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Effective syntheses of quinoline-7,8-diol, 5-amino-L-DOPA, and 3-(7,8-dihydroxyquinolin-5-yl)-L-alanine

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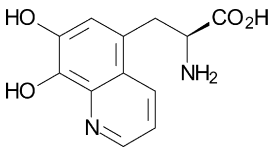
Dedicated to Professor Dieter Seebach on the occasion of his 65th birthday

Abstract—A modification of the Baeyer–Villiger reaction allows the conversion of aromatic 2-hydroxy-3-nitroketones and aldehydes into 3-nitrocatechols, which can be reduced to 3-aminocatechols. Reaction of the latter with acrolein yields quinoline-7,8-diols under exceptionally mild conditions. This new reaction sequence was successfully applied to the synthesis of the title compounds.

1. Introduction

Like the corresponding 8-hydroxy derivative,[1] (7,8-dihydroxyquinolin-5-yl)-L-alanine (**1**) can be expected to form metal complexes. In addition, **1** can participate in electron transfer reactions and may be regarded as a biosynthetic precursor of the cytotoxic marine alkaloid halitulin.[2–4] In this publication we describe an efficient synthesis of this interesting amino acid from L-tyrosine.



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2. Results and discussion

Our synthesis of **1** commences from 3-acetyl-L-tyrosine (**2**) which can be easily prepared by Friedel–Crafts acetylation of L-tyrosine[5] (Scheme 1). Esterification of **2** with methanol and treatment of the resulting ester **3** with trichloroethoxycarbonyl (Troc) chloride yielded the *N*-protected amino acid ester **4**. Nitration of **4** with 100% nitric acid in acetic acid[6] afforded the 3-acetyl-5-nitro-L-tyrosine derivative **5** in good yield.

Attempts to convert **5** with peracetic acid or *meta*-chloroperbenzoic acid into the desired DOPA derivative were unsuccessful,[7] and the starting material was recovered even after several days of exposure to the peracid. The reluctance of aromatic 2-hydroxy-3-nitroaldehydes and ketones to undergo the Baeyer–Villiger rearrangement is well known,[8] and in a comprehensive review[9] no successful example for this type of reaction is given. We were, therefore, pleased to obtain *O*-acetylcatechol **6** in up to 89% yield by treatment of ketone **5** with peracetic acid, followed by chromatography of the crude reaction mixture on a silica gel column (Scheme 2). Even more effective is the direct conversion of ketone **5** into the free catechol **7** by addition of a solution of ammonia in methanol to the mixture of **5** and the peracid.

Our procedure is of general value for the synthesis of 3-nitrocatechols.[3] Thus far, compounds of this type have only been accessible by more complicated[10] or uneconomic[11] routes. Mechanistically, the action of ammonia or silica gel on the reaction mixture may assist the formation and breakdown of the crucial epoxy intermediate **10**[12] from the phenolic precursor **9** (Scheme 3).

Methylation of the dihydroxyphenylalanine (DOPA) derivative **7** with dimethyl sulfate yielded the dimethyl ether **8**. In the same manner, acetate **6** may be used to prepare mono *O*-protected derivatives of **7**.

Hydrogenation of the 5-nitro-DOPA derivatives **7** and **8** with Pd–C (10%) in 0.2 M methanolic HCl yielded the 5-amino derivatives **11** and **12**, respectively, in form of their hydrochlorides. Neutral conditions led to partial dechlorination of the N-protecting group. The hydrobromide of free 5-amino-L-DOPA (**13**) was obtained by heating **11** in 48% aqueous HBr. The amine **12**, prepared from L-tyrosine in 30% overall yield, is a valuable starting material for the synthesis of 5-substituted DOPA derivatives. Thus, diazotation under standard conditions yielded the crystalline

Keywords: Baeyer–Villiger reaction; 3-aminocatechols; quinolines; L-DOPA derivatives.

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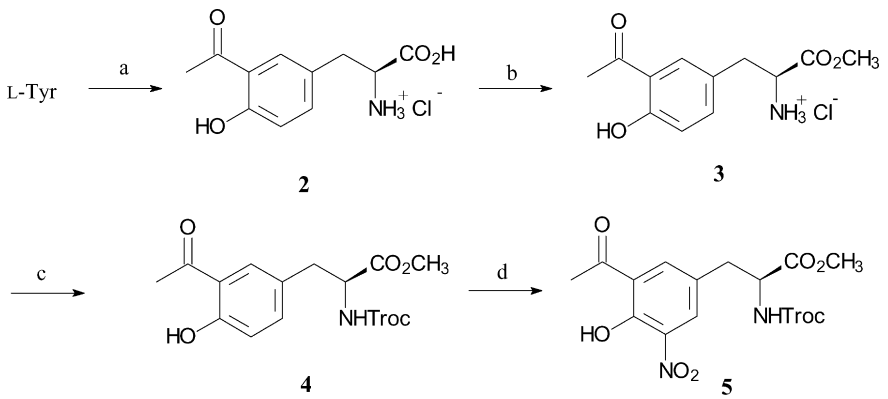
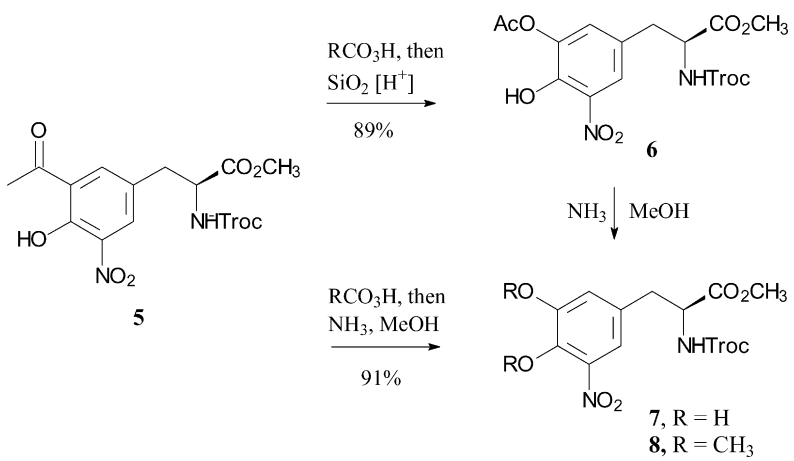
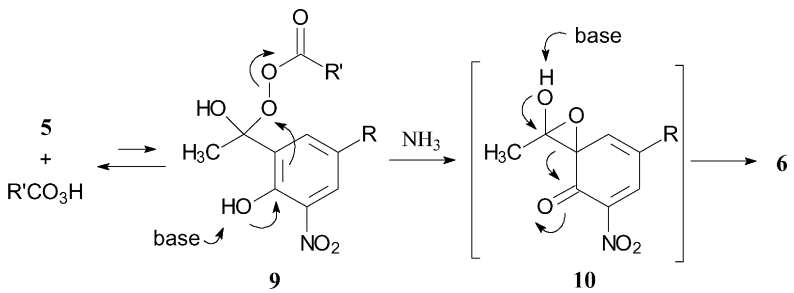


