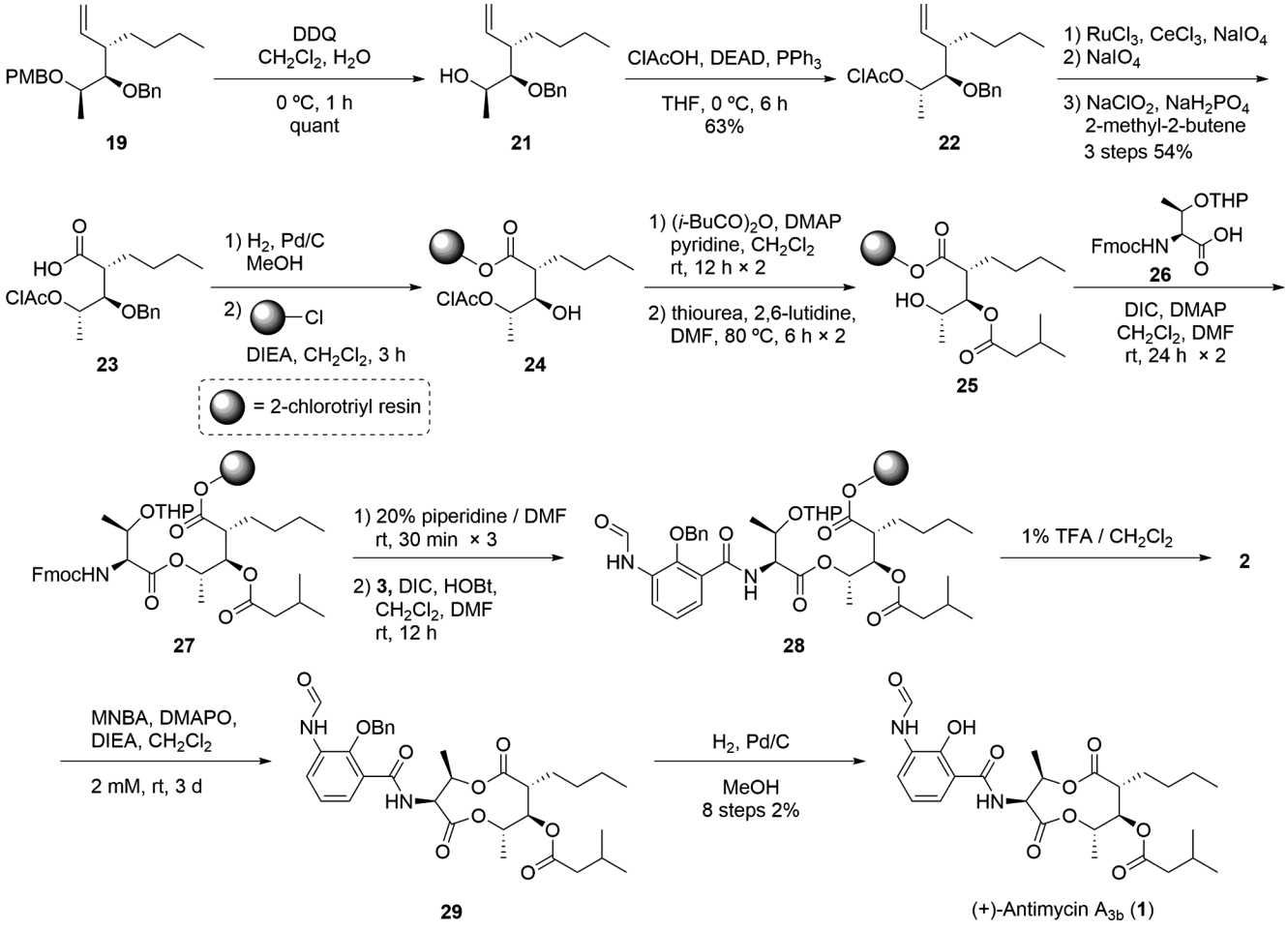


Scheme 2. Synthesis of the model compound.

to avoid γ-lactone formation. In a preliminary study, we investigated the macrolactonization of the *N*- and C-8 *O*-acylated *seco* acid. D-Lactaldehyde, used immediately after the oxidation of the corresponding alcohol, reacted with alkenyl stannane **9**[21] to obtain product **12** as an analytically pure stereoisomer (Scheme 2).[20] The stereochemistry was checked by converting **12** into known lactone **20**.[22] After C-8 *O*-acylation and deprotection of the *p*-methoxybenzyl (PMB) group, the threonine derivative **15** was added to achieve the Mitsunobu reaction, which produced inversion of the stereocenter C-9 in moderate yield. After deprotection of THP, the alkene was converted into the corresponding carboxylic acid by consecutive oxidation. RuO_4-catalyzed oxidation[23] of **16** gave a mixture of diol and aldehyde. This mixture was treated by $NaIO_4$, followed by Pinnick oxidation[24] to give the *N*-acylated *seco* acid **17**. Macrolactonization was performed by using Shiina's method.[19] In the presence of 2-methyl-6-nitrobenzoic anhydride (MNBA) and 4-(dimethylamino)pyridine (DMAP), macrolactonization did not proceed. However, in the presence of 4-(dimethylamino)pyridine *N*-oxide (DMAPO) and *N*,*N*-diisopropylethylamine (DIEA) instead of DMAP, macrolactone **18** was obtained in good yield. We confirmed that the macrolactonization proceeded after all diversity points were introduced.

In the next stage, we performed the total synthesis of antimycin A_{3b} on solid support. The PS-2-chlorotrityl resin, which would avoid undesirable cleavage from the solid support by γ-lactone formation, was selected as the solid support. The chloroacetyl group was selected as the protecting group of the C-9 OH moiety, the alkene was converted into the corresponding carboxylic acid, and the fragment was attached to the solid support. However, direct Mitsunobu inversion with threonine afforded unsatisfactory results both in the solution phase and on the solid support, probably because of steric hindrance. Therefore, the stereochemistry of C-9 was inverted in advance by the Mitsunobu reaction with chloroacetic acid.

The PMB group of **19** was removed and the chloroacetyl group was introduced by Mitsunobu reaction with inversion of the C-9 stereochemistry to give **22** (Scheme 3). The carboxylic acid **23** was synthesized by oxidative cleavage[23,24] of the alkene of **22**. After removal of the Bn group, the compound was immediately attached to the PS-2-chlorotrityl resin. Migration of the C-9 *O*-chloroacetyl group to 8-OH was observed when the loading reaction was performed for 12 h. We therefore set the reaction time as 3 h and used an excess amount of resin to suppress the migration of the protecting group. Isovalerate was introduced and the chloroacetate was removed on the solid support. Fmoc-



Scheme 3. Total synthesis of (+)-antimycin A_{3b} on solid supports.

threonine **26** was esterified and the progress of the reaction was checked by performing the Fmoc test. After deprotection of the Fmoc group followed by amidation of the salicylic acid derivative **3**, *seco* acid **2** was cleaved from the solid support by the application of 1% trifluoroacetic acid (TFA). After the removal of the volatile compounds, the crude *seco* acid **2** was directly exposed to the cyclization conditions. Thus, the reagents were added to a solution of crude **2** and the cyclization reaction proceeded without the formation of detectable amounts of cyclic dimer. This simplified method to perform efficient and rapid library synthesis minimized the treatment in the solution phase. Finally, the benzyl group of **29** was removed by hydrogenation to give (+)-antimycin A_{3b} (**1**). The structures of antimycin A_{3b} (**1**) were confirmed by ^{1}H NMR, ^{13}C NMR, IR, and HRMS analyses.[16,25]

Conclusions

A straightforward, diversity-oriented total synthesis of (+)-antimycin A_{3b} (**1**) was accomplished. The consecutive stereogenic centers from C-7 to C-9 were synthesized by Keck's allylation and Mitsunobu reaction, stereoselectively. All fragments were assembled on a solid support. The key macrolactonization step was performed with a simple procedure to minimize manipulations in the solution phase. This solid-phase procedure could be valuable for the combinatorial synthesis of a library of antimycin analogues.

