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NOTE

Synthesis of New DOPA Derivative from L-Tyrosine for Construction of Bioactive Compound

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A practical synthetic method of new DOPA derivative was developed with L-tyrosine as starting material. The new DOPA analogue could be used in building bioactive compounds.

Key Words: Bioactive compound, L-DOPA analogue, Synthesis, L-Tyrosine.

DOPA and its analogues have been useful unit in many biologically active natural products, such as the inhibitor of FPTase, pepticinnamin E[1], OF4949-I[2] (Fig. 1).

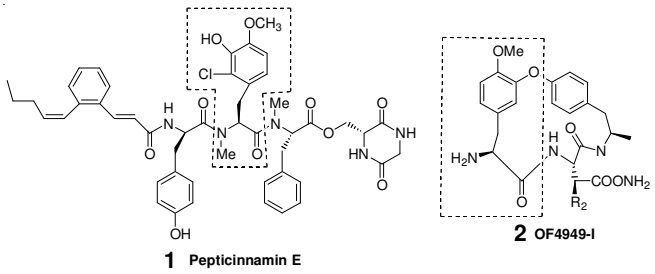

Fig. 1

Many methods have been reported for preparation of DOPA analogue[3], such as traditional Schollköpf method for preparation of chiral amino acid; the improved synthesis of selectively protected L-DOPA derivatives from L-tyrosine, *via* Reimer-Tiemann to obtain compound **5** and Dakin reaction and Baeyer-Villiger oxidation to obtain selectively O-benylation L-DOPA derivatives **7** reported by Jung and Lazarova[4] (Fig. 2):

In above procedure, the compound **5** was prepared according to Reimer-Tiemann process, such reaction had to run refluxing in solution of sodium hydroxide (6 equive) in water and chloroform for 4 h, so risking in substantial racemization (15-20 %) according to the report of Boger[5] even under the reaction conditions (2 equive of K_2CO_3, acetone, 60 ºC); furthermore, the O-benzylation of tyrosine phenol in compound **5** also need vigorous reaction conditions (4.4 equive of K_2CO_3,

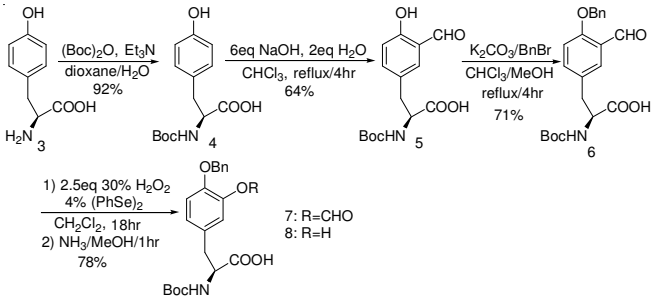

Fig. 2

2/1 chloroform/methanol, reflux 4 h), which may cause racemization as well.

Wilcoxen[6] reported an another synthetic method of O-benzylation L-DOPA derivative from L-tyrosine based on the conditions described by Boger[5] by utilizing warm conditions (2.5equiv of BnBr, 2.5equiv of K_2CO_3, 0.1 equiv of Et_4NI, DMF, 25 ºC) to minimize possible racemization. However no efficient methods have been report to prepare O-methylated, N-methylated L-DOPA analogue even they are very useful building block for the total synthesis of many biological active natural compounds.

Herein, we reported an efficient method for synthesis O-methylation, N-methylation chlorinated L-DOPA derivative, which could be utilized as key intermediate in the total synthesis of natural products and their derivatives, such as analogues of pepticinnamin E **1**. In our prior study of total synthesis of pepticinnamin E, we obtained the novel DOPA analogue through catalytic hydrogenation of the dehydroamino acids (DDAA)[7]. In this paper, we report the other strategy to

obtain new DOPA analogue by starting from nature amino acid. We employed L-tyrosine as starting material *via* synthetic strategy based on Baeyer-Villiger oxidation, methylation under Coggins's condition[8] and finally chlorination by Cl_2 gas in dichloromethane to give new DOPA analogue **16** (Fig. 3).

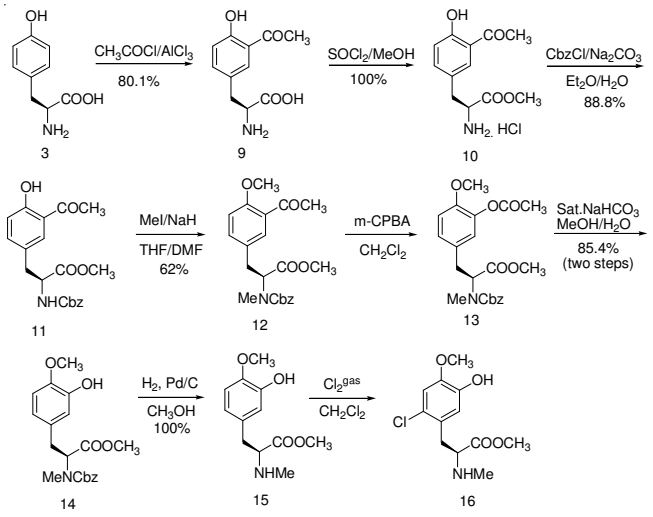

Fig. 3

Melting points were determined with an electrothermal digital melting point apparatus and were uncorrected. Optical rotation were recorded on a Perkin-Elmer Model 341 polarimeter, at the sodium D line. NMR and spectra were run either on Bruker-200 and Bruker-300 or on Varian-400.

Compound **9**[9], **10**[9], **11**[9a], **12**[5], **13**[10], **14**[7], **15**[11] were prepared based on the procedures reported in literatures.

Preparation of L-N-methyl-3-hydroxy-4-methoxy-6-chlorophenylalanine methyl ester **16**: To a stirred solution of compound **15** (0.24 g, 1 mmol) in dichloromethane was bubbled chlorine at 0 ºC until **15** was converted completed showed by TLC plate. The yellow reaction solution was concentrated at 0 ºC to give slight yellow oil, which was chromato-graphed to yield final product **16** as pale yellow oil, 107 mg, yield 39.1 %. ^{1}H NMR ($CDCl_3$, 400 Hz) δ ppm: 6.82 (s, 1H, Ar-H), 6.79(s, 1H, Ar-H), 3.85(s, 3H, COOMe), 3.68 (s, 3H, OMe), 3.63-3.48 (m, 1H, CH), 3.05-2.93 (m, 2H, CH_2), 2.39 (s, 3H, NMe).

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