Pergamon

Tetrahedron Letters 39 (1998) 5679–5682

TETRAHEDRON LETTERS

Enzymatic Oxidative Coupling of Hydroxyphenylglycine Derivatives

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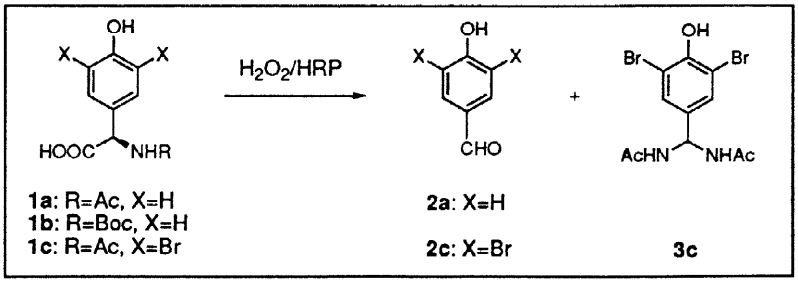
Received 27 April 1998; revised 22 May 1998; accepted 26 May 1998

Abstract: In contrast to N-protected tyrosine derivatives, N-protected hydroxy-D-phenylglycine derivatives underwent decarboxylation to give 4-hydroxybenzaldehyde under the normal incubation conditions. When both the carboxyl and amino groups of hydroxy-D-phenylglycine are blocked, the C–C and C–O coupling products were obtained in 48% and 32% yields respectively. No racemization of the chiral center was observed for all the substrates examined.

Bioactive cyclopeptides and cyclodepsipeptides, such as Bastadins,[1a] K-13,[1b] OF 4949,[1c] Bouvardin,[1d] and Vancomycin,[1e] are made up of building blocks derived from the oxidative coupling of phenolic amino acids or their derivatives. The C–C and C–O coupling products of tyrosine residues also contribute to the crosslinked properties of many structural proteins.[2] Consequently, considerable efforts have been devoted to the development of different strategies especially for the synthesis of the diaryl ether linkage present in these target molecules.[3]

We recently reported a novel efficient enzymatic method for the C–O coupling of dibromo- and dichlorotyrosine derivatives to yield the isodityrosine framework.[4] To further investigate the scope of this technology, we have examined the enzymatic oxidative coupling of hydroxy-D-phenylglycine derivatives because they are present in the diaryl ether linkages of many glycopeptide antibiotics.[3b] Moreover, it is important to determine whether racemization of the benzylic chiral center in this series of compounds occurs under different reaction conditions.

In a series of experiments, we first examined the action of soybean and horseradish peroxidases (HRP) on N-protected hydroxy-D-phenylglycine derivatives **1a** and **1b** at pH 6 and 9. By analogy to the results obtained with the N-protected tyrosine derivatives, we expected the corresponding C–C coupled product to be formed predominantly. Somewhat to our surprise, the major product formed was 4-hydroxybenzaldehyde, **2a**, in yields as high as 91%. Similarly, when N-acetyl-2,6-dibromohydroxy-D-phenyl-



1a: R=Ac, X=H
1b: R=Boc, X=H
1c: R=Ac, X=Br

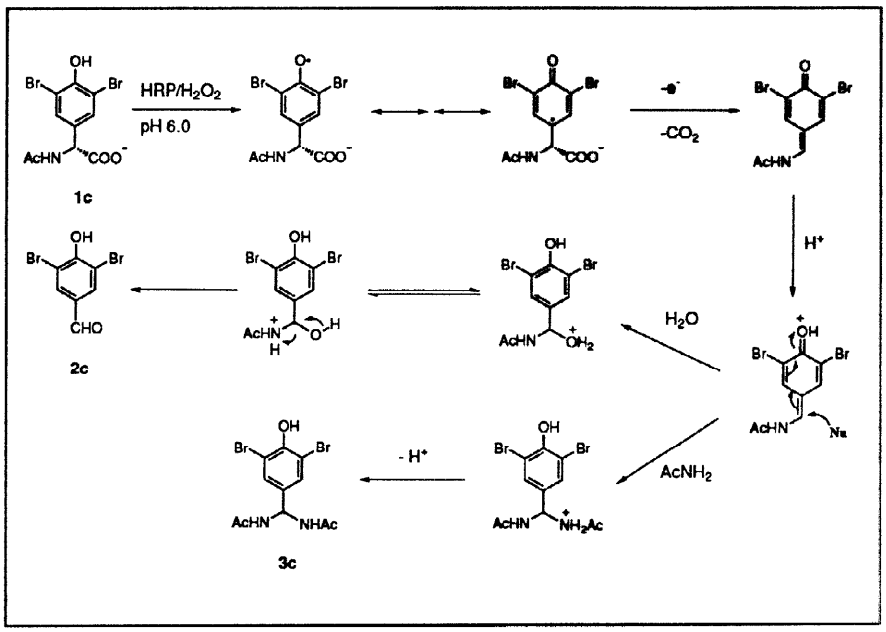
2a: X=H
2c: X=Br

3c

0040-4039/98/$19.00
PII: S0040-4039(98)01144-7

glycine, **1c**, was exposed to HRP at pH 6, the major product (**2c**) was isolated in 43% yield, accompanied by 12% of an interesting new compound, which was characterized as **3c** on the basis of its spectroscopic data.[5]

These results revealed that the N-protected hydroxy-D-phenylglycine derivatives were highly susceptible to oxidative decarboxylations under the reaction conditions. A plausible mechanism for the formation of **2c** and **3c** from **1c** is illustrated in Scheme 1.