Experimental Section

General Experimental Methods: NMR spectra were recorded at 270 or 400 MHz for ^{1}H, and 67.5, 100 or 125 MHz for ^{13}C nuclei in the indicated solvent. Chemical shifts are reported in parts per million (ppm) relative to the signal for internal tetramethylsilane (δ = 0 ppm) in $CDCl_3$. ^{1}H NMR spectrum data are reported as follows: $CDCl_3$ (δ =7.26 ppm). ^{13}C NMR spectrum data are reported as follows: $CDCl_3$ (δ =77.0 ppm). Multiplicities are reported by using the following abbreviations: s: singlet, d: doublet, t: triplet, q: quartet, sept: septet, m: multiplet, br: broad, coupling constants (J) are reported in Hertz. Only the strongest and/or structurally important IR peaks are reported (in cm^{-1}). Anhydrous CH_2Cl_2 was obtained from solvent purification columns.

(2*R*,3*R*,4*S*)-4-Butyl-2-(4-methoxybenzyloxy)hexa-5-en-3-ol (12): To a stirred mixture of (*R*)-2-(4-methoxybenzyloxy)propan-1-ol (**11**; 591 mg, 3.01 mmol, 1.00 equiv.), KBr (35.8 mg, 0.301 mmol, 0.100 equiv.), and TEMPO (23.5 mg, 0.151 mmol, 0.0500 equiv.) in CH_2Cl_2 (23.0 mL) and saturated aq. $NaHCO_3$ (23.0 mL) was added 10 wt.-% aq. NaClO (4.60 mL, 6.02 mmol. 2.00 equiv.) at 0 °C. After stirring at 0 °C for 30 min, the reaction mixture was poured into water. The aqueous layer was extracted with two portions of CH_2Cl_2 and the combined extract was washed with brine, dried with $MgSO_4$, filtered, and the solvents evaporated in vacuo. The residue was used for the next reaction without further purification.

To a stirred mixture of the residue (3.01 mmol, 1.00 equiv.) and $MgBr_2{\cdot}OEt_2$ (1.01 g, 3.91 mmol, 1.30 equiv.) in CH_2Cl_2 (6.00 mL) was added a solution of (*E*)-tri(*n*-butyl)(hept-2-en-1-yl)stannane (5.94 g, 3.91 mmol, 1.30 equiv.) in CH_2Cl_2 (3.00 mL) at –30 °C. After stirring at the same temperature for 30 min, the reaction mixture was poured into saturated aq. $NaHCO_3$. The aqueous layer was extracted with two portions of CH_2Cl_2 and the combined extract was washed with brine, dried with $MgSO_4$, filtered, and the solvents evaporated in vacuo. The residue was purified by chromatography on silica gel (hexane/ethyl acetate, 97:3) to give **12** (534 mg, 1.83 mmol, two steps 61%) as a colorless oil. $[\alpha]_D^{30}$ = –21.7 (c = 0.910, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 (d, J = 8.7 Hz, 2 H), 6.88 (d, J = 8.7 Hz, 2 H), 5.59 (dt, J = 16.9, 9.9 Hz, 1 H), 5.04 (dd, J = 9.9, 1.9 Hz, 1 H), 4.96 (dd, J = 16.9, 1.9 Hz, 1 H), 4.56 (d, J = 11.1 Hz, 1 H), 4.33 (d, J = 11.1 Hz, 1 H), 3.80 (s, 3 H), 3.63 (dq, J = 3.6, 6.2 Hz, 1 H), 3.20 (dt, J = 3.6, 6.9 Hz, 1 H), 2.16–2.22 (m, 2 H), 1.64–1.67 (m, 1 H), 1.11–1.31 (m, 8 H), 0.88 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2, 140.2, 130.6, 129.4, 116.2, 113.8, 77.9, 74.5, 70.5, 55.3, 47.8, 29.4 (×2), 22.8, 16.4, 14.1 ppm. IR (KBr): $\tilde{\nu}$ = 3560, 3074, 2956, 2931, 2859, 1614, 1514, 1249, 1068, 1037, 998, 913, 822 cm^{-1}. HRMS (ESI-TOF): m/z calcd. for $C_{18}H_{29}O_3$ $[M + H]^+$ 293.2117; found 293.2120.

(2*R*,3*R*,4*S*)-4-Butyl-2-(4-methoxybenzyloxy)hexa-5-en-3-yl 3-Methylbutanoate (13): To a stirred mixture of **12** (307 mg, 1.05 mmol, 1.00 equiv.), pyridine (425 μL, 5.25 mmol, 5.00 equiv.), and DMAP (6.41 mg, 0.0525 mmol, 0.0500 equiv.) in CH_2Cl_2 (5.30 mL) was added isovaleric anhydride (629 μL, 3.15 mmol, 3.00 equiv.) at room temperature. After stirring at the same temperature for 6 h, the reaction mixture was poured into 1 N aq. $NaHCO_3$. The aqueous layer was extracted with two portions of hexane and the combined extract was washed with brine, dried with $MgSO_4$, filtered, and the solvents evaporated in vacuo. The residue was purified by chromatography on silica gel (hexane/ethyl acetate, 97:3) to give **13** (313 mg, 0.830 mmol, 79%) as a colorless oil. $[\alpha]_D^{17}$ = +9.86 (c = 0.950, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 (d, J = 8.7 Hz, 2 H), 6.87 (d, J = 8.7 Hz, 2 H), 5.51 (dt, J = 17.2, 10.1 Hz, 1 H), 5.05 (dd, J = 10.1, 1.9 Hz, 1 H), 4.98 (dd, J = 17.2, 1.9 Hz, 1 H), 4.81 (dd, J = 9.2, 2.4 Hz, 1 H), 4.52 (d, J = 11.4 Hz, 1 H), 4.33 (d, J = 11.4 Hz, 1 H), 3.80 (s, 3 H), 3.70 (dq, J = 2.4, 6.3 Hz, 1 H), 2.53–2.59 (m, 1 H), 2.26 (d, J = 6.8 Hz, 2 H), 2.20 (m, 1 H), 1.09–1.37 (m, 9 H), 0.97 (d, J = 6.8 Hz, 6 H), 0.85 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.1, 159.1, 138.6, 130.7, 129.5, 117.1, 113.6, 78.0, 73.1, 70.5, 55.2, 44.9, 43.4, 29.7, 29.0, 25.5, 22.7, 22.4, 16.0, 14.0 ppm. IR (KBr): $\tilde{\nu}$ = 2959, 2935, 1734, 1614, 1515, 1467, 1294, 1250, 1067, 994, 822 cm^{-1}. HRMS (ESI-TOF): m/z calcd. for $C_{23}H_{37}O_4$ $[M + H]^+$ 377.2692; found 377.2690.

