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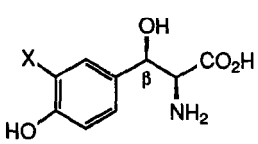
A NEW ENTRY TO THE SYNTHESIS OF β-HYDROXYTYROSINES VIA A NOVEL BENZYLIC HYDROXYLATION

Keiko Shimamoto and Yasufumi Ohfune*
Suntory Institute for Bioorganic Research
Shimamoto-cho, Mishima-gun, Osaka 618, Japan

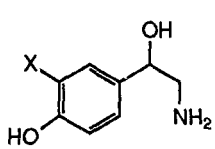
Summary: Highly stereoselective introduction of a hydroxyl group into the benzylic position of N-*tert*-butoxycarbonyl-L-tyrosine derivatives was achieved by the use of $K_2S_2O_8/CuSO_4$ system to give the threo cyclic carbamates. These were converted into β-hydroxytyrosine and octopamine, efficiently.

Aromatic amino acids and amines represented by catecholamines have received much attention from synthetic organic chemists due to their important role in biological systems. Recently, β-Hydroxytyrosine and its analogues, which are plausible biogenetic intermediates of the above family of compounds and have attracted considerable interest as medicinal compounds,[1,2] have been isolated as a key constituent of peptide antibiotics such as vancomycine[3] and monobactums.[4] As an extension of our work related to the stereocontrolled syntheses of 1,2- and/or 1,3-amino hydroxyl systems from readily available α-amino acids,[5] we focused on the synthesis of these important amino acids from L-tyrosine. We describe here the highly stereoselective syntheses of threo-β-hydroxy-L-tyrosine and octopamine via a novel benzylic oxidation.

Previous methods for the synthesis of β-hydroxytyrosines were mainly based on the condensation of an aryl aldehyde with a glycine equivalent and were non-stereoselective.[6] In addition, no methods have been reported for the direct introduction of a hydroxyl group into the benzylic position of tyrosine and phenylalanine derivatives. Our strategy was based on the benzylic oxidation of tyrosine derivatives, but initial attempts were accompanied by difficulties which resulted in the recovery of the starting material or cleavage of the C-C



1a X=H
1b X=Cl (vancomycine fragment)
1c X=OH (L-DOPS)



2a X=H (octopamine)
2b X=OH (noradrenaline)

Table I. Benzylic oxidation of L-tyrosine derivatives **3a-3i**.[a]

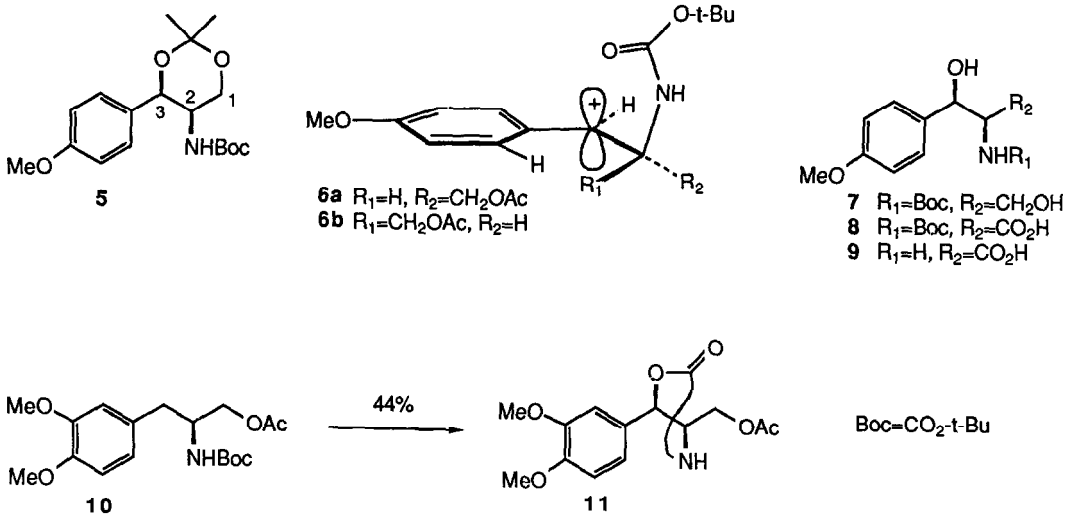
entry	substrate	R_1	R_2	R_3	product	yield (%)[b](erythro/threo)[c]
1	**3a**	Boc	CO_2Me	OMe	**4a**	55 (1/49)
2	**3b**	Z[d]	CO_2Me	OMe	**4b**	4
3	**3c**	CO_2Et	CH_2OAc	OMe	**4c**	0
4	**3d**	Boc	CH_2OAc	OMe	**4d**	76 (1/37)
5	**3e**	Boc	CH_2OSi	OMe	**4e**	0
6	**3f**	Boc	H	OMe	**4f**[e]	75
7	**3g**	Boc	CH_2OAc	OAc	**4g**	4
8	**3h**	Boc	CH_2OAc	OMEM	**4h**	0
9	**3i**	Boc	CH_2OAc	H	**4i**	0

