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Synthesis of the Side Chain Cross-Linked Tyrosine Oligomers Dityrosine, Trityrosine, and Pulcherosine

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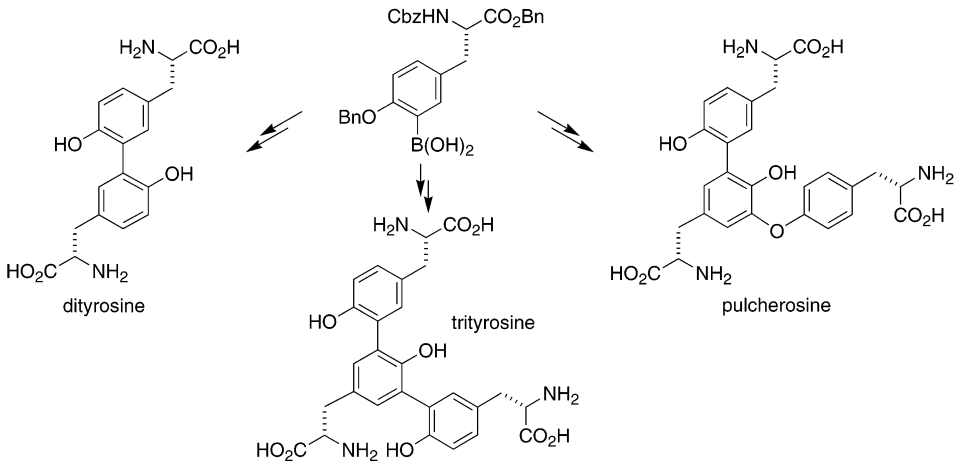

An efficient synthesis of dityrosine and the first syntheses of the tyrosine trimers trityrosine and pulcherosine have been achieved. Protected 3-iodotyrosine underwent tandem Miyaura borylation–Suzuki coupling to give protected dityrosine. The choice of benzyl carbamate, ester, and ether protecting groups enabled a one-step global deprotection to give dityrosine. Suzuki coupling of protected 3,5-diiodotyrosine and tyrosine-3-boronic acid derivatives gave the corresponding trityrosine, but in low yield. However, use of a potassium tyrosine-3-trifluoroborate derivative in place of the corresponding pinacol boronate ester, in combination with protecting group variation, gave protected trityrosine in good yield. Access to pulcherosine was achieved through copper-catalyzed coupling of phenylalanine-4-boronic acid and 4-*O*-protected dopa derivatives to give an isodityrosine derivative. Selective halogenation followed by Suzuki coupling with the potassium tyrosine-3-trifluoroborate gave protected pulcherosine. Global deprotection of the protected trityrosine and pulcherosine derivatives completed the first syntheses of the corresponding tris-α-amino acids.

Introduction

In recent years the presence of a number of unheralded structures in a variety of peptides and proteins has been unveiled. Many of these peptides and proteins incorporate cross-linked tyrosine residues in their structures. These cross-links are believed to impart a wide range of properties to the modified peptides and proteins, ranging from stabilization against degradation and denaturation[1] to modification of electronic properties of enzyme active sites[2] and conformational restriction of cyclic peptides.[3] The unusual chemical structure and biological activity of these peptides and proteins engenders great interest in the development of methods for the preparation of these pivotal functionalized tyrosine derivatives and determination of their physiological roles.

Dityrosine **1**,[4] a tyrosine dimer formed by 3,3′-biaryl bond formation, occurs naturally in fungal cell wall proteins,[5] invertebrate egg/oocyte envelopes,[6] and verte-

