This article is dedicated to Professor Satoshi Ōmura in celebration of his 2015 Nobel Prize.

Note

Total Synthesis of Thailandepsin B, a Potent HDAC Inhibitor Isolated from a Microorganism

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Thailandepsin B, a bicyclic depsipeptide histone deacetylase inhibitor, was efficiently synthesized in 51% overall yield in eight steps, starting from commercially available *D*-norleucine methyl ester and known (*S,E*)-3-(4-methoxybenzyloxy)-7-(tritylthio)hept-4-enoic acid. The method features a convergent approach in which the corresponding *seco*-acid, a key precursor in macrolactonization, is directly assembled through the condensation of a *D*-*allo*-isoleucine-*D*-cysteine-containing segment with a *D*-norleucine-containing segment.

Key words thailandepsin B; histone deacetylase inhibitor; natural product; bicyclic depsipeptide; total synthesis

In 2011, Cheng and colleagues reported the isolation and structural elucidation of the two bicyclic depsipeptide histone deacetylase (HDAC) inhibitors, thailandepsins A (**1**) and B (**2**)¹⁾ (Chart 1). These compounds were identified through the systematic overexpression of transcription factors associated with natural product gene clusters encoded within *Burkholderia thailandensis* E264.¹⁾ Almost simultaneously, Brady and colleagues independently reported the identification of the two bicyclic depsipeptide HDAC inhibitors, burkholdacs A (**3**) and B (**1**), using the same bacterial strain and gene clusters but a different technical approach.²⁾ Coincidentally, burkholdac B was identical to thailandepsin A.^{1,2)} Thailandepsins A and B exhibit comparable HDAC inhibitory activity to that of FK228 (**4**; romidepsin),¹⁾ which is an anticancer agent that has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of cutaneous T-cell lymphoma.^{3,4)} Note that isozyme selectivity of thailandepsins is superior to that of **4**¹⁾; isozyme selectivity is critically important for developing new HDAC inhibitors as anticancer agents with reduced undesirable side effects.^{4,5)} Thailandepsins, therefore, can be considered as intriguing and valuable targets for total synthesis. To date, the total synthesis of thailandepsin A (**1**; burkholdac B) has been reported by Ganesan and colleagues⁶⁾ and our group.⁷⁾ However, the total synthesis of thailandepsin B (**2**) has only been reported once in the patent literature.⁸⁾

During our efforts synthesizing and biologically evaluating bicyclic depsipeptide HDAC inhibitors including burkholdacs A (**3**),⁷⁾ B (**1**, thailandepsin A),⁷⁾ FK228 (**4**, romidepsin)⁹⁾ and spiruchostatins A (**5**),^{9,10)} B (**6**),^{9,11)} C (**7**)¹²⁾ and D (**8**)¹²⁾ we became interested in the synthesis of thailandepsin B (**2**) and its analogues with the aim of identifying novel mechanism-based anticancer agents. In this study, we describe our total synthesis of **2** using a synthetic strategy developed previously in our laboratory.^{7,9–12)}

i-Pr = isopropyl, *s*-Bu = *sec*-butyl, and *t*-Bu = isobutyl.

Chart 1. Structures of Thailandepsins A (**1**, Burkholdac B), B (**2**), Burkholdac A (**3**), FK228 (**4**; Romidepsin), and Spiruchostatins A–D (**5**–**8**)

Results and Discussion

Retrosynthetic analysis of thailandepsin B (**2**) is illustrated in Chart 2. We envisioned that target molecule **2** could be synthesized *via* the macrolactonization of the corresponding *seco*-acid **9** followed by internal disulfide bond formation. The

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TBS=*tert*-butyldimethylsilyl; Tr=triphenylmethyl; PMB=4-methoxybenzyl.

Chart 2. Retrosynthetic Analysis of Thailandepsin B (2)

key macrolactonization precursor **9** could be prepared through the direct condensation of the *D-allo*-isoleucine- and *D*-cysteine-containing segment **10** with the *D*-norleucine-containing segment **11**. Segment **11** could be formed by the condensation of commercially available *D*-norleucine methyl ester hydrochloride (**12**) with the known carboxylic acid **13** (previously prepared from *L*-malic acid in our laboratory^{7,9-12}). Segment **10** was obtained as previously described in our total synthesis of **1** and **6**.^{7,9}

We initially pursued the synthesis of the key segment **11**, which is the coupling partner of **10**, as shown in Chart 3. The condensation of **12** with **13**^{7,9-12} afforded the desired coupling product **14** in excellent yield (98%). Subsequent saponification of the methyl ester moiety in **14** furnished the requisite segment **11** in 90% yield.

