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Tetrahedron Letters 44 (2003) 7949–7952

TETRAHEDRON LETTERS

Synthesis and structural revision of eurypamides isolated from the Palauan sponge *Microciona eurypa*

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Received 25 July 2003; revised 25 August 2003; accepted 29 August 2003

Abstract—Eurypamides A and B, **1** and **2**, were successfully synthesized by employing $Tl(NO_3)_3$ (TTN) oxidation of the corresponding halogenated phenols, **9**, **16**, and **26**. This investigation revealed that the dihydroxyarginine residue of **1** should be revised to possess (2*S*,3*R*,4*S*)-configuration. In addition, the synthesis of **2** provided a pure sample, which was previously characterized in a mixture.

Eurypamides A–D, **1**–**4**, isolated from the Palauan sponge *Microciona eurypa*,[1] are typical members of such cyclic isodityrosines, as vancomycin, K-13, and OF-4949s. Eurypamide A **1** consists of isodityrosine and a novel dihydroxyarginine: the stereochemistry of the (3*S*,4*R*)-dihydroxyl unit was deduced from theoretical calculation. The other three congeners were unfortunately not separated, and their structures were determined by direct spectroscopic measurement of a mixture, although the pure data of **3** carrying L-serine, were obtained from a synthetic sample[2] (Fig. 1).

In contrast to diverse biological activities of the cyclic isodityrosines involving antimicrobial, cytotoxic, and enzyme-inhibitory activities, eurypamides have been reported not to have such activities. Against this background, we initiated study of the chemistry of the eurypamides, as part of our extensive investigation of the isodityrosine-class natural products from the standpoints of synthetic methodology employing phenolic oxidation, as well as molecular recognition related to MRSA.[3] We describe herein the findings obtained in the synthesis of eurypamides A and B, **1** and **2**.

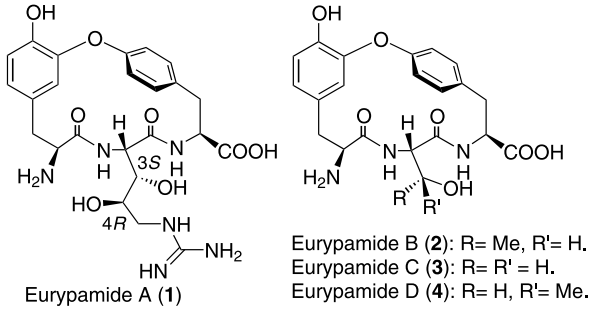

Figure 1. Proposed structures of eurypamides.

Synthesis of eurypamide B 2. At the outset, a synthesis of eurypamide B **2**, was performed to confirm the feasibility of our phenolic oxidation approach employing TTN as an oxidant.[3] In addition, the synthetic sample obtained would contribute to assessment of its biological activities. Thus, the dibromotyrosine derivative **5**[4] was coupled with Boc-L-threonine **6** under BOP conditions to give dipeptide **7**, which on connection with the diiodotyrosine **8**[5] gave the desired tripeptide **9** (Scheme 1).

The TTN oxidation of **9** in THF–MeOH effected the cyclization to give the 17-membered ring product **10** in 50% yield:[6] the required cyclization mode was confirmed by an EI mass spectrum indicating the existence of two bromines and one iodine, along with the high-field shift (δ 5.77) of the aromatic proton signal (*) by the anisotropy effect of another aromatic ring in its ^1H NMR spectrum. Compound **10** was submitted to hydrogenolysis, followed by successive alkaline and TFA treatments to provide eurypamide B **2**[7] in good overall yield. Amino acid analysis of a crude product of the acid hydrolysis of **2** clearly indicated the existence