Scheme 1. Proposed mechanism for the formation of **2c** and **3c**.

To prevent decarboxylation, we prepared substrates **4a-c**, in which both the amino and carboxyl groups were blocked for our C–C coupling investigations. The results of Table 1 showed that the expected dimeric C–C coupled products were obtained in yields ranging from 9% to 48% depending on reaction conditions. At pH values less than 9, some trimeric C–C coupled products were also formed besides recovered starting material.

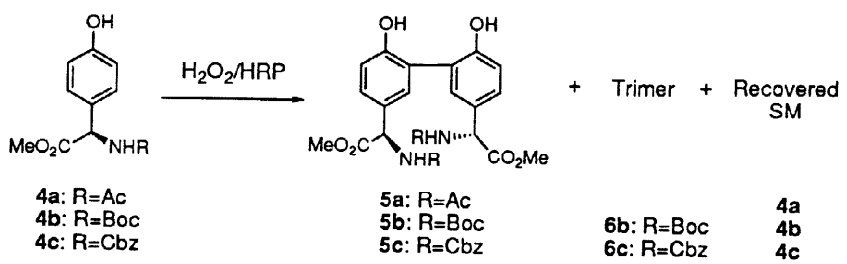
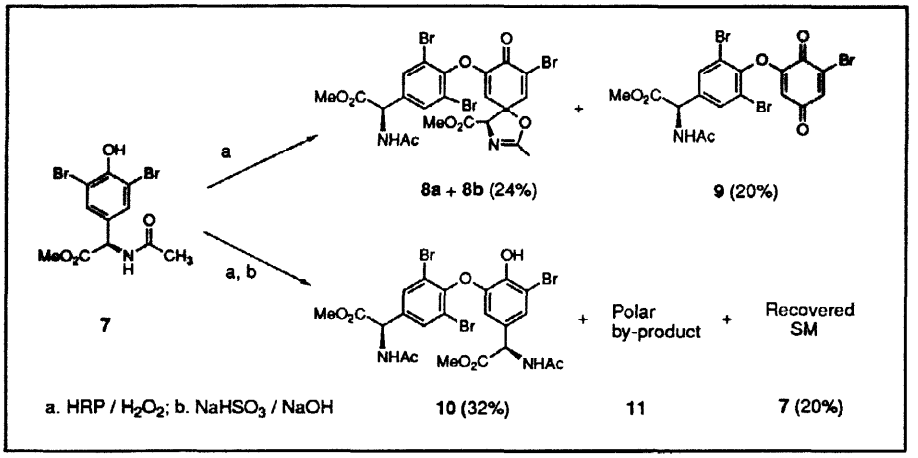


Table 1. HRP-catalyzed C–C Coupling of **4**

R	pH	Co-solvent	HRP/SM (units/μmol)	Time (min)	Scale (mmol SM)	Isolated Yield (%) 5	6	4
Ac	9.0	10% dioxane	3	5	1	9	–	11
Boc	9.0	30% dioxane	3	10	1	22	–	–
Boc	8.4	20% CH_3CN	5	10	5	48	3	10
Cbz	6.0	20% CH_3CN	0.5	20	3	26	14	48

Having successfully achieved the C–C coupling of hydroxy-D-phenylglycine derivatives, we turned our attention to the synthesis of diaryl ethers using the appropriately protected dibromo derivative **7** as substrate. As shown in Scheme

2, HRP-catalyzed oxidative coupling of 7 afforded a pair of diastereomeric derivatives, **8a** and **8b** in 24% yield and the quinone derivative **9** (20%).[6a]



Scheme 2. HRP-catalyzed C-O coupling of 7

To optimize the enzymatic C-O coupling reaction of 7, the reaction conditions were carefully studied and the intermediates, such as **8a** and **8b**, were reduced *in situ* with $NaHSO_3$ to generate the diaryl ether **10** directly.[6b] After much experimentation, we found that the best obtainable yield of **10** was around 32%.

Although the yields of enzymatic C-C and C-O coupling of hydroxy-D-phenylglycine derivatives are not as high as compared to the corresponding tyrosine series, the enzymatic oxidative C-O coupling methodology is more efficient than the electrochemical method wherein the desired diaryl ether was obtained in only 7% yield.[7] Further, we did not observe racemization of the chiral center in all of the substrates examined. The application of this oxidative coupling technology for the cyclization of peptides containing hydroxy-D-phenylglycine residues is currently under investigation.

