Pergamon

Tetrahedron Letters, Vol. 35, No. 45, pp. 8397-8400, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

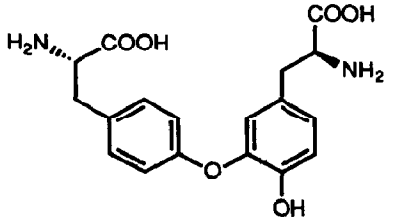
0040-4039(94)01793-X

Syntheses of Isodityrosine, Dityrosine and Related Compounds by Phenolic Oxidation of Tyrosine and Phenylglycine Derivatives Using an Electrochemical Method

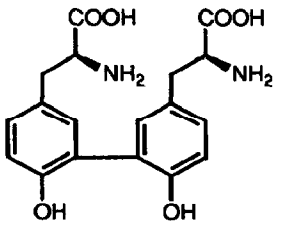
Shigeru Nishiyama,* Moon Hwan Kim, and Shosuke Yamamura*
Department of Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi, Yokohama 223 Japan

Abstract: The phenolic oxidation of L-tyrosine derivatives by electrolysis and zinc reduction produced the coupling products leading to isodityrosine and dityrosine. The oxidation mode could be controlled by altering halogen substituents (Br or I) at two *ortho* positions of phenol groups. Additionally, this methodology was applied to 4-hydroxy-D-phenylglycine derivatives, providing the corresponding oxidative products.

In our continuous synthetic investigation on isodityrosine-derived natural products such as piperazinomycin, K-13, OF-4949 III and vancomycins, biomimetic phenolic oxidation utilizing thallium (III) salts or electrochemical methodology has provided successful results to construct cyclic peptides by diaryl ether bond formation.[1] These natural products have also fascinated many synthetic groups for their challenging structures and concomitant biological activities, and usually their syntheses involved Ullmann condensations to produce diaryl ether units, followed by assembly of cyclic structures. However, contrary to these ingenious works, basic isodityrosine itself (**1**), contributing a cross-linked property of glycoprotein (extensin) of plant cell wall,[2,3] had been synthesized only by Fry,[3] Sano,[4] Jung[5] and Boger.[6] The latter three groups employed Ullmann reaction of tyrosine derivatives and/or appropriate arylic precursors, whereas Fry adopted phenolic oxidation using potassium ferric cyanide to afford **1** (1.8%) and dityrosine **2** (3.4%), which is also a component of native structural protein.[7] Under these situations, we planned to include syntheses of **1** and related compounds for accumulation of scope and limitation of our own phenolic oxidation methodology. We describe herein our synthetic process.



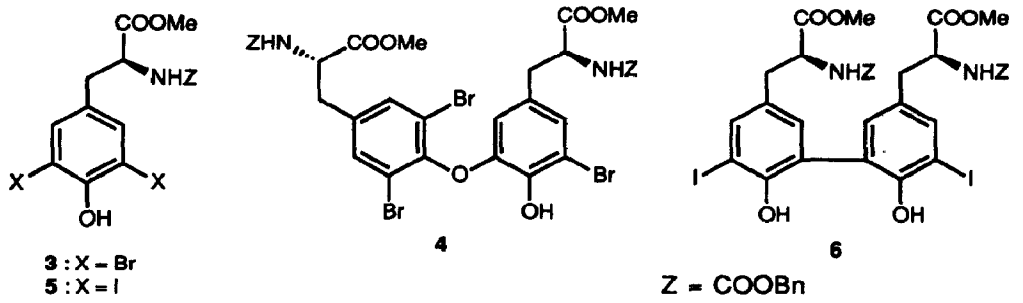
ISODITYROSINE (1)



DITYROSINE (2)

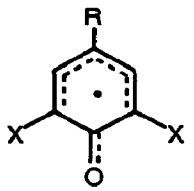
Oxidation of L-tyrosine derivatives.

Based on our investigation related to oxidative couplings of phenols, halogen atoms should be located at both *ortho* positions of a phenol function to control oxidative potentials.[1] Accordingly, L-tyrosine was submitted to simultaneous esterification and bromination, followed by protection of the amino group to provide **3** [1. Br_2 / MeOH; 2. ZCl, $NaHCO_3$ / aq. dioxane (89% in two steps)]. Anodic oxidation of **3** and subsequent zinc reduction afforded desired dimer **4**[8] in 45% yield.



Typical procedure: A mixture of **3** (100 mg, 0.21 mmol) and $LiClO_4$ (100 mg) in MeOH (20 ml) was electrolyzed [constant current electrolysis (CCE) at 5 mA, + 1038 → 1228 mV *vs* SCE, 3 h][9] under an argon atmosphere. After removal of the solvent, the residue was dissolved in THF (20 ml), and excess amounts of zinc powder and AcOH (1 ml) was added; the slurry was agitated at 0 °C for 3 h. The mixture was filtered, and the filtrate was evaporated to dryness. Chromatographic purification of the residue afforded **4** (41 mg, 45%).

