Efficient Synthesis of Selectively Protected L-Dopa Derivatives from L-Tyrosine via Reimer−Tiemann and Dakin Reactions

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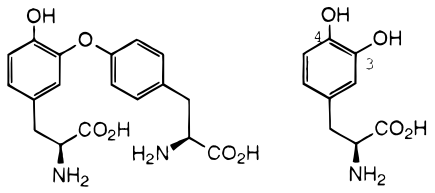
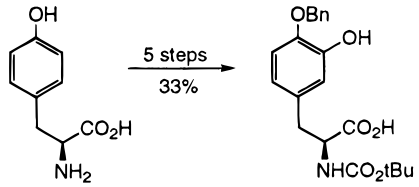
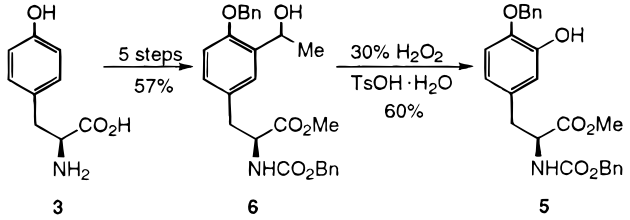
Isodityrosine (**1**) is a naturally occurring dimeric amino acid[2] that is a key structural unit of a large group of biologically active compounds, e.g., the antifungal agent piperazinomycin,[3] K-13, an inhibitor of angiotensin I converting enzyme,[4] the aminopeptidase B inhibitors, OF4949-I-IV,[5] the cytotoxic hexapeptides bouvardin and deoxybouvardin,[6] and the antitumor antibiotics, RA-I-IV.[7] All of these compounds have within their structure a unit of L-Dopa [L-3-(3,4-dihydroxyphenyl)alanine (**2**)] usually with the 3-hydroxyl group as an aryl ether. Indeed,



several synthetic approaches to these compounds[8] utilize an L-Dopa derivative in a key synthetic step. For this reason, routes to such L-Dopa derivatives in which the 4-hydroxyl group is selectively protected have been and continue to be of interest. We report herein a new and very efficient (33% overall yield) five-step synthesis of *N*-Boc-L-3-[3-hydroxy-4-(phenylmethoxy)phenyl]alanine (**4**) from inexpensive L-tyrosine (**3**) that utilizes a simple formylation (Reimer−Tiemann reaction) and a Dakin reaction as the key steps.



Several syntheses of selectively protected L-Dopa derivatives have been reported,[9,10] the best being that of Boger and Yohannes,[9] which afforded the 4-*O*-benzyl-*N*-Cbz-L-Dopa methyl ester **5** from L-tyrosine (**3**) in six steps and 34% overall yield. The key step in this approach involved the acid-promoted oxidative rearrangement of a benzylic hydroperoxide prepared by treatment of the secondary benzylic alcohol **6** with 30% hydrogen peroxide and tosic acid. Other routes have used a Baeyer−Villiger



oxidation of 3-acetyl-L-tyrosine derivatives,[10a−c] selective monoprotection of the catechol unit of L-Dopa,[10a,d−f] and conversion of 3-amino-L-tyrosine derivatives into the L-Dopa analogues via diazotization and displacement with hydroxide.[10a,g,h] It is interesting to note that even though the Baeyer−Villiger oxidation of 3-acetyl-L-tyrosine hydrochloride itself works quite well to give undifferentiated L-Dopa (75%),[10b] the Baeyer−Villiger oxidation of protected 3-acetyl-L-tyrosine derivatives is generally poor (∼30%), and thus, Boger used the higher-yielding two-step method of reduction and peroxide rearrangement instead.[9] We reasoned that one might obtain much higher yields of the desired phenol by an application of the Dakin reaction, namely the oxidation of aryl aldehydes having electron-rich aromatic rings. Thus, if one could produce the protected 3-formyl-L-tyrosine derivative in good yields, one should be able to produce the desired monoprotected L-Dopa derivative **4** in good yields from L-tyrosine (**3**) by this process.

Our synthesis (Scheme 1) begins with simple protection of L-tyrosine (**3**) to give in 92% yield the *N*-Boc derivative **7** (which is also commercially available). In general, formylation of phenols using a Reimer−Tiemann process[11] is quite often low-yielding.[12] However, use of the slightly hydrated solid−liquid medium conditions of Delmas,[12a] namely treatment of the phenol **7** with