After obtaining the key segment **11**, we directed our attention to the synthesis of the target thailandepsin B (**2**), as shown in Chart 4. The crucial condensation of **10** with **11** proceeded well under the mild conditions [*O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU) (1.3 equiv), 1-hydroxy-7-azabenzotriazole (HOAt) (1.3 equiv), *i*-Pr₂NEt (2.6 equiv), CH₂Cl₂, -30°C, 5 h] explored in our previous studies.^{7,9-12} The desired condensation product **15** was obtained in 90% yield without appreciable epimerization at the C2 stereogenic center (*D*-norleucine part in **15**). In this condensation reaction, the use of a combination of HATU and HOAt at low temperature was critical to effectively suppress unfavorable epimerization event.⁹ The condensation product **15** was then converted to the requisite *seco*-acid **9** with an overall yield of 82%, using the alcohol **16** by successive removal of both the 4-methoxybenzyl (PMB) and allyl-protecting groups. The subsequent macrolactonization of **9** was

a) PyBOP, *i*-Pr₂NEt, MeCN, rt, 98%; b) LiOH, MeOH, rt, 90%. PyBOP= (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate.

Chart 3. Synthesis of Segment **14**

(a) HATU, HOAt, *i*-Pr₂NEt, CH₂Cl₂, -30°C, 90%; (b) DDQ, CH₂Cl₂/H₂O, rt, 89%; (c) Pd(PPh₃)₄, morpholine, THF, rt, 92%; (d) MNBA, DMAP, CH₂Cl₂, rt, 85%; (e) I₂, CH₂Cl₂-MeOH, rt, 95%; (f) HF·pyridine, pyridine, rt, 90%. HATU=*O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate; HOAt=1-hydroxy-7-azabenzotriazole; DDQ=2,3-dichloro-5,6-dicyano-1,4-benzoquinone; MNBA=2-methyl-6-nitrobenzoic anhydride; DMAP=4-dimethylaminopyridine.

Chart 4. Synthesis of Thailandepsin B (2)

achieved by employing the Shiina method¹³⁻¹⁷ [2-methyl-6-nitrobenzoic anhydride (MNBA) (1.3 equiv), 4-dimethylaminopyridine (DMAP) (3.0 equiv), CH₂Cl₂ (1.0 mM), rt, 12 h], which resulted in the desired cyclization product **17** in 85% yield. Finally, simultaneous *S*-Tr deprotection and internal disulfide bond formation in **17** (95%), followed by the deprotection of the TBS group in the resulting disulfide **18** (90%) furnished thailandepsin B (**2**) with [α]_D²⁵ -28.4 (*c*=1.0, MeCN) {lit.¹ [α]_D²⁵ -22.8 (*c*=1.0, MeCN)}. The spectroscopic properties (infrared (IR), ¹H- and ¹³C-NMR, and MS) of the synthetic sample **2** were identical to those reported for natural **2**.¹

Conclusion

We have achieved the total synthesis of thailandepsin B (**2**) with 51% overall yield in eight steps, starting from commercially available D-norleucine methyl ester hydrochloride (**12**) and the known carboxylic acid **13**. The method is in highly convergent manner and features the condensation of a D-*allo*-isoleucine-D-cysteine-containing segment **10** with a D-norleucine-containing segment **11** to directly construct the requisite peptide framework **15** (**10**+**11**→**15**, Chart 4). The present study should be useful for producing thailandepsin analogues that possess various alkyl side chains. Further investigations concerning the synthesis and biological evaluation of thailandepsin analogues are currently under way and will be reported in due course.

Experimental

General Techniques All reactions involving air- and moisture-sensitive reagents were carried out using oven dried glassware and standard syringe-septum cap techniques. Routine monitorings of reaction were carried out using glass-supported Merck silica gel 60 F254 TLC plates. Flash column chromatography was performed on Kanto Chemical Silica Gel 60N (spherical, neutral 40–50 nm) with the solvents indicated.

All solvents and reagents were used as supplied with following exceptions. Tetrahydrofuran (THF) was freshly distilled from Na metal/benzophenone under argon. CH₂Cl₂, MeCN, pyridine and *i*-Pr₂NEt were distilled from calcium hydride under argon.

