ALKOXYLATION AT *META* POSITION TO HYDROXYL GROUP OF L-TYROSINE: PREPARATION OF ALKYL (*S*)-2,4-DIALKOXYPHENYL-ALANINATES¶

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Abstract----Treatment of dienone lactone (**2**), derived from L-tyrosine, with methanol in the presence of boron trifluoride etherate gave methyl *N*-protected (*S*)-2,4-dimethoxyphenylalaninate (**4**) in 76 % yield. Similarly, two homologues (**9** and **10**) were conventionally produced from **2**.

L-Tyrosine derivatives are well known to be a pharmacologically great important in themselves or as a unit of peptides. Especially, L-DOPA (**1**) is effectively used in therapy. Therefore, conventional method for production of those L-amino acids has been explored.[1]

In the course of our investigation on modification of L-tyrosine derivatives,[2] we found that formation of the title compounds smoothly proceeded by treatment of the dienone lactone (**2**) with alcohols in the presence of boron trifluoride etherate (BF_3·Et_2O). The present paper deals with alkoxylation at *meta* position to hydroxyl group of L-tyrosine.

The dienone lactone (**2**),[2a] readily obtained from (*S*)-*N*-benzyl-*N*-benzyloxycarbonyltyrosine (**3**), was refluxed in methanol in the presence of BF_3·Et_2O for 7 h to give rise to methyl *N*-protected dimethoxy-

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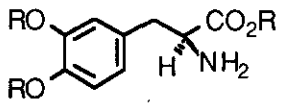
¶ This paper is dedicated to the memory of Professor Yoshio Ban.



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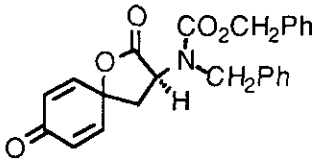

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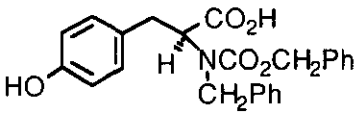

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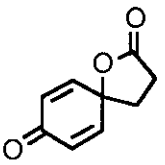

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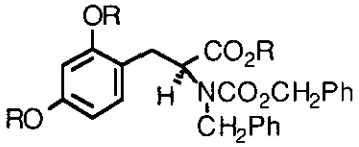
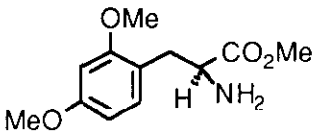


4 : R = Me
9 : R = Et
10 : R = *i*–Pr



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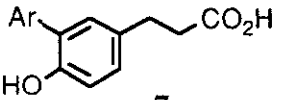

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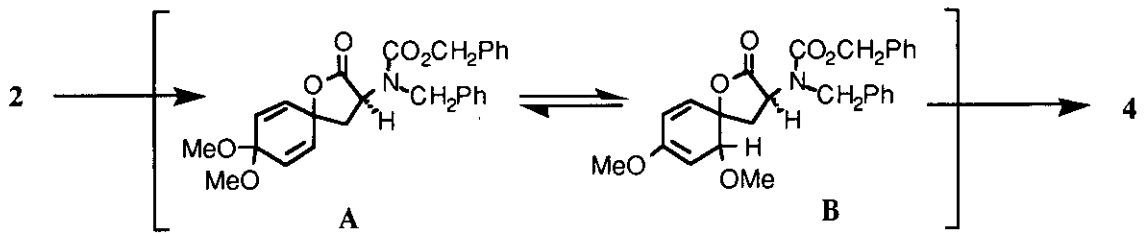
phenylalaninate (**4**) (76 %) as a sole product. Structure of **4** was determined as follows. Hydrogenolysis on 10% Pd-C of **4** afforded the deprotected amino ester (**5**), mp 164-166 °C (64 %). Previously, Tobinaga's group has reported that a simple dienone lactone (**6**) reacts with activated arenes to furnish 3-aryl-4-hydroxyphenylpropionic acids (**7**).[3] In consequence, substitution of arenes occurs at *ortho* position to the hydroxyl group. However, the product (**5**) was not identical with *O,O*-dimethyl-L-DOPA methyl ester (**8**) by comparison of both spectral data. ^{1}H-Nmr spectrum of **5** shows that two aromatic protons appear in higher field than another one. It indicates that structure of the diether should be **5** among theoretically possible diethers. In order to determine unambiguously the site of newly introduced methoxyl groups, racemic 2,4-dimethoxyphenylalanine derivative [(±)-**5**] was prepared *via* an azlactone in an unequivocal manner.[4] Spectral charts (ir and ^{1}H-nmr) of the racemate are expectedly superimposed on those of optically active product (**5**) described above, respectively.