Scheme 1. Synthesis of the 3-acetyl-5-nitro-L-tyrosine derivative **5**. *Reagents and conditions*: (a) AcCl, $AlCl_3$, $PhNO_2$, 100°C, 80%. (b) $SOCl_2$, MeOH, reflux, 100%. (c) Cl_3CCH_2OCOCl, $NaHCO_3$, NaCl, $CHCl_3$, H_2O, 0°C, 92%. (d) HNO_3, AcOH, 15°C→rt, 45–63%. Troc=2,2,2-trichloroethoxycarbonyl.



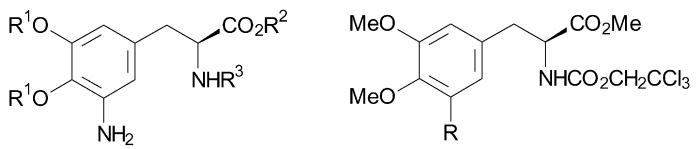
Scheme 2. Oxidation of nitroketone **5** with peracids.



Scheme 3. Proposed mechanism for the base-catalysed formation of nitrocatechol **6**.

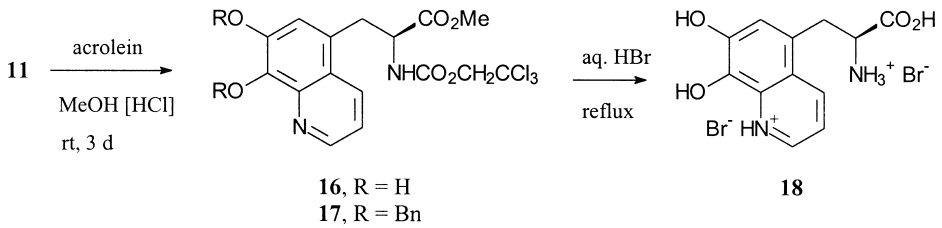
tetrafluoroborate **14**, which afforded the 5-fluoro-L-DOPA derivative **15**[13] on heating in xylenes. Experiments aimed at exploiting this reaction in the preparation of the ^{18}F-labelled compound are under investigation.

Treatment of amine **11** with acrolein in 1.3 M methanolic HCl for three days at rt yielded the quinoline derivative **16** (Scheme 4), which can be converted into dibenzyl ether **17** by treatment with benzyl bromide. Due to the orthogonal



11, R^1 = H, R^2 = Me, R^3 = Troc
12, R^1 = R^2 = Me, R^3 = Troc
13, R^1 = R^2 = R^3 = H

14, R = $N_2^+ BF_4^-$
15, R = F



Scheme 4. Synthesis of (7,8-dihydroxyquinolin-5-yl)-L-alanine dihydrobromide (**18**).

protecting groups, **17** may be used directly for the synthesis of peptides containing (7,8-dihydroxyquinolin-5-yl)-L-alanine (**1**). Indeed, the dihydrobromide salt, **18**, of the amino acid can be obtained by heating **16** in 48% aqueous HBr.

In the same manner, 3-aminocatechol hydrochloride (**20**), prepared from 5-bromo-3-nitrocatechol (**19**)[3] by hydrogenolysis with Pd/C, gave quinoline-7,8-diol (**21**)[14] in good yield (Scheme 5).

The formation of quinoline-7,8-diols from the corresponding 3-aminocatechols is a mild variant of the Skraup reaction, in which air acts as oxidant for the dihydroquinoline intermediate. The dehydrogenation step is meditated by the catechol unit which forms a redox system with the corresponding *ortho*-quinone. Compared to the classical Skraup synthesis, the reaction does not depend on the presence of an added oxidizing agent. When the reaction is applied to the dimethyl ether **12**, the yield is far lower.

The biological activities of **1** and peptides derived therefrom are now under investigation.

3. Conclusions

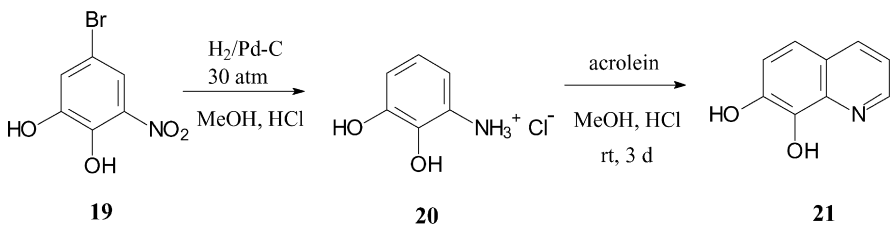
In summary, we have achieved a modification of the Baeyer–Villiger reaction which allows the conversion of aromatic 2-hydroxy-3-nitroketones and aldehydes into 3-nitrocatechols. Reduction of the latter yields 3-aminocatechols,[10,11] which represent valuable starting materials for the synthesis of quinoline-7,8-diols, hitherto only be accessible from pre-existing quinoline derivatives using rather severe reaction conditions.[14] The new methodology was applied to the first syntheses of 3-(7,8-dihydroxyquinolin-5-yl)-L-alanine (**1**), 5-amino-L-DOPA (**13**), and the complex marine alkaloid halitulin.[3]