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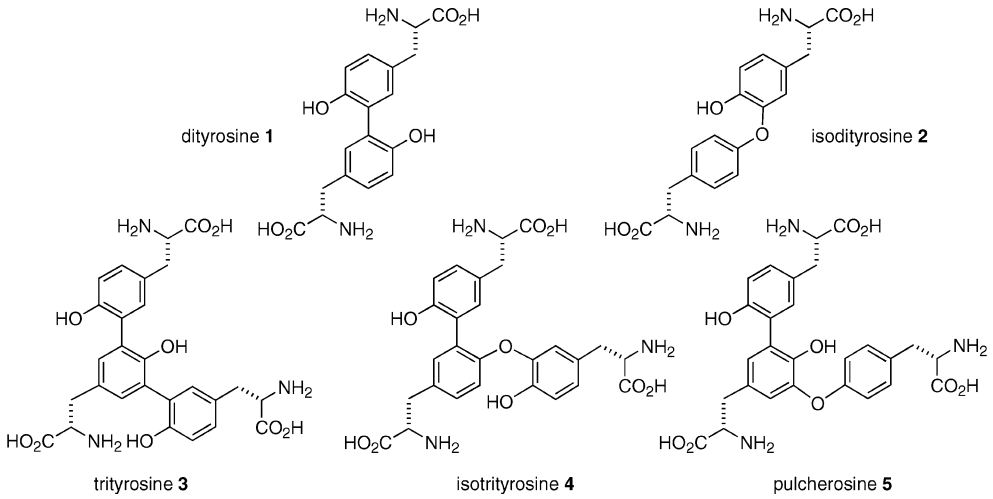

FIGURE 1. Cross-linked tyrosine residues in proteins.

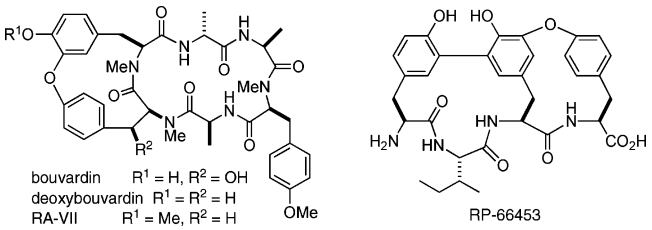

FIGURE 2. Cross-linked tyrosine residues in cyclic peptides.

brate proteins such as elastin and collagen.[7] In these examples the formation of dityrosine is believed to accord a strengthening and/or defensive role to the proteins.[8] Dimerization of proteins through dityrosine linkages is also necessary for the proper functioning of proteins such as thyroglobulin, the precursor to the thyroid hormone thyroxine.[9] Isodityrosine **2**, a tyrosine dimer in which the tyrosine units are linked through a biaryl ether moiety, occurs in plant cell wall proteins and presumably conveys a similar structural/defensive role.[10] Oxidatively coupled trimers of tyrosine−trityrosine **3**, isotrityrosine **4** and pulcherosine **5** (Figure 1)−have also been isolated from bacteria,[11] plants,[10] yeast,[12] and metazoans.[6]

Although many of these cross-links are formed specifically by the organisms for strength and protective purposes, the formation of tyrosine cross-links in proteins has also been associated with a variety of diseases and disorders, including the neurodegenerative Alzheimer's and Parkinson's diseases,[1,13] cystic fibrosis,[14] atherosclerosis,[15] and cataract formation.[16] In these conditions nonspecific formation of cross-linked tyrosine residues has been shown to be a biological marker of oxidative stress and plays a critical role in the signaling of protein degradation and cellular damage.[15]

Cross-linked tyrosine residues are also common in biologically active cyclic peptides, including the cyclo-isodityrosine-containing bouvardins,[17] RA-series compounds,[1,18] and the neurotensin antagonist RP-66453,[19] which contains a pulcherosine moiety. The functionalized tyrosine derivatives in these complex peptides are believed to be of critical importance to their three-dimensional structure and biological activity.

Recently, we communicated the synthesis of dityrosine **1** through a tandem Miyaura borylation−Suzuki coupling of 3-iodotyrosine derivatives.[20] Shortly thereafter Yoburn and Van Vranken[21] independently reported a closely related synthesis of dityrosine-containing peptides. We hereby present a full account of the expedient synthesis of dityrosine **1** and the elaboration of this approach to the first syntheses of the tyrosine trimers trityrosine **3** and pulcherosine **5**.