Measurements of optical rotations were performed with a Anton Paar MCP-100 automatic digital polarimeter. ¹H- and ¹³C-NMR spectra were measured with a JEOL AL-400 (400 MHz) and JEOL LA-600 (600 MHz) spectrometers. Chemical shifts were expressed in ppm using Me₄Si (δ=0) as an internal standard. The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and broad (br). IR spectral measurements were carried out with a JASCO FT/IR-4100 spectrometer. Low- and high-resolution mass spectra (LR-HR-MS) were measured on a JEOL JMS-700 high resolution mass spectrometer.

(R)-Methyl 2-[(S,E)-3-(4-Methoxybenzyloxy)-7-(tritylthio)-hept-4-enamido]hexanoate (14) *i*-Pr₂NEt (0.33 mL, 1.9 mmol) was added dropwise to a stirred solution of D-norleucine methyl ester hydrochloride (**12**) (88.0 mg, 0.48 mmol)¹⁸ and (S,E)-3-(4-methoxybenzyloxy)-7-(tritylthio)hept-4-enoic acid (**13**)^{7,9–12} (174 mg, 0.32 mmol) in MeCN (6.5 mL) containing (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP) (252 mg, 0.48 mmol) at 0°C under argon, and stirring was continued for 2 h at room temperature. The reaction mixture was diluted with EtOAc (30 mL), and the organic layer was washed successively with 10% aqueous HCl (2×10 mL), saturated aqueous NaHCO₃ (2×10 mL) and brine (2×10 mL), then dried over Na₂SO₄. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane–EtOAc 2:1) to give **14** (211 mg, 98%) as a colorless viscous oil. [α]_D²⁵ –6.5 (*c*=1.0, CHCl₃); IR (neat) cm^{–1}: 3309, 3057, 2953, 2929, 2860, 1743, 1652, 1613, 1514, 1443, 1362, 1248, 1080, 821, 744, 700; ¹H-NMR (400 MHz, CDCl₃) δ: 0.83 (3H, t, *J*=7.1 Hz), 1.14–1.28 (4H, m), 1.53–1.60 (1H, m), 1.70–1.77 (1H, m), 2.04–2.25 (4H, m), 2.38 (1H, dd, *J*=15.4, 3.2 Hz), 2.51 (1H, dd, *J*=15.4, 8.8 Hz), 3.71 (3H, s), 3.78 (3H, s), 4.10 (1H, td, *J*=8.3, 3.4 Hz), 4.31 (1H,

d, *J*=10.7 Hz), 4.51 (1H, d, *J*=10.7 Hz), 4.55 (1H, td, *J*=7.7, 5.2 Hz), 5.32 (1H, dd, *J*=15.6, 8.3 Hz), 5.59 (1H, dt, *J*=15.1, 6.6 Hz), 6.81–6.84 (2H, m), 6.95 (1H, d, *J*=8.3 Hz), 7.19–7.29 (11H, m), 7.41–7.45 (6H, m); ¹³C-NMR (100 MHz, CDCl₃) δ: 13.8, 22.2, 27.4, 31.2, 31.4, 32.0, 42.7, 52.0, 52.1, 55.2, 66.6, 70.1, 76.8, 113.8 (2C), 126.6 (3C), 127.9 (6C), 129.5 (6C), 129.7 (2C), 130.0, 130.3, 132.9, 144.9 (3C), 159.2, 170.5, 173.0; HR-FAB-MS *m/z*: 688.3087 (Calcd for C₄₁H₄₇NO₅Sn [M+Na]⁺: 688.3073).