(2*R*,3*R*,4*S*)-4-Butyl-2-hydroxyhexa-5-en-3-yl 3-Methylbutanoate (14): To a stirred mixture of **13** (313 mg, 0.830 mmol, 1.00 equiv.) in CH_2Cl_2 (8.30 mL) and water (8.30 mL), was added DDQ (283 mg, 1.24 mmol, 1.50 equiv.) at 0 °C. After stirring at the same temperature for 1 h, the reaction mixture was poured into saturated aq. $NaHCO_3$. The aqueous layer was extracted with two portions of CH_2Cl_2 and the combined extract was washed with brine, dried with $MgSO_4$, filtered, and the solvents evaporated in vacuo. The residue was purified by chromatography on silica gel (hexane/ethyl acetate, 95:5) to give **14** (207 mg, 0.807 mmol, 97%) as a colorless oil. $[\alpha]_D^{18}$ = +2.02 (c = 1.65, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.63–5.54 (m, 1 H), 5.13–5.17 (m, 2 H), 4.73 (dd, J = 9.2, 2.4 Hz, 1 H), 3.97 (dq, J = 2.4, 6.3 Hz, 1 H), 2.47 (dq, J = 2.9, 9.2 Hz, 1 H), 2.28 (d, J = 6.8 Hz, 2 H), 2.20 (sept, J = 6.8 Hz, 1 H), 1.11–1.41 (m, 9 H), 0.99 (d, J = 6.8 Hz, 6 H), 0.86 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.9, 138.4, 117.5, 78.4, 66.8, 45.3, 43.4, 29.7, 29.0, 25.6, 22.5, 22.4, 20.2, 13.9 ppm. IR (KBr): $\tilde{\nu}$ = 3472, 2960, 2934, 1736, 1467, 1924, 1190,

1047, 993, 917 cm^{-1}. HRMS (ESI-TOF): *m*/*z* calcd. for $C_{15}H_{29}O_3$ $[M + H]^+$ 257.2117; found 257.2110.

(1*S*,2*R*,3*S*)-1-Methyl-2-(3-methylbutyryloxy)-3-vinylheptyl (2*S*,3*R*)-2-Benzoylamino-3-hydroxybutylate (16): To a stirred mixture of **14** (36.1 mg, 0.141 mmol, 1.00 equiv.), *N*-benzoyl-*O*-(tetrahydro-2*H*-pyran-2-yl)-L-threonine (**15**; 41.4 mg, 0.306 mmol, 2.17 equiv.), and triphenylphosphine (40.6 mg, 0.155 mmol, 1.10 equiv.) in THF (0.700 mL) was added DEAD (ca. 2.2 M in toluene, 76.8 μL, 0.169 mmol, 1.20 equiv.) at 0 °C. After stirring at room temperature for 12 h, the reaction mixture was poured into water and the aqueous layer was extracted with two portions of ethyl acetate. The combined extract was washed with brine, dried with $MgSO_4$, filtered, and the solvents evaporated in vacuo. The residue was used for the next reaction without further purification.

To a stirred solution of the residue (0.141 mmol, 1.00 equiv.) in methanol (1.40 mL) was added CSA (1.64 mg, 0.00705 mmol, 0.0500 equiv.) at 0 °C. After stirring at room temperature for 12 h, the reaction mixture was poured into saturated aq. $NaHCO_3$. The aqueous layer was extracted with two portions of ethyl acetate and the combined extract was washed with brine, dried with $MgSO_4$, filtered, and the solvents evaporated in vacuo. The residue was purified by chromatography on silica gel (hexane/ethyl acetate, 70:30) to give **16** (24.1 mg, 0.0522 mmol, two steps 37%) as a colorless oil. $[\alpha]_D^{18}$ = –9.87 (*c* = 0.930, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.86 (d, *J* = 7.2 Hz, 2 H), 7.51 (t, *J* = 7.2 Hz, 1 H), 7.44 (t, *J* = 7.2 Hz, 2 H), 6.90 (d, *J* = 9.7 Hz, 1 H), 5.59 (dt, *J* = 16.9, 9.7 Hz, 1 H), 5.08–5.20 (m, 4 H), 4.73 (d, *J* = 9.7 Hz, 1 H), 4.26–4.30 (m, 1 H), 3.49 (d, *J* = 5.3 Hz, 1 H), 2.31 (d, *J* = 7.2 Hz, 2 H), 2.12–2.19 (m, 2 H), 1.11–1.43 (m, 12 H), 1.02 (d, *J* = 6.3 Hz, 6 H), 0.85 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.6, 170.3, 167.9, 136.8, 134.0, 131.7, 128.5, 127.2, 118.1, 75.4, 72.5, 66.8, 58.0, 46.0, 43.6, 30.5, 28.4, 25.7, 22.5, 22.3, 19.7, 13.9, 12.1 ppm. IR (KBr): $\tilde{\nu}$ = 3397, 2960, 2935, 1740, 1668, 1527, 1488, 1295, 1165, 920, 714 cm^{-1}. HRMS (ESI-TOF): *m*/*z* calcd. for $C_{26}H_{40}NO_6$ $[M + H]^+$ 462.2856; found 426.2850.

(2*R*,3*R*,4*S*)-4-[(2*S*,3*R*)-2-Benzamido-3-hydroxybutanoyloxy]-2-butyl-3-(3-methylbutanoyloxy)pentanoic Acid (17): To a stirred suspension of $NaIO_4$ (5.28 mg, 24.7 μmol, 1.20 equiv.) in water (60.0 μL) was added $CeCl_3 \cdot 7H_2O$ (0.767 mg, 2.06 μmol, 0.100 equiv.) at room temperature. After stirring at 35 °C for 10 min, acetonitrile (190 μL), ethyl acetate (100 μL), and $RuCl_3$ (0.1 M in water, 10.3 μL, 1.03 μmol, 0.0500 equiv.) was added to the reaction mixture at 0 °C. After stirring at the same temperature for 2 min, a solution of **16** (9.50 mg, 20.6 μmol, 1.00 equiv.) in ethyl acetate (90.0 μL) was added to the reaction mixture at 0 °C. After stirring at the same temperature for 5 min, the reaction mixture was filtered and poured into 10% aq. $Na_2S_2O_3$. The aqueous layer was extracted with two portions of ethyl acetate and the combined extract was washed with brine, dried with $MgSO_4$, filtered, evaporated in vacuo, and purified by short-pad column chromatography ($CHCl_3$/methanol, 97:3) to give a mixture of diol and aldehyde. This mixture was used for the next reaction without further purification.

To a stirred solution of the mixture (20.6 μmol, 1.00 equiv.) in THF (400 μL) and water (100 μL) was added $NaIO_4$ (8.78 mg, 41.2 μmol, 2.00 equiv.) at 0 °C. After stirring at the same temperature for 12 h, the reaction mixture was poured into water and the aqueous layer was extracted with two portions of ethyl acetate. The combined extract was washed with brine, dried with $MgSO_4$, filtered, and the solvents evaporated in vacuo. The residue was used for the next reaction without further purification.

