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Total synthesis of eurypamides, marine cyclic-isodityrosines from the Palauan sponge *Microciona eurypa*

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Abstract—Total synthesis of eurypamides A, B, and D, **1**, **2**, and **4**, has been successfully accomplished. The $Tl(NO_3)_3$ (TTN) oxidation of the halogenated bisphenols, **14a**, **14b**, **24**, and **43**, effected regio-controlled cyclization to provide the corresponding diaryl ethers, **15a**, **15b**, **25**, and **46**. This investigation revealed a structural revision of eurypamide A as to possess (2″*S*,3″*R*,4″*S*)-configuration (**47**), along with the spectral data of pure **2** and **4**, which were previously characterized in a mixture.

1. Introduction

The isodityrosine-type natural products are known to exhibit antimicrobial, cytotoxic, and enzyme-inhibitory activities. In such cyclic members, as K-13, OF 4949, and vancomycin, the diaryl ether moiety plays an important role to support the stereochemistry of the peptide chains which regulate their biological activities. In this context, we have extensively synthesized these isodityrosine-type natural products employing phenolic oxidation with TTN, as a key step,[1] which can assemble the cyclic structures by production of the diaryl ether linkage in the desired manner. Upon oxidation of **A** with TTN in MeOH, the corresponding product **B** is produced, and the following Zn-reduction afforded the diaryl ether **C** (Fig. 1). In particular, the ether linkage is exclusively constructed at the iodine position.[2]

We initiated the synthesis of eurypamides, as part of our extensive investigation. Among eurypamides A–D, **1**–**4**, isolated from the Palauan sponge, *Microciona eurypa*,[3] **1** consists of isodityrosine and the unprecedented (2″*S*,3″*S*,4″*R*)-dihydroxyarginine unit. The other three congeners were not isolated, and their structures were determined by direct spectroscopic measurement of a mixture. While eurypamide C **3** was synthesized by Itokawa et al.,[4] no synthetic investigation of the others has been reported. In addition, eurypamides might be expected to possess biological activities by their structural similarity to other cyclic isodityrosine-members, although no such information has been reported, to our knowledge. We describe herein the synthesis of eurypamides A, B, and D, **1**, **2**, and **4**.[5]

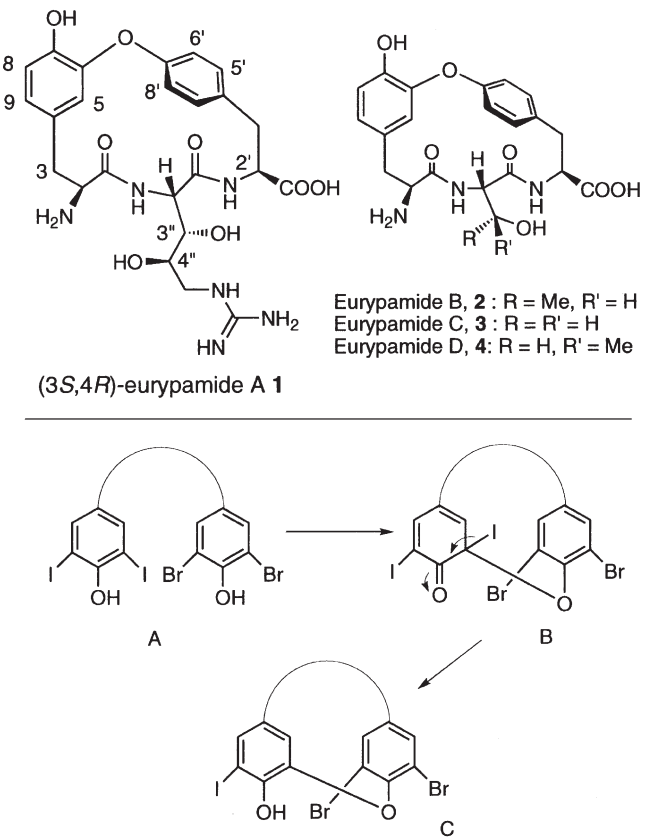

Figure 1.

2. Results and discussion

In our retrosynthetic analysis, the cyclic structure would be constructed by ring-closing at the ether linkage by means of the TTN oxidation of **5** (Scheme 1). The substrate **5** would

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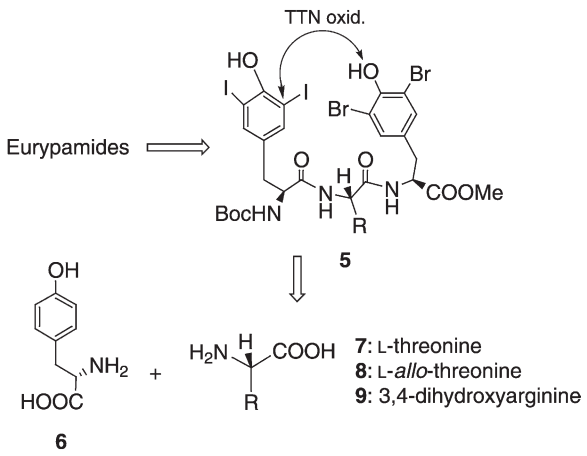


Scheme 1. Retrosynthetic analysis of eurypamides A, B, and D, **1**, **2**, and **4**.

be synthesized from L-tyrosine **6** and, L-threonine **7** for **2**, L-*allo*-threonine **8** for **4**, or (3*S*,4*R*)-dihydroxyarginine unit **9** for **1**, a guanidine group of which would be introduced at the final step.

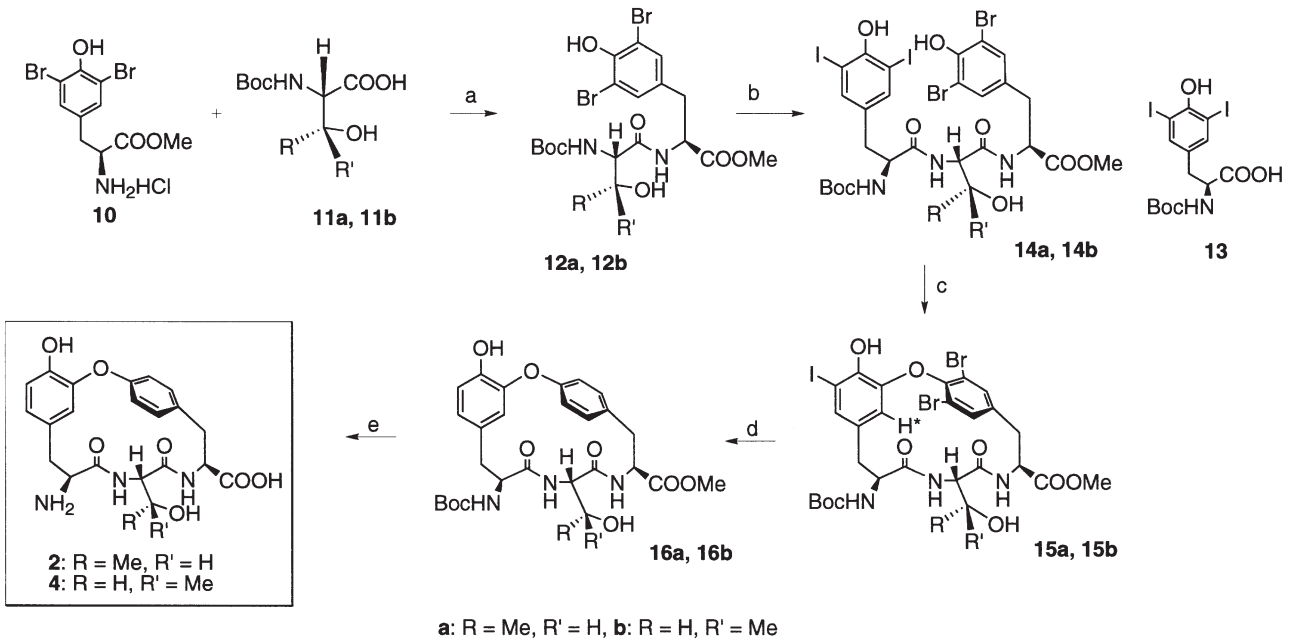
2.1. Synthesis of eurypamide B 2 and D 4

The first synthetic target was the relatively simple eurypamide B **2** to confirm the feasibility of our phenolic oxidation approach employing TTN as an oxidant (Scheme 2). Accordingly, connection of the brominated tyrosine derivative **10**[6] with *N*-Boc-L-threonine **11a** under BOP conditions, provided the dipeptide **12a**. After removal of the Boc group of **12a**, an ammonium salt was further coupled with the diiodotyrosine derivative **13** to give the tripeptide **14a**. TTN oxidation of **14a** in THF–MeOH smoothly proceeded to afford the desired cyclic product **15a** in 72% yield. The structure was determined by the mass and ^{1}H NMR spectra: the high-field shift (δ 5.77) of the aromatic proton signal (*) by the anisotropy effect of another aromatic ring in addition to existence of two Br and one I groups by the mass spectroscopic evidence. Dehalogenation of **15a** was accomplished by Pd-mediated hydrogenolysis, followed by alkaline hydrolysis and TFA treatment to give **2** in good yield. After acid hydrolysis of **2**, gas-chromatographic analysis of the resultant mixture indicated the existence of L-threonine: the phenolic oxidation of **14a** gave rise to cyclization without serious racemization and/or elimination reactions even in the presence of a labile L-threonine.

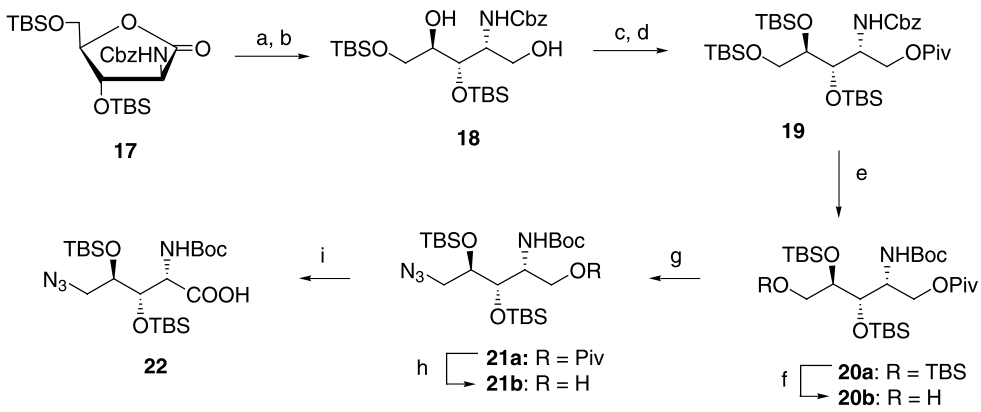
In the next stage, synthesis of eurypamide D **4** was attempted. Tripeptide **14b**, a substrate of the TTN oxidation, was produced essentially as the same procedure as in the case of **14a**, as depicted in Scheme 2. The oxidation of **14b** gave the desired cyclic compound **15b** in 61% yield, which was successively submitted to hydrogenolysis (**16b**), alkaline hydrolysis, and TFA treatment to provide eurypamide D **4**. Based on these successful results, our attention turned to synthesis of eurypamide A **1**.

2.2. Synthesis of eurypamide A 1

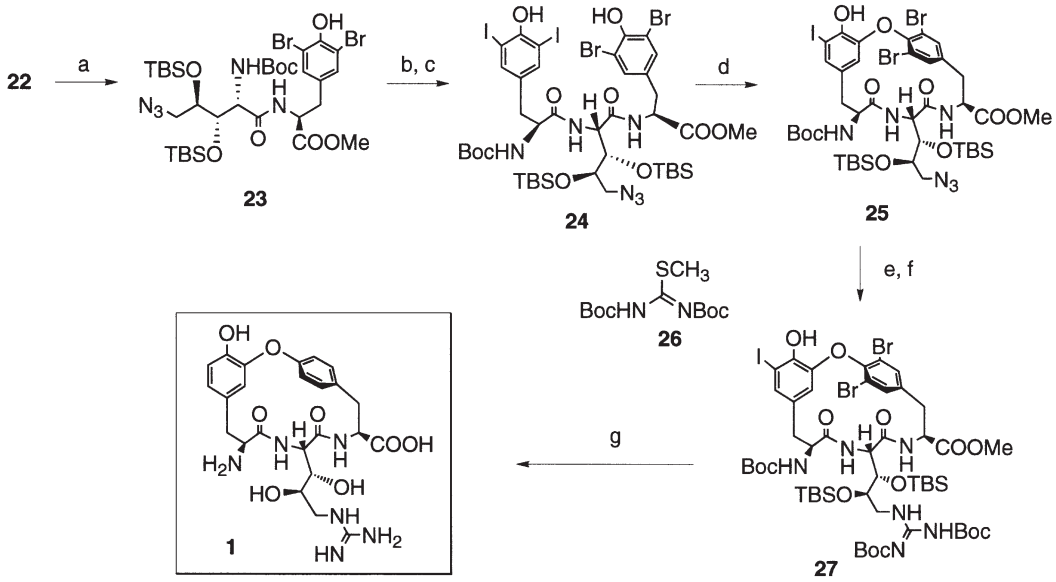
Synthesis of **1** was started from preparation of the (3*S*,4*R*)-dihydroxyarginine derivative. Thus, **17**[7] was produced by condensation of 2,3-*O*-isopropylidene-D-glyceraldehyde with methyl isocyanoacetate. Reduction of **17** with DIBAL-H and $NaBH_4$, gave diol **18**. Selective protection of the primary hydroxyl group as a pivaloyl ester, followed by introduction of TBS groups, afforded **19**. After conversion of the Cbz group into the Boc group (**20a**), the primary TBS group was selectively removed (**20b**), followed by azidation (**21a**) and removal of the pivaloyl group to give the primary alcohol **21b**, which on oxidation with TEMPO afforded the amino acid **22** (Scheme 3).



