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Total Synthesis of (*S*,*S*)-Isodityrosine[1]

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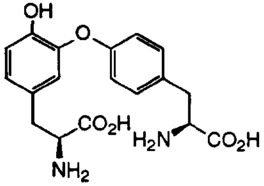
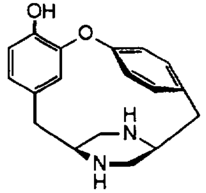
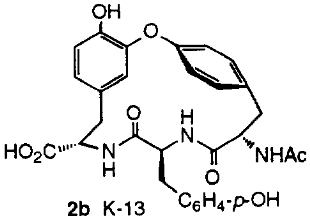
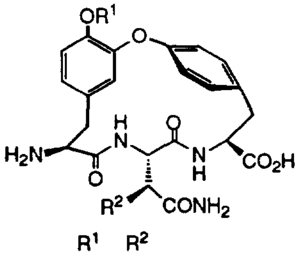
Abstract: The novel dimeric amino acid isodityrosine 1 has been synthesized by a route which uses a new method of diaryl ether preparation. Nucleophilic addition of a protected tyrosine to cyclohexenone oxide and the Pd(0)-catalyzed coupling of an aryl iodide with a protected iodoalanine derivative are the key steps in this synthesis. This represents one of the first efficient syntheses of this molecule beginning with two naturally-occurring amino acids as inexpensive starting materials © 1997 Elsevier Science Ltd.

Isodityrosine[4] (**1**), the key structural subunit which defines a large class of biologically active natural products, was isolated in the early 1980's from extensin, a plant cell wall glycoprotein. Piperazinomycin[5] (**2a**) possesses antimicrobial and antifungal activity, the cyclic tripeptide K-13[6] (**2b**) is a potent, noncompetitive inhibitor of angiotensin I converting enzyme, and OF4949-I – OF4949-IV[7] (**2c-f**) are inhibitors of aminopeptidase B and also exhibit immunopotentiating and antitumor activity. The bicyclic hexapeptides bouvardin[8] (**2g**) and deoxybouvardin[8] (**2h**) are members of a large class of potent antitumor antibiotics, including RA-I – RA-IV[9] (**2i-l**).

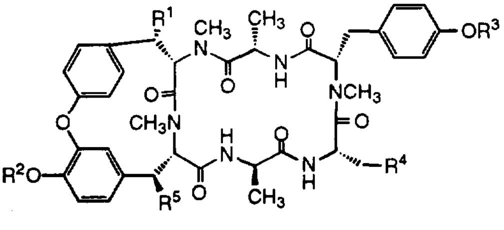

1 Isodityrosine


2a Piperazinomycin


2b K-13



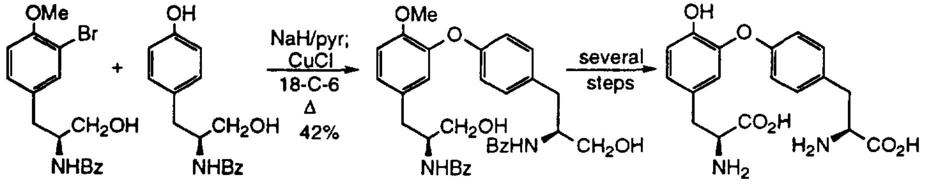
	R¹	R²	
2c	CH_3	OH	OF4949-I
2d	H	OH	OF4949-II
2e	CH_3	H	OF4949-III
2f	H	H	OF4949-IV



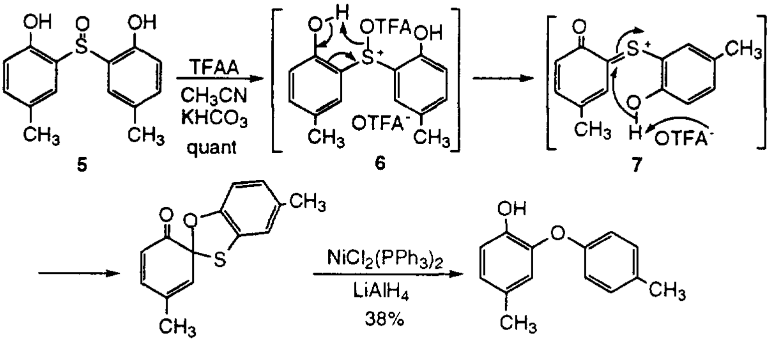
	R¹	R²	R³	R⁴	R⁵	
2g	OH	H	CH_3	H	H	Bouvardin
2h	H	H	CH_3	H	H	Deoxybouvardin
2i	H	H	CH_3	OH	H	RA-I
2j	H	CH_3	H	H	H	RA-II
2k	H	CH_3	CH_3	OH	H	RA-III
2l	H	CH_3	CH_3	H	OH	RA-IV

The foremost synthetic challenge posed by these targets is the construction of the diaryl ether moiety. As a result, the efforts of a wide group of chemists[10] have been aimed toward the development of new methodology and the expansion of current technologies. Several syntheses of isodityrosine,[11] piperazinomycin,[12] K-13,[13] OF-4949-III,[14] bouvardin,[15] deoxybouvardin,[16] and RA-VII[17] have been published, utilizing a variety of creative strategies. Much work has also been applied to the more complex but structurally related vancomycin[18] group of antibiotics. Several different approaches have been used to build the diaryl ether moiety,[10] e.g., Ullmann-type couplings,[19] nucleophilic displacements of *o*-nitro-substituted aryl fluorides[20] or bromobenzoquinones,[21] oxidative phenol couplings,[22] Diels-Alder reactions,[23] displacement of areneruthenium complexes,[24] etc.