To a stirred mixture of the residue (20.6 μmol, 1.00 equiv.) and NaH_2PO_4 (19.9 mg, 111 μmol, 5.40 equiv.) in *t*BuOH (400 μL), 2-methyl-2-butene (400 μL) and water (400 μL), was added $NaClO_2$ (7.73 mg, 85.5 μmol, 4.15 equiv.) at 0 °C. After stirring at the same temperature for 4 h, the reaction mixture was poured into water and the aqueous layer was extracted with two portions of $CHCl_3$. The combined extract was washed with brine, dried with $MgSO_4$, filtered, and the solvents evaporated in vacuo. The residue was purified by preparative thin-layer chromatography ($CHCl_3$/methanol, 9:1) to give **17** (3.20 mg, 6.67 μmol, three steps 32%) as a colorless oil. $[\alpha]_D^{20}$ = –1.24 (*c* = 0.450, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 7.2 Hz, 2 H), 7.51 (t, *J* = 7.2 Hz, 1 H), 7.43 (t, *J* = 7.2 Hz, 2 H), 7.08 (d, *J* = 9.2 Hz, 1 H), 5.34 (dd, *J* = 10.1, 3.9 Hz, 1 H), 5.13 (dq, *J* = 3.9, 6.3 Hz, 1 H), 4.80 (dd, *J* = 9.2, 1.9 Hz, 1 H), 4.40 (dq, *J* = 1.9, 6.8 Hz, 1 H), 2.55 (dt, *J* = 3.9, 10.1 Hz, 1 H), 2.27 (d, *J* = 6.8 Hz, 2 H), 2.13 (sp, *J* = 6.8 Hz, 1 H), 1.48–1.59 (m, 2 H), 1.24–1.29 (m, 10 H), 0.99 (d, *J* = 6.8 Hz, 6 H), 0.85 (t, *J* = 6.5 Hz, 3 H) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 173.3, 170.3, 168.4, 133.7, 131.8, 128.5, 127.4, 73.8, 72.2, 70.5, 67.2, 57.9, 47.5, 43.4, 28.9, 28.5, 25.7, 22.5, 22.4, 22.3, 19.7, 14.2, 13.8 ppm. IR: $\tilde{\nu}$ = 3363, 2960, 2031, 2873, 1742, 1648, 1531, 1466, 1293, 1188, 1165(KBr) cm^{-1}. HRMS (ESI-TOF): *m*/*z* calcd. for $C_{25}H_{38}NO_8$ $[M + H]^+$ 480.2597; found 480.2609.

(3*S*,4*R*,7*R*,8*R*,9*S*)-3-Benzamido-7-butyl-4,9-dimethyl-8-(3-methylbutanoyloxy)-2,6-dioxo-1,5-dioxacyclononane (18): To a stirred mixture of MNBA (2.37 mg, 6.89 μmol, 3.00 equiv.), DMAPO (0.629 mg, 4.59 μmol, 2.00 equiv.) and DIEA (4.79 μL, 27.5 μmol, 12.0 equiv.) in CH_2Cl_2 (780 μL), was added **17** (1.1 mg, 2.3 μmol, 1.00 equiv.) in CH_2Cl_2 (160 μL) at room temperature. After stirring at the same temperature for 3 days, the reaction mixture was evaporated in vacuo. The residue was purified by chromatography on silica gel (toluene/acetone, 90:10) to give **18** (1.0 mg, 2.2 μmol, 95%) as a colorless oil. $[\alpha]_D^{20}$ = +5.13 (*c* = 0.150, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 7.2 Hz, 2 H), 7.54 (t, *J* = 7.2 Hz, 1 H), 7.47 (t, *J* = 7.2 Hz, 2 H), 6.84 (d, *J* = 7.7 Hz, 1 H), 5.75 (dq, *J* = 7.2,7.2 Hz, 1 H), 5.34 (t, *J* = 7.7 Hz, 1 H), 5.09 (t, *J* = 10.1 Hz, 1 H), 4.99 (dq, *J* = 10.1, 6.3 Hz, 1 H), 2.47–2.52 (m, 1 H), 2.25 (d, *J* = 6.8 Hz, 2 H), 2.13 (t sept, *J* = 6.8 Hz, 1 H), 1.67–1.73 (m, 1 H), 1.02–1.44 (m, 11 H), 0.99 (d, *J* = 6.8 Hz, 6 H), 0.86 (t, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.1, 171.6, 170.6, 133.3, 132.1, 128.8, 127.1, 75.6, 74.5, 71.5, 54.1, 50.2, 43.3, 29.7, 29.2, 28.2, 25.5, 22.4, 17.9, 15.9, 13.8 ppm. IR (KBr): $\tilde{\nu}$ = 3332, 2959, 2858, 1737, 1644, 1532, 1466, 1370, 1185, 1167 cm^{-1}. HRMS (ESI-TOF): *m*/*z* calcd. for $C_{25}H_{36}NO_7$ $[M + H]^+$ 462.2492; found 462.2493.

(2*R*,3*R*,4*S*)-3-Benzyloxy-2-(4-methoxybenzyloxy)-4-butylhexa-5-ene (19): To a stirred mixture of **12** (3.00 g, 10.3 mmol, 1.00 equiv.) and NaH (63% in oil, 549 mg, 14.4 mmol, 1.40 equiv.) in DMF (30.0 mL), was added benzyl bromide (1.47 mL, 12.4 mmol, 1.20 equiv.) at 0 °C. After stirring at room temperature for 6 h, the reaction mixture was poured into 1 N HCl and Et_2O. The aqueous layer was extracted with two portions of Et_2O and the combined extract was washed with 1 N HCl, saturated aq. $NaHCO_3$, and brine, dried with Na_2SO_4, filtered, and the solvents evaporated in vacuo. The residue was purified by chromatography on silica gel (hexane/ethyl acetate, 95:5) to give **19** (3.42 g, 8.94 mmol, 87%) as a colorless oil. $[\alpha]_D^{30}$ = +10.4 (*c* = 2.23, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.34 (m, 7 H), 6.84 (d, *J* = 8.7 Hz, 2 H), 5.70–5.72 (m, 1 H), 4.96–5.02 (m, 2 H), 4.72 (d, *J* = 11.1 Hz, 1 H), 4.60 (d, *J* = 11.1 Hz, 1 H), 4.54 (d, *J* = 11.1 Hz, 1 H), 4.42 (d, *J* = 11.1 Hz, 1 H), 3.80 (s, 3 H), 3.70 (dq, *J* = 5.7, 5.7 Hz, 1 H), 3.26 (t, *J* = 5.7 Hz, 1 H), 2.31–2.39 (m, 1 H), 1.19–1.44 (m, 9 H), 0.87 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ =

159.0, 140.7, 139.1, 131.1, 129.2, 128.1, 127.7, 127.3, 115.4, 113.6, 86.2, 76.3, 74.3, 71.0, 55.2, 45.9, 29.5, 28.6, 22.7, 16.5, 14.1 ppm. IR (KBr): $\tilde{\nu}$ = 2956, 2933, 2860, 1613, 1514, 1455, 1091, 1037, 913, 822, 735, 698 cm^{-1}. HRMS (ESI-TOF): *m*/*z* calcd. for $C_{25}H_{35}O_3$ $[M + H]^+$ 383.2586; found 383.2589.