Scheme 2. Reagents and conditions: (a) BOP, Et_3N, DMF: **12a**, 90%; **12b**, 85%. (b) i. TFA, CH_2Cl_2; ii. **13**, BOP, Et_3N, DMF: **14a**, 91% in 2 steps; **14b**, 91% in 2 steps. (c) TTN, THF–MeOH (4:1): **15a**, 72%; **15b**, 61%. (d) H_2, NaOAc, 10% Pd–C, MeOH: **16a**, 100%; **16b**, 100%. (e) i. 1 M aq. NaOH, MeOH, quant; ii. TFA, CH_2Cl_2: **2**, 90% in 2 steps; **4**, 92% in 2 steps.



Scheme 3. Reagents and conditions: (a) DIBAL-H, CH_2C1_2. (b) $NaBH_4$, MeOH, 84% from **21**. (c) PivCl, pyr, 80%. (d) TBSOTf, 2,6-lutidine, CH_2Cl_2, 85%. (e) H_2, 10% Pd–C, MeOH; Boc_2O, $NaHCO_3$ aq., dioxane, 100%. (f) PPTS, MeOH, 77%. (g) MsCl, pyr; NaN_3, DMF, 77%. (h) DIBAL-H, CH_2Cl_2, 90%. (i) TEMPO, KBr, NaClO, $NaHCO_3$ aq., acetone, 83%.



Scheme 4. Reagents and conditions: (a) **10**, BOP, Et_3N, DMF, 85%. (b) TFA, CH_2C1_2. (c) **13**, BOP, Et_3N, DMF, 65% in 2 steps. (d) TTN, THF–MeOH (4:1), 63%. (e) Ph_3P, H_2O, THF. (f) $HgCl_2$, Et_3N, DMF, 60% in 2 steps. (g) i. H_2, NaOAc, 10% Pd–C, MeOH; ii. TBAF, THF, 65% in 2 steps; iii. 1 M aq. NaOH, MeOH; iv. TFA, CH_2Cl_2, quant in 2 steps.

Amino acid **22** was connected with **10** to give the dipeptide **23** in 85% yield (Scheme 4). After selective removal of the Boc group, the second coupling with **13** afforded the desired tripeptide **24**. TTN oxidation of **24** effected the cyclization to give the cyclic diaryl ether **25** in 63% yield. Upon monitoring by TLC, there were no remarkable byproducts except highly polar-products, which might be produced by polymerization. The azide group of **25** was selectively reduced, followed by introduction of the guanidine group to give **27**. Removal of the halogen atoms and the TBS groups, followed by successive hydrolysis for the ester and the N-protecting group, gave (3″*S*,4″*R*)-eurypamide A **1**. Comparison of the ^{1}H NMR data of the synthetic sample with those reported (Table 1), indicated a clear difference in the region of the methine protones of the dihydroxyarginine moiety while the respective ^{13}C NMR spectra and optical rotations were similar ($[\alpha]_D^{20}$ −17.8 (*c* 0.23, MeOH), lit.[3] $[\alpha]_D$ −21.5 (*c* 0.23, MeOH)).

Faulkner described that the rigid system of eurypamide A **1** enabled determination of the stereochemistry, with the exception of those at the C-3 and 4 positions.[3] The acetonide derivative of **1** was used to determine the stereochemistry of the C-3 and 4 positions; both H-3 and H-4 showed NOE correlations to the same acetonide-methyl group. This observation revealed that the C-3 and 4 positions should have (3″*S*,4″*R*)- or (3″*R*,4″*S*)-configuration. Although they adopted a more energetically preferred (3″*S*,4″*R*)-configuration in the molecular modeling calculation, we expected **1** might possess a more labile (3″*R*,4″*S*)-stereochemistry. Based on this working-hypothesis, the corresponding arginine derivative carrying (3″*R*,4″*S*)-configuration was synthesized from D-ribose.

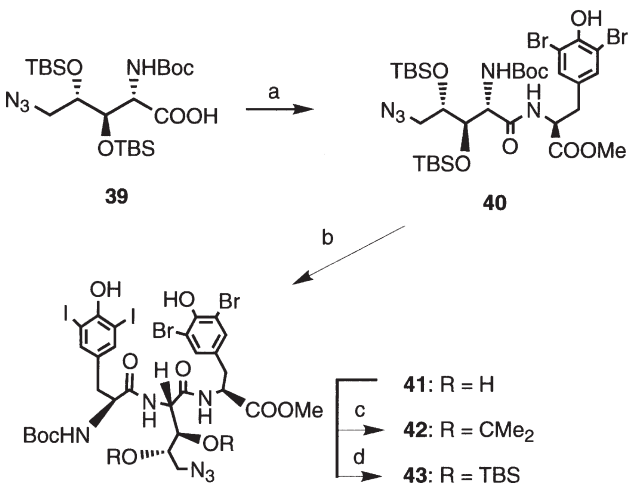
2.3. Synthesis of (3″*R*,4″*S*)-eurypamide A 47

Introduction of an azide group at the free hydroxyl group position of **28**[8] under the Mitsunobu conditions provided **29** (Scheme 5). Reduction of the azide and successive Boc protection afforded **30**. Debenzylation (**31**) and selective

Table 1. Comparison of the ^{1}H NMR data (CD_3OD) of the synthetic **1** with the reported data (Ref. 3)

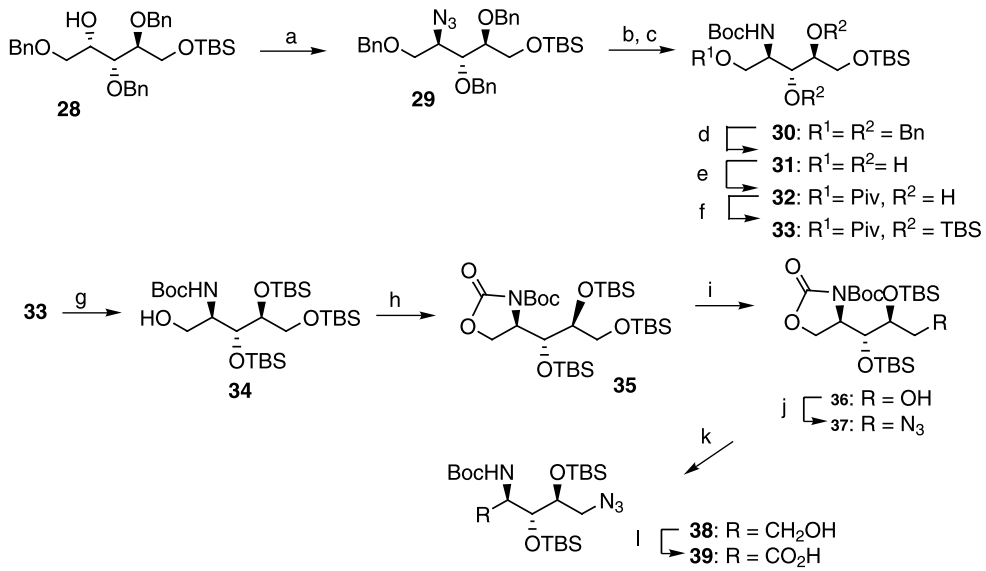
	Synthetic 1		Natural data (ref. 3)	
H	δ_H		δ_H	
3'	2.71	1H, t, 12.7	2.70	1H, t, 12.5
3	2.95	1H, dd, 5, 15	2.98	1H, dd, 6, 15
3	3.20	1H, d, 13	3.20	1H, d, 15
3'			3.35	1H, dd, 7, 12.5
3'	3.32	1H [a)]	3.46	1H, dd, 3, 12.5
5"	3.43-3.52	3H, complex	3.47	1H, dd, 2, 12.5
3"			3.70	1H, dd, 4.5, 8
4"	3.93	1H, dd, 2, 9	3.87	1H, ddd, 2, 7, 8
2	4.20	1H, m	4.15	1H, d, 6
2"	4.75	1H, m	4.70	1H, d, 4.5
2'	4.85	1H, m	4.78	1H, dd, 3, 12.5
5	5.91	1H, d, 2	5.95	1H, d, 2
9	6.67	1H, dd, 2, 8	6.68	1H, dd, 2, 8
8	6.84	1H, d, 8	6.85	1H, d, 8
8'	6.87	1H, dd, 2, 8	6.89	1H, dd, 2, 8
6'	7.03	1H, dd, 2, 8	7.05	1H, dd, 2, 8
9'	7.22	1H, dd, 2, 8	7.22	1H, dd, 2, 8
5'	7.42	1H, dd, 2, 8	7.43	1H, dd, 2, 8

protection with a pivaloyl (**32**) and TBS groups, gave **33**. After selective removal of the primary TBS group, an alcohol generated was submitted to mesylation and azidation. However, the required substitution did not proceed. Based on our working-hypothesis of influence of the amide proton, protection of the amide proton would effect the desired introduction of an azide group. Thus, after removal of the pivaloyl group of **33**, alcohol **34** was treated with NaH, followed by Boc protection to give the oxazolidinone **35**. The primary TBS ether was selectively removed (**36**), followed by successive mesylation and azidation to give the desired **37**. Hydrolysis of the oxazolidinone proceeded under Cs_2CO_3 conditions, and the resulted primary alcohol (**38**) was oxidized with TEMPO to give the amino acid **39**.

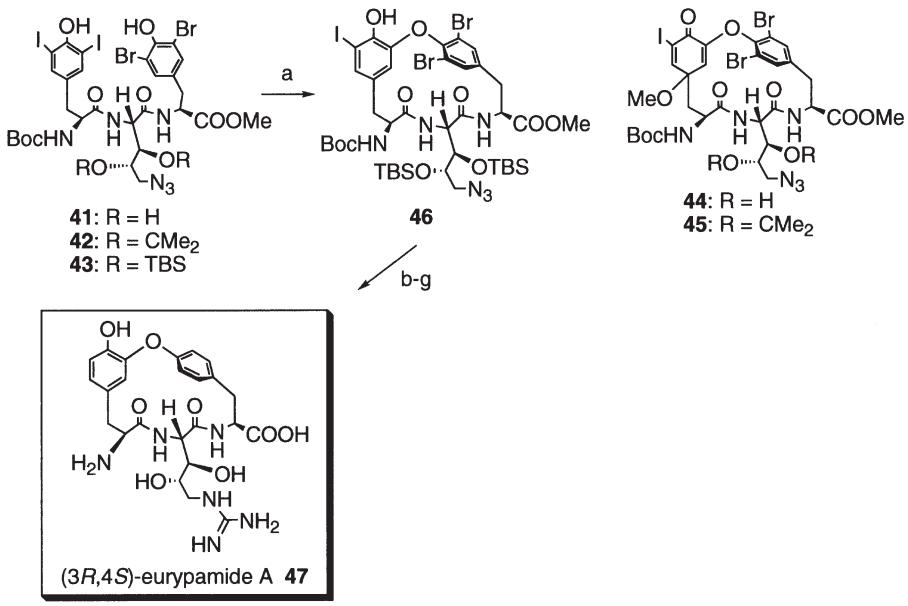


Scheme 6. Reagents and conditions: (a) **10**, BOP, Et_3N, DMF, 81%. (b) i. TBAF, THF; ii. TFA, CH_2C1_2, **13**, EDC, HOBt, Et_3N, DMF, 85% in 3 steps. (c) 2,2-dimethoxypropane, cat. TsOH, DMF, 47%. (d) i. TBSOTf, 2,6-lutidine, CH_2Cl_2; ii. K_2CO_3, MeOH, 60%.