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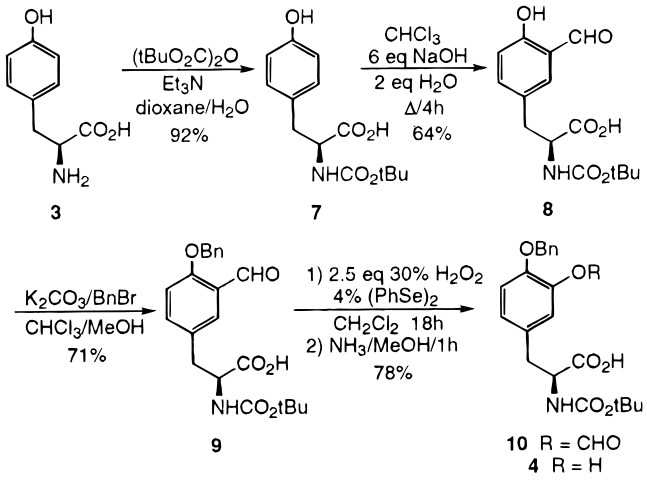
Scheme 1



chloroform and solid sodium hydroxide in the presence of a small amount of water, gave the desired 2-formyl compound **8** in 64% yield based on unrecovered starting material. Benzylation of the phenol of **8** was easily accomplished using potassium carbonate and benzyl bromide to give the benzyl ether aldehyde **9** in 71% yield. The final transformation is the Dakin oxidation of the aryl aldehyde to give the required phenol. Many sets of conditions have been developed[13] to raise the yield of this oxidation, and we investigated several of these before choosing the Syper process[13e] of using arylselenium compounds as activators for this oxidation. Therefore, treatment of the aldehyde **9** with 2.5 equiv of 30% hydrogen peroxide in the presence of 4% diphenyl diselenide in dichloromethane for 18 h gave the desired aryl formate **10** in excellent yield. This ester was cleaved by treatment with methanolic ammonia for 1 h to afford the desired phenol **4** in an overall yield of 78% for the two steps. This final conversion of the aldehyde **9** into **4** could be accomplished without isolation of the formate by allowing the oxidation mixture to stir for an extended period of time, e.g., 36 h, but at a slight cost in the yield. Thus, in either four or five operations, one can convert L-tyrosine (**3**) into the selectively monoprotected L-Dopa derivative, *N*-Boc-L-3-[3-hydroxy-4-(phenylmethoxy)phenyl]alanine (**4**), in 33% overall yield. Compounds such as **4** have been used in the synthesis of isodityrosine antibiotics.[8]

Thus, we have developed a new route to the important selectively protected L-Dopa derivative **4** from L-tyrosine (**3**) via applications of the Reimer−Tiemann reaction and the Dakin oxidation. The use of this compound for the synthesis of such derivatives is under investigation in our laboratories and will be reported in due course.

Experimental Section

Dichloromethane and methanol were distilled prior to use, the former from calcium hydride and the latter from magnesium. Dioxane and chloroform were of analytical grade and were used without further purification. Other reagents were used as provided. All reactions were carried out under a positive nitrogen pressure. Flash chromatography was performed on ICN silica 32−63.

***N*-[(1,1-Dimethylethoxy)carbonyl]-L-tyrosine (7).** Triethylamine (5.81 mL, 41.4 mmol) was added to a solution of L-tyrosine (**3**) (Aldrich, 5 g, 27.6 mmol) in 1/1 dioxane/water (100 mL). The reaction flask was cooled to 0 °C with an ice/water bath, and di-*tert*-butyl dicarbonate (6.6 g, 30.4 mmol) was added in one batch. After 30 min, the cold bath was removed, and the reaction mixture was stirred at ambient temperature for 18 h. The reaction mixture was then concentrated on a rotary evaporator and the residue diluted with water and ethyl acetate. The aqueous layer was washed with ethyl acetate, acidified to pH 1 with 1 N HCl, and back-extracted with ethyl acetate. The organic extracts were washed with brine, dried over $MgSO_4$, and evaporated to give the protected amino acid, *N*-Boc-L-tyrosine (**7**) as a white foam (7.12 g, 92%), which was used in the next step without further purification: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.0 (2H, d, J = 7.8 Hz, C3-H, C5-H), 6.74 (2H, d, J = 7.8 Hz, C2-H, C6-H), 5.92 (1H, bs, OH), 5.06 (1H, bs, NH), 4.58 (unresolved m, 1H, αH), 3.02 (2H, unresolved m, βH), 1.42 (9H, s, Boc); ^{13}C NMR (MeOD, 90 MHz) δ 175.5, 157.7, 157.1, 131.2, 129.1, 116.1, 80.5, 57.8, 37.8, 28.6; IR (neat) ν_{max} 3445, 2962, 1690, 1518 cm^{-1}.

