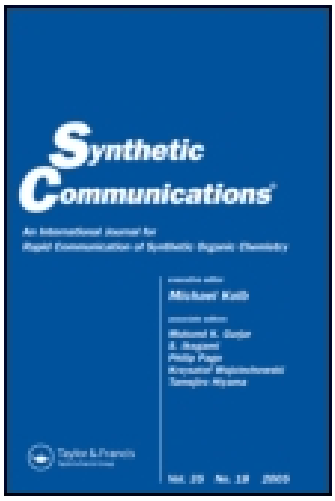

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A CONVENIENT PREPARATION OF SELECTIVELY PROTECTED L-DOPA DERIVATIVES FROM 3-IODO-L-TYROSINE

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A CONVENIENT PREPARATION OF SELECTIVELY PROTECTED L-DOPA DERIVATIVES FROM 3-IODO-L-TYROSINE

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ABSTRACT

Palladium-catalyzed hydroformylation of 3-iodo-L-tyrosine derivatives **la**,**b** followed by protection of the free phenol as its benzyl ether and Baeyer-Villiger oxidation of the 3-formyl group provided the desired L-Dopa derivatives **4b**,**c** in 71 and 68% overall yields, respectively.

L-Dopa derivatives in which the 4-OH group is selectively protected are useful building blocks for the synthesis of a series of biologically active natural products, in particular those containing the key structural unit isodityrosine such as piperazinomycin,[1] K-13,[2] OF4949-I-IV,[3] bouvardin and deoxybouvardin,[4] and RA-I-XVI.[5]

Past syntheses of selectively protected L-Dopa derivatives have involved monoprotection of the unsymmetrical catechol moiety,[6] diazotization of 3-amino-L-tyrosine derivatives followed by copper(I)-promoted phenol introduction[6d,7] and Baeyer-Villiger oxidation of 3-acetyl-L-tyrosine[8]

* Corresponding author.

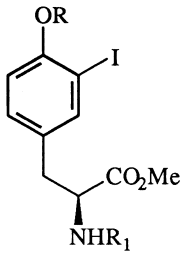
and furnished the desired compounds in 30% yield or less. A benzylic hydroperoxide rearrangement has been later utilized by Boger to obtain **4c** from L-tyrosine in six steps and 34% overall yield.[9] More recently, a five-step synthesis of 4-*O*-benzyl-*N*-Boc-L-Dopa from L-tyrosine via Reimer-Tiemann formylation followed by Dakin oxidation has been described by Jung.[10] The Reimer-Tiemann formylation step afforded however a low yield of the 3-formyl derivative (33%). Eventually, a method based on a modified Baeyer-Villiger oxidation of *N*-Boc-3-acetyl-L-tyrosine benzyl ester has been reported by Chen, Zhu, and Wilcoxen.[11] Although *m*-CPBA oxidation of the acetyl group was very clean (81% yield), it was rather sluggish, requiring 7 days at room temperature.

Following our previous papers on the palladium-catalyzed elaboration of α-amino acids,[12] we report here an alternative and convenient procedure for the preparation of **4b**,**c** from the commercially available and rather inexpensive 3-iodo-L-tyrosine which utilizes as the key step a palladium-catalyzed hydroformylation reaction.

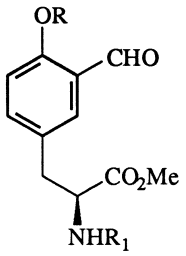
First attempts were made on a fully protected 3-iodo-L-tyrosine (**1c**), adopting a procedure similar to that developed originally by Kotsuki[13] for aryl triflates and applied successfully by us to the preparation of **4**-hydroxymethyl-L-phenylalanine.[12b] Reaction of **1c** with carbon monoxide and trioctylsilane in the presence of $Pd(OAc)_2$/dppp[14] as the catalyst in DMF at 80°C and atmospheric pressure resulted however in premature catalyst decomposition and low conversion. The use of 2 mol of dppp per mole of palladium prolonged the lifetime of the catalyst enough to allow a near complete conversion after 24 h, but afforded the desired aldehyde **2c** along with the concomitant reduction product **3** in 34 and 50% yields, respectively. Faster conversions were observed with dppe[15] and, especially, dppf[15] as the ligands, but again the main reaction product was **3**, nor could the selectivity be improved by slow addition of the organosilane.