Our research efforts in this area have focused on three general methods for the synthesis of diaryl ethers: a) the Ullmann coupling of two protected L-tyrosinol derivatives **3a** and **3b** (both readily available from L-tyrosine) to give the protected isodityrosinediol **4**, with eventual reoxidation of the primary alcohols to acids to give **1**;[11a] b) an internal trapping of the α-ketosulfonium salt **7** prepared by a Pummerer-type rearrangement (via **6**) of the symmetrical 2-(phenylsulfinyl)phenol **5** to give the orthoquinone mono(hemithioketal) **8**, which was then hydrogenolyzed to give the *o*-aryloxyphenol **9** in an overall yield of 38%.[25] This type of chemistry has also led to a facile synthesis of substituted phenols and biaryls by a process of 'vicarious substitution' e.g., reaction of **11** (prepared by the same route from the 2-(phenylsulfinyl)phenol **10**) with nucleophiles to give **12** [where X = Cl, OAc, or (2-OH-5-MeC$_6$H$_3$)];[25b] and c) the opening of cyclohexenone oxides with phenols followed by oxidation to afford the desired *o*-aryloxyphenols, e.g., reaction of **13** with a phenol **14** (including a protected tyrosine) under two-phase conditions with sonication to give the 2-aryloxycyclohexenone **15** which could be oxidized by several methods to the *o*-aryloxyphenol **16**.[26]

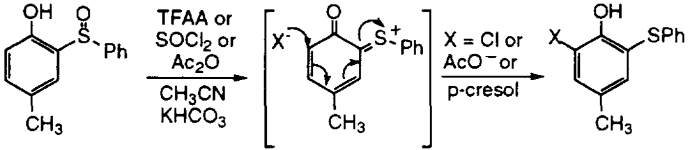


3a **3b** **4** **1**

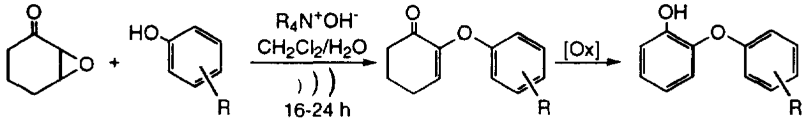


5 **6** **7**

8 **9**



10 **11** **12**

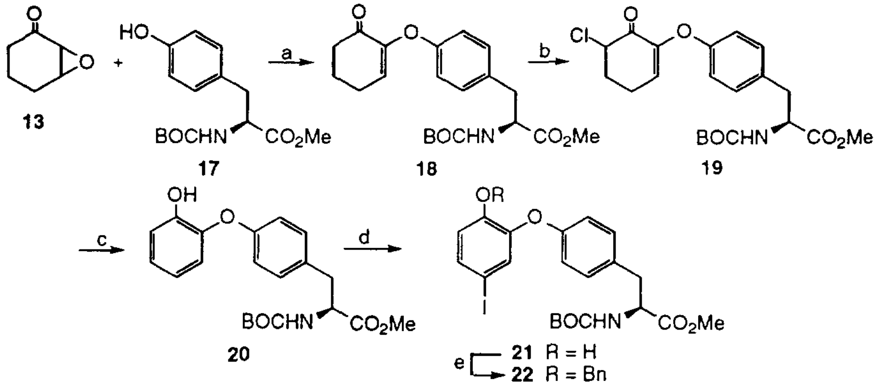


13 **14** **15** **16**

We now report the application of this final methodology for the preparation of *o*-aryloxyphenols to the total synthesis of isodityrosine.[27]