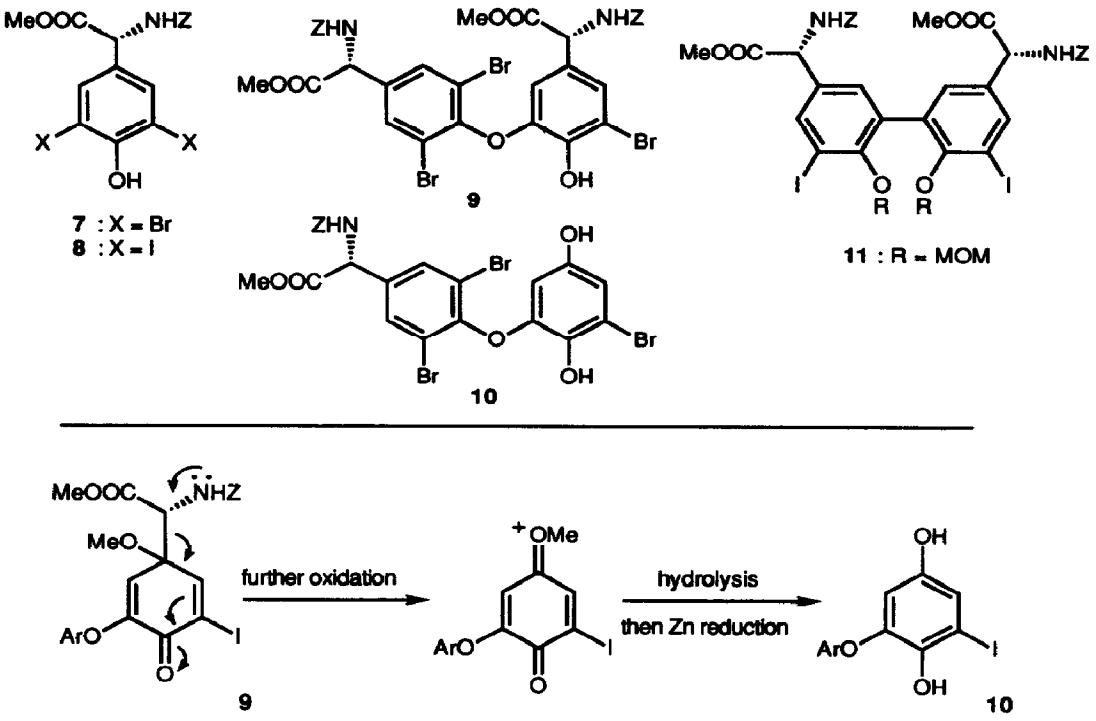
Alternatively, **4** was also obtained in 38% yield by thallium (III) trinitrate oxidation (8 eq in MeOH) and subsequent zinc reduction process. Upon catalytic hydrogenation, **4** underwent debromination and deprotection of the amino groups, and the following acidic hydrolysis produced isodityrosine (**1**)[8] [1. H_2, 10% Pd-C / MeOH - aq. HCl; 2. 6M HCl (quantitative yield in two steps)]. Since ready accessibility (six steps from L-tyrosine) to isodityrosine (**1**) could be demonstrated by our phenolic oxidation methodology, our attention was turned to effects of other halogen atoms to product distribution of the phenolic oxidation. Particularly, of interest was iodo derivatives which might provide a diverse result for a stability of an iodonium ion.[1] Thus, diiodide **5** was synthesized from L-tyrosine in three steps [1. $SOCl_2$ / MeOH; 2. ZCl, $NaHCO_3$ / H_2O - dioxane; 3. NIS / acetone, -76 °C (82% in three steps)]. Electrolysis of **5**, followed by zinc reduction [1. CCE at 20 mA, + 822 → 1295 mV *vs* SCE; 2. Zn powder, AcOH] produced **6**[10] (28%) as a sole product,[11] which on catalytic hydrogenation followed by acidic hydrolysis gave dityrosine (**2**)[10] [1. H_2, 10% Pd-C / MeOH - aq. HCl (72%); 2. 6MHCl (quantitative yield)]. Interestingly, depending on halogen atoms, one electron oxidations of **3** and **5** gave the different products (**4** and **6**), probably *via* the radical species of type **A**. Detailed evaluation of these reaction process are in progress, and would be published elsewhere.



X = Br or I
Radical intermediate (**A**)

Oxidation of D-phenylglycine derivatives.