Then, we propose the following mechanism for the *meta* methoxyl introduction (Scheme). At first, acid catalyzed acetalization on dienone carbonyl occurs to give a dimethoxy lactone (**A**), which may be in equilibrium with another dimethoxy lactone (**B**). Finally, lactone-ring opening of **B** with simultaneous

Scheme



aromatization and subsequent esterification forms **4**.

Optical purity of **5** {$[\alpha]_D^{33}$ = +9.05° (c=0.574, $CHCl_3$)} was confirmed to be 88% ee[5] by hplc analysis [DAICEL CHIRALCEL OJ; hexane-EtOH (1:1)] after converting into its (+)-MTPA amide.

Similar treatment of the dienone lactone (**2**) with ethanol and 2-propanol in the presence of BF_3·Et_2O, afforded the corresponding dialkoxy-L-phenylalanine esters (**9** and **10**) in the yield of 80 and 55%, respectively. Alkoxylated sites of the products were deduced on the basis of their spectral evidence. Thus, a new method for alkoxylation at *meta* position to hydroxyl group of L-tyrosine was developed. Reaction of the dienone lactone (**2**) with other nucleophiles is now in progress.

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EXPERIMENTAL

GENERAL--- All melting points were measured on a Büchi melting point apparatus and are uncorrected. Ir spectra were taken with a Hitachi model 260-10 spectrophotometer in $CHCl_3$ solution. ^{1}H-Nmr spectra were recorded on a JEOL model FX-100 or GSX-500 spectrometer in $CDCl_3$ solution using Me_4Si as internal standard. Ms were measured on a Hitachi M-80 or M-80A spectrometer. HRms were measured on a Hitachi M-80 spectrometer.

(*S*)-*N*-Benzyl-*N*-Cbz-tyrosine (3) --- Concentrated sulfuric acid (7 ml) was added drop by drop into a stirred solution of (*S*)-*N*-benzyltyrosine[6] (10 g, 37 mmol) in MeOH (150 ml). The mixture was refluxed for 10 h and evaporated *in vacuo*. Then water (100 ml) was added to the residue and the whole was basified to pH 8 with $NaHCO_3$ (powder). AcOEt (100 ml) was added and the mixture was stirred. Insoluble material was filtered off and aqueous layer was extracted with AcOEt. Combined organic layer was washed with brine and dried over $MgSO_4$. The solvent was evaporated *in vacuo* to give methyl *N*-benzyl-L-tyrosinate as colorless crystals (9.25 g, 88%, mp 55-57 °C). A solution of benzyl chloroformate (12.5 g, 73.5 mmol) in acetone (25 ml) was added dropwise to a stirred mixture of the ester (9.25 g, 32.6 mmol), anhydrous K_2CO_3 (12 g, 87 mmol), acetone (135 ml) and water (65 ml) during 30 min at room temperature. After stirring was further continued for 30 min, reaction mixture was diluted with water. The product was extracted with benzene and the organic layer was washed with brine and dried over $MgSO_4$. The solvent was evaporated *in vacuo* to give methyl (*S*)-*N*-benzyl-*N*-Cbz-tyrosinate as a pale yellow oil (18.3 g), to a solution of which in MeCN (65 ml) and MeOH (65 ml) was added 2N NaOH solution (81 ml, 162 mmol) and the whole was stirred at room temperature for 2 h. Reaction mixture was diluted with water (100 ml) and washed twice with benzene. Aqueous layer was acidified to pH 3 with 6N HCl (*ca.* 23 ml) and the product was extracted with AcOEt. Organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* to afford a yellowish brown oil, which was triturated in a mixture of AcOEt and hexane to give the title compound (**3**) as crystals (13.1 g, quantitative). Recrystallization from AcOEt-hexane yielded colorless prisms; mp 127-129 °C; ir 3600 (OH), 3350 (COOH), 1700 (N-$COOCH_2Ph$) cm^{-1}; ^{1}H-nmr δ 3.16 (2H, d, J = 7.1 Hz, N-CH-CH_2Ar), 3.84 (2H, AB type, J = 11.4 Hz, NCH_2Ph), 4.13 (1H, t, J = 7.1 Hz, N-C*H*-CH_2Ar), 5.17 (2H, AB type, J = 10 Hz, $NCOOCH_2Ph$), 6.61 (2H, d, J = 8.6 Hz, 3- and 5-H), 6.71-7.36 (12H, m, 12 x ArH); $[\alpha]_D^{27}$ = -139.3° (c=1, MeOH); ms (*m/z*) 405 (M^+). *Anal.* Calcd for $C_{24}H_{23}NO_5$: C, 71.09; H, 5.72; N, 3.46. Found: C, 71.19; H, 5.55; N, 3.63.