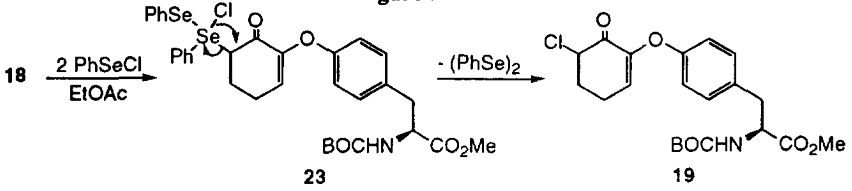
The framework of the diaryl ether was constructed by nucleophilic addition of the readily available protected tyrosine, *N*-BOC-L-Tyr-OMe, **17**, to cyclohexenone oxide **13**, as shown in Scheme 1. As reported previously,[26] sonication of a two-phase system, water and dichloromethane, in the presence of a tetraalkylammonium hydroxide base, followed by treatment with methyl iodide to reesterify *in situ*, affords the 2-aryloxy enone **18** in an isolated yield of 44%. In this coupling reaction, a reasonable amount of the starting tyrosine derivative is isolated while the cyclohexenone oxide is completely consumed, so that the yield based on recovered tyrosine is much higher. We explored several methods for the oxidation of the cyclohexenone derivative **18** to the desired phenol **20**. Our previous method for simple systems, namely, a two-step process of silyl enol ether formation and Pd(II)-promoted oxidation,[26] was unsuccessful here. We found only limited success in the use of cupric bromide/lithium bromide in refluxing acetonitrile,[28] which provided a 34% yield of **20**, along with an equal amount of free tyrosine. Therefore, we decided to introduce a phenylseleneny group in the α position using the mild reaction conditions reported by Sharpless, namely treatment of **18** with phenylselenenyl chloride in ethyl acetate.[29] We did not observe formation of the desired α-phenylselenenyl ketone in good yield. Instead, we discovered that treatment of the enone **18** with two equivalents of phenylselenenyl chloride in ethyl acetate furnished the α-chloro derivative **19** in excellent yield. Presumably, the expected phenylselenation occurs but is then followed by addition of a second equivalent of phenylselenenyl chloride to the selenium atom to give the hypervalent selenium species **23** (Figure 1). Such compounds are known to undergo a 1,2-shift of chlorine from selenium to the α-carbon,[30] with loss of diphenyl diselenide. Although its formation was unexpected, the chloride **19** proved equally useful for the introduction of the required unsaturation and readily underwent elimination upon treatment with DBU to give the *o*-aryloxyphenol **20** in high yield. Iodination in the *para*

Scheme 1



(a) i. $BnEt_3NCl$, NaOH, CH_2Cl_2, H_2O))), 2d; ii. MeI, 6h, 44%; (b) PhSeCl (2 eq), EtOAc, 5h, 80%; (c) DBU, THF, 16h, 86%; (d) NaI, Chloramine-T, DMF, 2h; (e) BnBr, TBAI, K_2CO_3, DMF, 16h, 91% over two steps.

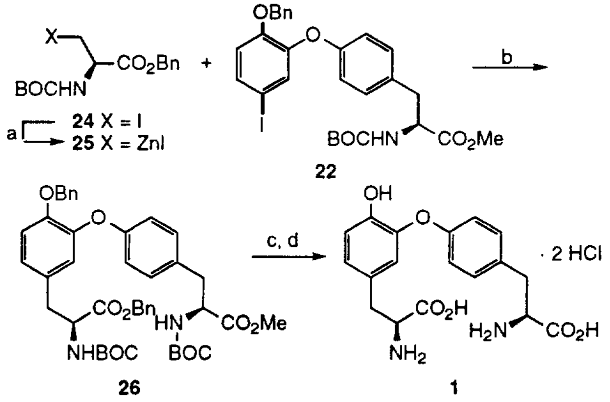
Figure 1



position, followed by protection of the phenol, would provide the desired substrate **22** for a palladium-catalyzed coupling with the zinc reagent prepared from iodoalanine and used by Jackson.[31] We found after some experimentation that the amino acid side chain tolerated the neutral, mild conditions of sodium iodide and Chloramine-T and we obtained excellent yields of the desired *para* iodide **21**, which was unfortunately inseparable from the tosylamide byproduct. However, treatment of this crude product mixture with potassium carbonate and excess benzyl bromide in DMF produced the desired iodo benzyl ether **22** and the easily removed *N,N*-dibenzyltosylamide. Thus the aryl iodide **22** is available in only four operations from cyclohexenone oxide and a readily available protected tyrosine.

We planned to use the new method of Jackson,[31] namely the Pd-mediated coupling of an organozinc reagent derived from serine (an iodoalanine derivative) to the aryl iodide **22**, to produce the second tyrosine unit. Our initial results with this mixed metal coupling reaction were disappointing, giving poor yields of the desired product. We found that the use of dimethylacetamide[32] was required for zinc insertion into *N*-BOC-L-iodoalanine benzyl ester **24**[31,32] (Scheme 2). The zinc dust was activated according to the procedure of Knochel, using dibromoethane and chlorotrimethylsilane (TMSCl).[33] Addition of the aryl iodide **22** and *in situ* formation of the palladium(0) catalyst by addition of $Pd_2(dba)_3$ and *o*-tol_3P[34] gave the desired coupled product **26** in 64% yield. An alternate procedure, namely adding the aryl iodide along with the iodoalanine benzyl ester to the activated zinc mixture, followed by addition of the palladium catalyst, gave the coupled product **26** in 71% yield, implying that the insertion of the zinc into the primary iodide was much faster than the insertion into the aryl iodide. This may provide the opportunity to carry out intramolecular couplings of primary, aryl diiodides of this type in the future. The benzyl ether and ester protecting groups were removed by hydrogenolysis and the methyl ester and BOC groups by acidic hydrolysis[11c] without isolation of intermediates to produce isodityrosine, **1**, isolated as its bis hydrochloride salt, in 90% yield for the two deprotection steps.