(2*R*,3*R*,4*R*)-4-Butyl-3-hydroxy-γ-valerolacone (20): To a stirred suspension of $NaIO_4$ (71.0 mg, 0.332 mmol, 1.50 equiv.) in water (0.400 mL) was added $CeCl_3·7H_2O$ (8.20 mg, 22.1 μmol, 0.100 equiv.) at room temperature. After stirring at 35 °C for 10 min, acetonitrile (1.30 mL), ethyl acetate (0.800 mL), and $RuCl_3$ (0.1 M in water, 0.111 mL, 11.1 μmol, 0.0500 equiv.) was added to the reaction mixture at 0 °C. After stirring at the same temperature for 2 min, a solution of **19** (84.6 mg, 0.221 mmol, 1.00 equiv.) in ethyl acetate (0.500 mL) was added to the reaction mixture at 0 °C. After stirring at the same temperature for 5 min, the reaction mixture was filtered and poured into 10% aq. $Na_2S_2O_3$. The aqueous layer was extracted with two portions of ethyl acetate and the combined extract was washed with brine, dried with $MgSO_4$, filtered, evaporated in vacuo, and purified by short-pad column chromatography (hexane/ethyl acetate, 60:40). The residue was used for the next reaction without further purification.

To a stirred solution of the residue (0.221 mmol, 1.00 equiv.) in MeOH (1.30 mL) and water (0.500 mL) was added $NaIO_4$ (71.0 mg, 0.332 mmol, 1.50 equiv.) at 0 °C. After stirring at the same temperature for 12 h, the reaction mixture was poured into water. The aqueous layer was extracted with two portions of ethyl acetate and the combined extract was washed with brine, dried with $MgSO_4$, filtered, and the solvents evaporated in vacuo. The residue was used for the next reaction without further purification.

To a stirred mixture of the residue (0.221 μmol, 1.00 equiv.) and NaH_2PO_4 (215 mg, 1.20 mmol, 5.43 equiv.) in *t*BuOH (2.20 mL), 2-methyl-2-butene (2.20 mL) and water (2.20 mL), was added $NaClO_2$ (83.0 mg, 0.917 mmol, 4.15 equiv.) at 0 °C. After stirring at the same temperature for 4 h, the reaction mixture was poured into water. The aqueous layer was extracted with two portions of $CHCl_3$ and the combined extract was washed with brine, dried with $MgSO_4$, filtered, and the solvents evaporated in vacuo. The residue was used for the next reaction without further purification.

To a stirred solution of a part of the residue (47.0 mmol) in methanol (1.00 mL) was added 10 wt.-% Pd/C (5.00 mg). The reaction mixture was hydrogenated for 12 h under H_2 gas. The reaction mixture was filtered, and the solvents evaporated in vacuo. The residue was purified by chromatography on silica gel (hexane/ethyl acetate, 85:15) to give **20** (5.00 mg, 29.1 mmol, four steps 20%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.63 (dq, *J* = 6.6, 4.8 Hz, 1 H), 4.21 (dd, *J* = 4.8, 3.4 Hz, 1 H), 2.54 (ddd, *J* = 8.2, 6.3, 3.4 Hz, 1 H), 1.70–1.79 (m, 1 H), 1.25–1.50 (m, 8 H), 0.92 (t, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.7, 78.3, 74.2, 49.3, 29.4, 28.2, 22.6, 14.0, 13.9 ppm {ref.[22] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.65 (dq, *J* = 6.7, 4.8 Hz, 1 H), 4.21 (ddd, *J* = 4.8, 4.3, 3.2 Hz, 1 H), 2.63 (d, *J* = 4.3 Hz, 1 H), 2.55 (ddd, *J* = 8.2, 6.6, 3.2 Hz, 1 H), 1.65–1.78 (m, 1 H), 1.20–1.63 (m, 8 H), 0.92 (t, *J* = 7.3 Hz, 3 H) ppm}. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.3, 78.6, 73.9, 49.2, 29.3, 28.1, 22.4, 13.9, 13.8 ppm.

(2*R*,3*R*,4*S*)-3-Benzyloxy-4-butylhexa-5-en-2-ol (21): To a stirred mixture of **19** (1.03 g, 2.70 mmol, 1.00 equiv.) in CH_2Cl_2 (14.0 mL) and water (14.0 mL) was added DDQ (919 mg, 4.05 mmol, 1.50 equiv.) at 0 °C. After stirring at the same temperature for 1 h, the reaction mixture was poured into saturated aq. $NaHCO_3$. The aqueous layer was extracted with two portions of CH_2Cl_2 and the combined extract was washed with brine, dried with $MgSO_4$, filtered, and the solvents evaporated in vacuo. The residue was purified by chromatography on silica gel (hexane/ethyl acetate, 95:5) to give **21** (705 mg, 2.69 mmol, quant.) as a colorless oil. $[\alpha]_D^{31}$ = –5.57 (*c* = 1.93, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.35 (m, 5 H), 5.66–5.76 (m, 1 H), 5.06–5.11 (m, 2 H), 4.71 (d, *J* = 11.1 Hz, 1 H), 4.57 (d, *J* = 11.1 Hz, 1 H), 3.86 (m, 1 H), 3.14 (dd, *J* = 4.3, 6.3 Hz, 1 H), 2.34–2.39 (m, 1 H), 2.21 (d, *J* = 6.8 Hz, 1 H), 1.14–1.37 (m, 9 H), 0.88 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.0, 138.3, 128.4, 127.8, 116.4, 86.7, 74.7, 67.7, 46.4, 29.6, 29.3, 22.7, 20.4, 14.0 ppm. IR (KBr): $\tilde{\nu}$ = 3454, 3068, 2930, 1639, 1455, 1378, 1068, 914, 734, 698 cm^{-1}. HRMS (ESI-TOF): *m*/*z* calcd. for $C_{17}H_{27}O_2$ $[M + H]^+$ 263.2011; found 263.2055.