(R)-2-[(S,E)-3-(4-Methoxybenzyloxy)-7-(tritylthio)-hept-4-enamido]hexanoic Acid (11) One mol LiOH (1.30 mL, 1.3 mmol) was added dropwise to a stirred solution of **14** (211 mg, 0.32 mmol) in MeOH (6.3 mL) at room temperature. After 3 h, 10% aqueous HCl was added to the mixture at 0°C until pH was 6. The resulting mixture was extracted with EtOAc (3×30 mL), and the combined extracts were washed with saturated aqueous NaHCO₃ (2×20 mL) and brine (2×20 mL), then dried over Na₂SO₄. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (CHCl₃–MeOH 15:1) to give **11** (186 mg, 90%) as a colorless amorphous solid. [α]_D²⁵ –2.4 (*c*=1.0, CHCl₃); IR (neat) cm^{–1}: 3340, 3057, 2955, 2930, 2862, 1732, 1614, 1514, 1449, 1443, 1248, 1079, 1034, 974, 822, 745, 701; ¹H-NMR (400 MHz, CDCl₃) δ: 0.82 (3H, t, *J*=6.8 Hz), 1.21–1.27 (4H, m), 1.53–1.62 (1H, m), 1.75–1.84 (1H, m), 2.04–2.24 (4H, m), 2.41 (1H, dd, *J*=15.4, 3.2 Hz), 2.52 (1H, dd, *J*=15.1, 8.8 Hz), 3.76 (3H, s), 4.10 (1H, td, *J*=8.2, 3.4 Hz), 4.27 (1H, d, *J*=10.7 Hz), 4.46–4.50 (2H, m), 5.30 (1H, dd, *J*=15.4, 8.0 Hz), 5.58 (1H, dt, *J*=15.1, 6.8 Hz), 6.79–6.83 (2H, m), 7.12 (1H, d, *J*=7.3 Hz), 7.18–7.29 (11H, m), 7.39–7.42 (6H, m); ¹³C-NMR (100 MHz, CDCl₃) δ: 13.8, 22.2, 27.4, 31.2, 31.37, 31.40, 42.4, 52.4, 55.2, 66.6, 70.1, 76.6, 113.9 (2C), 126.6 (3C), 127.9 (6C), 129.5 (6C), 129.7, 129.8 (2C), 130.1, 133.1, 144.9 (3C), 159.3, 171.6, 175.8; HR-FAB-MS *m/z*: 652.3094 (Calcd for C₄₀H₄₆NO₅S [M+H]⁺: 652.3097).

(7S,11R,14S,17R,18S,E)-Allyl 17-[(S)-*sec*-Butyl]-11-butyl-18-(*tert*-butyldimethylsilyloxy)-7-(4-methoxybenzyloxy)-9,12,15-trioxo-1,1,1-triphenyl-14-(tritylthiomethyl)-2-thia-10,13,16-triazaisicos-5-en-20-oate (15) *i*-Pr₂NEt (0.12 mL, 0.72 mmol) was added dropwise to a stirred solution of (3S,4R,5S)-allyl-4-[(S)-2-amino-3-(tritylthio)propanamido]-3-(*tert*-butyldimethylsilyloxy)-5-methylheptanoate (**10**)^{7,9} (187 mg, 0.28 mmol) and **11** (186 mg, 0.28 mmol) in CH₂Cl₂ (5.6 mL) containing HATU (137 mg, 0.36 mmol) and HOAt (49.1 mg, 0.36 mmol) at –30°C under argon. After 5 h, the reaction mixture was diluted with CHCl₃ (50 mL). The organic layer was washed successively with 10% aqueous HCl (2×20 mL), saturated aqueous NaHCO₃ (2×20 mL) and brine (2×20 mL), then dried over MgSO₄. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane/EtOAc 1:1) to give **15** (328 mg, 90%) as a colorless viscous liquid. [α]_D²⁵ +13.1 (*c*=1.0, CHCl₃); IR (neat) cm^{–1}: 3285, 3060, 2956, 2930, 2857, 1734, 1637, 1541, 1515, 1490, 1458, 1444, 1387, 1249, 1173, 1085, 1036, 938, 830, 744, 700; ¹H-NMR (400 MHz, CDCl₃) δ: 0.00 (3H, s), 0.07 (3H, s), 0.77–0.81 (6H, m), 0.83–0.88 (12H, m), 1.05–1.28 (6H, m), 1.36–1.41 (1H, m), 1.64–1.69 (1H, m), 1.75–1.81 (1H, m), 2.07–2.17 (2H, m), 2.20–2.25 (2H, m), 2.34 (1H, dd, *J*=15.6, 3.4 Hz), 2.40–2.58 (4H, m), 2.77 (1H, dd, *J*=12.7, 7.8 Hz), 3.77 (3H, s), 3.91–3.96 (2H, m), 4.01 (1H, td, *J*=8.0, 3.3 Hz), 4.10–4.20 (3H, m), 4.38 (1H, d, *J*=10.7 Hz), 4.44–4.55 (2H, m),