Scheme 2



(a) Zn dust, THF/DMAC (1:1), 35 °C, 15 min; (b) $Pd_2(dba)_3$, *o*-tol_3P **22** (0.5 eq), 55 °C, 2h, 64%; (c) 10% Pd(C) (10% wt eq), H_2 (1 atm), THF, 16h; (d) 6*N* HCl, 60 °C, 6h, 90%, isolated as bis hydrochloride.

This ends a very direct and efficient synthesis of **1**, involving only six operations, and in which all of the chirality in the molecule is derived directly from the two amino acids L-tyrosine and L-serine. Thus our new preparation of *o*-aryloxyphenols has successfully been applied to the total synthesis of isodityrosine. This novel approach opens the door to the synthesis of the many isodityrosine-derived natural products and to unique analogues as well.

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Experimental Section

General Methods. ^{1}H NMR spectra were recorded on a Bruker AF-200, AM-360, or ARX-400 spectrometer, operating at 200.132 MHz, 360.134 MHz or 400.132 MHz, respectively and are so indicated. ^{13}C NMR spectra were recorded on the AF-200, the AM-360, or the ARX-400, operating at 50.323 MHz, 90.556 MHz, or 100.622 MHz, respectively, and are also so noted. Infrared spectra were recorded on a Nicolet 510 FT-IR as liquid films (neat). High resolution mass spectra (HRMS) were recorded on a VG Analytical Autospec instrument and are electron impact (EI) or fast atom bombardment (FAB). Optical resolutions were obtained on a Perkin-Elmer 241 MC polarimeter at 20 °C and referenced to the sodium D line (589 nm). Melting points were taken on a Büchi melting point apparatus and are uncorrected. Sonication was performed using a Brasonic 521 cleaning bath. ^{1}H and ^{13}C NMR data are reported in parts per million (δ) downfield from tetramethylsilane and the line spacings are given in Hertz (Hz). The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent. Second order spectra in which couplings cannot be obtained by inspection are reported as multiplets, with the center of the signal indicated by the δ value given. IR data are reported in wavenumbers (cm^{-1}) and only significant peaks were recorded. The following abbreviations are used to indicate qualitative intensities: s = strong, m = medium, w = weak, br = broad. Thin layer chromatography (TLC) was performed using Merck silica gel 60 F_{254} 0.2 mm plates with visualization by ultraviolet light or an acid-based stain, prepared from *p*-anisaldehyde (5 mL), conc. sulfuric acid (5 mL) and glacial acetic acid (0.5 mL) in 95% ethanol (90 mL). Flash column chromatography (FCC) was done by the method of Still,[35] using E. Merck silica gel 60 (230–400 mesh) with solvent systems reported as volume percent mixtures. Concentration *in vacuo* refers to the removal of solvent using a Büchi rotary evaporator at aspirator pressure. All inorganic solutions are aqueous and concentrations are indicated in percent weight, except saturated aqueous sodium chloride (brine). The following solvents and reagents were distilled from the indicated agent under dry nitrogen: tetrahydrofuran (THF) and diethyl ether (Et_2O) from sodium benzophenone ketyl; benzene, dichloromethane, chloroform, acetonitrile, pyridine and triethylamine from calcium hydride; methanol from magnesium; diisopropylamine from sodium hydroxide. *N,N*-dimethylformamide (DMF) and *N,N*-dimethylacetamide were distilled from calcium sulfate and barium oxide, respectively, under reduced pressure and stored over 4 Å molecular sieves. All other reagents were purified by literature procedures. All reactions were performed under an inert atmosphere of dry nitrogen.

Cyclohexenone oxide, 13.[36] To a well-stirred solution of cyclohexenone (9.7 mL, 100 mmol, 1.0 eq) in 100 mL methanol, cooled to 0 °C, was added 30% aq. hydrogen peroxide (300 mmol, 3.0 eq). After the reaction was stirred for 10 min, 20% aq. sodium hydroxide (0.15 mL, 0.75 mmol, 7.5 meq) was added and the resulting mixture stirred at 0 °C for 15 min longer. The reaction mixture was poured into a 1 L separatory funnel, filled with 200 mL brine and 150 g ice. The product was extracted with cold dichloromethane (3 x 80 mL). The combined organic fractions were dried over $MgSO_4$ and the solvent was removed by distillation through a 15 cm Vigreux column. The remaining yellow residue was distilled through a 15 cm Vigreux column, under vacuum, to give 9.4 g product **13** (84 mmol, 84% yield) as a colorless oil. The spectral data matched that reported in the literature.[36] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.51 (m, 1H), 3.12 (m, 1H), 2.44 (dm, 1H, *J* = 17.4 Hz), 2.18 (m, 1H), 2.00 (m, 1H), 1.85 (m, 2H), 1.59 (m, 1H). ^{13}C NMR (90 MHz, $CDCl_3$) δ: 206.7, 59.6, 55.8, 37.1, 23.6, 17.7. IR (film) 3011 (w), 2949 (m), 2886 (w), 1713 (s), 820 (s) cm^{-1}.