The hydroformylation reaction using $Pd(OAc)_2$/2dppf as the catalytic system was then tried on the free phenol **1a**. The reaction went to completion in 6 h and appeared uncontaminated from the reduction product, even by fast introduction of silane reagent. Beside the aldehyde **2a** (52% yield), the trioctylsilyl ether **2b** was produced (26% yield) as the result of the silylation of the free phenol by Oct_3SiI arising from hydroformylation reaction. Subjecting the carbonylation reaction mixture to a fluoride ion-induced desilylation before work-up, we were able to isolate **2a** in 77% yield. Even more gratifying was however the use of Et_3SiH instead of Oct_3SiH. The reaction went to completion in 1.5 h and afforded **2a** in 85% yield.

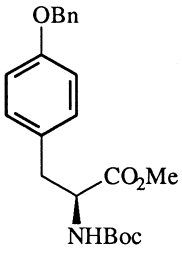
Thus, in contrast to Kotsuki's findings, the use of dppf as the ligand and of Et_3SiH as the hydride donor did not 'prove to be too reactive to control the reaction selectivity'.[13] Triethylsilane has been previously



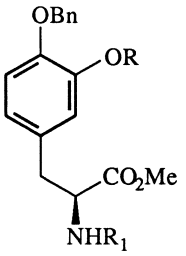
1a: R = H; R_1 = Boc
1b: R = H; R_1 = Cbz
1c: R = Bn; R_1 = Boc



2a: R = H; R_1 = Boc
2b: R = $SiOct_3$; R_1 = Boc
2c: R = Bn; R_1 = Boc
2d: R = H; R_1 = Cbz
2e: R = Bn; R_1 = Cbz



3



4a: R = CHO; R_1 = Boc
4b: R = H; R_1 = Boc
4c: R = H; R_1 = Cbz

employed as hydride donor in the carbonylation of arenediazonium salts[16] and aryl iodides,[17] but pressurized CO had to be used to obtain satisfactory yields of aldehydes in the former case, while in the carbonylation of aryl iodides a Pd-Co bimetallic system was investigated and the major products were either benzyl silyl ethers or 1,2-diaryl-1,2-disiloxyethanes.

Benzylation of the free phenol was accomplished utilizing Boger's conditions ($BnBr/K_2CO_3/n$-Bu_4NI/DMF, rt)[9] to minimize possible racemization and provided **2c** in near quantitative yield. Baeyer-Villiger oxidation of **2c** with 1.5 equiv of *m*-chloroperbenzoic acid in CH_2Cl_2 at room temperature was complete in **7 h** to give the corresponding formate **4a** in 88% yield. The formate group was smoothly cleaved by treatment with methanolic ammonia at room temperature for 0.5 h to afford **4b** in 95% yield. The two-step reaction sequence leading from **2c** to **4b** can be conveniently conducted as a one-pot operation that omits the isolation of the formate. The monoprotected L-Dopa derivative **4b** was isolated in 84% yield from **2c**.

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Thus, in a four-step procedure, **4b** was obtained from 3-iodo-L-tyrosine derivative **1a** in 71% overall yield.