5.17–5.31 (3H, m), 5.45 (1H, dt, $J=15.3, 6.6$ Hz), 5.82–5.91 (1H, m), 6.10 (1H, d, $J=10.2$ Hz), 6.49 (1H, d, $J=7.8$ Hz), 6.80–6.84 (2H, m), 7.00 (1H, d, $J=7.3$ Hz), 7.14–7.45 (32H, m); ^{13}C -NMR (100 MHz, CDCl_3) δ : –4.8, –4.5, 11.7, 13.6, 13.7, 17.9, 22.3, 25.8 (3C), 27.2, 27.6, 31.1, 31.2, 31.4, 32.9, 34.1, 40.0, 42.4, 52.4, 53.2, 55.2, 56.0, 65.1, 66.6, 67.0, 69.5, 70.1, 76.5, 113.9 (2C), 118.2, 126.6 (3C), 126.8 (3C), 127.8 (6C), 128.0 (6C), 129.48 (6C), 129.50 (6C), 129.66, 129.73 (2C), 130.0, 132.1, 133.0, 144.3 (3C), 144.8 (3C), 159.3, 169.7, 171.2, 171.5, 171.8; HR-FAB-MS m/z : 1308.6550 (Calcd for $\text{C}_{79}\text{H}_{98}\text{N}_3\text{O}_8\text{S}_2\text{S} [\text{M}+\text{H}]^+$ 1308.6565).

(7S,11R,14S,17R,18S,E)-Allyl 17-[(S)-sec-Butyl]-11-butyl-18-(tert-butyl dimethylsilyloxy)-7-hydroxy-9,12,15-trioxo-1,1,1-triphenyl-14-(tritylthiomethyl)-2-thia-10,13,16-triazacos-5-en-20-oate (16) 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (112 mg, 0.50 mmol) was added in small portions to a stirred solution of **15** (324 mg, 0.25 mmol) in CH_2Cl_2 – H_2O 9:1 (12 mL) at room temperature. After 3 h, the mixture was diluted with CHCl_3 (60 mL), and the organic layer was washed with saturated aqueous NaHCO_3 (2×20 mL) and brine (2×20 mL), then dried over MgSO_4 . Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane–EtOAc, 2:1) to give **16** (262 mg, 89%) as a colorless viscous liquid. $[\alpha]_{\text{D}}^{25} +11.6$ ($c=1.0$, CHCl_3); IR (neat) cm^{-1} : 3272, 3060, 2956, 2929, 2856, 1737, 1672, 1634, 1542, 1490, 1444, 1387, 1254, 1181, 1084, 1035, 985, 938, 836, 743, 699; ^1H -NMR (400 MHz, CDCl_3) δ : 0.00 (3H, s), 0.06 (3H, s), 0.77–0.87 (19H, m), 1.06–1.12 (1H, m), 1.18–1.33 (5H, m), 1.48–1.57 (1H, m), 1.73–1.81 (2H, m), 2.04–2.09 (2H, m), 2.17–2.22 (3H, m), 2.31 (1H, dd, $J=13.7, 2.4$ Hz), 2.41 (1H, dd, $J=16.1, 6.8$ Hz), 2.54–2.63 (2H, m), 3.14 (1H, d, $J=3.4$ Hz), 3.88–3.98 (2H, m), 4.14 (1H, td $J=7.4, 3.4$ Hz), 4.27 (1H, td, $J=8.2, 4.7$ Hz), 4.32–4.36 (1H, m), 4.42 (1H, ddt, $J=8.4, 4.5, 1.9$ Hz), 4.50 (1H, ddt, $J=8.4, 4.4, 2.0$ Hz), 5.17–5.20 (1H, m), 5.27 (1H, dq, $J=17.1, 1.5$ Hz), 5.35 (1H, dd, $J=15.4, 6.1$ Hz), 5.48 (1H, dt, $J=15.3, 6.7$ Hz), 5.79–5.89 (1H, m), 5.95 (1H, d, $J=10.2$ Hz), 6.02 (1H, d, $J=7.8$ Hz), 6.92 (1H, d, $J=8.3$ Hz), 7.15–7.43 (30H, m); ^{13}C -NMR (100 MHz, CDCl_3) δ : –4.8, –4.5, 11.7, 13.7, 13.8, 18.0, 22.3, 25.8 (3C), 27.1, 27.7, 31.3, 31.4 (2C), 33.1, 34.1, 40.0, 44.0, 52.5, 53.7, 56.1, 65.2, 66.6, 67.0, 69.4, 69.7, 118.3, 126.6 (3C), 126.8 (3C), 127.8 (6C), 128.1 (6C), 129.5 (6C), 129.6 (6C), 129.9, 132.1, 132.6, 144.3 (3C), 144.9 (3C), 170.1, 171.5, 171.59, 171.61; HR-FAB-MS m/z : 1210.5809 (Calcd for $\text{C}_{71}\text{H}_{89}\text{N}_3\text{O}_7\text{S}_2\text{SiNa} [\text{M}+\text{Na}]^+$ 1210.5809).