Methyl *N*-([(1,1-dimethyl)ethoxy]carbonyl)-L-tyrosinate (*N*-BOC-Tyr-OMe), 17. To a stirred suspension of L-tyrosine (6.3 g, 34.8 mmol, 1.0 eq) in distilled water (50 mL) was added triethylamine (9.7 mL, 69.6 mmol, 2.0 eq) and dioxane (50 mL). This mixture was cooled to 0 °C and di-*t*-butyldicarbonate (12 mL, 52.2 mmol, 1.5 eq) was added. The reaction mixture was stirred at 0 °C for 30 min and then at 25 °C for 24 h, during which time it became a clear, pale yellow solution. This was concentrated *in vacuo* and the oily residue taken up in 200 mL distilled water and washed with ethyl acetate (2 x 50 mL). The aqueous layer was then acidified to pH 1 with 1 *N* HCl and the product extracted with ethyl acetate (3 x 100 mL). These extracts were combined, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give a quantitative yield of *N*-BOC-L-tyrosine as a white powder (9.8 g, 34.8 mmol). ^{1}H NMR (400 MHz, CD_3OD) δ: 6.92 (d, 2H, *J* = 8.4 Hz), 6.58 (d, 2H, *J* = 8.4 Hz), 4.16 (m, 1H), 2.93 (dd, 1H, *J* = 13.9, 5.0 Hz), 2.70 (dd, 1H, *J* = 13.9, 8.8 Hz), 1.28 (s, 9H). ^{13}C NMR (100 MHz, CD_3OD) δ: 176.4, 158.5, 158.1, 132.1, 130.1, 117.0, 81.3, 57.4, 38.8, 29.5.

To a suspension of $NaHCO_3$ (329 mg, 3.9 mmol, 1.1 eq) in 15 mL dry DMF was added *N*-BOC-L-tyrosine (1.0 g, 3.6 mmol, 1.0 eq) and methyl iodide (0.24 mL, 3.9 mmol, 1.1 eq).[37] This mixture was stirred at 25 °C for 20 h. Distilled water (100 mL) was added and the product extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with distilled water and then dried over $MgSO_4$ and concentrated *in vacuo* to 1.4 g pale yellow oil. This was purified by FCC (eluent 15% Et_2O/dichloromethane) to give 891 mg of product **17** (3.0 mmol, 85%) as a white powder. This compound can also be prepared from methyl L-tyrosinate hydrochloride with di-*t*-butyldicarbon-ate and aq. sodium hydroxide in THF, by the procedure of Jackson.[31a] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.97 (m, 2H), 6.73 (m, 2H), 5.8–5.3 (br, 1H), 4.99 (m, 1H), 4.53 (m, 1H), 3.71 (s, 3H), 3.03 (dd, 1H, *J* = 13.9, 5.8 Hz), 2.96 (dd, 1H, *J* = 13.9, 6.1 Hz), 1.42 (s, 9H). $[\alpha]_D^{20}$ = +48.2° (c=1.0, $CHCl_3$).

Methyl *N*-([(1,1-dimethyl)ethoxy]carbonyl)-*O*-(6-oxo-1-cyclohexenyl)tyrosinate, 18. To a solution of *N*-BOC-L-tyrosine methyl ester **17** (6.07 g, 20.6 mmol, 1 eq) in 90 mL dichloromethane was added benzyltriethylammonium chloride (4.69 g, 20.6 mmol, 1 eq), cyclohexenone oxide **13** (4.1 mL, 41.2 mmol, 2 eq), 1 *N* sodium hydroxide (30.9 mL, 30.9 mmol, 1.5 eq) and 60 mL distilled water. This 2-phase mixture was placed in a sonicator cleaning bath and sonicated for 2 days, reaching a final bath temperature of 36 °C. Methyl iodide (6.4 mL, 103 mmol, 5 eq) was added and sonication was continued for 6 h. The organic layer was removed and the product extracted with additional dichloromethane (3 x 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude yellow oil was purified by FCC (eluent 10% Et_2O in dichloromethane) to give 3.74 g of compound **18** (9.6 mmol, 47% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.03 (d, 2H, *J* = 8.4 Hz), 6.84 (d, 2H, *J* = 8.4 Hz), 6.24 (t, 1H, *J* = 4.5 Hz), 4.98 (br d, 1H, *J* = 7.3 Hz), 4.71 (br s, 1H, minor conformer), 4.52 (app dt, 1H, *J* = 7.3, 6.1 Hz), 4.31 (br s, 1H, minor conformer), 3.67 (s, 3H), 3.03 (dd, 1H, *J* = 13.9, 5.6 Hz), 2.96 (dd, 1H, *J* = 13.9, 6.3 Hz), 2.55 (app t, 2H, *J* = 6.3 Hz), 2.43 (dt, 2H, *J* = 6.3, 4.5 Hz), 2.03 (tt, 2H, *J* = 6.3, 6.3 Hz), 1.39 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ: 193.6, 172.2, 155.4, 155.0, 149.8, 130.8, 130.4, 129.9, 118.1, 79.8, 54.4, 52.1, 38.7, 37.6, 28.2, 24.7, 22.8. IR (film): 3364 (br), 2976 (m), 1746 (s), 1703 (s), 1693 (s), 1508 (s), 1366 (s) cm^{-1}. HRMS (EI): 389.183750 (M^+) [$C_{21}H_{27}NO_6$ calcd 389.183838]. $[\alpha]_D^{20}$ = 37.9° (c=1.0, $CHCl_3$).