(*S*)-3-(*N*-Benzyl-*N*-Cbz-amino)-1-oxaspiro[4.5]deca-6,9-diene-2,8-dione (2) --- *Iodo*-benzene bis(trifluoroacetate) (1.825 g, 2.75 mmol) was added in one portion to a solution of **3** (1.013

g, 2.5 mmol) in MeCN-H_2O (4:1) (25 ml) at room temperature. The mixture was stirred for 1 h at the same temperature and diluted with water (20 ml). The product was extracted with EtOAc and the organic layer was washed with brine. After drying over $MgSO_4$, the solvent was evaporated *in vacuo*. The residue (1.58 g) was purified by silica gel column chromatography [eluent; hexane-EtOAc (2:1)] to give pale yellow crystals (**2**) (634 mg, 63%), which were recrystallized from benzene-hexane to yield colorless crystals; mp 104-106 °C; ir 1785 (lactone C=O), 1690, 1670 (NHCOO and dienone CO) cm^{-1}; ^{1}H-nmr δ (2H, m, N-CH-CH_2), 4.16 (1H, t, J = 10 Hz, N-CH-CH$_2$), 4.64 (2H, AB type, J = 15.7 Hz, NCH_2Ph), 5.21 (2H, s, OCH_2Ph), 6.16 (2H, m, O=C-CH=CH), 6.58 (2H, m, O=C-CH=CH), 7.26 (10H, m, 10 x Ar-H); $[\alpha]_D^{25}$ = -2.18° (c=1, $CHCl_3$); ms (*m/z*) 403 (M^+). *Anal.* Calcd for $C_{24}H_{21}NO_5$: C, 71.45; H, 5.25; N, 3.47. Found: C, 71.68; H, 5.41; N, 3.45.

General procedure for preparation of alkyl (*S*)-*N*-benzyl-*N*-Cbz-2,4-dialkoxyphenyl-alaninates (4, 9 and 10) --- To a solution of the dienone lactone (**2**) (100 mg, 0.25 mmol) in anhydrous alcohols (10 ml), was added BF_3·Et_2O (1 ml, 7.9 mmol) at room temperarure. The whole was refluxed on an oil bath for 7 h. Reaction mixture was neutrallized with 5% aqueous $NaHCO_3$ solution and the product was extracted with $CHCl_3$. Organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the solvent *in vacuo* gave crude product, which was purified by silica gel column chromatography [eluant: hexane-AcOEt (1 : 1)] to afford alkyl (*S*)-*N*-benzyl-*N*-Cbz-2,4-dialkoxyphenyl-alaninates.

Methyl (*S*)-*N*-benzyl-*N*-Cbz-2,4-dimethoxyphenylalaninate (**4**) : a pale yellow oil (72 mg, 76 %); ir 1745 (ester C=O), 1700 (NHCOO) cm^{-1}; ^{1}H-nmr δ 3.20 (2H, br s, Ar-CH_2-CH), 3.36 (2H, s, NCH_2Ph), 3.60 (6H, s, 2 x OCH_3), 3.76 (3H, s, OCH_3), 4.36 (1H, br s, COCHN-), 5.16 (2H, s, OCH_2Ph), 6.10-6.36 (2H, m, 3- and 5-H), 6.64-6.90 (1H, m, 6-H), 7.12, 7.24 (each 5H, s, 10 x Ar-H); ms (*m/z*) 463 (M^+). HRms *m/z* calcd for $C_{27}H_{29}NO_6$(M^+): 463.1993, found: 463.2012.