(7S,11R,14S,17R,18S,E)-17-[(S)-sec-Butyl]-11-butyl-18-(tert-butyl dimethylsilyloxy)-7-hydroxy-9,12,15-trioxo-1,1,1-triphenyl-14-(tritylthiomethyl)-2-thia-10,13,16-triazacos-5-en-20-oic Acid (9) Morpholine (38.7 μL , 0.44 mmol) was added dropwise to a stirred solution of **16** (262 mg, 0.22 mmol) in THF (11 mL) containing $\text{Pd}(\text{PPh}_3)_4$ (25.5 mg, 22 μmol) at room temperature under argon. After 1 h, the reaction mixture was diluted with EtOAc (30 mL), and the organic layer was washed with 10% aqueous HCl (2×10 mL) and brine (2×10 mL), then dried over Na_2SO_4 . Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (CHCl_3 –MeOH 40:1) to give **9** (234 mg, 92%) as a colorless amorphous solid. $[\alpha]_{\text{D}}^{25} +0.6$ ($c=1.0$, CHCl_3); IR (neat) cm^{-1} : 3284, 3059, 3018, 2957, 2929, 2857, 1714, 1635, 1541, 1490, 1444, 1254, 1217, 1185, 1094, 1034, 951, 836, 753, 700; ^1H -NMR (400 MHz, CDCl_3) δ : 0.05 (6H, s), 0.80 (3H, d, $J=6.8$ Hz), 0.83–0.88 (15H, m), 1.06–1.14

(1H, m), 1.19–1.28 (5H, m), 1.54–1.59 (1H, m), 1.78–1.84 (2H, m), 2.03–2.08 (2H, m), 2.17–2.26 (3H, m), 2.32 (1H, dd, $J=13.7, 2.9$ Hz), 2.39 (1H, dd, $J=16.1, 3.9$ Hz), 2.45 (1H, dd, $J=12.4, 5.6$ Hz), 2.54 (1H, dd, $J=16.3, 6.6$ Hz), 2.75 (1H, dd, $J=12.0, 7.6$ Hz), 3.92 (1H, td, $J=13.2, 4.8$ Hz), 4.06–4.14 (2H, m), 4.30–4.35 (2H, m), 5.34 (1H, dd, $J=15.4, 6.1$ Hz), 5.46 (1H, dt, $J=15.3, 6.6$ Hz), 6.36 (2H, d, $J=9.8$ Hz), 7.02 (1H, brs), 7.15–7.42 (30H, m); ^{13}C -NMR (100 MHz, CDCl_3) δ : –4.9, –4.3, 11.8, 13.4, 13.8, 17.9, 22.3, 25.7 (3C), 27.2, 27.8, 29.7, 31.3, 31.4, 33.1, 34.2, 40.3, 44.1, 53.1, 53.8, 57.0, 66.6, 67.0, 68.9, 69.7, 126.6 (3C), 126.9 (3C), 127.9 (6C), 128.1 (6C), 129.5 (6C), 129.6 (6C), 130.0, 132.3, 144.3 (3C), 144.9 (3C), 170.3, 171.9 (2C), 172.3; HR-FAB-MS m/z : 1170.5470 (Calcd for $\text{C}_{68}\text{H}_{85}\text{N}_3\text{O}_7\text{S}_2\text{SiNa} [\text{M}+\text{Na}]^+$ 1170.5496).