Results and Discussion

Tyrosine-3-boronic acid derivatives were chosen as common precursors to a variety of cross-linked tyrosines, as these functionalized tyrosine derivatives are suitable for the preparation of biaryl-linked tyrosines, through

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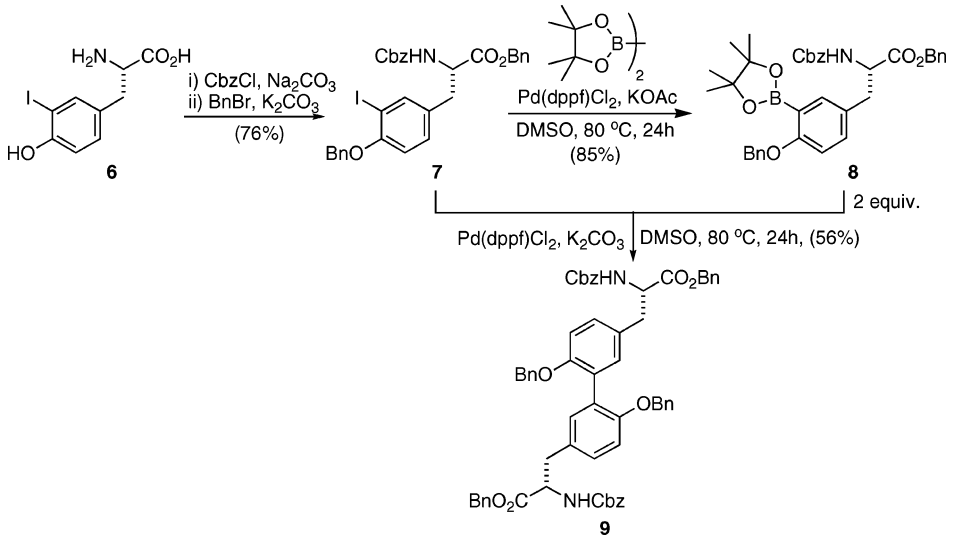
SCHEME 1



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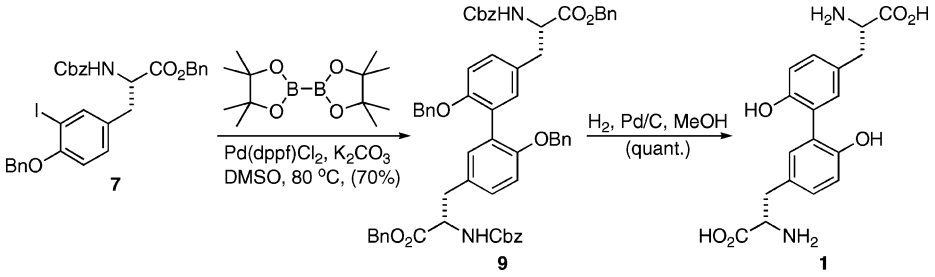

Suzuki coupling, and biaryl ether-linked tyrosines, through copper(II)-catalyzed coupling with tyrosine derivatives. Additionally, the tyrosine-3-boronic acid derivatives are available through borylation of the corresponding 3-iodotyrosine derivatives, which constitute the other coupling partner in the formation of biaryl-linked tyrosines, thereby providing a highly convergent overall process.

A. Synthesis of Dityrosine. Following protection of 3-iodo-L-tyrosine **6** under standard conditions, Miyaura borylation[22] with bis(pinacolatodiboron) gave the tyrosine-3-boronate derivative **8**. Suzuki coupling[23] of the tyrosine-3-boronate **8** and 3-iodo-L-tyrosine derivative **7** then gave the protected dityrosine **9** in reasonable yield (Scheme 1). This procedure was not optimized as a more efficient route to the symmetrical biaryl compound **9** was developed through a one-pot, tandem Miyaura borylation−Suzuki coupling from the 3-iodo-L-tyrosine derivative **7**. In theory, treatment of an aryl iodide with 0.5 equiv of bis(pinacolato)diboron under standard Suzuki coupling conditions should result in 50% of the iodide being transformed to the corresponding boronate, which then couples with the remaining iodide to give the symmetrical biaryl product. In practice, optimization of the amount of the diboron reagent is required for different iodide substrates due to the differing relative rates of conversion of the iodide to the boronate intermediate, protodeborylation, and Suzuki coupling. The optimum conditions for the one-pot conversion of iodotyrosine derivative **7** to dityrosine derivative **9** were found to be the use of 0.95 equiv of bis(pinacolato)diboron, giving dityrosine derivative **9** in 70% yield (Scheme 2).