4. Experimental

4.1. General

All reactions requiring anhydrous conditions were conducted in flame or oven-dried apparatus under an atmosphere of argon. Reactions were monitored by TLC using commercially available aluminium-backed plates, precoated with a layer of silica gel containing a fluorescent indicator (Merck). Column chromatography was carried out on silica gel 60 (40–63 μm, 230–400 mesh, Merck). Hexanes refers to the fraction of petroleum ether with bp 40–60°C. Melting points were measured on a Reichert Thermovar hot-stage microscope and are uncorrected. IR spectra were measured on a Perkin–Elmer FT spectrometer Spectrum-1000. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$, CD_3OD, [D_6]DMSO, or [D_6]acetone using a Bruker ARX 300, Varian VXR 400S or Bruker AMX 600 spectrometer. Chemical shifts are reported relative to $CDCl_3$ (δ_H 7.26, δ_C 77.0), CD_3OD (δ_H 3.35, δ_C 49.3), [D_6]DMSO (δ_H 2.49, δ_C 39.5) or [D_6]acetone (δ_H 2.06, δ_C 29.8). Mass spectra (EI, FAB, ESI) were recorded on a Finnigan MAT 90 or MAT 95Q spectrometer.

4.1.1. 3-Acetyl-L-tyrosine methyl ester hydrochloride (3). $SOCl_2$ (4.38 mL, 7.14 g, 60.0 mmol) was added dropwise to a solution of 3-acetyl-L-tyrosine hydrochloride (**2**)[5a] (10.39 g, 40.0 mmol) in dry methanol maintained at 0°C. After heating the reaction mixture at reflux for 8 h, the solvents were removed under reduced pressure to give **3** as a colourless solid (10.94 g, 100%); R_f=0.6 ($CHCl_3$–MeOH, 10:1, v/v); IR (KBr) 3045br, 1752s, 1639s, 1490s, 1446m, 1372m, 1302s, 1253s, 1235s, 1130w, 1061w, 848m, 810m, 635m, 616m cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 2.70 (s, 3H), 3.23 (dd, J=14.5, 6.9 Hz, 1H), 3.31 (m, 1H), 3.87 (s, 3H), 4.40 (dd, J=6.9, 6.4 Hz, 1H), 6.99 (d, J=8.6 Hz, 1H), 7.45 (dd, J=8.6, 2.3 Hz, 1H), 7.86 (d, J=2.3 Hz, 1H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 27.5, 36.6, 54.0, 55.4, 120.0, 121.5, 126.1, 133.6, 138.7, 163.07, 170.7, 206.5; MS (EI, 70 eV) *m/z* (rel. int.): 237 (3, M^+), 178 (18), 150 (37), 149



Scheme 5. Synthesis of quinoline-7,8-diol (**21**).

(100), 131 (25), 107 (11), 88 (31), 36 (65); HRMS (EI) calcd for $C_{12}H_{15}NO_4$ 237.1001, found 237.0998.

4.1.2. 3-Acetyl-*N*-(2,2,2-trichloroethoxycarbonyl)-L-tyrosine methyl ester (4). A chilled (0°C) solution of **3** (4.00 g, 14.6 mmol) in H_2O (100 mL) and $CHCl_3$ (100 mL) was treated with $NaHCO_3$ (2.45 g, 29.2 mmol), NaCl (4.00 g), and 2,2,2-trichloroethyl chloroformate (2.11 mL, 15.3 mmol). The reaction mixture was stirred for 2 h at 0°C, then the phases were separated and the aq. layer extracted with $CHCl_3$ (2×50 mL). The combined organic phases were washed with H_2O and dried ($MgSO_4$). Concentration under reduced pressure gave **4** as a colourless oil (5.53 g, 92%); R_f=0.85 ($CHCl_3$–MeOH, 10:1, v/v); $[\alpha]_D^{20}=-9.7$ (*c* 0.8, MeOH); IR (KBr) 3340m, 3009m, 2956m, 1738s, 1732s, 1644s, 1532m, 1488s, 1437m, 1370m, 1299s, 1253s, 1219s, 1094m, 1047m, 820m, 769m, 722m, 634m, 568m cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.60 (s, 3H), 3.04 (dd, *J*=14.2, 6.1 Hz, 1H), 3.15 (dd, *J*=14.2, 5.6 Hz, 1H), 3.75 (s, 3H), 4.62 (d, *J*=12.1 Hz, 1H), 4.67 (m, 1H), 4.81 (d, *J*=12.1 Hz, 1H), 5.63 (d, *J*=8.3 Hz, 1H), 6.90 (d, *J*=8.5 Hz, 1H), 7.23 (dd, *J*=8.5, 2.2 Hz, 1H), 7.48 (d, *J*=2.2 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 26.6, 37.4, 52.6, 54.9, 74.5, 95.3, 118.7, 119.5, 125.8, 131.2, 137.4, 153.8, 161.5, 171.3, 204.2; MS (EI, 70 eV) *m/z* (rel. int.): 413 (1) [M^+, $C_{15}H_{16}NO_6^{37}Cl^{35}Cl_2^+$], 411 (1) [$M^+$, $C_{15}H_{16}NO_6^{35}Cl_3^+$], 354 (1), 352 (1), 264 (4), 220 (14), 150 (10), 149 (100), 131 (13); HRMS (EI) calcd for $C_{15}H_{16}NO_6^{35}Cl_3$ 411.0043, found 411.0044.

4.1.3. 3-Acetyl-*N*-(2,2,2-trichloroethoxycarbonyl)-5-nitro-L-tyrosine methyl ester (5). A solution of **4** (22.68 g, 55.0 mmol) in AcOH (100 mL) maintained at 12°C was treated, dropwise over 15 min, with 100% HNO_3 (3.42 mL, 82.5 mmol). The mixture was warmed up to rt over 1 h, diluted with H_2O (300 mL), and extracted with $CHCl_3$ (3×150 mL). The combined organic phases were washed with H_2O and sat. NaCl solution, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (EtOAc–hexanes, 1:1, v/v) to give **5** (11.33–15.86 g, 45–63%) as well as 20–25% starting material.