(2S,6R,9S,12R,13S)-12-[(S)-sec-Butyl]-6-butyl-13-(tert-butyl dimethylsilyloxy)-2-[(E)-4-(tritylthio)but-1-en-1-yl]-9-tritylthiomethyl-1-oxa-5,8,11-triazacyclopentadecane-4,7,10,15-tetraone (17) A solution of **9** (191 mg, 0.17 mmol) in CH_2Cl_2 (17 mL) was added very slowly to a stirred solution of MNBA (74.4 mg, 0.22 mmol) in CH_2Cl_2 (170 mL, 1.0 mm concentration) containing DMAP (61.0 mg, 0.50 mmol) at room temperature over 14 h. After 1 h, the mixture was diluted with CH_2Cl_2 (200 mL), and the organic layer was washed successively with saturated aqueous NaHCO_3 (2×80 mL), water (2×80 mL) and brine (2×80 mL), then dried over MgSO_4 . Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane–EtOAc, 2:1) to give **17** (160 mg, 85%) as a colorless amorphous solid. $[\alpha]_{\text{D}}^{25} -6.4$ ($c=1.0$, CHCl_3); IR (neat) cm^{-1} : 3286, 3059, 3031, 2956, 2928, 2857, 1733, 1652, 1539, 1490, 1444, 1258, 1198, 1098, 1034, 990, 834, 743, 700 cm^{-1} ; ^1H -NMR (400 MHz, CDCl_3) δ : –0.10 (3H, s), 0.00 (3H, s), 0.76 (3H, d, $J=6.8$ Hz), 0.79–0.86 (15H, m), 0.98–1.05 (1H, m), 1.12–1.19 (1H, m), 1.25–1.38 (4H, m), 1.58–1.66 (1H, m), 1.75–1.86 (2H, m), 2.00–2.07 (2H, m), 2.16–2.20 (2H, m), 2.30 (1H, dd, $J=16.6, 5.9$ Hz), 2.35–2.43 (2H, m), 2.48 (1H, dd, $J=13.9, 3.2$ Hz), 2.55–2.62 (1H, m), 3.24–3.28 (2H, m), 3.70 (1H, td, $J=10.2, 2.0$ Hz), 3.99–4.04 (1H, m), 4.10–4.15 (1H, m), 5.34 (1H, dd, $J=15.6, 7.3$ Hz), 5.51–5.56 (1H, m), 5.66 (1H, dt, $J=15.3, 6.7$ Hz), 6.13 (1H, d, $J=7.8$ Hz), 6.82 (1H, d, $J=5.9$ Hz), 7.19–7.43 ppm (31H, m); ^{13}C -NMR (100 MHz, CDCl_3) δ : –4.9, –3.9, 12.0, 13.0, 13.8, 17.9, 22.4, 25.8 (3C), 27.4, 27.9, 30.9, 31.0, 31.3, 31.9, 34.0, 41.8, 41.9, 54.0, 56.6, 58.1, 66.6, 66.8, 68.7, 71.8, 126.6 (3C), 126.8 (3C), 127.9 (6C), 128.0 (6C), 128.1, 129.48 (6C), 129.53 (6C), 133.4, 144.4 (3C), 144.8 (3C), 169.5, 170.2, 170.4, 173.0; HR-FAB-MS m/z : 1152.5363 (Calcd for $\text{C}_{68}\text{H}_{83}\text{N}_3\text{O}_6\text{S}_2\text{SiNa} [\text{M}+\text{Na}]^+$ 1152.5390).

(1S,5S,6R,9S,20R,E)-6-[(S)-sec-Butyl]-20-butyl-5-(tert-butyl dimethylsilyloxy)-2-oxa-11,12-dithia-7,19,22-triazabicyclo[7.7.6]docos-15-ene-3,8,18,21-tetraone (18) A solution of **17** (156 mg, 0.14 mmol) in CH_2Cl_2 –MeOH 9:1 (35 mL) was added dropwise to a vigorously stirred solution of I_2 (350 mg, 1.4 mmol) in CH_2Cl_2 –MeOH 9:1 (280 mL, 0.5 mm concentration) over 10 min at room temperature. After 10 min, the reaction was quenched with 10% aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (60 mL) at room temperature. The resulting mixture was diluted with CH_2Cl_2 (150 mL), and the organic layer was washed with saturated aqueous NaHCO_3 (2×60 mL) and brine (2×60 mL), then dried over MgSO_4 . Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (CHCl_3 –MeOH 40:1) to give **18** (84.2 mg, 95%) as a