Keywords: *Microciona eurypa*; isodityrosine; phenolic oxidation; thallium(III) nitrate; dihydroxyarginine.
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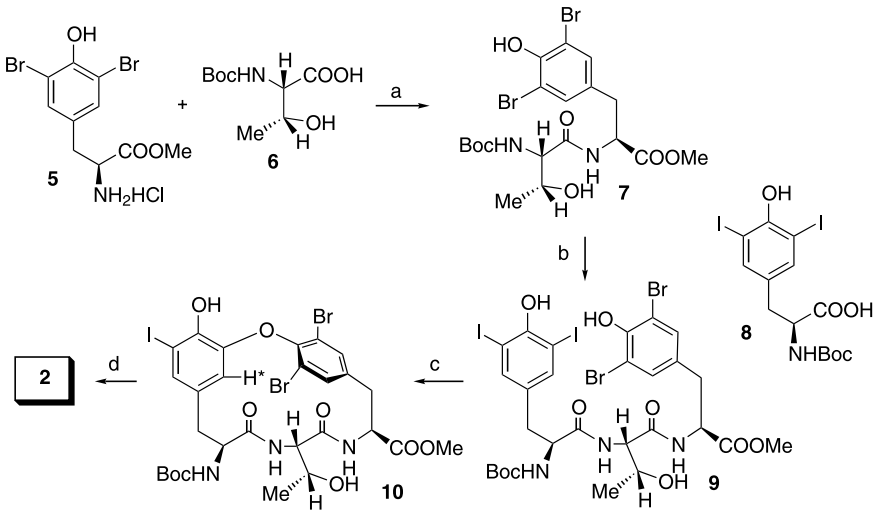
doi:10.1016/j.tetlet.2003.08.105

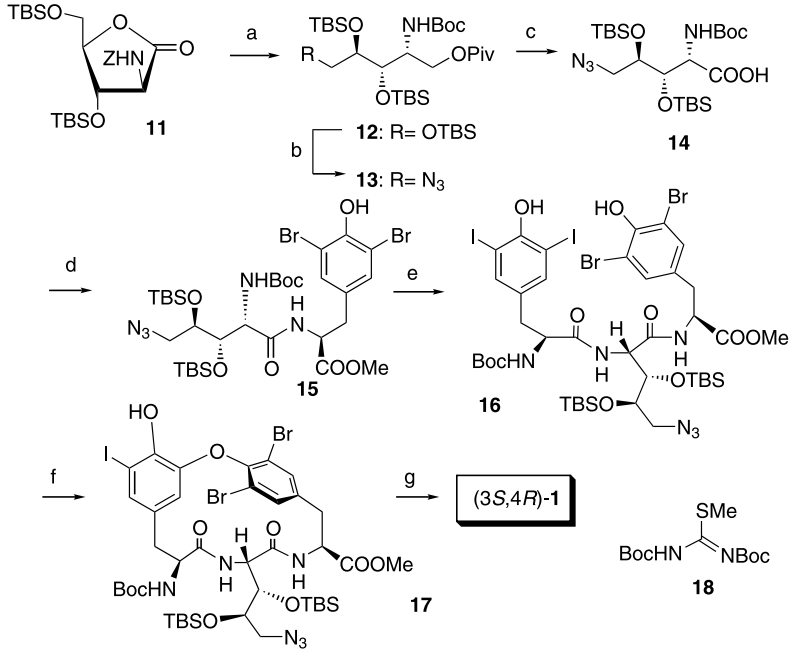


Scheme 1. *Reagents and conditions*: a. BOP, Et_3N/DMF, 90%. b. i) TFA/CH_2Cl_2; ii) **8**, BOP, Et_3N/DMF, 39% in two steps. c. TTN/MeOH–THF (1:4), 50%. d. i) H_2, NaOAc, 10% Pd–C/MeOH, 82%; ii) 1 M aq. NaOH/MeOH, 98%; iii) TFA/CH_2Cl_2, quant.

of L-threonine: the phenolic oxidation of **9** carrying a relatively labile L-threonine residue, gave rise to cyclization without serious racemization and/or elimination reactions. These results prompted us to undertake the synthesis of eurypamide A **1**.