Compound **5**. Yellow solid, mp 72°C; R_f=0.65 (EtOAc–hexanes, 1:1, v/v); $[\alpha]_D^{20}=-17.8$ (*c* 0.6, MeOH); IR (KBr) 3335m, 3076w, 3010m, 2958m, 1740br, 1702s, 1657s, 1589m, 1535s, 1462m, 1439m, 1361s, 1346s, 1279s, 1225s, 1094s, 1047m, 978m, 820m, 774m, 731m, 569m cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.69 (s, 3H), 3.09 (dd, *J*=14.3, 6.6 Hz, 1H), 3.26 (dd, *J*=14.3, 5.3 Hz, 1H), 3.80 (s, 3H), 4.60 (d, 1H, *J*=12.0 Hz), 4.67 (m, 1H), 4.79 (d, 1H, *J*=12.0 Hz), 5.80 (d, *J*=7.8 Hz, 1H), 7.68, 7.98 (each d, *J*=2.2 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 28.2, 36.9, 52.9, 54.7, 74.5, 95.1, 123.6, 126.3, 132.0, 137.3, 137.4, 153.8, 155.1, 170.8, 202.4; MS (EI) *m/z* (rel. int.): 456 (0.03) [M^+, $C_{15}H_{15}N_2O_8^{35}Cl_3^+$], 440 (2) [$M^+-H_2O$, $C_{15}H_{13}N_2O_7^{37}Cl^{35}Cl_2^+$], 438 (3) [$M^+-H_2O$, $C_{15}H_{13}N_2O_7^{35}Cl_3^+$], 309 (3), 308 (4), 265 (24), 250 (8), 195 (11), 194 (100), 176 (11), 148 (11), 105 (15); HRMS (EI) calcd for $C_{15}H_{15}N_2O_8^{35}Cl_3$ 455.9894. found 455.9865.

4.1.4. 3-*O*-Acetyl-*N*-(2,2,2-trichloroethoxycarbonyl)-5-nitro-L-DOPA methyl ester (6). A solution of **5** (0.93 g, 2.03 mmol) in CH_2Cl_2 (150 mL) was treated with *meta*-chloroperbenzoic acid (70%, 1.25 g, 5.08 mmol). The resulting mixture was stirred for 24 h at rt and then concentrated under reduced pressure. The residue was directly applied to the top of a silica gel column which was eluted with EtOAc–hexanes (2:3, v/v) to yield **6** (0.67–0.86 g, 70–89%) as well as recovered starting material (10–30%). During the chromatography, the formation of bubbles inside the column was observed.

Compound **6**. Light yellow oil; R_f=0.75 (EtOAc–hexanes, 1:1, v/v); $[\alpha]_D^{20}=-7.4$ (*c* 1.0, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 2.36 (s, 3H), 3.08 (dd, *J*=14.1, 6.1 Hz, 1H), 3.23 (dd, *J*=14.1, 5.6 Hz, 1H), 3.79 (s, 3H), 4.64 (d, *J*=12.1 Hz. 1H), 4.65 (m, 1H), 4.83 (d, *J*=12.1 Hz, 1H), 5.62 (d, *J*=7.4 Hz, 1H), 7.21, 7.98 (each d, *J*=2.0 Hz, 1H), 10.53 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.4, 37.0, 52.9, 54.7, 74.6, 95.2, 122.6, 127.0, 131.7, 134.3, 140.7, 147.1, 153.8, 168.2, 170.7; MS (EI) *m/z* (rel. int.): 474 (0.1) [M^+, $C_{15}H_{15}N_2O_9^{37}Cl^{35}Cl_2^+$], 472 (0.1) [$M^+$, $C_{15}H_{15}N_2O_9^{35}Cl_3^+$], 414 (1), 412 (1), 325 (2), 297 (2), 282 (22), 252 (5), 239 (100), 223 (24), 193 (4), 168 (67), 149 (29), 138 (9), 122 (8); HRMS (EI) calcd for $C_{15}H_{16}N_2O_9^{35}Cl_3^+$ 472.9922, found 472.9911.

4.1.5. *N*-(2,2,2-Trichloroethoxycarbonyl)-5-nitro-L-DOPA methyl ester (7). A solution of **5** (1.00 g, 2.19 mmol) in CH_2Cl_2 (40 mL) was treated with peracetic acid (39% in AcOH, 0.74 mL, 4.38 mmol) under an argon atmosphere. The resulting mixture was stirred for 2 h at rt and then treated with NH_3 (2.8 M in MeOH, 4.1 mL, 11.5 mmol). The ensuing intense red solution was stirred under argon for an additional hour at rt and then quenched with 1N HCl (20 mL). The organic phase was separated and concentrated under reduced pressure. The resulting red oil was diluted with EtOAc (40 mL), washed with sat. aq. $Na_2S_2O_3$ (2×30 mL), H_2O (20 mL), sat. aq. NaCl (20 mL), and dried (Na_2SO_4). Evaporation and drying of the residue under reduced pressure gave **7** (0.86 g, 91%) as an orange–brown foam; R_f=0.6 (EtOAc–hexanes, 1:1, v/v); $[\alpha]_D^{20}=-5.1$ (*c* 0.8, MeOH); IR (KBr) 3433s, 3331m, 2957w, 1734s, 1720s, 1545s, 1440m, 1348s, 1286s, 1242s, 1162m, 1092m, 1043m, 820m, 799m, 764m, 726m, 570m cm^{-1}; ^1H NMR (300 MHz, [D_6]DMSO) δ 2.81 (dd, *J*=13.9, 10.3 Hz, 1H), 3.00 (dd, *J*=13.9, 4.9 Hz, 1H), 3.63 (s, 3H), 4.27 (ddd, *J*=10.3, 8.3, 4.9 Hz, 1H), 4.72, 4.77 (each d, *J*=12.0 Hz, 1H), 6.98, 7.23 (each d, *J*=2.1 Hz, 1H), 8.22 (d, *J*=8.3 Hz, 1H), 10.01, 10.06 (each s, 1H); ^{13}C NMR (75.5 MHz, [D_6]DMSO) δ 35.2, 52.1, 55.3, 73.4, 96.0, 115.0, 120.9, 128.0, 136.6, 140.6, 147.4, 154.4, 171.6; MS (EI) *m/z* (rel. int.): 432 (0.5) [M^+, $C_{13}H_{13}N_2O_8^{37}Cl^{35}Cl_2^+$], 430 (0.5) [$M^+$, $C_{13}H_{13}N_2O_8^{35}Cl_3^+$], 414 (1), 412 (1), 397 (2), 395 (2), 373 (3), 371 (3), 337 (1), 335 (2), 283 (11), 264 (7), 262 (7), 240 (12), 239 (100), 168 (36), 151 (18), 133 (14), 131 (14); HRMS (EI) calcd for $C_{13}H_{13}N_2O_8^{35}Cl_3$ 429.9738, found 429.9745.