Amino acid **39** was coupled with **10** to give dipeptide **40** (Scheme 6). After deprotection of the Boc group, coupling reaction with **13** was attempted. Unfortunately, no expected product was obtained under several reaction conditions. Accordingly, the TBS and Boc groups of **40** were removed, and the resulting amino alcohol was submitted to coupling with **13** to give tripeptide **41** in good yield. To examine



Scheme 5. Reagents and conditions: (a) Ph_3P, DEAD, DPPA, THF, 92%. (b) Ph_3P, H_2O, THF. (c) Boc_2O, $NaHCO_3$, H_2O–dioxane, 92% in 2 steps. (d) H_2, 10% Pd–C, EtOH. (e) PivCl, pyr., 66% in 2 steps. (f) TBSOTf, 2,6-lutidine, CH_2Cl_2, 89%. (g) DIBAL-H, CH_2Cl_2, 92%. (h) i. NaH, THF, 93%; ii. Boc_2O, DMAP, Et_3N, THF, 86%. (i) CSA, MeOH, 67%. (j) i. MsCl, pyr.; ii. NaN_3, DMF, 80%. (k) Cs_2CO_3, MeOH, 85%. (l) TEMPO, KBr, NaClO, $NaHCO_3$ aq., acetone, 85%.



Scheme 7. Reagents and conditions: (a) TTN, THF–MeOH (4:1), **44**: 56%, **45**: 47%, **46**: 56%. (b) i. Ph_3P, H_2O, THF; ii. $HgCl_2$, Et_3N, DMF, 72%; iii. H_2, NaOAc, 10% Pd–C, MeOH, quant; iv. TBAF, THF, 70%; v. 1 M aq. NaOH, MeOH, quant; vi. TFA, CH_2Cl_2, quant.

adaptability to the TTN cyclization, acetonide **42** and TBS derivative **43** were produced from **41**. Among the oxidation reactions of **41**, **42** and **43**, **41** and **42** provided not the desired cyclic isodityrosine but the spirodienone-type compounds **44** and **45** in moderate yields, while the TBS derivative **43** provided the desired product **46** in 56% yield. Compound **46** in hand was derivatized by essentially the same procedure as in the case of **24** to afford (3″*R*,4″*S*)-eurypamide A **47** (Scheme 7). Under the full range of spectroscopic data, the synthetic sample was superimposable to those of the reported data.

3. Conclusion

Eurypamides A **1**, B **2**, and D **4**, were successfully synthesized by employing the TTN-mediated oxidative cyclization of the corresponding phenols **14a**, **14b**, **24**, and **43**. In addition to supplying the spectroscopic data of pure **2** and **4**, structural revision of **1** was accomplished: the dihydroxyarginine residue of **1** possesses (2″*S*,3″*R*,4″*S*)-configuration **47**.

4. Experimental

4.1. General

All reactions were carried out under an argon atmosphere unless otherwise noted. Optical rotations were measured on a Jasco DIR-360 digital polarimeter with a sodium (D line) lamp. IR spectra were recorded on a Jasco Model A-202 spectrophotometer. ^{1}H NMR spectra and ^{13}C NMR spectra were obtained on JNM-EX270 and JNM-GX400 spectrometers in $CDCl_3$ using tetramethylsilane as an internal standard, as otherwise stated. High-resolution mass spectra were obtained on a Hitachi M-80B GC-MS spectrometer operating at the ionization energy of 70 eV or JEOL JMS-700 (FAB) spectrometers. Preparative and analytical TLCs were carried out on silica gel plate (Kieselgel 60 PF_{254}, E. Merck AG. Germany) using UV light and 5% molybdophosphoric acid in ethanol or 2% ninhydrin in 1-propanol for detection. Kanto Chemical silica 60 N (spherical, neutral, 63–210 μm) was used for column chromatography.

4.2. Synthesis of eurypamide B 2 and D 4

4.2.1. *N*-*tert*-Butoxycarbonyl-L-threonyl-*o*,*o*′-dibromo-L-tyrosine methyl ester 12a. A mixture of **11a** (1.83 g, 8.4 mmol), **10** (3.63 g, 8.4 mmol), BOP reagent (3.69 g, 8.35 mmol), and Et_3N (2 mL, 15 mmol) in DMF (17 mL) was stirred overnight. After the addition of 5% $KHSO_4$ aq., the mixture was extracted with EtOAc, then washed with brine. The organic layer was dried (Na_2SO_4), and evaporated. The residue was purified by silica-gel column chromatography (1/1 hexane/EtOAc) to give **12a** as an oil (4.15 g, 90%): IR (film) 3392, 1662, 1477, 1367, 1241, 1162 cm^{-1}; δ_H 1.20 (3H, d, *J*=6.4 Hz), 1.45 (9H, s), 2.90 (1H, s), 2.93 (1H, dd, *J*=5.6, 14 Hz), 3.09 (1H, dd, *J*=5.6, 14 Hz), 3.76 (3H, s), 4.05 (1H, m), 4.39 (1H, m), 4.75 (1H, m), 5.43 (1H, d, *J*=8.1 Hz), 5.92 (1H, s), 7.12 (1H, d, *J*=7.3 Hz), 7.24 (2H, s); δ_C 18.4, 28.3, 36.3, 52.6, 53.3, 58.3, 66.8, 80.5, 109.9, 130.2, 132.6, 148.5, 156.2, 171.0; HREIMS *m*/*z* 553.0159, calcd for $C_{19}H_{27}{}^{79}Br_2N_2O_7$ (M^++H) 553.0185.

4.2.2. *N*-*tert*-Butoxycarbonyl-*o*,*o*′-diiodo-L-tyrosyl-L-threonyl-*o*,*o*′-dibromo-L-tyrosine methyl ester 14a. A solution of **12a** (524 mg, 0.94 mmol) in TFA (2 mL)–CH_2Cl_2 (6 mL) was stirred at 0 °C for 3 h. After evaporation, the residue was dissolved in DMF (0.6 mL), containing **13** (504.2 mg, 0.94 mmol), BOP reagent (418 mg, 0.94 mmol) and Et_3N (0.27 mL, 1.9 mmol) were added at 0 °C. After being stirred overnight, the reaction was quenched by the addition of 5% $KHSO_4$ aq., extracted with

EtOAc, and washed with brine. The organic layer was dried (Na_2SO_4), and evaporated. The residue was purified by silica-gel column chromatography (2/3 hexane/EtOAc) to give **14a** as an amorphous solid (850 mg, 91% in 2 steps): $[\alpha]_D^{20}$ +4.2 (*c* 1.00, $CHCl_3$); IR (film) 3388, 1650, 1519, 1477, 1457, 1241, 1160 cm^{-1}; δ_H 1.10 (3H, d, *J*=6.8 Hz), 1.43 (9H, s), 2.94 (2H, complex), 3.05 (1H, dd, *J*=5.6, 14 Hz), 3.75 (3H, s), 4.31 (3H, complex), 4.72 (1H, m), 4.96 (1H, d, *J*=7.6 Hz), 5.72 (1H, s), 5.96 (1H, s), 6.96 (1H, d, *J*=7.6 Hz), 7.14 (1H, d, *J*=7.8 Hz), 7.24 (2H, s), 7.51 (2H, s); δ_C 19.8, 28.7, 36.8, 36.9, 52.8, 55.1, 56.3, 57.1, 59.7, 68.5, 80.9, 85.1, 112.0, 131.9, 134.0, 134.6, 141.4, 151.1, 155.3, 157.6, 171.9, 172.7, 173.7; HRFABMS *m/z* 967.8734, calcd for $C_{28}H_{34}{}^{79}Br_2I_2N_3O_9$ (M^++H) 967.8751. Found: C, 34.75; H, 3.68; N, 4.22. Calcd for $C_{28}H_{33}Br_2I_2N_3O_9$: C, 34.70; H, 3.43; N, 4.34.

4.2.3. Cyclic tripeptide 15a. To a solution of **14a** (329.2 mg, 0.34 mmol) in THF (140 mL) and MeOH (35 mL) was added TTN (420 mg, 1.0 mmol) at 0 °C. After being stirred for 1 h, Na_2SO_3 and H_2O (1drop) were added. The mixture was passed through a Celite pad, and evaporated to give a residue. Purification by silica-gel column chromatography (1/2 hexane/EtOAc) gave **15a** as an oil (206.6 mg, 72%): $[\alpha]_D^{20}$ +6.5 (*c* 1.00, $CHCl_3$); IR (film) 3332, 1654, 1490, 1455, 1276, 1253, 1172 cm^{-1}; δ_H 1.00 (3H, d, *J*=6.4 Hz), 1.49 (9H, s), 2.57 (1H, t, *J*=12.8 Hz), 2.72 (1H, d, *J*=12.4 Hz), 3.19 (1H, dd, *J*=4.8, 13.2 Hz), 3.35 (1H, dd, *J*=4.0, 13.2 Hz), 3.62 (1H, m), 3.85 (3H, s), 4.05 (1H, m), 4.37 (1H, m), 4.51 (1H, m), 5.01 (1H, m), 5.46 (1H, d, *J*=7.2 Hz), 5.75 (1H, d, *J*=2 Hz), 6.32 (1H, s), 6.71 (1H, d, *J*=7.6 Hz), 7.06 (1H, d, *J*=1.6 Hz), 7.36 (1H, d, *J*=1.6 Hz), 7.56 (1H, d, *J*=9.6 Hz), 7.66 (1H, s); δ_C 17.2, 28.5, 37.0, 38.8, 52.7, 53.0, 53.7, 56.2, 56.2, 67.7, 79.8, 82.7, 113.5, 116.8, 128.9, 133.8, 134.3, 135.0, 137.0, 142.8, 146.9, 155.0, 168.4, 169.2; HRFABMS *m/z* 841.9602, calcd for $C_{28}H_{33}{}^{79}Br^{81}BrIN_3O_9$ (M^++H) 841.9608.

4.2.4. *N-tert*-Butoxycarbonyl-eurypamide B methyl ester 16a. A solution of **15a** (90.6 mg, 0.11 mmol) in MeOH (1 mL) containing catalytic amounts of 10% Pd/C and NaOAc (26.5 mg, 0.32 mmol) was stirred overnight at ambient temperature in a hydrogen atmosphere. After filtration, the filtrate was evaporated. The residue was purified by silica-gel column chromatography (20/1 $CHCl_3$/MeOH) to give **16a** as an oil (66.3 mg, 100%): $[\alpha]_D^{20}$ +22.4 (*c* 1.00, MeOH); IR (film) 3311, 1654, 1508, 1438, 1367, 1276, 1226, 1166 cm^{-1}; δ_H (CD_3OD) 1.11 (3H, d, *J*=6.4 Hz), 1.42 (9H, s), 2.66 (1H, t, *J*=12.8 Hz), 2.90 (2H, m), 3.29–3.36 (3H, complex), 3.80 (3H, s), 4.06 (1H, m), 4.39 (2H, complex), 4.80 (1H, m), 5.37 (1H, d, *J*=8.4 Hz), 5.88 (1H, d, *J*=1.6 Hz), 6.52 (1H, dd, *J*=2.4, 8.4 Hz), 6.76 (1H, d, *J*=8.4 Hz), 6.87 (1H, dd, *J*=2.4, 8.4 Hz), 7.01 (1H, dd, *J*=2.4, 8.4 Hz), 7.17 (1H, dd, *J*=2.4, 8.4 Hz), 7.37 (1H, dd, *J*=2.4, 8.4 Hz), 7.85 (1H, d, *J*=9.6 Hz), 8.33 (1H, d, *J*=10.4 Hz); δ_C (CD_3OD) 19.7, 28.7, 38.3, 39.5, 52.9, 54.7, 54.9, 58.6, 69.6, 80.7, 116.5, 117.1, 122.7, 123.4, 124.7, 127.9, 131.6, 133.1, 135.0, 146.3, 149.2, 155.3, 156.9, 170.9, 172.2, 173.0; HRFABMS *m/z* 558.2467, calcd for $C_{28}H_{36}N_3O_9$ (M^++H) 558.2451.

4.2.5. Eurypamide B 2. A solution of **16a** (17 mg, 0.03 mmol) in MeOH (0.5 mL)–1 M NaOH aq. (0.5 mL) at 0 °C was stirred for 30 min. After treatment with Amberlite IR 120B (H^+), evaporation gave a residue, which was dissolved in CH_2Cl_2 (1 mL)–TFA (1 mL). After being stirred at 0 °C for 2 h, the mixture was evaporated to give **2** as an oil (12 mg, 90%): $[\alpha]_D^{20}$ −22.1 (*c* 1.00, MeOH); IR (film) 3407, 1653, 1508, 1384, 1220 cm^{-1}; δ_H (CD_3OD) 1.14 (3H, d, *J*=6.4 Hz), 2.66 (1H, t, *J*=13 Hz), 2.93 (1H, dd, *J*=5, 15 Hz), 3.20 (1H, broad d, *J*=15 Hz), 3.42 (1H, dd, *J*=4, 13 Hz), 4.16 (2H, complex), 4.43 (1H, d, *J*=2.4 Hz), 4.72 (1H, dd, *J*=4, 13 Hz), 5.94 (1H, d, *J*=2 Hz), 6.65 (1H, d, *J*=2, 8 Hz), 6.83 (1H, d, *J*=8 Hz), 6.86 (1H, d, *J*=2, 8 Hz), 7.02 (1H, dd, *J*=2, 8 Hz), 7.19 (1H, d, *J*=2, 8 Hz), 7.41 (1H, d, *J*=2, 8 Hz); δ_C (CD_3OD) 19.9, 36.9, 39.8, 53.9, 58.7, 58.8, 69.5, 116.7, 117.0, 122.7, 123.4, 124.5, 124.9, 131.8, 133.0, 135.7, 147.2, 149.7, 154.8, 168.4, 168.5, 170.7; HRFABMS *m/z* 444.1758, calcd for $C_{22}H_{26}N_3O_7$ (M^++H) 444.1771.