Methyl *N*-[(1,1-dimethylethoxy)carbonyl]-*O*-(5-chloro-6-oxo-1-cyclohexenyl)tyrosinate, 19. To a suspension of K_2CO_3 (645 mg, 4.67 mmol, 1.1 eq) in 20 mL ethyl acetate was added the enone **18** (1.65 g, 4.24 mmol, 1.0 eq) and phenylselenenyl chloride (1.79 g, 9.35 mmol, 2.2 eq). The resulting brown mixture was stirred at 25 °C for 9 h, during which it became a yellow slurry. The mixture was diluted with 200 mL ethyl acetate, filtered and poured into distilled water. The aqueous layer was extracted once with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by FCC (eluent 7-10% Et_2O in dichloromethane gradient) gave 1.46 g of compound **19** (3.45 mmol, 81% yield) as a colorless oil and ~1.2 g diphenyl diselenide (3.8 mmol, 91% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.03 (d, 2H, *J* = 8.4 Hz), 6.85 (d, 2H, *J* = 8.4 Hz), 6.31 (t, 1H, *J* = 4.4 Hz), 5.00 (br d, 1H, *J* = 7.9 Hz), 4.77 (br s, 1H, minor conformer), 4.50 (m, 1H), 4.47 (dd, 1H, *J* = 6.3, 3.5 Hz), 4.31 (br s, 1H, minor conformer), 3.66 (s, 3H), 3.02 (dd, 1H, *J* = 13.9, 5.3 Hz), 2.95 (dd, 1H, J = 13.9, 5.7 Hz), 2.79–2.71 (m, 1H), 2.47–2.38 (m, 2H), 2.35–2.28 (m, 1H), 1.38 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 186.2, 172.1, 155.1, 155.0, 147.3, 131.0, 130.4, 130.4, 117.6, 79.7, 59.1, 54.3, 52.1, 34.5, 31.4, 28.1, 21.3. IR (film): 2990 (w), 1744 (s), 1703 (s), 1509 (s), 1219 (m), 1167 (m) cm^{-1}. HRMS (EI): 423.142872 (M$^+$) [$C_{21}H_{26}NO_6{}^{35}Cl$ calcd 423.144866]. $[\alpha]^{20}_{D}$ = +38.3° (c=1.0, $CHCl_3$).

Methyl *N*-[(1,1-dimethylethoxy)carbonyl]-*O*-(2-hydroxyphenyl)tyrosinate, 20. To a stirred solution of the chloride **19** (1.17 g, 2.76 mmol, 1.0 eq) in 40 mL THF was added dropwise DBU (0.66 mL, 4.42 mmol, 1.6 eq). The reaction darkened immediately and a precipitate formed within 15 min. The reaction mixture was stirred at 25 °C for 18 h and then concentrated *in vacuo*. The foamy residue was partitioned between ethyl acetate and water (50 mL each) and the aqueous layer was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with 30 mL portions each of 0.5 *N* HCl, saturated aq. $NaHCO_3$ and brine, then dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified by FCC (eluent 10% Et_2O in dichloromethane) to give 920 mg of **20** (2.38 mmol, 86% yield) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.06 (d, 2H, J = 8.5 Hz), 7.03 (m, 2H), 6.91 (d, 2H, J = 8.5 Hz), 6.87–6.79 (m, 2H), 5.90 (s, 1H), 5.05 (br d, 1H, J = 7.9 Hz), 4.81 (br s, 1H, minor conformer), 4.55 (m, 1H), 4.37 (br s, 1H, minor conformer), 3.70 (s, 3H), 3.08 (dd, 1H, J = 13.8, 5.5 Hz), 2.98 (dd, 1H, J = 13.8, 6.2 Hz), 1.41 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.2, 155.9, 155.0, 147.6, 143.3, 131.0, 130.6, 124.8, 120.5, 119.1, 117.8, 116.3, 80.0, 54.4, 52.2, 37.5, 28.2. IR (film): 3380 (br), 1742 (s), 1698 (s), 1507 (s), 1497 (s) cm^{-1}. HRMS (EI): 387.167680 (M$^+$) [$C_{21}H_{25}NO_6$ calcd 387.168188]. $[\alpha]^{20}_{D}$ = 39.9° (c=1.0, $CHCl_3$).