Repetition of the same four-step procedure on **1b** led to *N*-Cbz-4-*O*-benzyl-L-Dopa methyl ester (**4c**) in 68% overall yield. Physical data for **4c** were in good agreement with the values reported in the literature.[9]

EXPERIMENTAL SECTION

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Optical rotations were measured at 25°C with a Schmidt-Haensch Polartronic D polarimeter (1 dm-cell) in 1% $CHCl_3$ solutions, unless otherwise indicated. IR spectra were recorded on a Perkin-Elmer 983 spectrophotometer as $CHCl_3$ solutions. ^1H and ^{13}C NMR spectra were obtained on a Varian Mercury 300 spectrometer using $CDCl_3$ as solvent and TMS as internal standard. Microanalyses have been performed by Dr. L. Petrilli of Servizio Microanalisi del C.N.R., Area della Ricerca di Roma, 00016 Monterotondo Stazione, Roma, Italy.

***N*-[(1,1-Dimethylethoxy)carbonyl]-3-iodo-L-tyrosine Methyl Ester (1a)**. Dry HCl was slowly bubbled through a stirred suspension of 3-iodo-L-tyrosine (2.00 g, 6.51 mmol) in dry MeOH (30 mL) for 2 h at 0°C. The final solution was evaporated under reduced pressure to leave a white solid (2.31 g, 99%) which was used in the next step without further purification. A suspension of the above methyl ester hydrochloride in dry CH_2Cl_2 (25 mL) was treated with Et_3N (2.73 mL, 19.5 mmol) and di-*tert*-butyl dicarbonate (1.77 g, 8.12 mmol) at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure and the residue was diluted with Et_2O. The ethereal solution was washed with 10% aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated. The residue (2.84 g) was purified by chromatography on silica gel (57 g) using hexane/AcOEt = 7/3 as eluent to give 2.47 g (90%) of **1a**: mp 111–112°C (CH_2Cl_2/hexane); $[\alpha]_D$ + 46°, +14° (c 1.0, MeOH) {lit.[18] mp 101–103°C; $[\alpha]^{19-26}{}_{246}$ +19° (c 1.0, MeOH)}; IR 3497, 3432, 2984, 1741, 1711, 1487, 1367, 1170 cm^{-1}; ^1H NMR δ 1.43 (9H, s, *t*-Bu), 2.93 (1H, dd, J = 14.1, 6.0 Hz, C<u>H</u>H), 3.03 (1H, dd, J = 14.1, 6.0 Hz, CH<u>H</u>), 3.73 (3H, s, CO_2Me), 4.51 (1H, m, α-CH), 5.04 (1H, d, J = 7.5 Hz, NH), 5.88 (1H, m, OH), 6.86 (1H, d, J = 8.1 Hz, ArH), 6.99 (1H, dd, J = 8.1, 2.1 Hz, ArH), 7.43 (1H, br s, ArH); ^{13}C NMR δ 28.32, 37.00, 52.34, 54.50, 80.21, 85.38, 115.05, 130.03, 130.97, 139.00, 154.19, 155.10, 172.20.

***N*-[(Phenylmethoxy)carbonyl]-3-iodo-L-tyrosine Methyl Ester (1b)**. Crude 3-iodo-L-tyrosine methyl ester hydrochloride, obtained as above from 3-iodo-L-tyrosine (2.00 g, 6.51 mmol), in a two-phase mixture of H_2O (32 mL) and Et_2O (26 mL) was treated with Na_2CO_3 (2.07 g, 19.5 mmol) and