Phenylglycines are one of the crucial factors consisting of vancomycin-class glycopeptide antibiotics.[12] Owing to unstable properties including a racemization, phenolic oxidation of this amino acid might be an intriguing subject. According to essentially the same procedure as in the case of L-tyrosine derivatives, dibromide **7** and diiodide **8** were synthesized from 4-hydroxy-D-phenylglycine [**7**: 1. Br_2 / MeOH; 2. ZCl, $NaHCO_3$ /aq. dioxane (81% in two steps). **8**: 1. $SOCl_2$ / MeOH; 2. ZCl, $NaHCO_3$ / aq. dioxane; 3. NIS / acetone (71% in three steps)]. When **7** was subjected to electrolysis (CCE at 5 mA, + 987 → 1383 mV *vs* SCE) - zinc reduction, two diaryl ethers [**9** (7%) and **10** (12%)][13] were obtained from a complex mixture.[11] Probably,



Scheme 1. Conversion of **9** into **10**.

the benzylic amide of **9** assisted abstraction of a side chain to produce the corresponding hydroquinone of **10** (Scheme 1). On the other hand, electrolysis - zinc reduction of diiodide **8** effected carbon - carbon bond formation in a similar manner to the case of **6**, leading to **11**[13] (21%) after protection with MOM groups [1. CCE at 23 mA, + 754 → 1350 mV *vs* SCE; 2. Zn powder, AcOH; 3. MOMCl, iPr_2NEt].

In conclusion, electrolysis - zinc reduction of dihalogeno-tyrosine and phenylglycine gave rise to the diaryl ethers (**4, 9, 10**) and the C–C diaryls (**6, 12**) of the corresponding amino acids. We could demonstrate the facile syntheses of isodityrosine and dityrosine, as well as the phenylglycine congeners, although the oxidation conditions have not yet been optimized. Particularly, information of the phenylglycine derivatives might promise a new methodology for synthetic studies on vancomycin-class antibiotics.

This research was financially supported by a Grant-in-Aid from the Ministry of Education, Science and Culture to whom grateful acknowledgment is made.

REFERENCES

1. Yamamura, S.; Nishiyama, S. *Studies in Natural Products Chemistry* (Atta-ur-Rahman Ed), Elsevier, **1992**, 629.
2. Fry, S. C. *Biochem. J.* **1982**, *204*, 449. Cooper, J. B.; Varner, J. E. *Biochem. Biophys. Res. Commun.* **1983**, *112*, 161. Epstein, L.; Lamport, D. T. A. *Phytochemistry* **1984**, *23*, 1241.
3. Fry, S. C. *Meth. Enzymol.* **1984**, *107*, 388.