4.1.6. *N*-(2,2,2-Trichloroethoxycarbonyl)-3-*O*,4-*O*-dimethyl-5-nitro-L-DOPA methyl ester (8). A solution of catechol **7** (0.10 g, 0.23 mmol) in dry acetone (10 mL) maintained under argon was treated with dimethyl sulfate (0.13 mL, 1.4 mmol) and anhydrous K_2CO_3 (0.19 g, 1.4 mmol). After heating at reflux for 6 h, the cooled

reaction mixture was concentrated under reduced pressure and the residue treated with 1N HCl (20 mL) and EtOAc (30 mL). The phases were separated, and the organic layer was washed with H_2O (20 mL), sat. aq. NaCl (20 mL), and then dried (Na_2SO_4). Purification by silica gel flash chromatography (EtOAc–hexanes, 1:2, v/v) yielded **8** (83 mg, 79%) as a light brown solid, mp 76°C; R_f=0.4 (EtOAc–hexanes, 1:2, v/v); $[\alpha]_D$=−16.9 (*c* 0.8, MeOH); IR (KBr) 3338m, 3004w, 2950m, 1752s, 1708s, 1535s, 1450m, 1434m, 1348m, 1281s, 1225m, 1148m, 1090m, 1064m, 1042m, 996m, 825m, 730m, 571w cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.07 (dd, *J*=14.1, 6.3 Hz, 1H), 3.26 (dd, *J*=14.1, 5.4 Hz, 1H), 3.78, 3.89, 3.94 (each s, 3H), 4.61 (d, *J*=12.0 Hz, 1H), 4.68 (m, 1H), 4.83 (d, *J*=12.0 Hz, 1H), 5.63 (d, *J*=8.0 Hz, 1H), 6.89, 7.09 (each d, *J*=2.0 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 37.8, 52.8, 54.7, 56.5, 61.95, 74.6, 95.2, 116. 6, 117.0, 131.8, 142.0, 144.6, 153.8, 154.0, 170.9; MS (EI): *m/z* (rel. int.): 460 (3) [M^+, $C_{15}H_{17}N_2O_8^{37}Cl^{35}Cl_2^+$], 458 (3) [$M^+$, $C_{15}H_{17}N_2O_8^{35}Cl_3^+$], 311 (11), 268 (10), 267 (74), 196 (100), 180 (8), 135 (13), 90 (19); HRMS (EI) calcd for $C_{15}H_{17}N_2O_8^{35}Cl_3$ 458.0051, found 458.0079.

4.1.7. 5-Amino-*N*-(2,2,2-trichloroethoxycarbonyl)-3-*O*,4-*O*-dimethyl-L-DOPA methyl ester (12). A solution of **8** (0.23 g, 0.50 mmol) in dry MeOH was treated with 10% Pd/C (50 mg). After saturating the resulting mixture with hydrogen, HCl (1.25 M in MeOH, 1.0 mL) was added and the mixture stirred for 24 h under 50 atm of hydrogen. The reaction mixture was filtered through a short pad of Celite and concentrated under reduced pressure to give the hydrochloride of **12**, which was accompanied by less than 5% of the corresponding *N*-ethoxycarbonyl derivative. Treatment of the aq. hydrochloride solution with Na_2CO_3, extraction with CH_2Cl_2, and removal of the solvent yielded the free amine **12** (0.22 g, >95%) as a light brown oil; R_f=0.6 (EtOAc–hexanes, 1:1, v/v); $[\alpha]_D^{20}$=−6.1 (*c* 0.8, MeOH **12**-hydrochloride); IR (KBr) 3368m, 2953m, 1736s, 1617m, 1596m, 1511s, 1438m, 1360m, 1232m, 1135m, 1093m, 1047w, 1004w, 818w, 761w, 568w cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 2.83 (dd, *J*=13.8, 9.3 Hz, 1H), 3.06 (dd, *J*=13.8, 5.3 Hz, 1H), 3.75, 3.77, 3.82 (each s, 3H), 4.49 (dd, *J*=9.3, 5.3 Hz, 1H), 4.72, 4.81 (each d, *J*=12.3 Hz, 1H), 6.28, 6.33 (each d, *J*=2.0 Hz, 1H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 38.9, 53.1, 56.5, 57.4, 60.5, 75.7, 97.3, 104.7, 111.3, 134.4, 136.4, 142.3, 154.3, 156. 7, 173.9; MS (EI) *m/z* (rel. int.): 430 (4) [M^+, $C_{15}H_{19}N_2O_6^{37}Cl^{35}Cl_2$], 428 (4) [$M^+$, $C_{15}H_{19}N_2O_6^{35}Cl_3$], 281 (6), 280 (26) [$M^+-C_2H_3OCl_3$], 222 (13), 196 (22), 167 (13), 166 (100) [$C_9H_{12}NO_2$], 151 (9); HRMS (EI) calcd for $C_{15}H_{19}N_2O_6^{35}Cl_3$ 428.0309, found 428.0297.