***N*-[(1,1-Dimethylethoxy)carbonyl]-3-(3-formyl-4-hydroxyphenyl)-L-alanine (8).** Powdered sodium hydroxide (1.71 g, 42.72 mmol) was added to a suspension of *N*-Boc L-tyrosine (**7**) (2 g, 7.12 mmol), water (0.256 mL, 14.13 mmol), and chloroform (30 mL). The mixture was refluxed for 4 h. Additional sodium hydroxide was added (0.42 g, 10.68 mmol) after 1 and 1.5 h. The reaction was then diluted with water and ethyl acetate, and the aqueous layer was acidified to pH 1 with 1 N HCl and back-extracted with ethyl acetate. The organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. Flash column chromatography (silica gel, 12/1 $CHCl_3$/MeOH 1% acetic acid eluent) afforded the desired product **8** as a brown oil (0.72 g, 33%) and recovered starting material **7** (0.62 g, 31%). The yield of **8** based on recovered starting material was 66%: ^{1}H NMR ($CDCl_3$, 360 MHz) δ 10.90 (1H, s, OH), 9.84 (1H, s, CHO), 7.36 (1H, s, C2-H), 7.33 (1H, d, J = 8.3 Hz, C6-H), 6.93 (1H, d, J = 8.3 Hz, C5-H), 5.28 (1H, bs, NH), 4.96 (1H, unresolved m, αH), 3.17 (1H, unresolved m, βH), 3.04 (1H, unresolved m, βH), 1.40 (9H, s, Boc); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 196.6, 175.6, 160.5, 155.3, 138.1, 134.2, 127.6, 120.4, 117.7, 80.4, 54.2, 36.8, 28.2; IR (neat) ν_{max} 3400, 2980, 1713, 1659, 1489 cm^{-1}.

***N*-[(1,1-Dimethylethoxy)carbonyl]-3-[3-formyl-4-(phenylmethoxy)phenyl]-L-alanine (9).** A solution of anhydrous potassium carbonate (0.506 g, 3.66 mmol) in 2/1 chloroform/methanol (6 mL) was refluxed for 15 min. The 3-formyl-*N*-Boc-L-tyrosine **8** (0.257 g, 0.832 mmol) and benzyl bromide (0.148 mL, 1.25 mmol) were added, and the mixture was refluxed for 4 h. The reaction was then diluted with water and ethyl acetate. The aqueous layer was acidified to pH 1 with 1 N HCl and back-extracted with ethyl acetate. The organic extracts were washed with brine, dried over $MgSO_4$, and concentrated to give the desired product **9** as a yellow oil (0.237 g, 71%), which was used in the next step without further purification: ^{1}H NMR ($CDCl_3$, 360 MHz) δ 10.52 (1H, s, CHO), 7.67 (1H, s, C2-H), 7.41 (6H, m, C6-H, Ph), 7.04 (1H, d, J = 8.6 Hz, C5-H), 5.18 (2H, s, CH_2Ph), 4.98 (1H, bs, NH), 4.58 (1H, unresolved m, αH), 3.18 (1H, unresolved m, βH), 3.10 (1H, unresolved m, βH), 1.42 (9H, s, Boc); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 189.9, 175.3, 160.2, 155.3, 137.0, 136.0, 129.2, 128.7, 128.2, 127.3, 124.8, 113.3, 80.3, 70.5, 54.1, 36.9, 28.2; IR (neat) ν_{max} 3343, 2980, 1686, 1611, 1499 cm^{-1}.

***N*-[(1,1-Dimethylethoxy)carbonyl]-3-[3-hydroxy-4-(phenylmethoxy)phenyl]-L-alanine (4).** To a solution of the 3-formyl-4-(benzyloxy)-*N*-Boc-L-tyrosine **9** (0.096 g, 0.24 mmol) in dichloromethane (3 mL) were added diphenyl diselenide (0.003 g, 0.01 mmol) and 30% aqueous hydrogen peroxide (0.062 mL, 0.614 mmol). The reaction mixture was stirred at ambient temperature for 18 h. The mixture was then diluted with water and ethyl acetate, washed with brine, dried over $MgSO_4$, and concentrated on a rotary evaporator. The residue was dissolved in methanol (3 mL), and gaseous ammonia was bubbled through the solution for 20 min. The reaction mixture was then stirred at ambient temperature for 1 h. The mixture was then concentrated and the residue redissolved in water. The aqueous solution was acidified to pH 1 with 1 N HCl and back-extracted with ethyl acetate. The organic extracts were washed with

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brine, dried over $MgSO_4$, and concentrated to give the desired product **4** as a white foam (0.073 g, 78% for two steps): ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.39 (5H, m, Ph), 6.85 (1H, d, J = 8.2 Hz, C5-H), 6.76 (1H, s, C2-H), 6.64 (1H, d, J = 8.2 Hz, C6-H), 5.60 (1H, bs, OH), 5.28 (2H, s, CH_2Ph), 5.06 (1H, bs, NH), 4.53 (1H, unresolved m, αH), 3.04 (2H, unresolved m, βH), 1.40 (9H, s, Boc); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 176.0, 155.6, 145.7, 145.0, 136.4, 129.7, 128.6, 128.2, 127.7, 121.0, 115.9, 112.6, 80.1, 71.0, 55.0, 37.1, 28.2; IR (neat) ν_{max} 3355, 3034, 2979, 1709, 1593, 1511 cm^{-1}.

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