Synthesis of eurypamide A 1. The synthesis commenced with preparation of the appropriately protected (3*S*,4*R*)-dihydroxyarginine derivative, from which the tripeptide sequence of **1** was constructed by essentially the same procedure as **2** (Scheme 2).

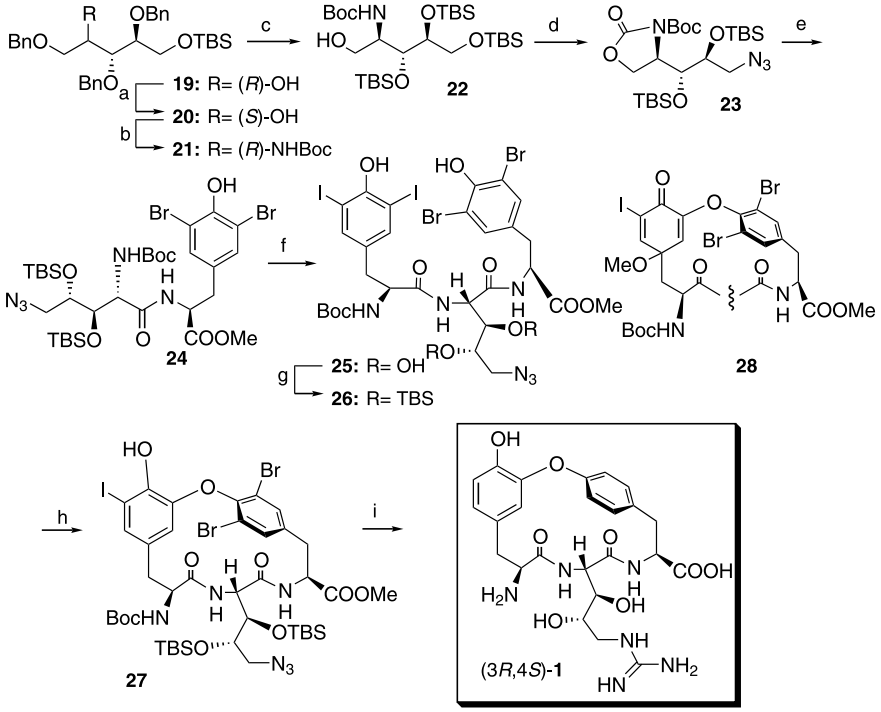
Thus, the optically active **11**, obtained by condensation of 2,3-*O*-isopropylidene-D-glyceraldehyde with methyl isocyanoacetate,[8] was converted into **12**. A TBS group at the terminal position was selectively removed, followed by esterification and azidation to give **13**, which on successive DIBAL reduction and TEMPO oxidation



Scheme 2. *Reagents and conditions*: a. i) DIBAL-H/CH_2Cl_2; ii) $NaBH_4$/MeOH, 84% in two steps; iii) PivCl, pyr., 80%; iv) TBSOTf, 2,6-lutidine/CH_2Cl_2, 85%; v) H_2, 10% Pd–C/MeOH; vi) Boc_2O, $NaHCO_3$/aq. dioxane, 100% in two steps. b. i) PPTS/MeOH, 62%; ii) MsCl, pyr.; iii) NaN_3/DMF, 79% in two steps. c. i) DIBAL-H/CH_2Cl_2, 90%; ii) TEMPO, KBr, NaClO, $NaHCO_3$/aq. acetone, 88%. d. **5**, BOP, Et_3N/DMF, 86%. e. i) TFA/CH_2Cl_2; ii) **8**, BOP, Et_3N/DMF, 65% in two steps. f. TTN/MeOH–THF (1:4), 63%. g. i) Ph_3P/aq. THF; ii) **18**, $HgCl_2$, Et_3N/DMF, 59% in two steps; iii) H_2, NaOAc, 10% Pd–C/MeOH, 88%; iv) TBAF, 77%; v) 1 M aq. NaOH/MeOH; iii) TFA/CH_2Cl_2, quant in two steps.