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benzyl chloroformate (0.92 mL, 6.51 mmol) and the resulting mixture was stirred for 3 h at room temperature. The mixture was then diluted with Et_2O, the organic layer was separated, washed with brine, dried (Na_2SO_4), and evaporated. The residue (2.90 g) was chromatographed on silica gel (28 g) with hexane/AcOEt = 75/25 as eluent to give 2.64 g (89%) of **1b**: mp 101–102°C (CH_2Cl_2/hexane); $[\alpha]_D$+49°, +2° (c 1.0, MeOH) {lit.[18] mp 99.5–101°C; $[\alpha]^{19-26}{}_{246}$+2° (c 1.0, MeOH)}; IR 3493, 3428, 2950, 1721, 1486, 1351 cm^{-1}; ^1H NMR δ 2.96 (1H, dd, J = 14.0, 6.0 Hz, CHH), 3.04 (1H, dd, J = 14.0, 6.0 Hz, CHH), 3.72 (3H, s, CO_2Me), 4.59 (1H, m, α-CH), 5.08 (1H, d, J = 12.1 Hz, PhCHHO), 5.12 (1H, d, J = 12.1 Hz, PhCHHO), 5.28 (1H, d, J = 7.8 Hz, NH), 5.59 (1H, br s, OH), 6.84 (1H, d, J = 8.2 Hz, ArH), 6.95 (1H, dd, J = 8.2, 2.1 Hz, ArH), 7.34–7.41 (6H, m, ArH); ^{13}C NMR δ 36.95, 52.42, 54.92, 67.13, 85.52, 115.11, 128.09, 128.25, 128.59, 128.84, 131.03, 136.18, 138.90, 154.20, 155.66, 171.79.

***N*-[(1,1-Dimethylethoxy)carbonyl]-3-formyl-L-tyrosine Methyl Ester (2a)**. A mixture of *N*-Boc-3-iodo-L-tyrosine methyl ester (**1a**, 421 mg, 1 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), dppf (55 mg, 0.10 mmol), and Et_3N (0.35 mL, 2.5 mmol) in DMF (5 mL) was purged with carbon monoxide for 5 min. Then, triethylsilane (0.32 mL, 2 mmol) was introduced in one portion by a syringe and the mixture was stirred under a CO balloon at 80°C for 1.5 h. The mixture was then diluted with brine and extracted with AcOEt. The organic phase was washed two times with brine, dried (Na_2SO_4), and evaporated. The residue (465 mg) was chromatographed on silica gel (14 g) using CH_2Cl_2/AcOEt = 95/5 as eluent to give 275 mg (85%) of **2a**: mp 85–86°C (CH_2Cl_2/hexane); $[\alpha]_D$ +57°; IR 3435, 2990, 1743, 1710, 1658, 1485, 1367, 1284, 1161 cm^{-1}; ^1H NMR δ 1.42 (9H, s, *t*-Bu), 3.01 (1H, dd, J = 13.8, 6.3 Hz, CHH), 3.15 (1H, dd, J = 13.8, 5.6 Hz, CHH), 3.73 (3H, s, CO_2Me), 4.58 (1H, m, α-CH), 5.07 (1H, d, J = 8.1 Hz, NH), 6.93 (1H, d, J = 8.4 Hz, ArH), 7.29–7.33 (2H, m, ArH), 9.86 (1H, s, CHO), 10.92 (1H, s, OH); ^{13}C NMR δ 28.29, 37.42, 52.39, 54.39, 80.19, 117.85, 120.49, 127.73, 134.10, 138.03, 155.03, 160.68, 172.08, 196.38. Anal. Calcd for $C_{16}H_{21}NO_6$ (323.4): C, 59.43; H, 6.55; N, 4.33. Found: C, 59.80; H, 6.81; N, 4.38.

***N*-[(Phenylmethoxy)carbonyl]-3-formyl-L-tyrosine methyl ester (2d)** could be prepared and isolated in a similar manner using *N*-Cbz-3-iodo-L-tyrosine methyl ester (**1b**, 455 mg, 1 mmol) as starting material. The reaction time was 3 h and the yield of **2d** was 82%: mp 75–77°C (Et_2O/petroleum ether); $[\alpha]_D$+47°; IR 3431, 2951, 2849, 1721, 1658, 1499, 1485, 1284 cm^{-1}; ^1H NMR δ 3.03 (1H, dd, J = 14.1, 6.3 Hz, CHH), 3.16 (1H, dd, J = 14.1, 5.7 Hz, CHH), 3.73 (3H, s, CO_2Me), 4.65 (1H, m, α-CH), 5.06 (1H, d, J = 12.0 Hz, PhCHHO), 5.12 (1H, d, J = 12.0 Hz, PhCHHO), 5.32 (1H, d, J = 7.2 Hz, NH), 6.89 (1H, d, J = 7.8 Hz, ArH), 7.24–7.34 (7H, m, ArH), 9.76