Methyl *N*-[(1,1-dimethylethoxy)carbonyl]-*O*-(2-hydroxy-5-iodophenyl)tyrosinate, 21. To a stirred solution of phenol **20** (900 mg, 2.33 mmol, 1.0 eq) and sodium iodide (384 mg, 2.56 mmol, 1.1 eq) in 10 mL DMF at 25 °C was added Chloramine-T (720 mg, 2.56 mmol, 1.1 eq) in three portions. The mixture was stirred at 25 °C for 1 h and changed from a tan to a plum color. The reaction mixture was diluted with 10 mL distilled water and 1 *N* HCl was added dropwise until pH 4–5 (turns pale yellow). This was diluted further with 75 mL distilled water and the product was extracted with ethyl acetate (3 x 70 mL). The combined organic layers were washed sequentially with 50 mL portions each of 10% aq. $Na_2S_2O_3$, distilled water and brine, then dried over $MgSO_4$ and concentrated *in vacuo*. The resulting crude oil, consisting of **21** and *p*-toluenesulfonamide, was taken on without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.27 (dd, 1H, J = 8.5, 2.0 Hz), 7.08 (d, 1H, J = 2.0 Hz), (d, 1H, J = 8.5 Hz), 6.59 (br s, 1H), 5.09 (br d, 1H, J = 8.0 Hz), 4.52 (br dt, 1H, J = 7.2, 6.1 Hz), 3.67 (s, 3H), 3.05 (dd, 1H, J = 13.8, 5.5 Hz), 2.96 (dd, 1H, J = 13.8, 6.3 Hz), 1.38 (s, 9H). Also seen were the absorptions for $TsNH_2$, δ: 7.92 (br s, 2H), 7.75 (d, 2H, J = 8.1 Hz), 7.24 (d, 2H, J = 8.1 Hz), 2.38 (s, 3H).

Methyl *N*-[(1,1-dimethylethoxy)carbonyl]-*O*-[5-iodo-2-(phenylmethoxy)phenyl]tyrosinate, 22. To a stirred solution of the crude iodophenol **21** (1.19 g, 2.33 mmol theoretical, 1.0 eq), containing tosyl amide (398 mg, 2.33 mmol theoretical, 1.0 eq) in 15 mL DMF was added tetrabutylammonium iodide (429 mg, 1.16 mmol, 0.5 eq) and K_2CO_3 (3.21 g, 23.3 mmol, 10 eq). To the resulting suspension was added benzyl bromide (1.38 mL, 11.6 mmol, 5.0 eq) dropwise. This mixture was stirred at 25 °C for 18 h. The reaction mixture was diluted with 100 mL ethyl acetate, filtered and poured into 150 mL distilled water. The aqueous layer was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with distilled water (3 x 50 mL) and brine, then dried over $MgSO_4$ and concentrated *in vacuo* to give a crude yellow oil which crystallized to spheres upon standing. The product was purified by FCC (eluent 5% Et_2O in dichloromethane) to give 1.28 g of compound **22** (2.12 mmol, 91% yield) as colorless crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36 (dd, 1H, J = 8.6, 2.1 Hz), 7.30–7.27 (m, 3H), 7.29 (d, 1H, J = 2.1 Hz), 7.20 (br dd, 2H, J = 6.8, 1.7 Hz), 7.07 (br d, 2H, J = 8.6 Hz), 6.87 (br d, 2H, J = 8.6 Hz), 6.76 (d, 1H, J = 8.6 Hz), 5.06 (s, 2H), 4.98 (br d, 1H), 4.57 (m, 1H), 3.69 (s, 3H), 3.09 (dd, 1H, J = 13.9, 5.9 Hz), 3.03 (dd, 1H, J = 13.9, 6.2 Hz), 1.43 (s, 9H). ^{13}C NMR (100 MHz, CDCl$_3$) δ: 172.2, 156.7, 155.0, 150.5, 146.4, 136.2, 133.6, 130.4, 130.1, 128.4, 128.3, 127.9, 127.0, 117.2, 117.0, 82.6, 79.9, 70.8, 54.4, 52.2, 37.5, 28.3. IR (film): 3434 (w), 3394 (br w), 2978 (m), 1746 (s), 1717 (s), 1507 (s), 1489 (s) cm^{-1}. HRMS (EI): 603.111645 (M$^+$) [$C_{28}H_{30}NO_6{}^{127}I$ calcd 603.111790]. mp: 111–112 °C. $[\alpha]^{20}_{D}$ = +27.8° (c=1.0, CHCl$_3$).