4.1.8. *N*-(2,2,2-Trichloroethoxycarbonyl)-5-diazonium-3-*O*,4-*O*-dimethyl-L-DOPA methyl ester tetrafluoroborate (14). A solution of amine **12** (0.32 g, 0.75 mmol) in HCl (0.4N, 3 mL) maintained at 0°C was treated with $NaNO_2$ (52 mg, 0.75 mmol). The resulting mixture was stirred for 5 min, and after the addition of tetrafluoroboric acid (32% aq. solution, 0.6 mL) stirring was continued for 30 min at 0°C. The precipitated solid thus formed was filtered off and re-precipitated from acetone/Et_2O to give the diazonium salt **14** (333 mg, 84%) as an orange–brown foam; R_f=0.2 ($CHCl_3$–MeOH, 10:1, v/v); $[\alpha]_D^{20}$=−18.7 (*c* 0.7, MeOH); IR (KBr): 3435s, 2959w, 2926w, 2854w, 2526w, 2268w, 1736m, 1637m, 1513m, 1438m, 1337m, 1292m, 1226m, 1149m, 1084m, 1061m, 904w, 820w, 765w, 723w, 570w 523w cm^{-1}; ^{1}H NMR (300 MHz, [D_6]acetone) δ 3.16 (dd, *J*=14.2, 9.7 Hz, 1H), 3.36 (dd, *J*=14.2, 5.1 Hz, 1H), 3.70, 4.06, 4.36 (each s, 3H), 4.60 (dd, *J*=9.7, 5.1 Hz, 1H), 4.71, 4.75 (each d, *J*=15.0 Hz, 1H), 7.95, 8.00 (each d, *J*=1.8 Hz, 1H); ^{13}C NMR (75.5 MHz, [D_6]acetone) δ 36.3, 52.3, 54.9, 57.2, 63.5, 74.2, 96.1, 106.6, 122.2, 128.1, 135.8, 152.0, 152.0, 154.7, 171.0; MS (FAB) *m/z* 442 [M^+, $C_{15}H_{17}N_3O_6^{37}Cl^{35}Cl_2$], 440 [$M^+$, $C_{15}H_{17}N_3O_6^{35}Cl_3$]; HRMS (ESI) *m/z* calcd for $C_{15}H_{17}N_3O_6^{35}Cl_3$ 440.0183, found 440.0178.

4.1.9. *N*-(2,2,2-Trichloroethoxycarbonyl)-5-fluoro-3-*O*,4-*O*-dimethyl-L-DOPA methyl ester (15). The diazonium salt **14** (221 mg, 0.42 mmol) was heated in xylenes (5 mL) at 130°C for 2 h and then cooled to rt. After concentration under reduced pressure, the residue was purified by column chromatography on silica gel (EtOAc–hexanes, 1:3, v/v) to give **15** (58 mg, 31%) as a colourless oil; R_f=0.35 (EtOAc–hexanes, 1:3, v/v); $[\alpha]_D^{20}$=−13.1 (*c* 1.1, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.02 (dd, *J*=14.0, 6.1 Hz, 1H), 3.11 (dd, *J*=14.0, 5.5 Hz, 1H), 3.76, 3.83 (each s, 3H), 3.89 (d, $^5J_{HF}$=1.0 Hz, 3H), 4.63 (d, *J*=12.0 Hz, 1H), 4.65 (m, 1H), 4.82 (d, *J*=12.0 Hz, 1H), 5.54 (d, *J*=8.1 Hz, 1H), 6.45 (dd, ^4J=1.8 Hz, $^5J_{HF}$=1.6 Hz, 1H), 6.49 (dd, $^3J_{HF}$=10.8 Hz, ^4J=1.8 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 37.9, 52.6, 54.8, 56.3, 61.4 (d, $^4J_{CF}$=3.5 Hz), 74.6, 95.3, 108.7 (d, $^4J_{CF}$=2.3 Hz), 109.9 (d, $^2J_{CF}$=20.2 Hz), 130.9 (d, $^3J_{CF}$=9.4 Hz), 135.9 (d, $^2J_{CF}$=12.9 Hz), 153.6 (d, $^3J_{CF}$=5.9 Hz), 153.8, 155.8 (d, $^1J_{CF}$=245.4 Hz), 171.2; MS (EI) *m/z* (rel. int.) 433 (1) [M^+, $C_{15}H_{17}NO_6^{37}Cl^{35}Cl_2F$], 431 (1) [$M^+$, $C_{15}H_{17}NO_6^{35}Cl_3F$], 284 (4), 283 (9) [$M^+-C_2H_3OCl_3$], 240 (8), 169 (100) [$C_9H_{10}O_2F$]; HRMS (EI) calcd for $C_{15}H_{17}NO_6^{35}Cl_3F$ 431.0106, found 431.0087.

4.1.10. 5-Amino-*N*-(2,2,2-trichloroethoxycarbonyl)-L-DOPA methyl ester hydrochloride (11). To a solution of **7** (100 mg, 0.23 mmol) in HCl (0.2 M in MeOH, 5 mL) was added 10% Pd/C (25 mg), and the resulting mixture was stirred under 1 atm of hydrogen. After completion of the reaction (TLC control), the catalyst was removed by filtration over a Celite pad. Concentration under reduced pressure gave **11** (96 mg, >95%) as a colourless solid, mp 95°C; R_f=0.4 ($CHCl_3$–MeOH, 10:1, v/v); $[\alpha]_D^{20}$=−6.6 (*c* 0.7, MeOH); IR (KBr) 3369s, 2956w, 2580m, 1727s, 1520s, 1440s, 1311s, 1224s, 1096m, 1049m, 820m, 767w, 727m, 569m cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 2.89 (dd, *J*=14.0, 9.1 Hz, 1H), 3.10 (dd, *J*=14.0, 5.6 Hz, 1H), 3.75 (s, 3H), 4.46 (dd, *J*=9.1, 5.6 Hz, 1H), 4.76 (m, 2H), 6.73, 6.81 (each d, *J*=1.4 Hz, 1H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 38.0, 53.2, 57.3, 75.7, 97.2, 115.8, 117.9, 119.6, 130.1, 140.1, 147.6, 156.7, 173.5; MS (EI) (rel. int.): 402 (5) [M^+, $C_{13}H_{15}N_2O_6^{37}Cl^{35}Cl_2^+$], 400 (6) [$M^+$, $C_{13}H_{15}N_2O_6^{35}Cl_3^+$], 253 (8), 252 (31) [$M^+-C_2H_3OCl_3$], 226 (6), 209 (9), 193 (21), 192 (7), 176 (8), 175 (15), 138 (100) [$C_7H_8NO_2^+$]; HRMS (EI) calcd for $C_{13}H_{15}N_2O_6^{35}Cl_3$ 399.9996, found 399.9986.

