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OXIDATIVE CYCLIZATION OF ISODITYROSINE TRIPEPTIDES: OPTIMIZED CONDITION AND APPLICATION OF ELECTROCHEMICALLY GENERATED THALLIUM(III) ION

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Abstract – Thallium(III) trinitrate oxidation of the tripeptide, which was a synthetic precursor of the 17-membered isodityrosine natural product, eurypamide, was investigated to give the desired cyclized compound in 96% yield at best. In addition, the thallium(III) species generated by electrochemical oxidation of thallium(I) successfully produced the target compounds.

From the viewpoints of novel structure and biological activity, natural products possessing isodityrosine or diaryl ether units are quite attractive. Eurypamides A-D isolated from the Palauan sponge, *Microciona eurypa*, are members of the 17-membered cyclic isodityrosine-class natural products.[1] Most of these 17-membered isodityrosine tripeptides have important biological activities, but to our knowledge, no conventional cytotoxic activity has been reported. For example, OF4949 I-IV were found to be potent aminopeptidase B inhibitors, and to possess immuno potentiating activity,[2] and K-13 has been reported to be a noncompetitive inhibitor of angiotensin I converting enzyme.[3] In this context, we have completed the total synthesis of eurypamides, and recently found the halogenated eurypamide B analogues showed inhibitory activity against lipid droplet accumulation in macrophages.[4] In addition, our recent total synthesis of verbenachalcone possessing an acyclic diaryl ether structure by employing anodic oxidation of suitably halogenated phenol derivatives, enabled the structure-activity relationship study as activators of nerve growth factor-mediated neurite outgrowth of PC12D cells.[5]

These diaryl ether moieties seem to be enzymatically formed by phenolic oxidative coupling of two L-tyrosine or phenol derivatives. We have extensively investigated the biomimetic oxidative coupling

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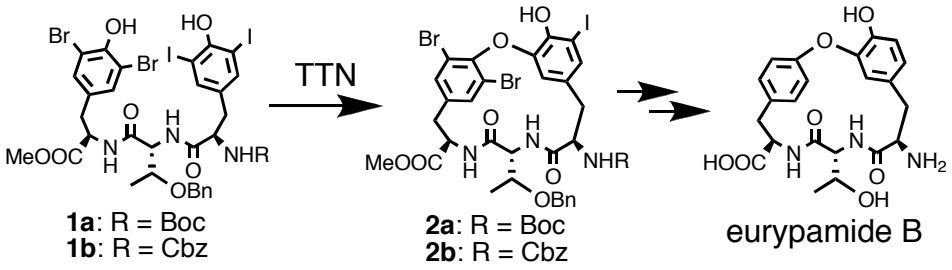
This paper is dedicated to Prof. Dr. Satoshi Ōmura in celebration of his 70th birthday.

by utilizing thallium(III) or anodic oxidation of halogenated phenol and L-tyrosine derivatives, as shown in reviews.[6] In thallium(III) trinitrate (TTN)-mediated phenolic coupling to provide diaryl ether macrocyclic compounds, utilization of *ortho,ortho'*-dihalophenol to control the oxidation potential and the regioselectivity is essential. The versatile availability of TTN oxidation for intramolecular oxidative coupling was proved by the successful total synthesis of OF-4949,[6] K-13,[6] and eurypamides.[4] Moreover, this TTN oxidative macrocyclization strategy was also adopted for vancomycin and related macromolecules.[7] Even so, a disadvantage of this method is the limitation of the reaction yield and toxicity of the thallium(III) salts.



Scheme 1. Construction of 17-membered cyclic isodityrosine by the TTN oxidative cyclization, and the structure of eurypamide B

To conquer this weak point of the thallium-mediated macrocyclization method, we investigated detailed reaction conditions to optimize the yield (up to 96%). Furthermore, we have set the ultimate goal of this thallium-mediated reaction to finalize up to catalytic reaction. From viewpoints of the green chemistry, we have selected electrochemical generation of the oxidant from thallium(I) salt and *in situ* reaction with phenols. We describe herein the accomplishment of this objective.