The use of benzyl carbamate, ester, and ether protecting groups was designed to enable a one-step global deprotection of the protected dityrosine derivative **9**. Accordingly, dityrosine **1** was prepared in quantitative yield by treatment of **9** with palladium-on-charcoal under an atmosphere of hydrogen. The overall procedure enables preparation of dityrosine **1** in just four steps and 53% yield from 3-iodo-L-tyrosine **6**.

B. Synthesis of Trityrosine. It was envisaged that an analogous Suzuki coupling of 3,5-diiodo-L-tyrosine derivative **12** (in place of 3-iodo-L-tyrosine derivative **7)** with excess tyrosine-3-boronate **8** would provide the corresponding protected trityrosine derivative **17**. Accordingly, several methods were investigated toward the preparation of protected 3,5-diiodo-L-tyrosine derivative **12**. Protection of commercially available 3,5-diiodo-L-tyrosine **10** was initially attempted, with Cbz-protection under standard conditions proceeding to give Cbz-3,5-diiodo-L-tyrosine in 99% crude yield. However, the benzylation of Cbz-3,5-diiodo-L-tyrosine by treatment with excess benzyl bromide in acetone in the presence of potassium carbonate (Scheme 3) gave the fully protected compound **12** in low yield (19%), along with 28% of the intermediate phenol **11**. Use of cesium carbonate as base in DMF improved the yield of the fully protected diiodotyrosine derivative **12** to a moderate level (32%). The difficulty in forcing this reaction to completion is presumably due to the steric hindrance around the phenolic

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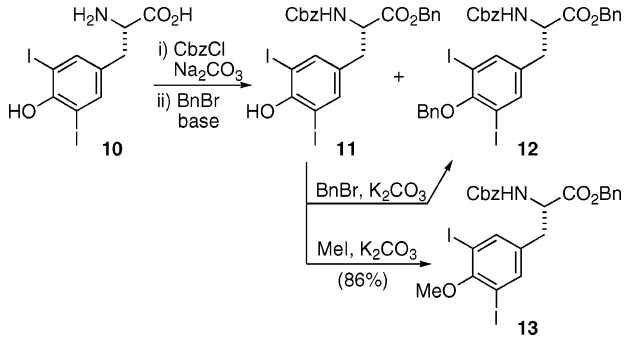
SCHEME 3



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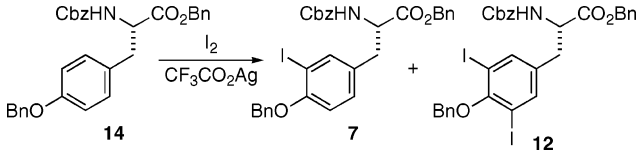