4.1.11. 5-Amino-L-DOPA (13). The protected amino acid **11** (50 mg, 0.11 mmol) was dissolved in 48% aq. HBr (5 mL) and heated at reflux for 6 h. After removal of the

solvent under reduced pressure and drying of the residue in vacuo, the hygroscopic dihydrobromide of **13** (39 mg, 91%) was obtained as a brown foam.

Compound **13**-dihydrobromide. $[\alpha]_D=-6.6$ (*c* 0.3, MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ 3.13 (dd, *J*=14.5, 7.3 Hz, 1H), 3.25 (dd, *J*=14.5, 6.0 Hz, 1H), 4.28 (m, 1H), 6.86 (d, *J*=2.0 Hz, 1H), 6.92 (d, *J*=2.0 Hz, 1H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 36.8 (CH_2), 55.4 (CH), 116.4 (CH), 118.1 (CH), 120.0 (C_q), 127.4 (C_q), 141.1 (C_q), 148.2 (C_q), 171.2 (C_q); MS (ESI) *m*/*z* 213.1 [M^++H]; HRMS (ESI) calcd for $C_9H_{13}N_2O_4$ 213.0875, found, 213.0867.

4.1.12. *N*-(2,2,2-Trichloroethoxycarbonyl)-3-(7,8-dihydroxyquinolin-5-yl)-L-alanine methyl ester hydrochloride (16). A solution of **11** (2.10 g, 4.81 mmol) in HCl (1.25 M in MeOH, 30 mL) was treated, dropwise at 0°C, with acrolein (2.39 mL, 36 mmol). The ice-bath was removed and the solution stirred for at least 4 days at rt (^{1}H NMR control). After careful concentration and drying in vacuo, crude **16** was obtained as a reddish brown foam, which was directly converted into the dibenzyl derivative **17**. Purification of an analytical sample of **16** was carried out by HPLC on a Prontosil 120-5-C18-SH column [5.0 μm, 250×20 mm; solvent gradient: 0–10 min: H_2O/CH_3CN 9:1 (+0.5% TFA)→50 min: 100% CH_3CN; flow rate 3 mL/min, R_t=32 min]. **16**-trifluoroacetate was obtained as a yellow oil, R_f=0.4 ($CHCl_3$–MeOH, 3:1, v/v); $[\alpha]_D^{20}=-7.8$ (*c* 0.2, MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ 3.46 (dd, *J*=14.6, 9.6 Hz, 1H), 3.78 (dd, *J*=14.6, 5.4 Hz, 1H), 3.79 (s, 3H), 4.61 (d, *J*=12.2 Hz, 1H), 4.66 (dd, *J*=9.6, 5.4 Hz, 1H), 4.75 (d, *J*=12.2 Hz, 1H), 7.51 (s, 1H), 7.86 (dd, *J*=8.5, 5.5 Hz, 1H), 8.91 (dd, *J*=5.5, 1.3 Hz, 1H), 9.24 (dd, *J*=8.5, 1.3 Hz, 1H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 34.7 (CH_2), 53.4 (CH/CH_3), 56.9 (CH/CH_3), 75.7 (CH_2), 97.2 (C_q), 119.2 (CH), 124.9 (CH), 125.1 (C_q), 129.3 (C_q), 132.6 (C_q), 133.9 (C_q), 143.8 (CH), 144.7 (CH), 145.0 (C_q), 156.7 (C_q), 172.9 (C_q); MS (FAB) *m*/*z* 439 [M^+, $C_{16}H_{15}N_2O_6^{37}Cl^{35}Cl_2$], 437 [$M^+$, $C_{16}H_{15}N_2O_6^{35}Cl_3$]; HRMS (FAB) calcd for $C_{16}H_{15}N_2O_6^{35}Cl_3$ 437.0074, found 437.0085.

4.1.13. 3-(7,8-Dibenzyloxyquinolin-5-yl)-*N*-(2,2,2-trichloroethoxycarbonyl)-L-alanine methyl ester (17). The crude hydrochloride **16** (2.5 g, ~2.75 mmol), obtained as described before, was dissolved in dry DMF (25 mL) at 0°C and treated with benzyl bromide (3.14 mL, 26.4 mmol) and anhydrous K_2CO_3 (4.39 g, 31.8 mmol). The ice-bath was removed and the mixture stirred for 24 h at rt. After the addition of sat. aq. $NaHCO_3$ (50 mL) and extraction with Et_2O (3×100 mL), the combined organic phases were washed with sat. aq. $NaHCO_3$ and H_2O and dried (Na_2SO_4). The solvents were removed under reduced pressure, and the residue was purified by silica gel flash chromatography (CH_2Cl_2–acetone, 15:1, v/v) to give **17** (0.40 g, 24% from **11**) as a light yellow oil; R_f=0.45 (CH_2Cl_2–acetone, 15:1, v/v); $[\alpha]_D^{20}=-10.0$ (*c* 0.2, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.49 (m, 2H), 3.54 (s, 3H), 4.65 (d, *J*=12.0 Hz, 1H), 4.70 (m, 1H), 4.76 (d, *J*=12.0 Hz, 1H), 5.21 (s, 2H), 5.39 (m, 2H), 5.73 (d, *J*=8.0 Hz, 1H), 7.17 (s, 1H), 7.25–7.44 (m, 9H), 7.51–7.57 (m, 2H), 8.36 (dd, *J*=8.5, 1.4 Hz, 1H), 8.97 (dd, *J*=4.2, 1.4 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 34.9 (CH_2), 52.5 (CH_3), 54.9 (CH), 72.4 (CH_2), 74.6 (CH_2), 76.1 (CH_2), 95.2 (C_q), 119.4 (CH), 119.8 (CH), 123.6 (C_q), 127.6 (2×CH), 127.8 (CH), 128.1 (2×CH), 128.2 (C_q), 128.6 (2×CH), 128.7 (2×CH), 132.7 (CH), 136.7 (C_q), 137.6 (C_q), 142.0 (C_q), 143.5 (C_q), 149.5 (CH), 150.5 (C_q), 153.8 (C_q), 171.2 (C_q) (only 25 of the 26 signals were observed); MS (EI) *m*/*z* (rel. int.): 618 (0.1) [M^+, $C_{30}H_{27}N_2O_6^{37}Cl^{35}Cl_2$], 616 (0.1) [$M^+$, $C_{30}H_{27}N_2O_6^{35}Cl_3$], 583 (0.1), 581 (0.1), 561 (0.1), 559 (0.2), 527 (5), 525 (5), 379 (13), 378 (55), 354 (6), 264 (4), 248 (4), 174 (10), 92 (9), 91 (100); HRMS (FAB) calcd for $C_{30}H_{27}N_2O_6^{35}Cl_3$ 616.0935, found 616.0938.