colorless amorphous solid. $[\alpha]_D^{25} +5.7$ ($c=1.0$, CHCl_3); IR (neat) cm^{-1} : 3339, 2957, 2930, 2858, 1747, 1661, 1542, 1463, 1433, 1362, 1257, 1158, 1138, 1080, 1027, 989, 949, 837, 810, 775, 755 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 0.09 (3H, s), 0.16 (3H, s), 0.88 (3H, d, $J=6.8\text{ Hz}$), 0.90–0.95 (15H, m), 1.21–1.28 (1H, m), 1.35–1.49 (5H, m), 1.64–1.72 (1H, m), 1.85–1.98 (2H, m), 2.58–2.62 (3H, m), 2.73–2.76 (3H, m), 2.92–3.13 (4H, m), 3.68 (1H, brs), 4.20–4.24 (1H, m), 4.86 (1H, dt, $J=10.2$, 3.4 Hz), 5.00–5.05 (1H, m), 5.65 (1H, d, $J=15.6\text{ Hz}$), 5.70–5.72 (1H, m), 5.81 (1H, d, $J=3.9\text{ Hz}$), 6.48 (1H, brs), 6.69 (1H, d, $J=9.8\text{ Hz}$), 7.09 ppm (1H, d, $J=6.8\text{ Hz}$); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ : -4.9, -4.3, 11.9, 13.8, 14.5, 17.9, 22.2, 25.7 (3C), 27.8, 28.5, 30.8, 34.9, 36.3, 39.6, 40.5, 41.2, 43.5, 53.4, 56.4, 61.1, 67.1, 68.7, 128.7, 133.0, 169.0 (2C), 170.5, 170.9; HR-FAB-MS m/z : 644.3228 (Calcd for $\text{C}_{30}\text{H}_{54}\text{N}_3\text{O}_6\text{S}_2$ $[\text{M}+\text{H}]^+$ 644.3223).

Thailandepsin B (2) HF·pyridine (1.3 mL) was added to a stirred solution of **18** (83.2 mg, 0.13 mmol) in pyridine (2.6 mL) at room temperature. After 22 h, the reaction mixture was diluted with EtOAc (60 mL), and the organic layer was washed successively with 3% aqueous HCl (3×15 mL), saturated aqueous NaHCO_3 (2×15 mL) and brine (2×15 mL), then dried over Na_2SO_4 . Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (CHCl_3 –MeOH 10:1) to give **2** (thailandepsin B) (61.2 mg, 90%) as a white amorphous solid. $[\alpha]_D^{25} -28.4$ ($c=1.0$, MeCN), {lit.¹⁾ $[\alpha]_D^{25} -22.8$ ($c=1.0$, MeCN)}. The IR, ^1H - and ^{13}C -NMR, and MS spectra were identical to those of natural thailandepsin B¹⁾; IR (neat) cm^{-1} : 3330, 2960, 2931, 2873, 1733, 1660, 1540, 1457, 1434, 1405, 1375, 1277, 1162, 1049, 1023, 981, 910, 731; $^1\text{H-NMR}$ (600 MHz, CDCl_3) δ : 0.91–0.95 (9H, m), 1.21–1.28 (1H, m), 1.36–1.49 (4H, m), 1.51–1.56 (1H, m), 1.60–1.74 (1H, m), 1.91–1.97 (1H, m), 2.08–2.12 (1H, m), 2.46–2.51 (1H, m), 2.59 (1H, dd, $J=13.2$, 1.1 Hz), 2.70–2.75 (4H, m), 2.86 (1H, d, $J=10.6\text{ Hz}$), 2.91–2.95 (1H, m), 3.08–3.12 (1H, m), 3.15–3.22 (1H, m), 3.36 (1H, dd, $J=13.4$, 7.1 Hz), 3.41–3.49 (1H, m), 4.17–4.20 (1H, m), 4.63–4.67 (1H, m), 4.94 (1H, td, $J=8.6$, 3.3 Hz), 5.50–5.51 (1H, m), 5.67 (1H, d, $J=15.4\text{ Hz}$), 5.90 (1H, d, $J=3.7\text{ Hz}$), 6.47 (1H, brs), 6.72 (1H, d, $J=9.5\text{ Hz}$), 7.25 (1H, d, $J=7.0\text{ Hz}$); $^{13}\text{C-NMR}$ (150 MHz, CDCl_3) δ : 11.6, 13.8, 15.3, 22.2, 27.1, 28.4, 30.6, 33.7, 36.3, 39.5, 40.5, 40.8, 41.9, 54.2, 56.6, 61.9, 68.3, 70.4, 128.3, 133.7, 169.1, 170.5, 170.7, 171.9; HR-FAB-MS m/z : 530.2360 (Calcd for $\text{C}_{24}\text{H}_{40}\text{N}_3\text{O}_6\text{S}_2$ $[\text{M}+\text{H}]^+$ 530.2359).

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Supplementary Materials The online version of this article contains supplementary materials.

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- 18) In this condensation reaction, we used 1.5 equiv. of **12** to smoothly complete the reaction. This is because the condensation partner **13** showed low reactivity to **12**. In addition, compound **13**, prepared from commercially available material *via* a ten-step sequence, was more valuable than compound **12**.