(2*S*,3*R*,4*S*)-3-Benzyloxy-4-butylhexa-5-en-2-yl Chloroacetate (22): To a stirred mixture of **21** (90.1 mg, 0.343 mmol, 1.00 equiv.), chloroacetic acid (48.7 mg, 0.515 mmol, 1.50 equiv.), and triphenylphosphine (180 mg, 0.687 mmol, 2.00 equiv.) in THF (1.00 mL), was added DEAD (ca. 2.2 M in toluene, 343 μL, 0.775 mmol, 2.20 equiv.) at 0 °C. After stirring at the same temperature for 6 h, the reaction mixture was poured into water. The aqueous layer was extracted with two portions of ethyl acetate and the combined extract was washed with brine, dried with $MgSO_4$, filtered, and the solvents evaporated in vacuo. The residue was purified by chromatography on silica gel (hexane/ethyl acetate, 98:2) to give **22** (73.8 mg, 0.218 mmol, 63%) as a yellow oil. $[\alpha]_D^{22}$ = +2.11 (*c* = 0.950, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.39 (m, 5 H), 5.58 (dt, *J* = 16.9, 9.7 Hz, 1 H), 5.19 (dq, *J* = 2.4, 6.3 Hz, 1 H), 5.11 (dd, *J* = 9.7, 1.5 Hz, 1 H), 5.05 (dd, *J* = 16.9, 1.5 Hz, 1 H), 4.79 (d, *J* = 11.1 Hz, 1 H), 4.59 (d, *J* = 11.1 Hz, 1 H), 4.02 (d, *J* = 14.5 Hz, 1 H), 3.98 (d, *J* = 14.5 Hz, 1 H), 3.47 (dd, *J* = 2.4, 9.7 Hz, 1 H), 2.10 (dq, *J* = 2.9, 9.7 Hz, 1 H), 1.78–1.83 (m, 1 H), 1.11–1.35 (m, 8 H), 0.88 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.5, 138.5, 128.3, 127.9, 127.6, 116.9, 82.9, 75.5, 74.8, 47.9, 41.0, 30.0, 29.0, 22.6, 14.0, 13.1 ppm. IR (KBr): $\tilde{\nu}$ = 2957, 2933, 2860, 1756, 1733, 1455, 1288, 1189, 1107, 1060, 919, 736, 699 cm^{-1}. HRMS (ESI-TOF): *m*/*z* calcd. for $C_{19}H_{28}O_3Cl$ $[M + H]^+$ 339.1727; found 339.1733.

(2*R*,3*R*,4*S*)-3-Benzyloxy-2-butyl-4-(chloroacetoxy)pentanoic Acid (23): To a stirred suspension of $NaIO_4$ (1.03 g, 4.80 mmol, 1.50 equiv.) in water (8.00 mL) was added $CeCl_3·7H_2O$ (149 mg, 0.400 mmol, 0.100 equiv.) at room temperature. After stirring at 35 °C for 10 min, acetonitrile (24.0 mL), ethyl acetate (20.0 mL), and $RuCl_3$ (0.1 M in water, 2.00 mL, 0.200 mmol, 0.0500 equiv.) was added to the reaction mixture at 0 °C. After stirring at the same temperature for 2 min, a solution of **22** (1.36 g, 4.00 mmol, 1.00 equiv.) in ethyl acetate (4.00 mL) was added to the reaction mixture at 0 °C. After stirring at the same temperature for 5 min, the reaction mixture was filtered and poured into 10% aq. $Na_2S_2O_3$. The aqueous layer was extracted with two portions of ethyl acetate and the combined extract was washed with brine, dried with $MgSO_4$, filtered, evaporated in vacuo, and purified by short-pad column chromatography (hexane/ethyl acetate, 60:40) to give a mixture of diol and aldehyde. This mixture was used for the next reaction without further purification.

To a stirred solution of the mixture (4.00 mmol, 1.00 equiv.) in THF (80.0 mL) and water (20.0 mL) was added $NaIO_4$ (1.28 mg, 6.00 mmol, 1.50 equiv.) at 0 °C. After stirring at room temperature for 12 h, the reaction mixture was poured into water. The aqueous layer was extracted with two portions of ethyl acetate and the combined extract was washed with brine, dried with $MgSO_4$, filtered, and the solvents evaporated in vacuo. The residue was used for the next reaction without further purification.

To a stirred mixture of the residue (4.00 mmol, 1.00 equiv.) and NaH_2PO_4 (3.88 g, 21.7 mmol, 5.43 equiv.) in *t*BuOH (40.0 mL), 2-

methyl-2-butene (40.0 mL) and water (40.0 mL), was added $NaClO_2$ (1.50 g, 16.6 mmol, 4.15 equiv.) at 0 °C. After stirring at the same temperature for 4 h, the reaction mixture was poured into water. The aqueous layer was extracted with two portions of $CHCl_3$, and the combined extract was washed with brine, dried with $MgSO_4$, filtered, and the solvents evaporated in vacuo. The residue was purified by chromatography on silica gel (hexane/ethyl acetate, 80:20) to give **23** (767 mg, 2.15 mmol, three steps 54%) as a colorless oil. $[\alpha]_D^{23}$ = +13.8 (c = 0.935, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.38 (m, 5 H), 5.08 (dq, J = 4.4, 6.3 Hz, 1 H), 4.75 (d, J = 11.1 Hz, 1 H), 4.63 (d, J = 11.1 Hz, 1 H), 4.01 (s, 2 H), 3.81 (dd, J = 8.3, 4.4 Hz, 1 H), 2.50–2.55 (m, 1 H), 1.61–1.84 (m, 2 H), 1.21–1.37 (m, 7 H), 0.88 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.0, 166.4, 137.7, 128.4, 128.0, 127.9, 80.9, 74.8, 74.3, 48.2, 40.9, 29.4, 28.1, 22.6, 14.8, 13.8 ppm. IR (KBr): $\tilde{\nu}$ = 3446, 3152, 2959, 2874, 1739, 1733, 1714, 1456, 1288, 1189, 1108, 1064, 960, 752, 700 cm^{-1}. HRMS (ESI-TOF): m/z calcd. for $C_{18}H_{26}O_5Cl$ $[M + H]^+$ 357.1469; found 357.1467.

(2*R*,3*R*,4*S*)-3-Benzyloxy-2-butyl-4-(chloroacetoxy)pentanoic Acid Attached to 2-Chlorotrityl Resin (24): To a stirred solution of **23** (28.0 mg, 74.1 μmol) in methanol (1.00 mL) was added 10 wt.-% Pd/C (0.500 mg). The reaction mixture was hydrogenated for 12 h under H_2 gas, then the reaction mixture was filtered and the solvents evaporated in vacuo. The residue was used for the next reaction without further purification.

To a suspension of 2-chlorotritylchloride resin (260 mg, 1.25 mmol/g, 0.325 mmol, 2.69 equiv.) in CH_2Cl_2 (5.40 mL) in a syringe-shaped vessel (Varian reservoir®) was added acetyl chloride (0.600 mL) at room temperature. After shaking at the same temperature for 3 h, the resin was filtered and washed with CH_2Cl_2 (× 5). To the resin was added a mixture of the residue (0.121 mmol, 1.00 equiv., 23.3 mM) and DIEA (84.3 μL, 0.484 mmol, 93.1 mM) in CH_2Cl_2 (5.20 mL) at room temperature. After shaking at the same temperature for 3 h, the resin was filtered and washed with CH_2Cl_2 (× 5). To the resin was added a mixture of acetic acid (20.6 mL, 0.363 mmol, 69.8 mM) and DIEA (253 μL, 1.45 mmol, 279 mM) in CH_2Cl_2 (5.20 mL) at room temperature and the mixture was shaken at the same temperature for 3 h. The resin was filtered, washed with CH_2Cl_2 (× 5), DMF (× 5), and CH_2Cl_2 (× 5), and dried under reduced pressure to give **24** attached to 2-chlorotrityl resin (0.288 mmol/g).