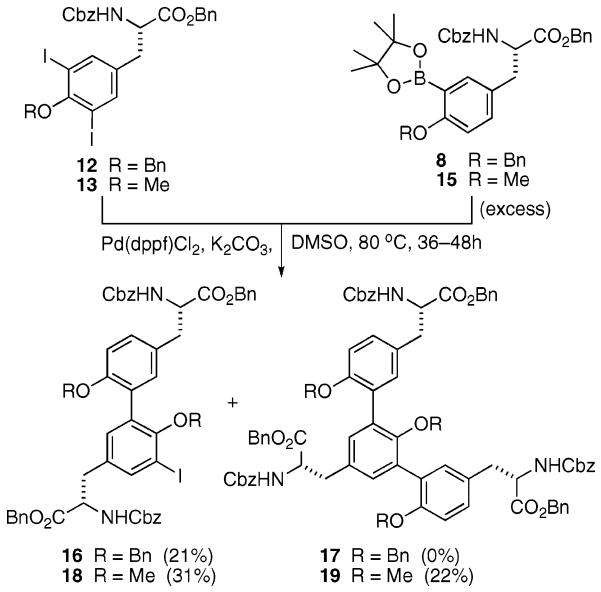
group by the two *ortho* iodine atoms. Evidence for this presumption was that the benzylation of **11** to give **12** was very slow, with mixtures of **11** and **12** being isolated despite the use of excess benzyl bromide and long reaction times. In contrast, the methylation of **11** with iodomethane proceeded to give **13** in good yield (86%) under similar conditions (Scheme 3).

An alternative approach to the fully protected diiodotyrosine derivative **12** through the iodination of tyrosine derivative **14** was also investigated, but again the reaction could not be driven to completion and mixtures of iodotyrosine **7** and diiodotyrosine **12** were obtained (Scheme 4).

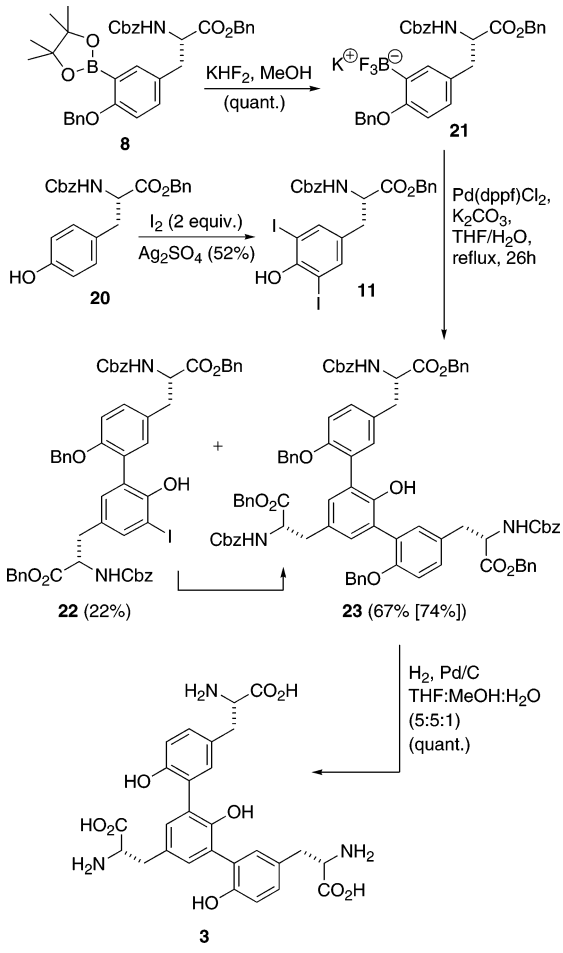
Despite the problems associated with the preparation of 3,5-diiodo-L-tyrosine derivative **12**, Suzuki coupling with tyrosine-3-boronate **8** was investigated. Treatment of **12** with excess tyrosine boronate **8** under standard Suzuki coupling conditions gave none of the doubly coupled product **17**, with the monocoupled iodo-dityrosine derivative **16** isolated in 21% yield (Scheme 5). Use of more forcing conditions (prolonged heating with excess boronate **8**) gave no improvement. Interestingly, coupling of the corresponding methyl ether compounds **13** and **15** gave the trityrosine derivative **19** in 22% yield, in addition to the iodo-dityrosine derivative **18** (31%). The successful preparation of the methyl ether protected trityrosine derivative **19** provides further evidence that the high degree of steric hindrance associated with the all-benzyl protected 3,5-diiodo-L-tyrosine derivative **12** gives rise to both the difficulty in its preparation and its subsequent lack of reactivity.