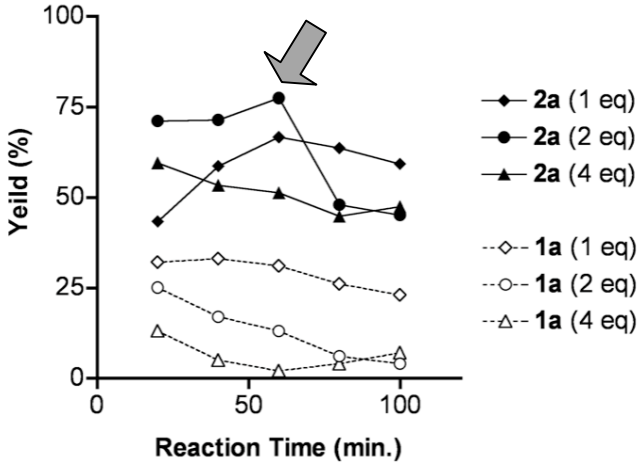
Chemical oxidation. The synthetic intermediates of eurypamides (**1a**, **1b**)[4] were adopted as substrates (Scheme 1). Such parameters as solvents, amount of reagent, reaction time, and temperature were examined in analytical scale[8] to obtain the cyclized compound. Accordingly, **1a** was treated with TTN in several solvents (Table 1).[9] Although solvents appropriate for solid-phase synthesis, such as NMP/MeOH, NMP, and DMF/MeOH, provided desired **2a** in high to moderate yields, due to the high boiling point, the solvent combination, THF/MeOH = 4/1 (56% yield), was adopted. Subsequently, comparison of amounts of the oxidant and reaction time indicated the optimized condition (2 equiv. mol of TTN at 0 °C, 60 min, 77% yield) (marked by the allow in Fig. 1). To check the effectiveness of the above reaction conditions, preparative scale reaction was examined by using **1a** and **1b** as substrate, and **2a**[4] and **2b**[10] were obtained in 69 % and 96% yields, respectively. The latter is the highest yield in our investigation of the thallium oxidation.

Table 1. Reaction yields *vs* solvent.

Solvents	Yield (%)	
	Recovered **1a**	**2a**
NMP/MeOH = 9/1	16	83
NMP	23	76
DMF/MeOH = 9/1	15	57
THF/MeOH = 4/1	24	56
THF/MeOH = 9/1	28	51
MeOH	7	37
dioxane/MeOH = 9/1	37	29
MeOH/H_2O = 9/1	3	5

NMP: N-methyl-2-pyrroridone

Figure 1. TTN amount and reaction time.



Electrochemical generation of thallium(III) species. In the next stage, our research direction moved on to the indirect electrochemical oxidation with thallium(I) salt. We have selected a tandem protocol involving anodic oxidation of thallium(I) salt and *in situ* reaction of thallium(III) species with phenols.

A trifluoroethanol (CF_3CH_2OH) solution of thallium(I) acetate (TlOAc) or thallium(I) nitrate ($TlNO_3$) possessing no oxidative activity, was added to the above-mentioned THF/MeOH = 4/1 solvent, and the mixture was electrolyzed to generate a thallium(III) species with tetrabutylammonium acetate (TBAOAc) or *n*-tetrabutylammonium nitrite ($TBANO_3$) as supporting salts. To this mixture was added substrate (**1b**), and the reaction was continued for 30 to 90 min.[11] As shown in Table 2, the combination of TlOAc with TBAOAc gave no reaction (entry 1). Upon using a combination of $TlNO_3$ with $TBANO_3$, the desired reaction proceeded smoothly, and **2b** was obtained in 57% yield, along with unreacted **1b** (entry 2). These results suggested the oxidative activity was conducted by the corresponding counter anion: the nitrate ions were more suitable than the acetate ions. Decrease of amounts of the thallium reagent from 10 to 6 equiv. mol reduced the product yield to 50% (entry 3). Under these conditions, the best reaction time was 45 min. When operating in shorter reaction time (30 min, entry 4), recovered **1b** was increased more than that of entry 2; however, even elongated reaction time to 90 min did not improve the yield (47%) of **2b**, along with recovered **1b** in 36% yield (entry 5).