Ethyl (*S*)-*N*-benzyl-*N*-Cbz-2,4-diethoxyphenylalaninate (**9**) : a pale yellow oil (122 mg, 80 %); ir 1740 (ester C=O), 1700 (NHCOO) cm^{-1}; ^{1}H-nmr δ 1.28 (3H, t, J = 7.1 Hz, CH_3), 1.40 (6H, t, J = 7.1 Hz, 2 x CH_3), 3.87 (2H, q, J = 7.1 Hz, OCH_2CH$_3$), 3.97 (4H, q, J = 7.1 Hz, 2 x OCH_2CH$_3$), 5.14 (2H,

br s, OCH_2Ph), 6.28 (2H, m, 3- and 5-H), 6.80 (1H, m, 6-H), 7.16, 7.24 (each 5H, br s, 10 x Ar-H); ms (*m/z*) 505 (M^+). HRms *m/z* calcd for $C_{30}H_{35}NO_6(M^+)$: 505.2462, found: 505.2462.

Isopropyl (*S*)-*N*-benzyl-*N*-Cbz-2,4-diisopropoxyphenylalaninate (10) : a pale yellow oil (75 mg, 55 %); ir 1745 (ester C=O), 1710 (NHCOO) cm^{-1}; ^{1}H-nmr δ 1.00-1.40 (18H, m, 6 x CH_3), 4.00-5.20 [3H, m, 3 x $OCH(CH_3)_2$], 5.10 (2H, br s, OCH_2Ph), 6.32 (2H, m, 3- and 5-H), 6.80 (1H, m, 6-H), 7.14, 7.32 (each 5H, br s, 10 x Ar-H); ms (*m/z*) 547 (M^+). HRms *m/z* calcd for $C_{33}H_{41}NO_6(M^+)$: 547.2931, found: 547.2932.

Methyl (*S*)-2,4-dimethoxyphenylalaninate (5) --- 10% Pd-C (20 mg) was added to a solution of **4** (100 mg, 0.22 mmol) in AcOEt (22 ml). Then the whole was shaken in an atmosphere of hydrogen until uptake of hydrogen was ceased. After the catalyst was filterd off, the filtrate was condenced *in vacuo*. 5% Aqueous $NaHCO_3$ solution was added to the residue and the product was extracted with $CHCl_3$. Organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent *in vacuo* gave a brown oil (50 mg), which was purified by preparative tlc [developing solvent: $CHCl_3$-MeOH (50 : 1)] to yield the title compound (**5**) as a pale brown oil (33 mg, 64 %); ir 3400 (NH_2), 1740 (ester C=O) cm^{-1}; ^{1}H-nmr δ 1.59 (2H, s, NH_2), 2.78 [1H, dd, *J* = 13.6, 8.1 Hz, ArC*H*(H)-CH], 3.05 [1H, dd, *J* = 13.6, 5.5 Hz, ArC*H*(H)-CH], 3.70, 3.79, 3.80 (each 3H, s, OCH_3), 3.76 (1H, dd, *J* = 8.1, 5.5 Hz, $ArCH_2$-C*H*), 6.42 (1H, dd, *J* = 8.1, 2.6 Hz, 5-H), 6.45 (1H, d, *J* = 2.6 Hz, 3-H), 7.02 (1H, d, *J* = 8.1 Hz, 6-H); $[\alpha]_D^{33}$ = +9.05° (c=0.574, $CHCl_3$); ms (*m/z*) 239 (M^+). HRms *m/z* calcd for $C_{12}H_{17}NO_4(M^+)$: 239.1156, found: 239.1159.

Methyl (±)-2,4-dimethoxyphenylalaninate [(±)-5] --- A mixture of (±)-2-benzamido-3-(2',4'-dimethoxyphenyl)propionic acid[4] (677 mg, 2.1 mmol), dioxane (10 ml) and 6N HCl (40 ml, 240 mmol) was refluxed for 12 h. After concentration, water was added to the residue, and the mixture was concentrated *in vacuo*. MeOH was added to the residue, and removal of the solvent *in vacuo* was repeated. Then the product was dissolved in MeOH (10 ml) and excess diazomethane ether solution was added to the stirred solution under ice-cooling. The whole was stirred at room temperature for 1 h, and the solvent was

evaporated *in vacuo*. 5% Aqueous $NaHCO_3$ solution was added to the residue and the product was extracted with $CHCl_3$. The organic layer was washed with brine and dried over K_2CO_3. Evaporation of the solvent gave a brown oil, which was purified on silica gel column chromatography with $CHCl_3$-MeOH (200:1-50:1) as eluent to afford a pale brown oil [(±)-**5**] (163 mg, 33 %). Ir and ^{1}H-nmr spectra of (±)-**5** were superimposable on those of (*S*)-**5**, respectively.

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