(2*R*,3*R*,4*S*)-2-Butyl-4-hydroxy-3-(3-methylbutanoyloxy)pentanoic Acid Attached to 2-Chlorotrityl Resin (25): To a **24** attached to 2-chlorotrityl resin (34.6 mg) in a syringe-shaped vessel (Varian reservoir®) was added a mixture of isovaleric anhydride (105 μL, 0.518 mmol, 0.370 M), pyridine (63.4 μL 0.784 mmol, 0.560 M), and DMAP (1.59 mg, 13.0 μmol, 9.30 mM) in CH_2Cl_2 (1.40 mL) at room temperature and the reaction mixture was shaken at the same temperature for 12 h (× 2). The resin was filtered and washed with CH_2Cl_2 (× 5), DMF (× 5), and CH_2Cl_2 (× 5) to give (2*R*,3*R*,4*S*)-2-butyl-4-(chloroacetoxy)-3-(3-methylbutanoyloxy)pentanoic acid attached 2-chlorotrityl resin.

To a (2*R*,3*R*,4*S*)-2-butyl-4-(chloroacetoxy)-3-(3-methylbutanoyloxy)pentanoic acid attached to 2-chlorotrityl resin packed in MicroKan, was added a mixture of 2,6-lutidine (304 mg, 4.00 mmol, 0.200 M) and thiourea (595 μL, 4.00 mmol, 0.200 M) in DMF (20.0 mL) at room temperature and the reaction mixture was shaken at 80 °C for 6 h (× 2). The resin was filtered and washed with DMF (× 5) and CH_2Cl_2 (× 5) to give **25** attached to 2-chlorotrityl resin (**25**).

(2*R*,3*R*,4*S*)-4-{[(2*S*,3*R*)-2-(9*H*-9-Fluoren-9-yl)methoxycarbonylamino-3-(tetrahydro-2*H*-pyran-2-yloxy)butanoyl]oxy}-2-butyl-3-(3-methylbutanoyloxy)pentanoic Acid Attached to 2-Chlorotrityl Resin (27): To **25** attached to 2-chlorotrityl resin packed in MicroKan was added a mixture of *N*-(9*H*-9-fluoren-9-yl)methoxycarbonyl-*O*-tetrahydro-2*H*-pyran-2-yl-L-threonine (**26**; 203 mg, 0.478 mmol, 0.150 M), DIC (150 μL, 0.956 mmol, 0.300 M), and DMAP (23.4 mg, 0.191 mmol, 0.0600 M) in CH_2Cl_2 (2.38 mL) and DMF (0.790 mL) at room temperature and the reaction mixture was shaken at the same temperature for 24 h (× 2). The resin was filtered and washed with CH_2Cl_2 (× 5), DMF (× 5), and CH_2Cl_2 (× 5) to give **27** attached to 2-chlorotrityl resin.

(2*R*,3*R*,4*S*)-4-{[(2*S*,3*R*)-2-(2-Benzyloxy-3-formamidobenzamido)-3-(tetrahydro-2*H*-pyran-2-yloxy)-butanoyl]oxy}-2-butyl-3-(3-methylbutanoyloxy)pentanoic Acid Attached to 2-Chlorotrityl Resin (28): To a **27** attached to 2-chlorotrityl resin packed in MicroKan was added 20% piperidine in DMF (4.00 mL) at room temperature and the reaction mixture was shaken at the same temperature for 30 min (× 3). The resin was filtered and washed with DMF (× 5) and CH_2Cl_2 (× 5) to give (2*R*,3*R*,4*S*)-4-[(2*S*,3*R*)-2-amino-3-(tetrahydro-2*H*-pyran-2-yloxy-butanoyl)oxy]-2-butyl-3-(3-methylbutanoyloxy)-pentanoic acid attached to 2-chlorotrityl resin.

To (2*R*,3*R*,4*S*)-4-{[(2*S*,3*R*)-2-amino-3-(tetrahydro-2*H*-pyran-2-yloxy)butanoyl]oxy}-2-butyl-3-(3-methylbutanoyloxy)pentanoic acid attached to 2-chlorotrityl resin packed in MicroKan was added a mixture of 2-benzyloxy-3-formamidobenzoic acid (**3**; 136 mg, 0.500 mmol, 0.100 M), DIC (77.4 μL, 0.500 mmol, 0.100 M), and HOBt·H_2O (76.6 mg, 0.500 mmol, 0.100 M) in CH_2Cl_2 (3.75 mL) and DMF (1.25 mL) at room temperature and the reaction mixture was shaken at the same temperature for 12 h. The resin was filtered and washed with CH_2Cl_2 (× 5), DMF (× 5), and CH_2Cl_2 (× 5) to give **28** attached to 2-chlorotrityl resin.

(+)-Antimycin A_{3b} (1): To **28** attached to 2-chlorotrityl resin packed in MicroKan was added 1% TFA in CH_2Cl (4.00 mL) at room temperature and the reaction mixture was shaken at the same temperature for 1 h. The reaction mixture was filtered and the resin was rinsed with CH_2Cl_2. The filtrate was evaporated in vacuo and the residue was filtered through a short pad of silica gel ($CHCl_3$/MeOH, 98:2) and the solvents evaporated. The residue was used for the next reaction without further purification.

To a solution of a part of the residue (21.9 mg, 0.0348 mmol, 1.00 equiv.) in CH_2Cl_2 (20.0 mL) was added a mixture of MNBA (34.9 mg, 0.105 mmol, 3.00 equiv.), DMAPO (9.56 mg, 0.0697 mmol, 2.00 equiv.), and DIEA (72.8 μL, 0.418 mmol, 12.0 equiv.) in CH_2Cl_2 (15.0 mL) at room temperature. After stirring at the same temperature for 48 h, the reaction mixture was evaporated in vacuo. The residue was filtered through a short pad of silica gel with $CHCl_3$, and the solvents evaporated. The residue was used for the next reaction without further purification.

To a stirred solution of a part of the residue (2.3 mg, 3.77 mmol) in methanol (0.200 mL) was added 10 wt.-% Pd/C (1.00 mg). The reaction mixture was hydrogenated for 12 h under H_2 gas. The reaction mixture was filtered, and the solvents evaporated in vacuo. The residue was purified by preparative reverse-phase HPLC to give (+)-antimycin A_{3b} (**1**; 0.8 mg, 1.53 mmol, eight steps 2%) as a white solid. $[\alpha]_D^{26.2}$ = +34.8 (c = 0. 035, $CHCl_3$); m.p. 171–172 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.62 (s, 1 H), 8.55 (d, J = 8.3 Hz, 1 H), 8.50 (d, J = 1.9 Hz, 1 H), 7.91 (s, 1 H), 7.23 (d, J = 1.5 Hz, 1 H), 7.07 (d, J = 7.3 Hz, 1 H), 6.92 (t, J = 8.0 Hz, 1 H), 5.73 (dq, J = 7.3, 6.7 Hz, 1 H), 5.28 (t, J = 7.5 Hz, 1 H), 5.09 (t, J = 10.2 Hz, 1 H), 4.99 (dq, J = 9.6, 6.3 Hz, 1 H), 2.51 (dt, J = 10.9, 2.9 Hz, 1 H), 2.25 (d, J = 6.8 Hz, 2 H), 2.21–2.09 (m, 1 H), 1.75–

1.65 (m, 1 H), 1.43–1.13 (m,5 H), 0.99 (d, J = 6.8 Hz, 6 H), 0.87 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.9, 171.6, 170.0, 169.4, 158.9, 150.6, 127.4, 124.8, 120.0, 119.0, 112.5, 75.4, 74.8, 70.9, 53.7, 50.1, 43.2, 29.2, 28.2, 25.4, 22.4, 22.4, 17.8, 15.0, 13.7 ppm. IR (KBr): $\tilde{\nu}$ = 3366, 2959, 2922, 2852, 1749, 1694, 1644, 1532, 1464, 1180, 1162 cm^{-1}. HRMS (ESI-TOF): *m/z* calcd. for $C_{26}H_{37}N_2O_9$ $[M + H]^+$ 521.2499; found 521. 2486.