Table 2. Reaction condition with electrochemically generated thallium

entry	Thallium salt	Amount (equiv.)	Supporting salt	Reaction time (min)	Yield (%)	
					Recovered **1b**	**2b**
1	TlOAc	10	TBAOAc	45	No reaction	
2	$TlNO_3$	10	$TBANO_3$	45	36	57
3	$TlNO_3$	6	$TBANO_3$	45	36	50
4	$TlNO_3$	10	$TBANO_3$	30	49	34
5	$TlNO_3$	10	$TBANO_3$	90	36	47

In conclusion, we have accomplished optimization of the TTN-mediated cyclization condition to construct the 17-membered cyclic isodityrosine tripeptide in 96% yield. We have also confirmed that thallium(III) electrochemically generated, has enough ability to perform the desired oxidative cyclization. With these attractive results, establishment of catalytic thallium reaction in combination with electroorganic chemistry will promise an efficient oxidation protocol by using catalytic amounts of toxic oxidants.

ACKNOWLEDGEMENTS

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REFERENCES AND NOTES

1. M. V. R. Reddy, M. K. Harper, and D. J. Faulkner, *Tetrahedron*, 1998, **54**, 10649.
2. S. Sano, K. Ikai, K. Katayama, K. Takesako, T. Nakamura, A. Obayashi, Y. Ezure, and H. Enomoto, *J. Antibiot.,* 1986, **39**, 1685; S. Sano, K. Ikai, Y. Yoshikawa, T. Nakamura, and A. Obayashi, *J. Antibiot.,* 1987, **40**, 512.
3. T. Yasuzawa, K. Shirahata, and H. Sano, *J. Antibiot.,* 1987, **40**, 455.
4. M. Ito, M. Yamanaka, N. Kutsumura, and S. Nishiyama, *Tetrahedron Lett.,* 2003, **44**, 7949; M. Ito, M. Yamanaka, N. Kutsumura, and S. Nishiyama, *Tetrahedron*, 2004, **60**, 5623; R. Obata, T. Ohshiro, H. Tomoda, and S. Nishiyama, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 4189.
5. T. Tanabe, F. Doi , T. Ogamino, and S. Nishiyama, *Tetrahedron Lett.,* 2004, **45**, 3477; T. Tanabe, T. Ogamino, Y. Shimizu, M. Imoto, and S. Nishiyama, *Bioorg. Med. Chem.*, 2006, **14**, 2753.
6. S. Yamamura and S. Nishiyama, 'Biomimetic Synthesis of Macrocyclic Oligopeptides Having Isodityrosine and Related Units', Studies in Natural Products Chemistry, Vol. 10 Stereoselective Synthesis (Part F), ed. by Atta-ur-Rahman, Elsevier, Amsterdam 1992, pp. 629-669; S. Yamamura and S. Nishiyama, *J. Synth. Org. Chem., Jpn.,* 1997, **55**, 1029; S. Yamamura and S. Nishiyama, *Synlett,* 2002, 533; R. Frlan and D. Kikelj, Synthesis, 2006, 2271.
7. D. A. Evans, J. C. Barrow, P. S. Watson, A. M. Ratz, C. J. Dinsmore, D. A. Evrard, K. M. DeVries, J. A. Ellman, S. D. Rychnovsky, and J. Lacour, *J. Am. Chem. Soc.*, 1997, **119**, 3419; T. Kai, N. Kajimoto, Y. Konda, Y. Harigaya, and H. Takayanagi, *Tetrahedron Lett.,* 1999, **40**, 6289.
8. HPLC: JASCO TRI ROTAR-V HPLC pump, 70% acetonitrile aqueous solution, 1.0 mL/min,

Senshu Pak PEGASIL ODS column (150 mm x 4.6 mm internal diameter), JASCO UVDEC-100-V UV Spectrophotometer, 280 nm detection, JASCO RC-228 Desktop recorder.