Given the problems associated with both the preparation and subsequent Suzuki coupling of **12**, attention was turned to the discovery of more reactive coupling partners. It was reasoned that the high degree of steric hindrance encountered through the presence of three adjacent, bulky aromatic substituents may be somewhat alleviated through the use of the 3,5-diiodo-L-tyrosine derivative containing a free phenolic group. That is, diiodotyrosine **11** should be both easier to access and more reactive in the double-Suzuki coupling reaction than the corresponding benzyl-ether **12**, while eliminating the need for a separate deprotection of the aryl-

SCHEME 5

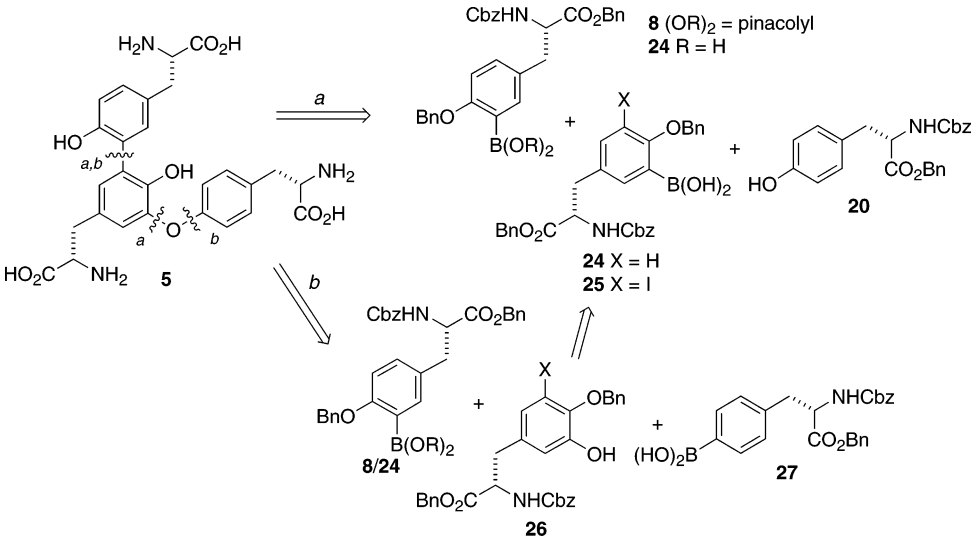


SCHEME 6



methyl ether as would be required from **13**. While the phenol **11** had already been prepared in low yield through mono-benzylation of *N*-Cbz-3,5-diiodo-L-tyrosine (Scheme 3), a more efficient procedure was found to be the diiodination of tyrosine derivative **20** (Scheme 6). Furthermore, recent reports by Molander[24] and Batey,[25] indicating that organotrifluoroborates are more reactive

SCHEME 7



coupling partners than the corresponding organoboronates, led us to investigate the reactivity of the potassium tyrosine-3-trifluoroborate salt **21**. The tyrosine-3-trifluoroborate **21** was synthesized in quantitative yield from the corresponding pinacol boronate derivative **8** by treatment with potassium hydrogen fluoride, according to the procedure of Vedejs et al.[26] Molander[24] found that optimal conditions for Suzuki couplings of organotrifluoroborates employed a solvent mixture of water and water-miscible polar solvents such as THF, 2-propanol, or methanol. Accordingly, the 3,5-diiodo-L-tyrosine derivative **11** was treated with 2 equiv of the tyrosine trifluoroborate **21** in THF/water to afford the trityrosine derivative **23** in 67% yield (Scheme 6). The monocoupled product **22** was also isolated in 22% yield. Protodeborylated product **14** and tyrosine boronic acid derivative **24** (arising from hydrolysis of the trifluoroborate salt) were isolated as minor byproducts. Resubjecting the iododityrosine **22** to the reaction conditions gave more of the trityrosine derivative, increasing the overall yield of **23** from **11** to 74%.