4.2.6. Chiral GC analysis of eurypamide B 2. Compound **2** (1 mg) in 6 M aq. HCl was heated at 120 °C overnight in the sealed tube. After evaporation, the residue was heated in HCl/MeOH for 1 h. The mixture was then evaporated, and the residue was treated with trifluoroacetic anhydride (0.5 mL) for 1 h under the same conditions. The mixture was evaporated, and the residue was dissolved in Et_2O (0.5 mL). The resulting solution was submitted to Chiral GC analysis using Chirasil–Val column (25 m×0.25 mm; the program rate: 50 °C (10 min), then 50–200 °C at 4 °C/min). The GC analysis for the amino acids established the presence of L-threonine (19.48 min).

4.2.7. *N-tert*-Butoxycarbonyl-L-*allo*-threonyl-*o*,*o*′-dibromo-L-tyrosine methyl ester 12b. A mixture of **11b** (65.2 mg, 0.3 mmol), **10** (129 mg, 0.3 mmol), BOP reagent (132 mg, 0.3 mmol), and Et_3N (0.084 mL, 0.6 mmol) in DMF (2 mL) was stirred overnight. Work-up and purification by silica-gel column chromatography (1/1 hexane/EtOAc) gave **12b** as an oil (140.1 mg, 85%): IR (film) 3382, 1658, 1479, 1241, 1160 cm^{-1}; δ_H 1.26 (3H, d, *J*=6.4 Hz), 1.44 (9H, s), 2.96 (1H, dd, *J*=6.8, 14 Hz), 3.06 (1H, dd, *J*=5.2, 14 Hz), 3.71 (1H, m), 3.73 (3H, s), 3.93 (1H, m), 4.05 (1H, m), 4.78 (1H, m), 5.53 (1H, d, *J*=8.0 Hz), 6.25 (1H, s), 7.06 (1H, d, *J*=7.6 Hz), 7.28 (2H, s); δ_C 19.8, 28.3, 36.2, 52.6, 52.7, 53.3, 58.5, 69.2, 76.6, 76.9, 77.2, 77.3, 80.5, 109.9, 130.3, 132.6, 148.6, 156.1, 171.1, 171.2; HREIMS *m/z* 553.0223, calcd for $C_{19}H_{27}{}^{79}Br_2N_2O_7$ (M^++H) 553.0185.

4.2.8. *N-tert*-Butoxycarbonyl-*o*,*o*′-diiodo-L-tyrosyl-L-*allo*-threonyl-*o*,*o*′-dibromo-L-tyrosine methyl ester 14b. To a solution of **12b** (213.3 mg, 0.385 mmol) in CH_2Cl_2 (1.5 mL) was added TFA (1.5 mL) at 0 °C. After being stirred for 1 h, the mixture was concentrated in vacuo. The residue was dissolved in DMF (3 mL), **13** (250 mg, 0.46 mmol), EDC (82.6 mg, 0.43 mmol), HOBt (70.6 mg, 0.43 mmol), and Et_3N (0.1 mL, 0.71 mmol) were added at 0 °C; the mixture was stirred overnight. Work-up and purification by silica-gel column chromatography (2/3 hexane/acetone) gave **14b** as an oil (340.4 mg, 91% in 2 steps): $[\alpha]_D^{20}$ +1.5 (*c* 1.00, MeOH); IR (film) 3361, 1564 cm^{-1}; δ_H (CD_3OD) 1.16 (3H, d, *J*=6.4 Hz), 1.38 (9H, s), 2.64 (1H, dd, *J*=10, 14 Hz), 2.94 (2H, complex),

3.04 (1H, dd, *J*=6.0, 14 Hz), 3.70 (3H, s), 3.97 (1H, m), 4.24 (1H, dd, *J*=6.0, 10 Hz), 4.33 (1H, d, *J*=6.4 Hz), 4.65 (1H, m), 7.34 (2H, s), 7.62 (2H, s); δ_C (CD_3OD) 19.7, 28.6, 28.7, 36.9, 37.0, 52.8, 55.2, 57.0, 59.8, 68.9, 80.8, 85.1, 112.0, 132.0, 134.1, 134.6, 141.4, 151.1, 155.4, 157.6, 171.7, 172.8, 173.6; HRFABMS *m/z* 969.8769, calcd for $C_{28}H_{34}{}^{79}Br^{81}BrI_2N_3O_9$ (M^++H) 969.8731.

4.2.9. Cyclic tripeptide 15b. To a solution of **14b** (95.7 mg, 0.1 mmol) in THF (40 mL) and MeOH (10 mL) was added TTN (110 mg, 0.24 mmol) at 0 °C. After being stirred for 1 h, the reaction was quenched by the addition of Na_2SO_3 and H_2O (1drop). The mixture was passed through a Celite pad, and evaporated. The residue was purified by silica-gel column chromatography (10/1 $CHCl_3$/MeOH) to give **15b** as an amorphous solid (50.9 mg, 61%): $[\alpha]_D^{20}$ +3.6 (*c* 1.00, $CHCl_3$); IR (film) 3332, 1656, 1490, 1455, 1421, 1367, 1253, 1170 cm^{-1}; δ_H 1.11 (3H, d, *J*=6.0 Hz), 1.44 (9H, s), 2.62 (2H, complex), 3.15 (1H, dd, *J*=6.4, 13 Hz), 3.36 (1H, dd, *J*=4.0, 13 Hz), 3.81 (3H, s), 4.39 (1H, m), 4.49 (1H, m), 4.97 (1H, m), 5.41 (1H, d, *J*=7.2 Hz), 5.66 (1H, s), 6.49 (1H, broad), 6.87 (1H, d, *J*=8 Hz), 7.05 (1H, broad s), 7.40 (1H, d, *J*=2 Hz), 7.58 (1 h, d, *J*=9 Hz), 7.64 (1H, broad s); δ_C 18.4, 19.5, 28.5, 36.8, 38.1, 52.9, 53.0, 53.5, 56.7, 58.4, 69.2, 79.8, 82.7, 113.5, 117.1, 118.5, 129.0, 133.4, 134.2, 134.9, 137.0, 142.8, 144.0, 146.9, 155.0, 169.1, 169.9, 171.1, 171.3; HRFABMS *m/z* 839.9646, calcd for $C_{28}H_{33}{}^{79}Br_2IN_3O_9$ (M^++H) 839.9628.

4.2.10. *N-tert*-Butoxycarbonyl-eurypamide D methyl ester 16b. A solution of **15b** (26 mg, 0.031 mmol) in MeOH (1 mL) containing catalytic amounts of 10% Pd/C and NaOAc (7.6 mg, 0.093 mmol) was stirred at ambient temperature overnight in a hydrogen atmosphere. Work-up and purification by silica-gel column chromatography (10/1 $CHCl_3$/MeOH) gave **16b** as an oil (21.1 mg, 100%): $[\alpha]_D^{20}$ +14.9 (*c* 1.00, MeOH); IR (film) 3419, 1656, 1508, 1438, 1367, 1276, 1226, 1166 cm^{-1}; δ_H (CD_3OD) 1.12 (3H, d, *J*=6.4 Hz), 1.43 (9H, s), 2.68 (1H, t, *J*=12.4 Hz), 2.85 (1H, d, *J*=14 Hz), 2.95 (1H, dd, *J*=7, 14 Hz), 3.34 (1H, dd, *J*=4, 13 Hz), 3.79 (3H, s), 3.92 (1H, m), 4.34 (1H, m), 4.44 (1H, m), 4.79 (1H, dd, *J*=4, 13 Hz) 5.46 (1H, d, *J*=8.4 Hz), 5.87 (1H, d, *J*=1.6 Hz), 6.53 (1H, dd, *J*=2.4, 8.4 Hz), 6.76 (1H, d, *J*=8 Hz), 6.88 (1H, dd, *J*=2.4, 8.4 Hz), 7.01 (1H, dd, *J*=2.4, 8.4 Hz), 7.19 (1H, dd, *J*=2.4, 8.4 Hz), 7.35 (1H, dd, *J*=1.6, 8 Hz), 7.95 (1H, d, *J*=9.2 Hz); δ_C (CD_3OD) 19.1, 28.7, 38.1, 39.1, 52.9, 54.7, 54.8, 55.4, 58.6, 69.5, 80.7, 116.6, 117.1, 119.3, 122.6, 123.3, 124.8, 128.1, 131.3, 133.1, 134.9, 146.4, 155.5, 170.5, 172.2, 172.9; HRFABMS *m/z* 558.2464, calcd for $C_{28}H_{36}N_3O_9$ (M^++H) 558.2451.

4.2.11. Eurypamide D 4. To a solution of **16b** (16.6 mg, 0.03 mmol) in MeOH (0.5 mL) was added 1 M NaOH aq. (0.5 mL) at 0 °C; the mixture was stirred for 30 min. After treatment with Amberlite IR 120B (H^+), evaporation gave a residue, which was dissolved in CH_2Cl_2 (1 mL)–TFA (1 mL) at 0 °C. After being stirred for 2 h, the mixture was evaporated, and the residue was co-evaporated several times with toluene to give **4** as an oil (12 mg, 92%): $[\alpha]_D^{20}$ −21.5 (*c* 1.00, MeOH); IR (film) 3297, 1666, 15081438, 1276, 1208 cm^{-1}; δ_H (CD_3OD) 1.14 (3H, d, *J*=6.4 Hz), 2.69 (1H, t, *J*=12.7 Hz), 2.94 (1H, dd, *J*=6.0, 15 Hz), 3.20 (1H, broad d, *J*=14 Hz), 3.40 (1H, dd, *J*=4.0, 13 Hz), 4.04 (1H, m), 4.09 (1H, m), 4.54 (1H, dd, *J*=6, 10 Hz), 4.75 (1H, m), 5.92 (1H, d, *J*=2 Hz), 6.66 (1H, dd, *J*=2, 8 Hz), 6.83 (1H, d, *J*=8 Hz), 6.88 (1H, dd, *J*=2, 8.4 Hz), 7.02 (1H, dd, *J*=2, 8.4 Hz), 7.22 (1H, dd, *J*=2, 8.4 Hz), 7.39 (1H, dd, *J*=2, 8.4 Hz), 8.20 (1H, d, *J*=10 Hz), 8.38 (1H, d, *J*=10 Hz); δ_C (CD_3OD) 18.9, 36.8, 37.8, 55.1, 58.7, 62.3, 69.2, 116.8, 117.0, 122.7, 123.4, 124.5, 124.9, 128.5, 131.7, 133.1, 135.6, 137.4, 147.2, 149.7, 154.8, 168.5, 176.7; HRFABMS *m/z* 444.1754, calcd for $C_{22}H_{26}N_3O_7$ (M^++H) 444.1771.

4.3. Synthesis of (3*S*,4*R*)-eurypamide A 1

4.3.1. 2-(*N*-Benzyloxycarbonyl)amino-2-deoxy-3,4,5-tri-(*tert*-butyldimethylsilyloxy)-1-pivaloyl-D-arabinitol 19. To a solution of **17** (2.1 g, 4.1 mmol) in CH_2Cl_2 (30 mL) was added DIBAL-H (6 mL, 1 M in toluene) at −78 °C; the mixture was stirred for 1 h. The reaction mixture was partitioned between EtOAc and H_2O. The organic layer was washed with Rochelle salt aq. and brine, dried (Na_2SO_4), then evaporated to give a residue, which was dissolved in MeOH (30 mL), and $NaBH_4$ (120 mg, 3 mmol) was added at 0 °C. After being stirred for 30 min at ambient temperature, the resulted mixture was partitioned between EtOAc and H_2O. Work-up and purification by silica-gel column chromatography (3/1 hexane/EtOAc) gave **18** as an oil (1.82 g, 84% in 2 steps): δ_H 0.07–0.16 (12H, complex), 0.90 (18H, s), 1.17 (9H, s), 3.53 (1H, dd, *J*=6.8, 9.6 Hz), 3.68 (1H, m), 3.78 (4H, complex), 4.00 (1H, m), 5.10 (2H, complex), 5.63 (1H, d, *J*=8.8 Hz), 7.35 (5H, complex). This compound was immediately submitted the next step.