afforded the amino acid **14** in good yield. The acid **14** was condensed with **5** to afford the dipeptide **15**. After removal of the Boc group, the second coupling with **8** furnished the expected tripeptide **16**. The TTN oxidation of **16** effected the cyclization, leading to **17** in 63% yield.[6] To introduce a guanidine group, the azide group was selectively reduced, and coupled with the thiourea derivative **18**. Successively, all of the protecting groups, as well as halogen atoms were removed stepwise to afford (3*S*,4*R*)-eurypamide A **1**.[9] However, comparison of the ^{1}H NMR data of the synthetic sample with those reported, indicated a clear difference in the region of the methine protones of the dihydroxyarginine moiety,[10] while the respective ^{13}C NMR spectra and optical rotations ($[\alpha]_D$: −17.8 (syn: *c* 0.23), −21.5 (nat: *c* 0.23)[1] in MeOH) were similar. Faulkner et al. mentioned 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, which should have (3*S*,4*R*)- or (3*R*,4*S*)-configuration by chemical and spectroscopic evidence.[1] Although they adopted a more preferred (3*S*,4*R*)-configuration in the molecular modeling calculation, we expected **1** might possess a more labile (3*R*,4*S*)-stereochemistry. According to this hypothesis, the corresponding arginine derivative carrying (3*R*,4*S*)-configuration was synthesized from **19**[11] (Scheme 3). Inversion of **19** with the Mitsunobu reaction, followed by solvolysis, provided **20**, which on introduction of an azide group, and reduction, gave **21** after protection. Four-step manipulation of the protecting groups afforded primary alcohol **22** in good yield. Selective introduction of an azide group was accomplished in five steps to provide **23**. After removal of the cyclic carbamate, the resulting alcohol was submitted to oxidation, followed by coupling with **5** to give the corresponding dipeptide **24**. After TFA treatment,[12] the resulting ammonium salt was coupled with **8** to provide **25**. Among TTN oxidation of **25** and its derivatives, the TBS derivative **26** provided the desired **27** in 57% yield, whereas **25** gave spirodienone **28** in 33% yield, and an acetonide derivative provided no cyclized product.[6] Compound **27** was derivatized by essentially the same procedure as in the case of **17** to afford (3*R*,4*S*)-**1** ($[\alpha]_D^{20}$ −19.4 (*c* 0.23, MeOH)), the spectral data of which was superimposable to those reported.[1] Accordingly, the stereochemistry of eurypamide A **1** should be revised as shown in Scheme 3.

In conclusion, eurypamides A and B, **1** and **2**, were successfully synthesized by using the TTN-cyclization of the halogenated diphenol derivatives, **10**, **16**, and **25**, as key steps. This synthesis enabled the structural revi-



Scheme 3. *Reagents and conditions*: a. i) iPrO$_2$C–N=N–CO$_2$$i$Pr, p-O$_2NC_6H_4CO_2H, Ph_3$P/THF, 90%; ii) NaOMe/MeOH, 80%. b. i) DEAD, DPPA, Ph$_3$P/THF, 88%; ii) Ph$_3$P/aq. THF; iii) Boc$_2$O, NaHCO$_3$/aq. dioxane, 92%. c. i) H$_2$, Pd(OH)$_2$–C, CaCO$_3$/EtOH; ii) PivCl·pyr., 53% in two steps; iii) TBSOTf, 2,6-lutidine/CH$_2$Cl$_2$, 89%; iv) DIBAL-H/CH$_2$Cl$_2$, 92%. d. i) NaH/THF, 93%; ii) Boc$_2$O, DMAP, Et$_3$N/THF, 86%; iii) CSA/MeOH, 75%; iv) MsCl·pyr.; v) NaN$_3$/DMF, 84% in two steps. e. i) Cs$_2$CO$_3$/MeOH, 85%; ii) TEMPO, KBr, NaClO, NaHCO$_3$/aq. acetone; iii) **5**, BOP, Et$_3$N/DMF, 85% in two steps. f. i) TBAF, quant; ii) TFA/CH$_2$Cl$_2$; **8**, BOP, Et$_3$N/DMF, 85% in two steps. g. TBSOTf, 2,6-lutidine/CH$_2$Cl$_2$; K$_2$CO$_3$/MeOH, 60%. h. TTN/MeOH–THF (1:4), 57%. i. i) Ph$_3$P/aq. THF, 76%; ii) **18**, HgCl$_2$, Et$_3$N/DMF, 72%; iii) H$_2$, NaOAc, 10% Pd–C/MeOH; iv) TBAF, 70% in two steps; v) 1 M aq. NaOH/MeOH; iii) TFA/CH$_2$Cl$_2$, quant in two steps.