With an efficient procedure for the preparation of protected trityrosine derivative **23** in hand, efforts were focused on a global deprotection to furnish trityrosine **3**. Initial attempts at the hydrogenolysis of trityrosine derivative **23** in methanol, as employed in the preparation of dityrosine **1**, were plagued by solubility problems resulting in the recovery of starting material and several partially deprotected compounds. Various solvent mixtures, including 5% acetic acid in methanol and THF/water were also unsuccessful due to solubility problems. Eventually, hydrogenolysis of **23** in a mixture of THF, methanol and water (5:5:1) was found to afford the fully deprotected product, trityrosine **3**, in quantitative yield (Scheme 6).

C. Synthesis of Pulcherosine. Pulcherosine **5** is a structural isomer of trityrosine in which the central tyrosine moiety is a 3,5-difunctionalized tyrosine, connected through a 3−3′-biaryl linkage to a second tyrosine moiety and through a biaryl ether linkage to the 4-oxygen of the third tyrosine moiety. It was envisaged that the biaryl linkage could be generated by Suzuki coupling of iodotyrosine and tyrosine boronic acid derivatives in a manner analogous to that developed for the syntheses of di- and trityrosine, while the biaryl ether could be generated by a copper(II)-catalyzed coupling[27] of a tyrosine-3-boronic acid with a tyrosine phenolic group. This retrosynthesis leads back to two tyrosine-3-boronic acid units (e.g., **24**) and a protected tyrosine unit (**20**) as the three constituent tyrosine moieties (Scheme 7, path *a*).

Although the tyrosine-3-pinacolyl boronate **8** had been prepared, the corresponding boronic acid **24** was required for the Cu(II)-catalyzed biaryl ether formation. The boronic acid **24** was prepared by transesterification of the pinacolyl boronate **8** with solid-supported boronic acid[28] or alternatively by borylation of the iodotyrosine derivative **7** with bis(neopentylglycolato)boron, followed by facile hydrolysis of the neopentylglycolyl boronate ester **28** (Scheme 8). Treatment of the tyrosine-3-boronic acid **24** with protected tyrosine **20** in the presence of $Cu(OAc)_2$, DMAP, and molecular sieves gave the isodityrosine derivative **29** in only 33% yield. Protected tyrosine **14**, generated by protodeborylation of **24**, was isolated in 15% yield, along with trace amounts of the dopa derivative **26** (X = H) (formed by oxidation of **24**). The formation of protodeborylated and oxidized byproducts is a known complication of the Cu(II)-catalyzed coupling of phenols and arylboronic acids when the arylboronic acid possesses an *ortho* heteroatom.[27c]

It was reasoned that switching the phenol and boronic acid groups would enable a more efficient coupling reaction as the arylboronic acid would no longer contain

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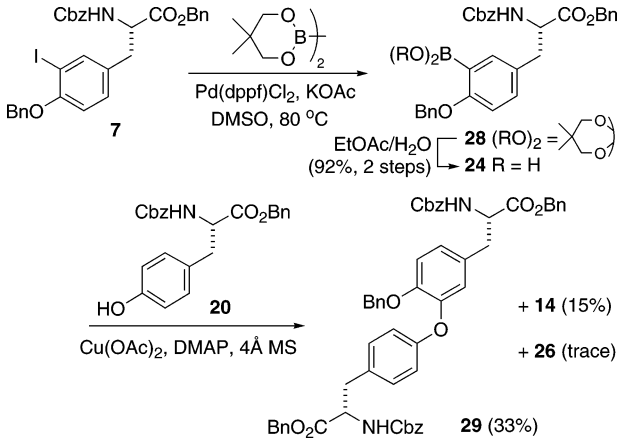
SCHEME 8