To a solution of **18** (421 mg, 0.82 mmol) in CH_2Cl_2 (8 mL) was added pivaloyl chloride (0.5 mL, 4.1 mmol) at 0 °C; the mixture was stirred at ambient temperature for 4 h. The reaction was quenched by the addition of 5% $KHSO_4$ aq., and extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$ aq. and brine, dried (Na_2SO_4), then evaporated. A mixture of the residue (392 mg, 0.66 mmol), 2,6-lutidine (0.6 mL, 5.2 mmol), and TBDMSOTf (0.6 mL, 2.6 mmol) in CH_2Cl_2 (6 mL) was stirred for 1 h. Work-up and purification by silica-gel column chromatography (20/1 hexane/EtOAc) gave **19** as an amorphous solid (398 mg, 85%): $[\alpha]_D^{20}$ +6.0 (*c* 1.00, $CHCl_3$); IR (film) 1733, 1471, 1255, 1149 cm^{-1}; δ_H 0.04 (3H, s), 0.05 83H, s), 0.06 (6H, s), 0.12 (3H, s), 0.87 (9H, s), 0.89 (9H, s), 0.91 (9H, s), 1.18 (9H, s), 3.55 (1H, dd, *J*=5.6, 11 Hz), 3.64 (1H, dd, *J*=5.2, 11 Hz), 3.71 (1H, m), 3.89 (1H, t, *J*=11 Hz), 3.99 (1H, d, *J*=2.8 Hz), 4.12 (2H, complex), 4.99 (1H, d, *J*=12.8 Hz), 5.12 (1H, d, *J*=12.8 Hz), 5.23 (1H, d, *J*=7.2 Hz), 7.33 (5H, complex); δ_C −5.1, −4.9, −4.7, −4.1, −3.7, 18.2, 18.3, 18.5, 25.8, 26.0, 27.3, 38.8, 50.2, 63.0, 64.7, 66.6, 71.0, 127.9, 128.1, 128.2, 128.3, 136.4, 155.5, 177.8; HREIMS *m/z* 712.4443, calcd for $C_{36}H_{70}NO_7Si_3$ (M^++H) 712.4460.

4.3.2. 2-(*N-tert*-Butoxycarbonyl)amino-2-deoxy-3,4,5-tri-(*tert*-butyldimethylsilyloxy)-1-pivaloyl-D-arabinitol 20a. A solution of **19** (0.8 g, 1.1 mmol) in MeOH (10 mL) containing of catalytic amounts of 10% Pd/C was stirred for 1 h at ambient temperature in a hydrogen atmosphere. The mixture was passed through a Celite pad, and evaporated. A mixture of the residue, $NaHCO_3$ (150 mg, 1.8 mmol), and Boc_2O (0.4 mL, 1.6 mmol) in H_2O (6 mL)–1,4-dioxane (6 mL) was stirred for 1 h. Work-up and purification by

silica-gel column chromatography (20/1 hexane/EtOAc) gave **20a** as an oil (0.77 g, 100%): $[\alpha]_D^{20}$ +1.4 (*c* 1.00, $CHCl_3$); IR (film) 1720, 1482, 1390, 1365, 1282, 1255, 1151 cm^{-1}; δ_H 0.06 (18H, complex), 0.89 (27H, complex), 1.18 (9H, s), 1.45 (9H, s), 3.53–3.71 (3H, complex), 3.84–4.11 (4H, complex), 5.00 (1H, d, *J*=7.2 Hz); δ_C −5.1, −4.9, −3.9, −3.7, 18.2, 18.3, 18.5, 26.1, 27.2, 27.5, 38.7, 49.9, 62.8, 64.8, 71.2, 76.1, 79.1, 154.9, 177.9; HREIMS *m/z* 678.4607, calcd for $C_{33}H_{72}NO_7Si_3$ (M^++H) 678.4616. Found: C, 58.79; H, 10.45; N, 1.97. Calcd for $C_{33}H_{71}NO_7Si_3$: C58.44; H, 10.55; N, 2.07.

4.3.3. 2-(*N*-*tert*-Butoxycarbonyl)amino-2-deoxy-3,4-di-(*tert*-butyldimethylsilyloxy)-1-pivaloyl-D-arabinitol 20b. To a solution of **20a** (760 mg, 1.1 mmol) in MeOH (10 mL) was added a catalytic amount of PPTS at 0 °C; the mixture was stirred overnight. Work-up and purification by silica-gel column chromatography (10/1 hexane/EtOAc) gave **20b** as an oil (640 mg, 77%): $[\alpha]_D^{20}$ +3.2 (*c* 1.00, $CHCl_3$); IR (film) 3450, 2956, 1720, 1482, 1390, 1255, 1155 cm^{-1}; δ_H 0.07–0.18 (12H, complex), 0.90 (18H, complex), 1.18 (9H, s), 1.42 (9H, s), 3.63 (1H, m), 3.69 (3H, complex), 3.89 (2H, complex), 4.07 (2H, complex), 4.88 (1H, d, *J*=7.8 Hz); δ_C −5.0, −4.8, −4.4, −4.2, −4.15, 18.1, 18.4, 25.9, 26.2, 27.2, 28.4, 38.7, 50.0, 62.5, 62.6, 70.7, 73.2, 79.4, 155.0, 177.8; HREIMS *m/z* 564.3778, calcd for $C_{27}H_{58}NO_7Si_2$ (M^++H) 564.3752. Found: C, 57.53; H, 10.07; N, 2.43. Calcd for $C_{27}H_{71}NO_7Si_2$: C, 57.51; H, 10.19; N, 2.48.

4.3.4. Azide 21a. To a solution of **20b** (557 mg, 0.99 mmol) in pyridine (5 mL) was added MsCl (0.1 mL, 1.3 mmol) at 0 °C. After being stirred for 2 h at the same temperature, the mixture was partitioned between EtOAc and H_2O, the organic layer was washed with 5% $KHSO_4$ aq., followed by brine. The organic layer was dried (Na_2SO_4), and concentrated in vacuo. A mixture of the residue and NaN_3 (514 mg, 7.9 mmol) in DMF (3 mL) was heated at 80 °C for 4 h. After being cooled to ambient temperature; the mixture was filtered. The filtrate was partitioned between EtOAc and H_2O, the organic layer was washed with brine. The organic layer was dried (Na_2SO_4), and evaporated. Purification of the residue by a silica gel column (40/1 hexane/EtOAc) gave **21a** as an oil (454 mg, 77%): $[\alpha]_D^{20}$ +13.1 (*c* 1.00, $CHCl_3$); IR (film) 3450, 2102, 1720, 1473, 1253 cm^{-1}; δ_H 0.09 (3H, s), 0.13 (3H, s), 0.15 (6H, s), 0.92 (9H, complex), 0.94 (9H, s), 1.21 (9H, s), 1.43 (9H, s), 3.27 (1H, dd, *J*=4.6, 13 Hz), 3.45 (1H, dd, *J*=3, 13 Hz), 3.79 (1H, m), 3.92 (1H, m), 4.07 (2H, complex), 4.81 (1H, d, *J*=7.6 Hz); δ_C −5.1, −5.0, −3.85, −3.8, 18.1, 18.5, 26.0, 26.3, 27.2, 28.4, 38.8, 49.2, 50.0, 53.4, 62.5, 72.0, 73.1, 79.6, 154.9, 177.8; HREIMS *m/z* 589.3830, calcd for $C_{27}H_{57}N_4O_6Si_2$ (M^++H) 589.3816.

4.3.5. Azide alcohol 21b. To a solution of **21a** (326 mg, 0.55 mmol) in CH_2Cl_2 (4 mL) was added DIBAL-H (2.0 mL, 1 M in toluene) at −78 °C; the mixture was stirred for 1 h. The reaction was quenched by the addition of EtOAc, and the mixture was partitioned between EtOAc and H_2O. The organic layer was washed with Rochelle salt aq., followed by brine. The organic layer was dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica-gel column chromatography (8/1–4/1 hexane/EtOAc) to give **21b** as an oil (252 mg, 90%): $[\alpha]_D^{20}$ +5.2 (*c* 1.0, $CHCl_3$); IR (film) 3446, 2102, 1697, 1496, 1473, 1390, 1367, 1255 cm^{-1}; δ_H 0.11 (3H, s), 0.15 (9H, s), 0.90 (9H, s), 0.93 (9H, s), 1.43 (9H, s), 2.94 (1H, m), 3.31 (1H, dd, *J*=4.8, 13 Hz), 3.45 (1H, dd, *J*=3.6, 13 Hz), 3.56 (1H, m), 3.72–3.81 (3H, complex), 3.93 (1H, dd, *J*=2, 5.2 Hz), 5.12 (1H, d, *J*=7.3 Hz); δ_C −4.9, −4.8, −4.1, −4.0, 18.1, 18.3, 26.0, 26.1, 28.4, 53.5, 53.9, 63.7, 72.1, 73.4, 79.8, 156.5; HREIMS *m/z* 505.3191, calcd for $C_{22}H_{48}N_4O_5Si_2$ (M^++H) 505.3241.

4.3.6. Amino acid 22. To a solution of **21b** (91.7 mg, 0.182 mmol) in acetone (0.5 mL) and 5% $NaHCO_3$ aq. (0.5 mL) were added TEMPO (35.7 mg, 0.20 mmol), KBr (2.8 mg, 0.018 mmol), and 8% NaClO aq. (0.5 mL). After being stirred for 3 h, the reaction was quenched by the addition of 5% $KHSO_4$ aq. The mixture was partitioned between EtOAc and H_2O, and the aqueous layer was extracted with EtOAc. The combined organic layer was dried (Na_2SO_4), then evaporated. The residue was purified by silica-gel column chromatography (20/1 hexane/EtOAc and 10/1 $CHCl_3$/MeOH) to give **22** as an oil (78 mg, 83%): IR (film) 2100, 1718, 1471, 1388, 1253 cm^{-1}; δ_H (CD_3OD) 0.07 (3H, s), 0.13 (3H, s), 0.16 (3H, s), 0.17 (3H, s), 0.89 (9H, s), 0.95 (9H, s), 1.43 (9H, s), 3.33 (1H, t, *J*=3.2 Hz), 3.55 (1H, dd, *J*=2.8, 13.2 Hz), 3.83 (1H, dd, *J*=3.6, 6.8 Hz), 4.33 (1H, broad d, *J*=6.8 Hz), 4.40 (1H, d, *J*=9.2 Hz), 5.55 (1H, d, *J*=9.2 Hz); δ_C (CD_3OD) −5.1, −4.4, −4.3, −4.2, −3.4, −3.3, 18.9, 19.1, 26.5, 26.6, 28.7, 54.0, 56.2, 73.7, 74.8, 80.9, 157.7, 174.4; HRFABMS *m/z* 519.3056, calcd for $C_{22}H_{47}N_4O_6Si_2$ (M^++H) 519.3034.

4.3.7. Dipeptide 23. To a solution of **22** (99.2 mg, 0.19 mmol) and **10** (102 mg, 0.22 mmol) in DMF (1.5 mL) were added BOP reagent (92.2 mg, 0.20 mmol) and Et_3N (0.10 mL, 0.68 mmol) at 0 °C, the reaction mixture was stirred overnight. Work-up and purification by silica-gel column chromatography (8/1 hexane/EtOAc) gave **23** as an oil (140.1 mg, 85%): $[\alpha]_D^{20}$ +15.7 (*c* 1.0, $CHCl_3$); IR (film) 3434, 2103, 1671, 1477 cm^{-1}; δ_H 0.05 (3H, s), 0.13 (6H, s), 0.16 (3H, s), 0.83 (9H, s), 0.90 (9H, s), 1.44 (9H, s), 2.95 (2H, complex), 3.28 (1H, dd, *J*=4.4, 12.8 Hz), 3.40 (1H, dd, *J*=3.2, 12.8 Hz), 3.72 (3H, s), 3.75 (1H, m), 4.26 (1H, m), 4.35 (1H, m), 4.76 (1H, m), 5.41 (1H, d, *J*=6.8 Hz), 5.91 (1H, s), 7.13 (1H, d, *J*=7.2 Hz), 7.22 (2H, s); δ_C −5.1, −4.8, −4.6, −3.9, 18.0, 18.1, 25.9, 28.2, 36.8, 52.4, 53.1, 53.3, 55.2, 72.4, 80.3, 100.5, 109.7, 130.6, 132.5, 148.4, 155.8, 170.2, 171.0; HRFABMS *m/z* 852.2023, calcd for $C_{32}H_{56}{}^{79}Br_2N_5O_8Si_2$ (M^++H) 852.2034.