sion of **1** to possess (2*S*,3*R*,4*S*)-configuration in the dihydroxyarginine residue.

Acknowledgements

This work was supported by Grant-in-Aid for the 21st Century COE program 'KEIO Life Conjugate Chemistry', as well as Scientific Research C from the Ministry of Education, Culture, Sports, Science, and Technology, Japan. The authors thank Mr. T. Ogamino for his technical assistance.

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5. Boc-L-tyrosine methyl ester was reacted with NIS in acetone (74%), followed by alkaline hydrolysis to give **8** in quantitative yield.
6. Upon monitoring by TLC, there were no remarkable by-products except highly polar-products, which might be produced by polymerization.
7. Although **2** carrying L-threonine was the major component in a mixture of **2**–**4**, Faulkner et al. reported no detailed spectroscopic data, with the exception of the ^{1}H NMR signals (δ 1.16, 4.18, and 5.94): the corresponding signals were observed in that of synthetic **2**. Selected data of **2**: $[\alpha]_D^{20}$ −22.1 (*c* 1.0, MeOH); IR (film) ν_{max} 3407, 1653 cm^{-1}; δ_H (CD_3OD, 400 MHz) 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, 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, dd, J=2, 8 Hz), 6.83 (1H, d, J=8 Hz), 6.86 (1H, dd, J=2, 8 Hz), 7.02 (1H, dd, J=2, 8 Hz), 7.19 (1H, dd, J=2, 8 Hz), 7.41 (1H, dd, J=2, 8 Hz); δ_C (CD_3OD, 100 MHz) 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.
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9. Selected data of (3*S*,4*R*)-**1**: $[\alpha]_D^{20}$ −17.8 (*c* 0.23, MeOH); IR (film) ν_{max} 3280, 1670 cm^{-1}; δ_H (CD_3OD, 400 MHz) 2.71 (1H, t, J=13 Hz), 2.95 (1H, dd, J=5, 15 Hz), 3.20 (1H, dd, J=2, 15 Hz), 3.4–3.48 (2H, complex), 3.50 (1H, dd, J=3, 13 Hz), 3.93 (1H, dd, J=2, 9 Hz), 4.20 (1H, broad dd, J=2, 5 Hz), 4.75 (1H, dt, J=2, 5 Hz), 4.8–4.9 (2H, complex overlapped with solvent signal), 5.91 (1H, d, J=2 Hz), 6.67 (1H, dd, J=2, 8 Hz), 6.84 (1H, d, J=8 Hz), 6.87 (1H, dd, J=2, 8 Hz), 7.03 (1H, dd, J=2, 8 Hz), 7.22 (1H, dd, J=2, 8 Hz), 7.42 (1H, dd, J=2, 8 Hz), 8.33 (1H, d, J=9 Hz), 8.39 (1H, d, J=10 Hz); δ_C (CD_3OD, 100 MHz) 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.
10. The appropriate signals were not observed, while the methine protons ascribed to the C-3, 4 positions, were resonated at δ 3.70 and 3.87, respectively.
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12. At this stage, a TBS group was removed to get tripeptide **26** in better yield.