Supporting Information (see footnote on the first page of this article): Analytical data (^{1}H, ^{13}C NMR and LC-MS charts) for the compounds are provided.

Acknowledgments

The authors acknowledge the financial support of this work from Adaptable and Seamless Technology transfer Program (A-STEP 9372). The authors thank Dr. Haruko Takahashi and Prof. Keisuke Suzuki for NMR spectroscopic assistance. Dr. Hiroshi Tanaka and Dr. Shinichiro Fuse are thanked for significant support in the preparation of this manuscript.

[1] C. Leben, G. W. Keitt, *Phytopathology* **1948**, *38*, 899–906.
[2] B. R. Dunshee, C. Leben, G. W. Keitt, F. M. Strong, *J. Am. Chem. Soc.* **1949**, *71*, 2436–2437.
[3] a) H. G. Schneider, G. M. Tener, F. M. Strong, *Arch. Biochem. Biophys.* **1952**, *37*, 147–157; b) J. L. Lockwood, C. Leben, G. W. Keitt, *Phytopathology* **1954**, *44*, 438–446.
[4] a) Y. Sakagami, S. Takeuchi, H. Yonehara, H. Sakai, M. Takashima, *J. Antibiot.* **1956**, *9*, 1–5; b) K. Watanabe, T. Tanaka, K. Fukuhara, N. Miyairi, H. Yonehara, H. Umezawa, *J. Antibiot., Ser. A* **1957**, *10*, 39–45; c) H. Yonehara, S. Takeuchi, *J. Antibiot., Ser. A* **1958**, *11*, 254–263.
[5] W.-C. Liu, F. M. Strong, *J. Am. Chem. Soc.* **1959**, *81*, 4387–4390.
[6] a) E. E. Van Tamelene, J. P. Dickie, M. E. Loomans, R. S. Dewey, F. M. Strong, *J. Am. Chem. Soc.* **1961**, *83*, 1639–1646; b) A. J. Birch, D. W. Cameron, Y. Harada, R. W. Rickards, *J. Chem. Soc.* **1961**, 889–895.
[7] M. Kinoshita, S. Asuraki, S. Umezawa, *J. Antibiot.* **1972**, *25*, 373–376.
[8] G. Schilling, D. Berti, D. Kluepfel, *J. Antibiot.* **1970**, *23*, 81–90.
[9] C. Barrow, J. Oleynek, V. Marinelli, H. H. Sun, P. Kaplita, D. M. Sedlock, A. M. Gillum, C. C. Chadwick, R. Cooper, *J. Antibiot.* **1997**, *50*, 729–733.
[10] K. Shiomi, K. Hatae, H. Hatanho, A. Matsumoto, Y. Takahashi, C.-L. Jiang, H. Tomoda, S. Kobayashi, H. Tanaka, S. Omura, *J. Antibiot.* **2005**, *58*, 74–78.
[11] N. Hosotani, K. Kumagai, H. Nakagawa, T. Shimatani, I. Saji, *J. Antibiot.* **2005**, *58*, 460–467.
[12] G. Chen, B. Lin, Y. Lin, F. Xie, W. Lu, W.-F. Fong, *J. Antibiot.* **2005**, *58*, 519–522.
[13] G. S. Kido, E. Spyhalski, *Science* **1950**, *112*, 172–173.
[14] M. K. F. Wikstrom, J. A. Berden, *Biochim. Biophys. Acta Bioenerg.* **1972**, *283*, 403–420.
[15] S.-P. Tzung, K. M. Kim, G. Basañez, C. D. Giedt, J. Simon, J. Zimmerberg, K. Y. J. Zhang, D. M. Hockenbery, *Nat. Cell Biol.* **2001**, *3*, 183–191.
[16] a) M. Kinoshita, M. Wada, S. Umezawa, *J. Antibiot.* **1969**, *22*, 580–582; b) M. Kinoshita, M. Wada, S. Aburagi, S. Umezawa, *J. Antibiot.* **1971**, *24*, 724–726; c) M. Kinoshita, S. Aburaki, M. Wada, S. Umezawa, *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1279–1287; d) T. Tsunoda, T. Nishii, M. Yoshizuka, C. Yamasaki, T. Suzuki, S. Ito, *Tetrahedron Lett.* **2000**, *41*, 7667–7671; e) T. Nishii, S. Suzuki, K. Yoshida, K. Araki, T. Tsunoda, *Tetrahedron Lett.* **2003**, *44*, 7829–7832; f) Y. Wu, Y. Yang, *J. Org. Chem.* **2006**, *71*, 4296–4301; g) Z. Hu, X. Jiang, W. Han, *Tetrahedron Lett.* **2008**, *49*, 5192–5195.
[17] M. Inai, T. Nishii, A. Tanaka, H. Kaku, M. Horikawa, T. Tsunoda, *Eur. J. Org. Chem.* **2011**, 2719–2729.
[18] M. Shimano, N. Kamei, T. Shibata, K. Inoguehi, N. Itoh, T. Ikari, H. Senda, *Tetrahedron* **1998**, *54*, 12745–12774.
[19] a) I. Shiina, M. Kubota, R. Ibuka, *Tetrahedron Lett.* **2002**, *43*, 7535–7539; b) I. Shiina, M. Kubota, H. Oshiumi, M. Hashizume, *J. Org. Chem.* **2004**, *69*, 1822–1830.
[20] G. E. Keck, E. P. Boden, *Tetrahedron Lett.* **1984**, *25*, 1879–1882.
[21] a) A. Barbero, P. Cuadrado, I. Fleming, A. M. González, F. J. Pulido, *J. Chem. Soc. Perkin Trans. 1* **1992**, 327–331; b) A. van der Klei, R. L. P. de Jong, J. Lugtenburg, A. G. M. Tielens, *Eur. J. Org. Chem.* **2002**, 3015–3023.
[22] a) P. M. Sibi, J. Lu, L. C. Talbacka, *J. Org. Chem.* **1996**, *61*, 7848–7855; b) S. Aburaki, N. Kinishi, M. Kinoshita, *Bull. Chem. Soc. Jpn.* **1975**, *48*, 1254–1259.
[23] B. Plietker, M. Niggemann, *J. Org. Chem.* **2005**, *70*, 2402–2405.
[24] B. S. Bal, W. E. Childers, H. W. Pinnick, *Tetrahedron* **1981**, *37*, 2091–2096.
[25] The specific rotation of (+)-antimycin A_{3b} synthesized by this solid-phase procedure is much lower than those reported in the literature (+34.8 < +80 degrees). However, the difference is the error within the allowable limits on small samples.

Received: April 16, 2014
Published Online: March 6, 2014