4.3.8. Tripeptide 24. To a solution of **23** (160.4 mg, 0.19 mmol) in CH_2Cl_2 (1 mL) was added TFA (1 mL) at 0 °C. After being stirred for 1 h, the mixture was evaporated. A mixture of the residue, **13** (112.3 mg, 0.210 mmol), BOP reagent (90.3 mg, 0.23 mmol) and Et_3N (0.10 mL, 0.71 mmol) in DMF (1.8 mL) was stirred overnight. Work-up and purification by silica-gel column chromatography (6/1 hexane/acetone) gave **24** as an oil (155 mg, 65% in 2 steps): $[\alpha]_D^{20}$ +5.1 (*c* 1.00, $CHCl_3$); IR (film) 3390, 2103, 1660, 1253 cm^{-1}; δ_H 0.01 (1H, s), 0.03 (3H, s), 0.11 (3H, s), 0.16 (3H, s), 0.84 (9H, s), 0.89 (9H, s), 1.43 (9H, s), 2.90 (1H, m), 2.93 (1H, dd, *J*=6.8, 13.2 Hz), 3.03 (1H, dd, *J*=6.8, 14 Hz), 3.10 (1H, m), 3.26 (1H, dd, *J*=3.2, 13 Hz),

3.41 (1H, dd, *J*=3.2, 13 Hz), 3.68 (1H, m), 3.73 (3H, s), 4.21 (1H, m), 4.33 (1H, d, *J*=6.8 Hz), 4.54 (1H, dd, *J*=2.4, 7.2 Hz), 4.76 (1H, m), 4.94 (1H, d, *J*=8.0 Hz), 5.71 (1H, s), 5.91 (1H, s), 6.90 (1H, d, *J*=7.8 Hz), 7.10 (1H, d, *J*=7.6 Hz), 7.22 (2H, s), 7.53 (2H, s); δ_C −4.9, −4.6, −3.8, 14.3, 18.0, 18.1, 21.1, 25.9, 26.8, 27.8, 28.3, 36.6, 52.5, 53.0, 53.5, 54.0, 55.7, 60.4, 71.7, 72.3, 80.5, 82.3, 109.9, 117.8, 132.6, 132.7, 140.0, 148.5, 152.5, 169.3, 1708, 171.0; HRFABMS *m/z* 1267.0624, calcd for $C_{41}H_{63}{}^{79}Br_2I_2N_6O_{10}Si_2$ (M^++H) 1267.0600.

4.3.9. Cyclic tripeptide 25. A mixture of **24** (149.5 mg, 0.12 mmol) and TTN (210 mg, 0.47 mmol) in THF (40 mL)–MeOH (10 mL) was stirred at 0 °C for 1 h. Work-up and purification by silica-gel column chromatography (4/1 hexane/EtOAc) gave **25** as an oil (85 mg, 63%): $[\alpha]_D^{20}$ +38.7 (*c* 1.00, $CHCl_3$); IR (film) 2103, 1681, 1486, 1255 cm^{-1}; δ_H −0.04 (3H, s), 0.08 (3H, s), 0.18 (3H, s), 0.37 (3H, s), 0.90 (9H, s), 1.00 (9H, s), 1.50 (9H, s), 2.41 (1H, t, *J*=12.8 Hz), 2.67 (1H, d, *J*=12.8 Hz), 3.23–3.40 (3H, complex), 3.53 (1H, dd, *J*=3.2, 12.8 Hz), 3.86 (3H, s), 3.91 (1H, m), 3.98 (1H, dd, *J*=3.2, 7.6 Hz), 4.27 (1H, m), 4.53 (1H, dd, *J*=2.8, 8.8 Hz), 4.92 (1H, m), 5.41 (1H, d, *J*=6.8 Hz), 5.87 (1H, d, *J*=1.6 Hz), 6.12 (1H, s), 6.18 (1H, d, *J*=8.8 Hz), 7.05 (1H, d, *J*=1.6 Hz), 7.19 (1H, d, *J*=2 Hz), 7.63 (1H, d, *J*=2 Hz); δ_C −5.3, −5.1, −5.0, −4.3, −3.3, 17.9, 18.0, 25.8, 26.2, 28.4, 36.7, 39.6, 52.8, 53.8, 72.5, 73.2, 79.5, 82.2, 114.0, 116.9, 117.3, 118.9, 128.2, 128.9, 133.9, 134.2, 134.3, 136.7, 142.6, 143.9, 147.0, 154.6, 167.5, 168.1, 170.9; HRFABMS *m/z* 1141.1490, calcd for $C_{41}H_{62}{}^{79}Br^{81}BrIN_6O_{10}Si_2$ (M^++H) 1141.1457.

4.3.10. Cyclic tripeptide 27. A mixture of **25** (73.2 mg, 0.064 mmol) and Ph_3P (52.5 mg, 0.2 mmol) in THF (0.7 mL)–H_2O (0.05 mL) was heated at 60 °C for 2 h. After evaporation, the residue was passed through silica-gel short column chromatography (2/1 hexane/$CHCl_3$). A mixture of the product, **26** (27.4 mg, 0.096 mmol) $HgCl_2$ (20.6 mg, 0.08 mmol), and Et_3N (0.03 mL, 0.21 mmol) in DMF (0.6 mL) was stirred at 0 °C for 1 h. Work-up and purification by silica-gel column chromatography (5/1 hexane/EtOAc) gave **27** as an oil (51.4 mg, 60%): δ_H 0.01–0.35 (12H, complex), 0.91 (9H,s), 1.03 (9H, s), 1.45 (27H, complex), 2.41 (1H, t, *J*=12.8 Hz), 2.66 (1H, d, *J*=14.0 Hz), 3.38 (4H, complex), 3.80 (1H, m), 3.83 (3H, s), 4.00 (1H, m), 4.23 (1H, m), 4.52 (1H, m), 4.93 (1H, m), 5.43 (1H, m), 5.92 (1H, s), 6.12 (1H, broad), 6.25 (1H, d, *J*=8.8 Hz), 7.03 (1H, s), 7.19 (1H, s), 7.53 (1H, m), 7.62 (1H, s), 8.55 (1H, d, *J*=7.0 Hz), 11.30 (1H, broad); δ_C −5.7, −5.3, −4.1, −4.0, 17.9, 25.8, 25.9, 26.1, 28.0, 28.3, 28.4, 28.5, 36.2, 39.7, 42.8, 52.8, 52.9, 53.8, 72.3, 72.6, 77.2, 79.0, 79.2, 82.1, 83.3, 113.9, 116.8, 118.8, 128.2, 128.9, 134.0, 134.2, 136.9, 142.6, 143.8, 146.9, 152.8, 154.4, 156.1, 163.2, 168.0, 170.6; HRFABMS *m/z* 1355.2855, calcd for $C_{52}H_{82}{}^{79}Br_2IN_6O_{14}Si_2$ (M^++H) 1355.2839.

4.3.11. Proposed eurypamide A 1. A solution of **27** (49 mg, 0.036 mmol) in MeOH (0.5 mL) containing catalytic amounts of 10% Pd/C and NaOAc (8.8 mg, 0.11 mmol) was stirred at ambient temperature overnight in a hydrogen atmosphere. The reaction mixture was filtered through a Celite pad, and evaporated. A mixture of the residue and TBAF (1 M in THF, 0.18 mL) in THF (0.6 mL) was stirred for 30 min. Work-up and purification by preparative TLC (1/2 hexane/EtOAc) gave a methyl ester (19.6 mg, 65%): $[\alpha]_D^{20}$ −23.9 (*c* 1.00, $CHCl_3$); IR (film) 3334, 1725, 1650, 1506, 1367, 1228, 1164 cm^{-1}; δ_H 1.43 (18H, complex), 1.50 (9H, s), 2.56 (1H, t, *J*=12 Hz), 2.83 (1H, dd, *J*=2, 14.4 Hz), 3.04 (1H, dd, *J*=6, 14 Hz), 3.26 (1H, m), 3.38 (1H, dd, *J*=3.6, 12.8 Hz), 3.62 (1H, d, *J*=9.2 Hz), 3.80 (3H, s), 4.42 (1H, m), 4.62 (1H, d, *J*=8.8 Hz), 4.90 (1H, m), 5.10 (1H, d, *J*=8.4 Hz), 5.78 (1H, s), 5.89 (1H, d, *J*=2 Hz), 6.55 (1H, dd, *J*=2, 8 Hz), 6.66 (1H, d, *J*=9.2 Hz), 6.85 (1H, d, *J*=8.0 Hz), 6.86 (1H, dd, *J*=2.4, 8.4 Hz), 6.90 (1H, d, *J*=8.4 Hz), 7.08 (2H, complex), 7.36 (1H, s), 7.40 (1H, dd, *J*=2, 8.0 Hz), 8.61 (1H, m), 11.4 (1H, s); δ_C 28.1, 28.2, 28.4, 37.4, 39.7, 43.3, 52.7, 53.3, 53.7, 53.8, 70.9, 71.1, 77.2, 79.6, 83.7, 114.6, 114.8, 121.5, 123.0, 124.1, 126.7, 128.2, 131.0, 132.0, 133.5, 144.2, 147.2, 152.7, 153.2, 155.1, 157.5, 162.1, 168.1, 171.0, 171.3; HRFABMS *m/z* 845.3948, calcd for $C_{40}H_{57}N_6O_{14}$ (M^++H) 845.3933.

To a solution of the protected **1** (19.6 mg, 0.023 mmol) in MeOH (0.3 mL) was added 1 M NaOH aq. (0.3 mL) at 0 °C. After being stirred for 30 min, the reaction was quenched by the addition of Amberlite IR 120B (H^+) and stirred for 15 min. The mixture was filtered, and the filtrate was evaporated. The residue was diluted with CH_2Cl_2 (0.5 mL), and TFA (0.5 mL) was added to the mixture at 0 °C. After being stirred for 2 h, the mixture was treated with essentially the same procedure as in the case of **2** to give (3*S*,4*R*)-**1** as an oil (15 mg, quant): $[\alpha]_D^{20}$ −17.8 (*c* 0.23, MeOH); IR (film) 3280, 1670, 15081438, 1203 cm^{-1}; δ_C (CD_3OD) 36.9, 39.7, 45.8, 53.9, 55.1, 55.4, 71.4, 74.2, 116.6, 117.1, 122.6, 123.5, 124.5, 124.9, 131.9, 133.0, 135.8, 147.2, 149.7, 154.7, 159.6, 169.3, 170.4, 174.8; HRFABMS *m/z* 531.2178, calcd for $C_{24}H_{31}N_6O_8$ (M^++H) 531.2203.

4.4. Synthesis of (3″*R*,4″*S*)-eurypamide A 47

4.4.1. 4-Azido-4-deoxy-2,3,5-tri-*O*-benzyl-1-*O*-*tert*-butyldimethylsilyl-D-ribitol 29. A mixture of **28** (6.14 g, 11 mmol), Ph_3P (4.48 g, 17 mmol), DPPA (3.5 mL, 17 mmol), and DEAD (7.5 mL, 17 mmol) in THF (80 mL) was stirred at ambient temperature for 2 h. Evaporation and purification by silica-gel column chromatography (15/1 hexane/EtOAc) gave **29** as an oil (5.9 g, 92%): IR (film) 2096, 1455, 1255 cm^{-1}; δ_H 0.05 (6H, s), 0.90 (9H, s), 3.67 (3H, complex), 3.76 (1H, dd, *J*=5.2, 10.8 Hz), 3.89 (1H, dd, *J*=4, 10.8 Hz), 3.97 (1H, m), 4.47 (1H, d, *J*=12 Hz), 4.50 (1H, d, *J*=12 Hz), 4.53 (1H, d, *J*=12 Hz), 4.63 (2H, s), 4.70 (1H, d, *J*=12 Hz), 7.35 (15H, complex); δ_C −5.2, 18.4, 26.0, 62.1, 62.3, 70.0, 72.4, 73.2, 73.9, 78.2, 79.4, 127.5, 127.6, 127.7, 127.9, 128.2, 137.8, 137.9, 138.1; HREIMS *m/z* 562.3121, calcd for $C_{32}H_{43}N_3O_4Si$ (M^++H) 562.3101.

4.4.2. 4-(*N*-*tert*-Butoxycarbonyl)amino-4-deoxy-2,3,5-tri-*O*-benzyl-1-*O*-*tert*-butyldimethylsilyl-D-ribitol 30. A mixture of **29** (1.91 g, 3.4 mmol) and Ph_3P (2.72 g, 10.2 mmol) in THF (30 mL)–H_2O (3 mL) was heated at 60 °C for 2 h. After evaporation, the residue was dissolved in H_2O (10 mL)–1,4-dioxane (30 mL), $NaHCO_3$ (0.87 g, 10.2 mmol) and Boc_2O (1.2 mL, 5.1 mmol) were added at 0 °C. After being stirred for 1 h, the mixture was partitioned

between EtOAc and H_2O. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by silica-gel column chromatography (50/1–10/1 hexane/EtOAc) to give **30** as an oil (1.99 g, 92%): $[\alpha]_D^{20}$ +3.4 (*c* 1.00, $CHCl_3$); IR (film) 3444, 1716, 1496, 1454, 1365, 1251, 1170 cm^{-1}; δ_H 0.09 (3H, s), 0.10 (3H, s), 0.94 (9H, s), 1.46 (9H, s), 3.54 (1H, d, *J*=4.4, 9.2 Hz), 3.70 (2H, complex), 3.85 (2H, complex), 4.00 (1H, m), 4.11 (1H, s), 4.47 (2H, complex), 4.61 (2H, complex), 4.77 (2H, complex), 5.04 (1H, d, *J*=8.8 Hz), 7.27–7.39 (15H, complex); δ_C −5.3, 18.3, 26.0, 28.4, 50.8, 62.7, 69.3, 72.4, 72.9, 73.5, 78.3, 79.0, 80.5, 100.4, 127.3, 127.4, 127.5, 127.6, 127.8, 128.1, 128.2, 138.1, 138.4, 138.6, 155.3; HREIMS *m/z* 635.3735, calcd for $C_{37}H_{53}NO_6Si$ (M^+) 635.3642.