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(1H, s, CHO), 10.91 (1H, s, OH); ^{13}C NMR δ 37.24, 52.51, 54.79, 67.09, 117.93, 120.50, 127.37, 128.18, 128.35, 128.58, 134.09, 136.15, 137.94, 155.56, 160.72, 171.70, 196.38. Anal. Calcd for $C_{19}H_{19}NO_6$(357.4): C, 63.86; H, 5.36; N, 3.92. Found: C, 64.03; H, 5.40; N, 3.97.

***N*-[(1,1-Dimethylethoxy)carbonyl]-3-formyl-*O*-(phenylmethyl)-L-tyrosine Methyl Ester (2c)**. A solution of **2a** (323 mg, 1 mmol), in dry DMF (4 mL) was treated with K_2CO_3 (276 mg, 2 mmol), *n*-Bu_4NI (37 mg, 0.1 mmol), and benzyl bromide (0.125 mL, 1.05 mmol). The resulting mixture was stirred at room temperature for 1.5 h, then partitioned between AcOEt and brine. The organic phase was washed twice with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue (460 mg) on silica gel (10 g) using hexane/AcOEt = 65/35 as eluent gave 409 mg (99%) of **2c**: colorless oil; $[\alpha]_D$+58°; IR 3434, 2950, 1738, 1703, 1610, 1494, 1367, 1163 cm^{-1}; ^{1}H NMR δ 1.41 (9H, s, *t*-Bu), 3.00 (1H, dd, J = 14.0, 6.0 Hz, CHH), 3.12 (1H, dd, J = 14.0, 5.4 Hz, CHH), 3.73 (3H, s, CO_2Me), 4.55 (1H, m, α-CH), 5.02 (1H, d, J = 6.9 Hz, NH), 5.17 (2H, s, PhCH_2O), 7.00 (1H, d, J = 9.0 Hz, ArH), 7.26–7.43 (6H, m, ArH), 7.60 (1H, br, s, ArH), 10.52 (1H, s, CHO); ^{13}C NMR δ 28.27, 37.40, 52.36, 54.42, 70.61, 80.07, 113.32, 125.00, 127.33, 128.33, 128.76, 128.86, 129.04, 136.04, 136.70, 155.02, 160.20, 172.09, 189.49. Anal. Calcd for $C_{23}H_{27}NO_6$(413.5): C, 66.81; H, 6.58; N, 3.39. Found: C, 67.10; H, 6.39; N, 3.20.

***N*-[(Phenylmethoxy)carbonyl]-3-formyl-*O*-(phenylmethyl)-L-tyrosine methyl ester (2e)** was prepared and isolated in a similar fashion from **2d** in 98% yield: mp 118–119°C (CH_2Cl_2/hexane); $[\alpha]_D$+59°; IR 3432, 2953, 2869, 1720, 1679, 1611, 1494, 1250 cm^{-1}; ^{1}H NMR δ 3.03 (1H, dd, J = 14.1, 6.1 Hz, CHH), 3.13 (1H, dd, J = 14.1, 5.2 Hz, CHH), 3.73 (3H, s, CO_2Me), 4.63 (1H, m, α-CH), 5.08 (2H, s, PhCH_2O_2C), 5.15 (2H, s, PhCH_2O), 5.29 (1H, d, J = 6.9 Hz, NH), 6.95 (1H, d, J = 8.4 Hz, ArH), 7.25–7.42 (11H, m, ArH), 7.59 (1H, d, J = 2.1 Hz, ArH), 10.50 (1H, s, CHO); ^{13}C NMR δ 37.21, 52.41, 54.75, 66.96, 70.54, 113.28, 124.96, 127.26, 128.03, 128.13, 128.27, 128.47, 128.69, 128.90, 135.93, 136.15, 136.59, 155.51, 160.15, 171.66, 189.34. Anal. Calcd for $C_{26}H_{25}NO_6$ (447.5): C, 69.79; H, 5.63; N, 3.13. Found: C, 70.08; H, 5.65; N, 3.17.