Methyl *N*-[(1,1-dimethylethoxy)carbonyl]-*O*-[*S*]-(5-[([2-(1,1-dimethylethoxy)carbonyl]amino)-2-([phenylmethoxy]carbonyl)ethyl]-2-[phenylmethoxy]phenyl)-L-tyrosinate, 26. Oven-dried zinc dust (325 mesh, 84 mg, 1.28 mmol, 6 eq) was placed in an oven-dried flask which was purged with Ar. To this was added 0.2 mL THF and 1,2-dibromoethane (5.5 µL, 64 µmol, 0.3 eq). The mixture was warmed briefly with a heat gun until the solvent began to boil, then was stirred vigorously for a few minutes. This procedure was repeated 5 times. It was then cooled to 35 °C, chlorotrimethylsilane (1.6 µL, 13 µmol, 0.06 eq) was added and the zinc suspension was stirred vigorously for 30 minutes before dropwise addition of *N*-BOC-L-iodoalanine benzyl ester **24** (173 mg, 0.43 mmol, 2.0 eq), in 1 mL of 1:1 THF/*N*,*N*-dimethylacetamide. Zinc insertion was followed by TLC (eluent 20% Et$_2$O in hexanes) and is complete within 15-30 min to give **25**. The iodide **22** (129 mg, 0.21 mmol, 1.0 eq) in 1 mL of 1:1 THF/*N*,*N*-dimethylacetamide was added followed by Pd$_2$(dba)$_3$ (11 mg, 10.6 µmol, 0.10 eq) and *o*-tol$_3$P (13 mg, 43 µmol, 0.20 eq). The resulting mixture was heated at 55 °C for 2 h and then diluted with 25 mL ethyl acetate, filtered and poured into 10 mL 1 *N* HCl. The organic layer was washed with distilled water (3 x 10 mL) and brine, then dried over MgSO$_4$ and concentrated *in vacuo*. The product was purified by FCC (eluent gradient 5-10% Et$_2$O in dichloromethane) to give 103 mg of compound **26** (0.14 mmol, 64% yield) as a colorless oil.

Alternate procedure: The above procedure was followed, except that the aryl iodide **22** was added along with the *N*-BOC-L-iodoalanine benzyl ester **24** to afford 71% of the product **26**. ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.37–7.22 (m, 8H), 7.18 (br d, 2H, J = 6.6 Hz), 7.03 (d, 2H, J = 8.5 Hz), 6.88 (m, 1H), 6.82 (d, 2H, J = 8.5 Hz), 6.76 (m, 2H), 5.07 (s, 2H), 5.03 (s, 2H), 4.99 (m, 2H), 4.56 (m, 2H), 3.67 (s, 3H), 3.04 (m, 2H), 3.02 (m, 1H), 2.96 (dd, 1H, J = 14.1, 5.9 Hz), 1.42 (s, 9H), 1.40 (s, 9H). ^{13}C NMR (100 MHz, CDCl$_3$) δ: 172.2, 171.5, 157.3, 155.0, 154.9, 149.6, 144.9, 136.7, 135.0, 130.2, 129.6, 129.4, 128.5, 128.4, 128.3, 127.7, 126.9, 125.7, 122.9, 116.8, 115.1, 79.9 (2 C's), 70.8, 67.1, 54.4, 52.1 (2 C's) 37.4, (2 C's), 28.2, (2 C's) (one low field carbon unresolved). IR (film): 3377 (br), 2982 (w), 1744 (m), 1715 (s), 1507 (s), 1271 (m), 1167 (s) cm^{-1}. HRMS (FAB): 755.3538 [(M+H)$^+$] [$C_{43}H_{51}N_2O_{10}$ calcd (M+H) 755.3544]. $[\alpha]^{20}_{D}$ = +29.5° (c=2.0, CHCl$_3$).

Isodityrosine, 1. To a flask containing **26** (103 mg, 0.14 mmol, 1.0 eq) was added 10% Pd-C (10 mg, 10 wt % eq). The vessel was evacuated and filled with hydrogen from a balloon. This procedure was repeated 5 times. To this was added THF (2 mL) and the mixture stirred at 25 °C for 18 h, under 1 atm of hydrogen. The reaction mixture was filtered through Celite and concentrated *in vacuo*. The resulting oil was treated with 2 mL of 6 *N* HCl and heated at 65 °C for 6 h, during which the milky suspension became a clear, tan solution. This solution was cooled, washed with ethyl acetate (3 x 3 mL), and concentrated *in vacuo* to give 54.4 mg (0.13 mmol, 92% yield) of isodityrosine **1** as its bis HCl salt. The spectral data was identical to that reported.[11c] ^{1}H NMR (400 MHz, CD$_3$OD) δ: 7.08 (d, 2H, J = 8.6 Hz), 6.80 (br s, 2H), 6.77 (d, 2H, J = 8.6 Hz), 6.75 (br s, 1H), 4.08 (dd, 1H, J = 7.3, 5.8 Hz), 4.02 (dd, 1H, J = 6.8, 6.1 Hz), 3.14–2.90 (m, 4H).

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2) American Chemical Society Arthur C. Cope Scholar, 1995.

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