4.4.3. 4-(*N*-*tert*-Butoxycarbonyl)amino-4-deoxy-1-*O*-*tert*-butyldimethylsilyl-5-*O*-pivaloyl-D-ribitol 32. A solution of **30** (2.18 g, 3.4 mmol) in EtOH (40 mL) containing catalytic amounts of 10% Pd/C was stirred for 30 min at ambient temperature in a hydrogen atmosphere. The reaction mixture was passed through a Celite pad, and evaporated. A mixture of crude **31** and pivaloyl chloride (0.5 mL, 3.83 mmol) in pyridine (15 mL) was stirred at ambient temperature for 1 day. Work-up and purification by silica-gel column chromatography (4/1–1/1 hexane/EtOAc) gave **32** as an oil (1.02 g, 66%): $[\alpha]_D^{20}$ −1.3 (*c* 1.00, $CHCl_3$); IR (film) 3384, 1716, 1508, 1253 cm^{-1}; δ_H 0.10 (6H, s), 0.90 (9H, s), 1.21 (9H, s), 1.43 (9H, s), 2.81 (1H, d, *J*=5.2 Hz), 3.50 (1H, d, *J*=5.6 Hz), 3.68 (2H, complex), 3.85 (2H, complex), 4.02 (1H, m), 4.25 (1H, dd, *J*=4, 11.2 Hz), 4.38 (1H, m), 4.93 (1H, d, *J*=8.8 Hz); δ_C −5.4, 18.3, 25.9, 27.2, 28.4, 38.9, 52.4, 63.6, 64.6, 70.9, 73.7, 79.9, 156.0, 178.5; HREIMS *m/z* 450.2903, calcd for $C_{21}H_{44}NO_7Si$ (M^++H) 450.2896.

4.4.4. 4-(*N*-*tert*-Butoxycarbonyl)amino-4-deoxy-1,2,3-tri-*O*-*tert*-butyldimethylsilyl-5-*O*-pivaloyl-D-ribitol 33. To a solution of **32** (0.82 g, 1.8 mmol) in CH_2Cl_2 (15 mL) was added 2,6-lutidine (1.3 mL, 11 mmol) and TBDMSOTf (1.1 mL, 5.5 mmol) at 0 °C; the mixture was stirred at 0 °C for 1 h. Work-up and purification by silica-gel column chromatography (10/1 hexane/EtOAc) gave **33** as an oil (1.1 g, 89%): $[\alpha]_D^{20}$ +6.1 (*c* 1.0, $CHCl_3$); IR (film) 3376, 1722, 1654, 1500, 1463, 1386, 1365, 1255, 1151 cm^{-1}; δ_H 0.10 (18H, complex), 0.90 (27H, complex), 1.19 (9H, s), 1.41 (9H, s), 3.47 (1H, m), 3.73 (2H, complex), 3.92 (1H, d, *J*=6.8 Hz), 4.09 (1H, m), 4.21 (2H, m), 5.11 (1H, d, *J*=12 Hz); HREIMS *m/z* 678.4587, calcd for $C_{33}H_{72}NO_7Si_3$ (M^++H) 678.4616. Found: C, 58.60; H, 10.38; N, 2.02. Calcd for $C_{33}H_{71}NO_7Si_3$: C58.44; H, 10.55; N, 2.07.

4.4.5. 4-(*N*-*tert*-butoxycarbonyl)amino-4-deoxy-1,2,3-tri-*O*-*tert*-butyldimethylsilyl-D-ribitol 34. A mixture of **33** (1.13 g, 1.7 mmol) DIBAL-H (5 mL, 1 M in toluene) in CH_2Cl_2 (10 mL) was stirred for 2 h at −78 °C. Work-up and purification by silica-gel column chromatography (10/1–4/1 hexane/EtOAc) to give **34** as an oil (0.91 g, 92%): $[\alpha]_D^{20}$ +6.2 (*c* 1.00, $CHCl_3$); IR (film) 3406, 1698 cm^{-1}; δ_H 0.08 (18H, complex), 0.89, (9H, s), 0.90, (9H, s), 0.91 (9H, s), 1.43 (9H, s), 3.01 (1H, m), 3.48 (1H, m), 3.65 (2H, complex), 3.80 (2H, complex), 3.98 (1H, m), 4.05 (1H, s), 5.47 (1H, d, *J*=7.6 Hz); δ_C −5.3, −5.0, −4.6, −4.4, −3.9, 18.2, 18.4, 26.0, 28.4, 53.4, 63.8, 64.3, 75.4, 79.1, 155.2; HREIMS *m/z* 594.4051, calcd for $C_{28}H_{64}NO_6Si_3$ (M^++H) 594.4041.

4.4.6. Oxazolidinone 35. To a solution of **34** (0.84 g, 1.4 mmol) in THF (15 mL) was added NaH (111 mg, 60% dispersion in mineral oil, 2.8 mmol) at 0 °C; the mixture was stirred overnight. The reaction was quenched by the addition of saturated NH_4Cl aq., and extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. A mixture of the residue, Et_3N (0.6 mL, 4.2 mmol), DMAP (catalytic amount), and Boc_2O (0.5 mL, 2.1 mmol) in THF (10 mL) was stirred for 1 h. Work-up and purification by silica-gel column chromatography (8/1 hexane/EtOAc) gave **35** as an oil (0.75 g, 86%): $[\alpha]_D^{20}$ +36.5 (*c* 1.00, $CHCl_3$); IR (film) 1797, 1720 cm^{-1}; δ_H 0.09 (18H, complex), 0.03 (3H, s), 0.90 (9H, s), 0.09 (3H, s), 0.10 (3H, s), 0.87 (9H, s), 0.90 (18H, s), 1.53 (9H, s), 3.45 (1H, dd, *J*=4.8, 10.4 Hz), 3.53 (1H, t, *J*=10.4 Hz), 3.71 (1H, dd, *J*=4.0, 8.4 Hz), 4.15 (1H, t, *J*=8.8 Hz), 4.35 (1H, s), 4.45 (1H, dd, *J*=4.0, 9.2 Hz), 4.65 (1H, dd, *J*=4.0, 8.4 Hz); δ_C −5.33, −5.31, −5.1, −4.8, −4.3, −4.2, 17.8, 18.0, 18.3, 25.9, 26.0, 27.4, 28.0, 55.7, 62.8, 64.1, 71.4, 77.9, 83.5, 85.2, 149.5, 152.5; HREIMS *m/z* 620.3794, calcd for $C_{29}H_{62}NO_7Si_3$ (M^++H) 620.3834.

4.4.7. Alcohol 36. To a solution of **35** (377.4 mg, 0.61 mmol) in MeOH (5 mL) was added catalytic amounts of CSA at 0 °C; the mixture was stirred for 3 h. Work-up and purification by silica-gel column chromatography (4/1 hexane/EtOAc) gave **36** as an oil (206 mg, 67%): $[\alpha]_D^{20}$ +58.9 (*c* 1.00, $CHCl_3$); IR (film) 3502, 1808, 1720, 1654, 1471, 1384, 1371, 1255 cm^{-1}; δ_H 0.04 (3H, s), 0.09 (6H, s), 0.11 (3H, s), 0.89 (9H, s), 0.90 (9H, s), 1.55 (9H, s), 2.21 (1H, dd, *J*=5, 8 Hz), 3.61 (2H, complex), 3.74 (1H, m), 4.18 (1H, t, *J*=12 Hz), 4.34 (1H, d, *J*=3.6 Hz), 4.63 (2H, complex); δ_C −5.0, −4.7, −4.4, −4.3, 17.9, 18.0, 25.8, 28.0, 55.6, 62.2, 63.7, 70.9, 76.0, 84.2, 150.1, 152.0; HREIMS *m/z* 506.2983, calcd for $C_{23}H_{48}NO_7Si_2$ (M^++H) 506.2969.

4.4.8. Azide 37. To a solution of **36** (309 mg, 0.61 mmol) in pyridine (4 mL) was added MsCl (0.1 mL, 1.3 mmol) at 0 °C. After being stirred for 2 h at the same temperature, the mixture was partitioned between EtOAc and H_2O. The organic layer was washed with 5% $KHSO_4$ aq. and brine, dried (Na_2SO_4), and evaporated. A mixture of the residue and NaN_3 (330 mg, 5.7 mmol) in DMF (1.0 mL) was heated at 70 °C overnight. Work-up and purification by silica-gel column chromatography (6/1 hexane/EtOAc) gave **37** as an oil (254 mg, 80%): $[\alpha]_D^{20}$ +29.0 (*c* 0.50, $CHCl_3$); IR (film) 2103, 1818, 1718, 1654, 1461, 1371, 1326, 1257, 1159, 1093 cm^{-1}; δ_H 0.05 (3H, s), 0.09 (3H, s), 0.11 (3H, s), 0.13 (3H, s), 0.90 (18H, s), 1.55 (9H, s), 3.28 (1H, dd, *J*=4.4, 8.8 Hz), 3.41 (1H, dd, *J*=6.8, 12.8 Hz), 3.72 (1H, m), 4.18 (1H, t, *J*=8.8 Hz), 4.23 (1H, d, *J*=2.4 Hz), 4.51 (1H, dd, *J*=4.4, 8.8 Hz), 4.59 (1H, dd, *J*=4.4, 8.8 Hz); δ C −5.0, −4.5, −4.4, −4.3, 18.0, 25.8, 28.0, 49.9, 53.6, 55.7, 62.1, 71.4, 75.0, 84.0, 149.3; HREIMS *m/z* 531.3054, calcd for $C_{23}H_{47}N_4O_6Si_2$ (M^++H) 531.3034.

4.4.9. Primary alcohol 38. To a solution of **37** (254 mg, 0.48 mmol) in MeOH (4 mL) was added Cs_2CO_3 (catalytic amount) at 0 °C; the mixture was stirred for 6 h. Work-up

and purification by silica-gel column chromatography (5/1–2/1 hexane/EtOAc) gave **38** as an oil (204 mg, 85%): $[\alpha]_D^{20}$ +1.6 (*c* 1.00, $CHCl_3$); IR (film) 3382, 2102, 1652, 1457, 1257, 1056 cm^{-1}; δ_H 0.12 (6H, s), 0.14 (3H, s), 0.15 (3H, s), 0.90 (9H, s), 0.92 (9H, s), 1.44 (9H, s), 2.47 (1H, m), 3.29 (1H, dd, *J*=6.8, 12.8 Hz), 3.54 (1H, dd, *J*=3.2, 12.8 Hz), 3.65 (2H, complex), 3.84 (1H, m), 3.90 (1H, m), 4.02 (1H, m), 5.18 (1H, d, *J*=8.0 Hz); δ_C −5.1, −4.4, −3.9, 18.1, 18.3, 25.9, 26.0, 28.4, 52.6, 53.7, 62.4, 73.9, 76.4, 79.6, 155.4; HREIMS *m/z* 505.3230, calcd for $C_{22}H_{49}N_4O_5Si_2$ (M^++H) 505.3241.

4.4.10. Amino acid 39. To a solution of **38** (204 mg, 0.4 mmol) in acetone (2 mL) and 5% $NaHCO_3$ aq. (1.5 mL) were added TEMPO (catalytic amount), KBr (111.1 mg, 0.93 mmol), and 8% NaClO aq. (1 mL, 1.6 mmol). After being stirred for 4 h, Work-up and purification by silica-gel column chromatography (2/1 hexane/EtOAc–10/1 $CHCl_3$/MeOH) gave **39** as an oil (177.4 mg, 85%): $[\alpha]_D^{20}$ +1.0 (*c* 1.00, MeOH); IR (film) 2102, 1716, 1384, 1367, 1255 cm^{-1}; δ_H (CD_3OD) 0.12 (3H, s), 0.15 (3H, s), 0.17 (3H, s), 0.18 (3H, s), 0.88 (9H, s), 0.95 (9H, s), 1.45 (9H, s), 3.55 (1H, dd, *J*=2.8, 13.2 Hz), 3.98 (1H, m), 4.05 (1H, m), 4.32 (1H, m), 6.59 (1H, dd, *J*=8.8 Hz); δ_C (CD_3OD) −4.8, −4.2, −4.1, −3.8, 19.1, 26.5, 26.6, 28.7, 54.6, 57.7, 74.3, 61.5, 77.4, 80.7, 157.0, 172.9; HRFABMS *m/z* 519.3066, calcd for $C_{22}H_{47}N_4O_6Si_2$ (M^++H) 519.3034.