[a] The reaction was carried out using 2 equiv $K_2S_2O_8$/0.2 equiv $CuSO_4$ at 50-70 °C for 1.5-4 h. [b] Isolated yield. [c] The products ratios were determined by a chromatographic isolation. [d] Z=CO_2CH_2Ph [e] Recovery of the starting material in which silyl ether was removed.

bond between C2 and C3 probably due to retro-aldol or over-oxidation. Finally, we found that the treatment of the N-*tert*-butoxycarbonyl (*t*-Boc) derivative **3a** with 2 equiv $K_2S_2O_8$ and 0.2 equiv $CuSO_4$[7] produced the cyclic carbamate **4a** (55% yield) in a highly stereoselective manner (**4a**:diastereomer=49:1). The configuration of the major isomer at C3 was determined to be (R) by conversion of **4a** into the corresponding acetonide **5** using the following sequence of reactions: (i) $LiAlH_4$/THF, (ii) $Ba(OH)_2$/80% EtOH, (iii) di-*tert*-butyldicarbonate (Boc_2O)/$NaHCO_3$ and (iv) *dl*-10-camphorsulfonic acid(CSA)/$(CH_3)_2C(OCH_3)_2$. The ^1H NMR data of **5** [360 MHz ($CDCl_3$) δ 3.80 (m, 1 H, 2-H), 3.86 (dd, 1 H, J=1.8, 12.2 Hz, 1αH or 1βH), 4.24 (dd, 1 H, J=1.9, 12.2 Hz, 1αH or 1βH), 5.10 (d, 1 H, J=1.6 Hz, 3-H)] indicated a threo stereochemistry.[8,9]

The following substituents are considered to be crucial to the success of this oxidation as summarized in Table I: (i) the *t*-Boc group for the amino protection and (ii) electron releasing groups such as methyl ether at para position [methoxymethyl (MEM) ether may chelate with Cu(II) resulting in no reaction (entry 8)].

Concerning the mechanism of this oxidation,[7b] the high threo selectivity in the cyclic carbamate formation (entries 1 and 4) suggests that the reaction proceeds via the more stable benzyl cation intermediate **6a**. The conformer **6b** is



more strained than **6a** by a severe steric interaction between the acetoxymethyl group and the ortho hydrogen analogous to $A^{1,3}$ strain.[10] Intramolecular trapping of this cation from a carboxyl oxygen and subsequent release of the *tert*-butyl cation which is more stable than the benzyl cation of **6a** may be a driving force for the formation of cyclic carbamates. Only poor yields were obtained from the other amino protecting groups such as benzyloxycarbonyl (Z) group (entries 3 and 4).

Next, we turned our attention to the conversion of these carbamates into β-hydroxytyrosines. Since cyclic carbamate **4a** was found to be labile under hydrolysis conditions to give glycine as the retro aldol product, the acetate **4d** was chosen for further transformations. Hydrolysis of **4d** with $Ba(OH)_2$/80% EtOH, 80 °C, 16 h followed by protection of the resulting amine with $Boc_2O/NaHCO_3$ gave the diol **7**: 100%; mp 69-72 °C; $[\alpha]_D^{23}$ -53.5° (*c* 1.0, $CHCl_3$). Oxidation of **7** with PtO_2/O_2, dioxane-H_2O, 40 °C, 24 h provided the β-hydroxy acid **8** (46%) which upon exposure to CF_3CO_2H gave the desired amino acid **9**: mp 75 °C (decomp), $[\alpha]_D$ -21° (*c* 0.50, H_2O). Octopamine was prepared in a conventional manner from the cyclic carbamate **4f**. This was carried out in one step with BBr_3/CH_2Cl_2/N,N-dimethylacetoamide[11] to give **2a** in 63% yield.[12]

In addition, it is noted that the reaction of an N-*t*-Boc-DOPA derivative **10** also yielded the threo carbamate **11** (44%; no erythro isomer was detected) which is equivalent with L-DOPS. Further studies are currently in progress.

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9. Experimental procedure for the conversion of **3d** to **4d**. To a solution of **3d** (2.0 g, 6.18 mmol) in CH_3CN under N_2 was added successively a solution of $K_2S_2O_8$ (3.34 g, 12.4 mmol) in 80 ml of water and $CuSO_4$ (200 mg, 1.24 mmol) in 10 ml of water. After stirring at 70 °C for 2.5 h, the reaction mixture was poured into water, and extracted with ethyl acetate for several times. The combined organic layer was washed with water, dried over $MgSO_4$, and concentrated in vacuo to give an oily residue which upon chromatography on SiO_2 (elution with ether) gave 1.22 g (74%) of **4d** as colorless crystals: mp 99.5-100.0 °C, $[\alpha]_D^{25}$ +58.8° (*c* 1.0, $CHCl_3$). The erythro diastereomer of **4d** was the by-product: 30 mg (2%).
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