Acknowledgment: This investigation was supported in part by a grant from the National Institutes of Health.

References and Notes

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5. ^{1}H NMR (DMSO-d_6) δ 9.85 (s, 1H), 8.65 (d, *J*=8, 2H), 7.50 (s, 2H), 6.25 (t, *J*=8, 1H), 1.90 (s, 6H); ^{1}H NMR (acetone-d_6-DMSO-d_6-D_2O) δ 7.51 (s, 2H), 6.54 (s, 1H), 2.03 (s, 6H); ^{13}C NMR (D_2O-NaOH) 177.1 (2C), 164.3, 133.6 (2C), 127.8, 118.6 (2C), 61.4, 25.7 (2C); FAB MS *m/z* (relative intensity) 383 (52), 381 (100), 379 ([M+H]$^+$, 62).

6. **a)** To a clear solution of **7** (230 mg, 0.6 mmol) in 69 mL of pH 4.0 buffer and 23 mL of dioxane, 3 mL of HRP (1000 unit/mL) was added, followed by 82 μL of 30% H_2O_2. The resulting mixture was stirred at 24°C for 5 min, quenched with 50 mL of 5% citric acid, and extracted with ethyl acetate (60 mL). The organic extract was washed with water (2 × 30 mL), dried over $MgSO_4$, and concentrated to dryness under reduced pressure. The residue was subjected to flash chromatography (CH_2Cl_2-acetone 1:0 to 1:1) to afford **9** (34 mg, 20%): ^{1}H NMR ($CDCl_3$) δ 7.63 (s, 2H), 7.25 (d, *J*=2.2, 1H), 6.76 (d, *J*=6.6, 2H), 5.62 (d, *J*=2.2, 1H), 5.57 (d, *J*=6.6, 2H), 3.82 (s, 3H), 2.10 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 184.3, 173.1, 170.1, 169.5, 154.3, 146.8, 138.5, 138.3, 134.8, 132.0 (2C), 117.2 (2C), 111.3, 54.9, 53.6, 23.1; FAB MS *m/z* (relative intensity) 594 (26), 592 (74), 590 (100), 588 ([M+Na]$^+$, 69), and a mixture of diastereoisomers **8a** and **8b** (1:1, 49 mg, 24%). The mixture was further subjected to flash chromatography (CH_2Cl_2-acetone 1:0 to 3:1) to afford the less polar portion as **8a**: ^{1}H NMR ($CDCl_3$) δ 7.61 (s, 1H), 7.22 (d, *J*=2.6, 1H), 6.80 (d, *J*=6.8, 1H), 5.58-5.55 (m, 2H), 4.71 (brs, 1H), 3.80 (s, 3H), 3.71 (s, 3H), 2.11 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 171.8, 170.1, 169.6, 168.2, 166.8, 147.5, 146.2, 143.3, 137.6, 131.9 (2C), 124.8, 118.1, 117.7 (2C), 83.3, 77.3, 55.0, 53.6, 52.9, 23.1, 14.2; FAB MS *m/z* (relative intensity) 683 (72), 681 (100), 679 (98), 677 ([M+H]$^-$, 62), and the more polar portion as **8b**: ^{1}H NMR ($CDCl_3$) δ 7.58 (s, 1H), 7.27 (d, *J*=2.8, 1H), 6.61 (d, *J*=6.4, 1H), 5.57-5.50 (m, 2H), 4.77 (brs, 1H), 3.82 (s, 3H), 3.65 (s, 3H), 2.10 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 171.8, 170.1, 169.5, 167.8, 167.0, 147.9, 147.1, 145.6, 137.5, 131.8 (2C), 124.6, 117.7 (2C), 114.4, 83.2, 75.8, 54.8, 53.5, 53.0, 23.1, 14.2; FAB MS *m/z* (relative intensity) 683 (50), 681 (100), 679 (85), 677 ([M+H]$^+$, 35). **b)** ^{1}H NMR ($CDCl_3$) δ 7.62 (s, 2H), 7.20 (s, 1H), 7.04 (brd, 1H), 6.68 (brd, 1H), 6.37 (s, 1H), 5.61 (d, *J*=7.0, 1H), 5.34 (d, *J*=7.4, 1H), 3.82 (s, 3H), 3.67 (s, 3H), 2.08 (s, 3H), 1.98 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.9, 170.2, 169.9, 169.7, 148.4, 143.8, 143.3, 137.2, 131.9 (2C), 129.0, 125.3, 118.5 (2C), 112.5, 110.2, 55.3, 54.9, 53.5, 52.9, 23.0, 22.9; FAB MS *m/z* (relative intensity) 707 (34), 705 (100), 703 (100), 701 ([M+Na]$^+$, 34).

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