4.4.11. Dipeptide 40. A mixture of **39** (52.9 mg, 0.1 mmol), **10** (71.8 mg, 0.16 mmol), BOP reagent (66.5 mg, 0.16 mmol), and Et_3N (0.05 mL, 0.34 mmol) in DMF (1.5 mL) was stirred overnight. Work-up and purification by silica-gel column chromatography (8/1 hexane/EtOAc) gave **40** as an oil (70.4 mg, 81%): $[\alpha]_D^{20}$ +12.2 (*c* 1.00, $CHCl_3$); δ_H 0.06 (3H, s), 0.12 (3H, s), 0.13 (3H, s), 0.16 (3H, s), 0.84 (9H, s), 0.93 (9H, s), 1.46 (9H, s), 2.99 (2H, complex), 3.17 (1H, dd, *J*=7.2, 12 Hz), 3.44 (1H, dd, *J*=4, 12 Hz), 3.71 (3H, s), 3.86 (1H, m), 4.12 (1H, broad d, *J*=6.4 Hz), 4.23 (1H, t, *J*=7 Hz), 4.72 (1H, dd, *J*=6.4, 14 Hz), 5.68 (1H, d, *J*=8 Hz), 5.85 (1H, s), 6.81 (1H, d, *J*=7.2 Hz), 7.23 (2H, s); δ_C −5.3, −4.7, −4.4, −4.1, 18.1, 25.6, 25.8, 25.9, 26.0, 28.3, 29.7, 37.0, 52.5, 53.3, 53.4, 58.0, 70.4, 74.6, 83.9, 109.8, 130.4, 132.5, 148.5, 169.7, 170.8; HRFABMS *m/z* 854.2011, calcd for $C_{32}H_{56}{}^{79}Br^{81}BrN_5O_8Si_2$ (M^++H) 854.2014.

4.4.12. Tripeptide 41. To a solution of **40** (106.8 mg, 0.13 mmol) in THF (1.5 mL) was added TBAF (1 M in THF, 0.5 mL) at 0 °C; the mixture was stirred for 30 min. The reaction mixture was partitioned between EtOAc and H_2O. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. A mixture of the residue and TFA (0.8 mL) in CH_2Cl_2 (0.8 mL), was stirred at 0 °C for 30 min, and evaporated. A mixture of the residue, **13** (130.6 mg, 0.25 mmol), EDC (46.2 mg, 0.24 mmol), HOBt (32.9 mg, 0.24 mmol) and Et_3N (0.08 mL, 0.61 mmol) in DMF (1.5 mL) was stirred overnight. Work-up and purification by silica-gel column chromatography (20/1 hexane/EtOAc) gave **41** as an oil (109.4 mg, 85%): $[\alpha]_D^{20}$ +0.4 (*c* 1.00, MeOH); IR (film) 3332, 2100, 1637, 1457, 1245, 1159 cm^{-1}; δ_H (CD_3OD) 1.39 (9H, s), 2.65 (1H, dd, *J*=8.4, 14 Hz), 2.85–2.98 (2H, complex), 3.04 (1H, dd, *J*=6.0, 14 Hz), 3.35 (1H, dd, *J*=6.0, 13.2 Hz), 3.50 (1H, m), 3.71 (3H, s), 3.74 (2H, complex), 4.25 (1H, m), 4.67 (2H, complex), 7.34 (2H, s), 7.63 (2H, s); δ_C (CD_3OD) 28.5, 28.7, 36.9, 52.9, 54.9, 55.0, 55.9, 57.1, 72.4, 73.7, 80.9, 85.1, 85.2, 112.0, 131.9, 134.1, 134.6, 141.3, 141.4, 151.1, 157.6, 170.9, 172.3, 173.4; HRFABMS *m/z* 1038.8856, calcd for $C_{29}H_{35}{}^{79}Br_2I_2N_6O_{10}$ (M^++H) 1038.8871.

4.4.13. Tripeptide 43. To a solution of **41** (30 mg, 0.03 mmol) in CH_2Cl_2 (3 mL) were added 2,6-lutidine (0.10 mL, 0.86 mmol) and TBDMSOTf (0.07 mL, 0.31 mmol) at 0 °C; the mixture was stirred at 0 °C for 1 h. The reaction was quenched by the addition of 5% $KHSO_4$ aq., and extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. A mixture of the residue and K_2CO_3 in MeOH (2 mL) was stirred for 2 h. Work-up and purification by silica-gel column chromatography (4/1 hexane/EtOAc) gave **43** as an oil (21.8 mg, 60%): $[\alpha]_D^{20}$ +6.8 (*c* 1.00, $CHCl_3$); IR (film) 3363, 2103, 1662, 1475, 1251, 1160 cm^{-1}; δ_H 0.09 (12H, complex), 0.82 (9H, s), 0.92 (9H, s), 1.44 (9H, s), 2.80 (1H, m), 2.91 (1H, dd, *J*=6.4, 13.2 Hz), 3.05 (2H, complex), 3.27 (1H, dd, *J*=6.8, 13.2 Hz), 3.54 (1H, dd, *J*=5.2, 12 Hz), 3.71 (3H, s), 3.74 (1H, m), 3.79 (1H, m), 4.06 (1H, broad d, *J*=4.4 Hz), 4.28 (1H, m), 4.56 (1H, dd, *J*=6.8, 8.4 Hz), 4.69 (1H, m), 4.84 (1H, d, *J*=7.2 Hz), 5.68 (1H, s), 5.87 (1H, s), 6.76 (1H, d, *J*=8.0 Hz), 7.02 (1H, d, *J*=8.0 Hz), 7.23 (2H, s), 7.53 (2H, s); δ_C −5.0, −4.6, −4.2, −4.1, 18.1, 18.2, 25.8, 26.0, 28.3, 36.9, 52.6, 52.8, 55.9, 73.0, 75.3, 80.8, 82.4, 109.9, 130.6, 132.6, 139.7, 139.8, 148.4, 152.6, 168.5, 170.5, 170.7; HRFABMS *m/z* 1266.0578, calcd for $C_{41}H_{63}{}^{79}Br_2I_2N_6O_{10}Si_2$ (M^++H) 1266.0600.

4.4.14. TTN oxidation of 41. A mixture of **41** (11 mg, 0.01 mmol) and TTN (30 mg, 0.06 mmol) in MeOH (1 mL)–THF (4 mL) was stirred at 0 °C for 4 h. Work-up and purification by preparative TLC (1/3 hexane/EtOAc) gave **44** as an oil (3.4 mg, 33%); δ_H 1.41 (9H, s), 1.98 (1H, broad d, *J*=14 Hz), 2.20 (1H, m), 2.59 (1H, t, *J*=12 Hz), 3.24 (3H, s), 3.85 (3H, s), 5.25 (1H, broad s), 7.34 (1H, broad s), 7.41 (1H, d, *J*=2 Hz), 7.53 (1H, broad s).

4.4.15. TTN oxidation of 42. A mixture of **41** (12.2 mg, 0.01 mmol) and 2,2-dimethoxypropane (0.1 mL) in DMF (0.5 mL) in the presence of catalytic amounts of TsOH was heated at 65 °C for 3.5 h: work-up gave **42** (6 mg, 47%). A mixture of **42** (7.8 mg, 0.007 mmol) and TTN (30 mg, 0.06 mmol) in MeOH (1 mL)–THF (4 mL) was stirred at 0 °C for 1 h. Work-up and purification by preparative TLC (20/1 $CHCl_3$/MeOH) gave **45** as an oil (1.8 mg, 25%); δ_H 1.40 (3H, s), 1.44 (9H, s), 1.66 (3H, s), 3.24 (3H, s), 3.84 (3H, s), 5.19 (1H, d, *J*=2.8 Hz), 6.42 (1H, d, *J*=10 Hz), 7.32 (1H, d, *J*=2 Hz), 7.40 (1H, d, *J*=2.8 Hz), 7.57 (1H, d, *J*=2 Hz).

4.4.16. Cyclic tripeptide 46. To a solution of **43** (57.9 mg, 0.046 mmol) in THF (20 mL) and MeOH (5 mL) was added TTN (57.8 mg, 0.13 mmol) at 0 °C; the mixture was stirred for 1 h. Work-up and purification by silica-gel column chromatography (4/1 hexane/EtOAc) gave **46** as an oil (29.0 mg, 56%): $[\alpha]_D^{20}$ +2.8 (*c* 1.00, $CHCl_3$); IR (film) 3374, 2103, 1671, 1455, 1255, 1106 cm^{-1}; δ_H 0.08 (6H, complex), 0.24 (6H, complex), 0.82 (9H, s), 1.00 (9H, s), 1.49 (9H, s), 2.56 (1H, t, *J*=12.8 Hz), 2.68 (1H, d,

J=12.8 Hz), 3.29 (2H, complex), 3.44 (1H, m), 3.80 (3H, s), 3.84 (2H, complex), 4.31 (1H, m), 4.56 (1H, d, J= 7.6 Hz), 4.99 (1H, m), 5.40 (1H, d, J=6.4 Hz), 5.72 (1H, d, J=1.6 Hz), 6.05 (1H, s), 6.64 (1H, d, J=7.2 Hz), 6.88 (1H, d, J=10 Hz), 7.09 (1H, s), 7.26 (1H, overlapped with solvent signal), 7.58 (1H, d, J=2 Hz); δ_C −4.5, −4.4, −4.0, −3.5, 18.1, 18.4, 25.6, 26.2, 28.4, 28.5, 36.3, 38.6, 52.8, 52.9, 53.8, 75.1, 76.4, 79.6, 82.6, 113.5, 116.9, 118.7, 128.8, 133.6, 134.4, 134.6, 136.9, 143.9, 146.9, 154.8, 166.9, 167.9, 170.7; HRFABMS m/z 1139.1438, calcd for $C_{41}H_{62}{}^{79}Br_2IN_6O_{10}Si_2$ (M^++H) 1139.1409.

4.4.17. (3″*R*,4″*S*)-Eurypamide A 47. To a solution of **46** (58.4 mg, 0.051 mmol) in THF (1 mL) and H_2O (0.1 mL) was added Ph_3P (40.7 mg, 0.2 mmol) at ambient temperature; the mixture was heated at 60 °C for 2 h. After evaporation, the residue was purified by silica-gel short column chromatography (30/1 $CHCl_3$/MeOH). A mixture of an amine, **26** (30.7 mg, 0.11 mmol), Et_3N (0.03 mL, 0.21 mmol), and $HgCl_2$ (28.6 mg, 0.11 mmol) in DMF (1 mL) was stirred at 0 °C for 1 h. The reaction mixture was diluted with EtOAc and H_2O, and filtered through a Celite pad. The filtrate was extracted with EtOAc, washed with brine, dried (Na_2SO_4), and evaporated. The residue was dissolved in MeOH (0.5 mL), containing catalytic amounts of 10% Pd/C and NaOAc (12.5 mg, 0.153 mmol), and the mixture was stirred at ambient temperature overnight in a hydrogen atmosphere. The reaction mixture was filtered through a Celite pad, and evaporated. To the residue in THF (0.6 mL) was added TBAF (1 M in THF, 0.18 mL) at 0 °C. After being stirred for 30 min, the mixture was partitioned between EtOAc and H_2O, and the organic layer was washed with brine. The organic layer was dried (Na_2SO_4), and evaporated. The residue was purified by preparative TLC (1/2 hexane/EtOAc) to give the corresponding methyl ester.

A mixture of the methyl ester (8.8 mg, 0.011 mmol) and 1 M NaOH aq. (0.3 mL) in MeOH (0.3 mL) was stirred at 0 °C for 30 min. After the addition of Amberlite IR 120B (H^+), the mixture was filtered. The filtrate was evaporated to give a residue, which was treated at 0 °C with TFA (0.5 mL) in CH_2Cl_2 (0.5 mL) for 2 h. Evaporation gave **47** as an oil (4.0 mg, 82%): $[\alpha]_D^{20}$ −20.5 (c 0.23, MeOH); IR (film) 3390, 1671, 1506, 1428, 1274, 1203 cm^{-1}; δ_H (CD_3OD) 2.67 (1H, t, J=12.7 Hz), 2.96 (1H, dd, J=6, 15 Hz), 3.20 (1H, d, J=15 Hz), 3.34 (1H, dd, J=6.8, 12.4 Hz), 3.44–3.48 (2H, complex), 3.68 (1H, dd, J=4.5, 8 Hz), 3.85 (1H, m), 4.12 (1H, d, J=6 Hz), 4.70 (1H, d, J=4.5 Hz), 4.74 (1H, dd, J=3, 12 Hz), 5.95 (1H, d, J=2 Hz), 6.67 (1H, dd, J=2, 8 Hz), 6.84 (1H, d, J=8 Hz), 6.88 (1H, dd, J=2, 8 Hz), 7.03 (1H, dd, J=2, 8 Hz), 7.20 (1H, dd, J=2, 8 Hz), 7.42 (1H, dd, J=2, 8 Hz); HRFABMS m/z 531.2180, calcd for $C_{24}H_{31}N_6O_8$ (M^++H) 531.2203.

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