***N*-[(1,1-Dimethylethoxy)carbonyl]-3-hydroxy-*O*-(phenylmethyl)-L-tyrosine Methyl Ester (4b)**. A solution of **2c** (413 mg, 1 mmol) and *m*-chloroperbenzoic acid (381 mg, 68%, 1.5 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 7 h. A 2M solution of NH_3 in MeOH (7.5 mL) was added and the mixture was stirred at room temperature for another 0.5 h. The solution was concentrated under reduced pressure and the residue was diluted with AcOEt, washed with saturated aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated. The residue (415 mg) was chromatographed on silica gel (13 g) with hexane/AcOEt = 73/

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27 as eluent to give 337 mg (84%) of **4b**: colorless oil; $[\alpha]_D$+49°; IR 3539, 3438, 3003, 1709, 1594, 1499, 1368, 1274, 1164 cm^{-1}; ^1H NMR δ 1.42 (9H, s, *t*-Bu), 2.98 (2H, m, β-CH_2), 3.71 (3H, s, CO_2Me), 4.53 (1H, m, α-CH), 5.01 (1H, d, J = 8.1 Hz, NH), 5.07 (2H, s, PhC$\underline{H}_2$O), 5.84 (1H, br s, OH), 6.57 (1H, dd, J = 8.1, 2.1 Hz, ArH), 6.71 (1H, d, J = 2.1 Hz, ArH), 6.83 (1H, d, J = 8.1 Hz, ArH), 7.36–7.40 (5H, m, ArH); ^{13}C NMR δ 28.31, 37.68, 52.17, 54.49, 71.20, 79.90, 112.36, 115.83, 120.76, 127.81, 128.38, 128.72, 129.58, 136.41, 145.01, 145.95, 155.16, 172.39. Anal. Calcd for $C_{22}H_{27}NO_6$ (401.5): C, 65.82; H, 6.78; N, 3.49. Found: C, 65.99; H, 6.87; N, 3.39.

Repetition of the two-step procedure on **2e** gave ***N*-[(phenylmethoxy)-carbonyl]-3-hydroxy-*O*-(phenylmethyl)-L-tyrosine methyl ester (4c)** in 85% overall yield: colorless oil; $[\alpha]_D$+44°, −14° (c 1.0, MeOH) {lit.[9] colorless oil; $[\alpha]^{22}_D$ −15.1° (c 1.0, MeOH)}; IR 3540, 3428, 2951, 1713, 1673, 1599, 1503, 1337, 1275 cm^{-1}; ^1H NMR δ 3.01 (2H, m, β-CH_2), 3.71 (3H, s, CO_2Me), 4.61 (1H, m, α-CH), 5.05 (2H, s, PhC$\underline{H}_2$O or PhC$\underline{H}_2O_2$C), 5.09 (2H, s, PhC$\underline{H}_2O_2$C or PhC$\underline{H}_2$O), 5.26 (1H, d, J = 8.1 Hz, NH), 5.74 (1H, br s, OH), 6.54 (1H, dd, J = 8.4, 2.1 Hz, ArH), 6.69 (1H, d, J = 2.1 Hz, ArH), 6.80 (1H, d, J = 8.4 Hz, ArH), 7.25–7.40 (10H, m, ArH); ^{13}C NMR δ 37.57, 52.29, 54.85, 66.96, 71.20, 112.36, 115.73, 120.77, 127.82, 128.08, 128.14, 128.40, 128.51, 128.73, 129.26, 136.35, 145.06, 145.99, 155.70, 172.01.

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