4.1.14. (7,8-Dihydroxyquinolin-5-yl)-L-alanine (1). Compound **16** (15 mg, 0.03 mmol) was dissolved in 48% aq. HBr (3 mL) and the resulting solution heated at reflux for 6 h. After removal of the solvent under reduced pressure and drying in vacuo, **1**-dihydrobromide (**18**) (10 mg, 81%) was obtained in high purity as a hygroscopic brown foam. Due to the intense colour and resulting concerns regarding accuracy, the optical rotation of **1** was not determined. ^{1}H NMR (600 MHz, CD_3OD) δ 3.71 (dd, *J*=15.1, 7.6 Hz, 1H), 3.86 (dd, *J*=15.1, 7.1 Hz, 1H), 4.42 (dd, *J*=7.6, 7.1 Hz, 1H), 7.64 (s, 1H), 7.93 (dd, *J*=8.5, 5.6 Hz, 1H), 8.98 (dd, *J*=5.6, 1.2 Hz, 1H), 9.26 (dd, *J*=8.5, 1.2 Hz, 1H); ^{13}C NMR (151 MHz, CD_3OD) δ 33.3 (CH_2), 55.1 (CH), 119.6 (C-3), 124.9 (C-4a), 125.5 (C-6), 126.5 (C-5), 132.8 (C-8a), 134.7 (C-8), 144.1 (C-2), 144.5 (C-4), 149.9 (C-7), 171.0 (CO_2H); MS (FAB) *m*/*z* 249 [M^++H]; HRMS (ESI) calcd for $C_{12}H_{13}N_2O_4$ 249.0875, found 249.0848.

4.1.15. 3-Aminocatechol hydrochloride (20). To a solution of bromonitrocatechol **19**[3] (0.96 g, 4.10 mmol) in dry MeOH (5 mL) was added 10% Pd/C (150 mg). After saturating the mixture with hydrogen, HCl (1.25 M in MeOH, 5.0 mL) was added and the mixture stirred for 24 h under 50 atm of hydrogen. The reaction mixture was filtered through a short pad of Celite and concentrated under reduced pressure to give **20** (0.63 g, >95%) as a light brown foam. ^{1}H NMR (300 MHz, CD_3OD) δ 6.78 (dd, 1H, *J*=8.0, 8.0 Hz), 6.86 (dd, 1H, *J*=8.0, 1.8 Hz), 6.93 (dd, 1H, *J*=8.0, 1.8 Hz); ^{13}C NMR (75.5 MHz, CD_3OD) δ 115.3 (CH), 117.1 (CH), 119.9 (C_q), 120.9 (CH), 141.3 (C_q), 147.8 (C_q); MS (EI) *m*/*z* (rel. int.): 126 (10) [M^++H], 125 (100) [M^+], 96 (12), 79 (55), 78 (5); HRMS (ESI) calcd for $C_6H_7NO_2$ 125.0477, found 125.0472.

4.1.16. 7,8-Dihydroxyquinoline (21). A solution of **20** (0.63 g, 3.90 mmol) in HCl (1.25 M in MeOH, 20 mL) was treated, dropwise at 0°C, with acrolein (1.90 mL, 29 mmol). The ice-bath was removed and the resulting solution stirred for at least 4 days at rt (^{1}H NMR control!). After careful concentration and drying in vacuo, crude **21**-hydrochloride (0.54 g, >70% as judged by ^{1}H NMR analysis) was obtained as a reddish brown foam. Recrystallization from acetonitrile/MeOH afforded the pure hydrochloride. The free base **21** was obtained by precipitation of the lead salt and treatment with H_2S.[14b]

Compound **21**×HCl. ^{1}H NMR (300 MHz, CD_3OD) δ 7.39 (d, *J*=9.1 Hz, 1H, 6-H), 7.54 (d, *J*=9.1 Hz, 1H, 5-H), 7.59 (dd, *J*=8.2, 5.2 Hz, 1H, 3-H), 8.72 (d, *J*=5.2 Hz, 1H, 2-H), 8.80 (d, *J*=8.2 Hz, 1H, 4-H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 119.3 (C-3), 122.0 (C-5), 123.3 (C-6), 126.0

(C-4a), 131.6 (C-8a), 134.5 (C-8), 144.1 (C-2), 148.2 (C-4), 150.5 (C-7). The assignments given were established by HMBC and HSQC experiments. MS-EI *m/z* (%): 161 (M^+, 48), 153 (10), 150 (6), 149 (10), 147 (6), 136 (36), 133 (17), 132 (12), 128 (8), 127 (7), 126 (7), 125 (7), 124 (5), 115 (3), 112 (22), 111 (9), 110 (100), 109 (11), 108 (17), 107 (21), 106 (18), 105 (19), 104 (15), 103 (6); HRMS-ESI calcd for $C_9H_7NO_2$ 161.0477, found 161.0471.

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