9. **General procedure of analytical scale reaction:** a) Investigation of the solvents: To a solution (4.5 mL) of **1a** (11 mg, 0.01 mmol) was added TTN (9 mg, 0.02 mmol in 0.5 mL solution); the mixture was stirred at 0 °C for 1 h. Na_2SO_3 (1 g) was added to the reaction mixture, and stirring was continued overnight from 0 °C to rt. The reaction mixture was passed through a celite cartridge (VARIAN, Chem Elut™ 5 mL, unbuffered), and the combined washings and filtrate were concentrated *in vacuo*. The residue was diluted with 70% aq. CH_3CN solution (11 mL) and 1 mL of each sample was passed through a membrane filter (Whatman syringe filter, 4 mm filter device, 0.45 μm PVDF membrane polypropylene housing) before injection to the HPLC. b) The 20 min intervals: From the reaction mixture, 1 mL aliquot was taken at each 20 min, and treated with Na_2SO_3 (200 mg) overnight respectively. The mixture was filtered, dried, diluted with 70% aq. CH_3CN solution (1 mL), and passed through a membrane filter before injection to the HPLC.
10. **Oxidation of 1b:** To a solution of **1b** (55 mg, 0.05 mmol) in THF/MeOH (20/5 mL) was added TTN (44 mg, 0.1 mmol in 1 mL MeOH solution) at 0 °C. After being stirred at 0 °C for 40 min, the reaction was quenched by the addition of Na_2SO_3 (5 g), and stirring was continued overnight at from 0 °C to rt. The reaction mixture was passed through a celite cartridge (VARIAN, Chem Elut™ 5 mL, unbuffered), and the combined washing and filtrate were concentrated *in vacuo*. The residue was purified by solid-phase extraction silica gel column (SPELCO, Supelclean™ LC-Si SPE Tubes, 1 g/6 mL, equilibrated, charged with $CHCl_3$). The charged sample was washed with $CHCl_3$, and eluted with EtOAc to give **2b** as colorless powder (46.5 mg, 96 %). No **1b** was detected on TLC. **2b:** ^{1}H-NMR (400 MHz, DMSO-d_6, δ): 1.02 (3H, d, J = 6.3 Hz), 2.65 (1H, t, J = 12.5 Hz), 2.72 (1H, d, J = 14 Hz), 2.87 (1H, dd, J = 5, 14 Hz), 3.30 (1H, m, overlapped with solvent), 3.65 (3H, s), 3.90 (1H, m), 4.38 (2H, m), 4.41 (1H, d, J = 12 Hz), 4.51 (1H, d, J = 12 Hz), 4.90 (1H, m), 4.98 (1H, d, J = 12.7 Hz), 5.12 (1H, d, J = 12.7 Hz), 5.55 (1H, s), 5.75 (1H, d, J = 6.8 Hz), 6.95 (1H, s), 7.26-7.38 (10H, m), 7.53 (1H, s), 7.79 (1H, s), 8.13 (1H, d, J = 9.3 Hz), 8.33 (1H, d, J = 10.3 Hz), 10.02 (1H, s). Anal. Calcd for $C_{38}H_{36}N_3O_9Br_2I•H_2O$: C, 46.41; H, 3.89; N, 4.27. Found: C, 46.43; H, 3.85; N, 4.16.
11. **General procedure of indirect electrochemical oxidation:** To a solution of $TlNO_3$ (50mg, 0.19 mmol) in THF/MeOH/CF_3CH_2OH (12/2.2/0.3 mL) was added $TBANO_3$ (350 mg, 1.15 mmol). The mixture was electrolized under the constant-current-electrolysis (CCE) conditions (10 mA, 6.5 F/mol) using platinum electrodes at rt. After electrolysis, the solution of **1a** in THF/MeOH (20/5 mL) was added at rt. After being stirred for 45 min, excess Na_2SO_3 powder was added, and the mixture was further stirred for 12 h. The mixture was filtered, and the filtrate was evaporated.

Purification by silica gel column chromatography (EtOAc/Hexane = 3/1) afforded **2a** (57%, convergent yield 89%) and **1a** (36%).