4. Sano, S.; Ikai, K.; Katayama, K.; Takesako, K.; Nakamura, T.; Obayashi, A.; Ezure, Y.; Enomoto, H. *J. Antibiot.*, **1986**, *39*, 1685.
5. Jung, M. E.; Jachiet, D.; Rohloff, J. C. *Tetrahedron Lett.* **1989**, *30*, 4211.
6. Boger, D. L.; Yohannes, D. *Tetrahedron Lett.* **1989**, *30*, 2053; *J. Org. Chem.*, **1990**, *55*, 6000.
7. Amadò, R.; Aeschbach, R.; Neukom, H. *Meth. Enzymol.* **1984**, *107*, 377.
8. **4** as needles mp 150 - 152 °C (hexane - EtOAc): $[\alpha]_D^{18}$ +49° (*c* 1.11, $CHCl_3$); IR (nujol) 3350, 1720, and 1585 cm^{-1}; δ_H ($CDCl_3$) 2.85 - 3.05 (3H, complex), 3.10 (1H, m), 3.59 (3H, s), 3.74 (3H, s), 4.52 (1H, m), 4.62 (1H, m), 5.06 (2H, s), 5.13 (2H, AB q), 5.19 (1H, d, J= 8 Hz), 5.45 (1H, d, J= 8 Hz), 6.01 (1H, s), 6.05 (1H, s), 6.97 (1H, s), 7.35 (12H, br s). **1**: $[\alpha]_D^{19}$ -2.5° (*c* 1.55, 1M HCl); δ_H (D_2O containing HCl) 3.00 (1H, dd, J= 14.6, 7.3 Hz), 3.07 (2H, complex), 3.20 (1H, dd, J= 14.6, 6.3 Hz), 4.13 (1H, dd, J= 7, 6.3 Hz), 4.20 (1H, dd, 7.5, 5.5 Hz), 6.83 (1H, s), 6.85 (2H, d, J= 8.5 Hz), 6.94 (2H, s), 7.16 (2H, d, J= 8.5 Hz); δ_C (D_2O containing HCl) 35.63, 35.67, 55.0, 55.1, 118.1, 118.6, 123.1, 127.5, 127.7, 129.4, 131.79, 144.0, 147.9, 157.8, 172.2, 172.4. The optical rotation of **1** might be sensitive to pH values of the solutions [-6.0° (1M HCl),[4] -28.2° (MeOH)[6]], and the optical purity of our synthetic sample was confirmed as a MTPA derivative.
9. Electrolysis was performed in an undivided cell which comprised a 30 ml glassy carbon beaker as an anode and a platinum wire as a cathode.
10. **6**: $[\alpha]_D^{19}$ +8.1° (*c* 1.17, $CHCl_3$); IR (film) 3380, 1720 (br), 1520 cm^{-1}; δ_H ($CDCl_3$) 2.80 (2H, dd, J= 8, 13.7 Hz), 3.13 (2H, dd, J= 4.9, 13.7 Hz), 3.75 (6H, s), 4.63 (2H, complex), 5.01 (4H, AB q), 5.36 (2H, d, J= 8.3 Hz), 6.28 (2H, broad s), 7.05 (2H, broad s), 7.30 (10H, complex), 7.50 (2H, s). **2**: $[\alpha]_D^{19}$ -10° (*c* 0.27, 2M HCl); δ_H (D_2O containing HCl) 3.08 (2H, dd, J= 14.6, 7.3 Hz), 3.18 (2H, dd, J= 14.6, 5.9 Hz), 4.13 (2H, dd, J= 7.3, 5.9 Hz), 6.89 (2H, d, J= 8.3 Hz), 7.03 (2H, d, J= 2.4 Hz), 7.12 (2H, dd, J= 8.3, 2.4 Hz); δ_C (D_2O containing HCl) 35.6, 55.4, 117.2, 126.5, 127.0, 131.3, 133.1, 153.5, 172.8.
11. Upon monitoring the reaction with TLC, majority of byproducts were located around high polarity region, presumably, owing to reactions such as polymerization.
12. Syntheses of phenylglycine derivatives related to vancomycins. Pearson, A. J.; Bruhn, P. R.; Gouzoules, F.; Lee, S.-H. *J. Chem. Soc. Chem. Commun.*, **1989**, 659. Pearson, A. J.; Bruhn, P. R. *J. Org. Chem.* **1991**, *56*, 7092. Pearson, A. J.; Shin, H. *Tetrahedron*, **1992**, *48*, 7527. Rao, A.V. R.; Chakraborty, T. K.; Joshi, S. P.; *Tetrahedron Lett.*, **1992**, *33*, 4045. Chakraborty, T. K.; Reddy, G. V. *J. Org. Chem.*, **1992**, *57*, 5462. Evans, D. A.; Dinsmore, C. J.; Evrard, D. A.; DeVries, K. M. *J. Am. Chem. Soc.*, **1993**, *115*, 6426. Zhu, J.; Beugelmans, R.; Bigot, A.; Singh, G. P.; B.-Choussy, M. *Tetrahedron Lett.*, **1993**, *34*, 7401.
13. **9**: $[\alpha]_D^{22}$ -90° (*c* 3.7, $CHCl_3$); IR (film) 3400, 1720 (br), 1590 cm^{-1}; δ_H ($CDCl_3$) 3.66 (3H, s), 3.80 (3H, s), 5.07 (2H, s), 5.12 (2H, AB q), 5.39 (1H, d, J= 7 Hz), 5.74 (1H, s), 6.02 (1H, s), 6.20 (1H, broad s), 6.38 (1H, s), 7.3 - 7.4 (10H, complex), 7.63 (2H, s). **10**: $[\alpha]_D^{22}$ -62° (*c* 0.56, $CHCl_3$); IR (film) 3500, 1730, 1615 cm^{-1}; δ_H ($CDCl_3$) 3.79 (3H, s), 5.07 (1H, d, J= 12.2 Hz, overlapped with 1H signal), 5.15 (1H, d, J= 12.2 Hz), 5.33 (1H, d, J= 6 Hz), 5.61 (1H, s), 5.93 (1H, br d, J= 2.4 Hz), 6.11 (1H, br d, J= 6 Hz), 6.74 (1H, d, J= 2.4 Hz), 7.36 (5H, s), 7.61 (2H, s). **11**: $[\alpha]_D^{20}$ -96.6° (*c* 2.14, $CHCl_3$); IR (film) 3350, 1740 (sh), 1720 (br) cm^{-1}; δ_H ($CDCl_3$) 2.95 (6H, s), 3.73 (6H, s), 4.75 (4H, s), 5.09 (4H, AB q), 5.32 (2H, d, J= 7.4 Hz), 5.94 (2H, broad s), 7.34 (12H, complex), 7.82 (2H, d, J= 2 Hz).

(*Received in Japan* 1 *June* 1994; *accepted* 1 *August* 1994)