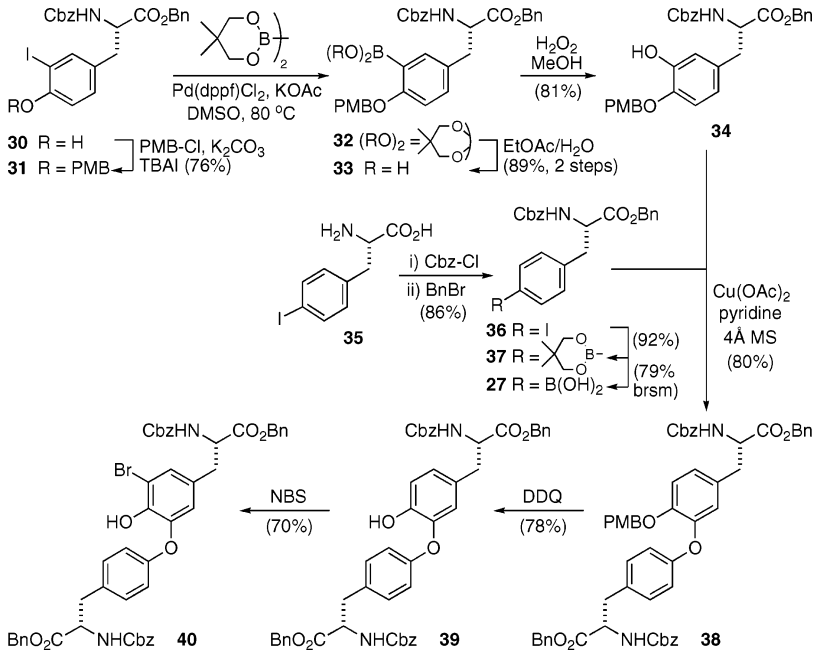
an *ortho* donating group (Scheme 7, path *b*). The biaryl ether linkage would therefore be generated by the coupling of a phenylalanine-4-boronic acid derivative (**27**) and a functionalized dopa derivative (**26**). Such a route to isodityrosine derivatives has previously been reported by Jung and Lazarova.[29] Furthermore, it was reasoned that the requisite differentially protected dopa derivative **26** would be easily accessible through oxidation of the corresponding tyrosine-3-boronic acid derivative **24**.[30] Disconnection of pulcherosine according to path *b* (Scheme 7) therefore leads back yet again to two tyrosine-3-boronic acid units, with a phenylalanine-4-boronic acid unit utilized as the third amino acid constituent. When employing this reworked strategy, the *p*-methoxybenzyl (PMB) group was chosen to protect the 4-oxygen of the central tyrosine in order that this group could specifically be removed in the presence of all the other benzyl protecting groups at a later stage in the synthesis (vide infra). Accordingly, PMB-protected iodotyrosine derivative **31** was prepared from **30** under standard conditions. Subsequent treatment with bis(neopentylglycolato)diboron in the presence of $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ and potassium acetate gave the neopentylglycolyl boronate **32**, which was immediately hydrolyzed to afford the tyrosine-3-boronic acid derivative **33** in good yield (Scheme 9). Treatment of **33** with 1 equiv of hydrogen peroxide for 30 min gave the 4-*O*-PMB protected dopa derivative **34** in 81% yield.[30]

The phenylalanine-4-boronic acid component **27** was prepared using a similar procedure to that employed for the preparation of tyrosine-3-boronic acids **24** and **33**. Protection of 4-iodophenylalanine (**35**) under standard conditions gave **36** in 86% yield. Borylation of iodide **36** with bis(neopentylglycolato)diboron gave the boronate ester **37**. Hydrolysis of the phenylalanine neopentylglycolyl boronate **37** was much slower than that of the corresponding tyrosine derivatives **28** and **32**, taking several days rather than several hours, but did afford the boronic acid **27** in 79% yield (based on recovered starting material).

Treatment of phenylalanine-4-boronic acid **27** with dopa derivative **34** in the presence of copper(II) acetate, pyridine, and 4 Å molecular sieves afforded the biaryl ether **38** in good yield (80%). Selective removal of the PMB group with DDQ then provided isodityrosine derivative **39** in 78% yield. Note that selective removal of the 4-*O*-protecting group was required as 3,4-*O,O*-dialkyl-protected dopa derivatives selectively halogenate at the 6-position,[31] whereas those only protected at the 3-position halogenate at the 5-position,[32] presumably as a result of the greater directing effect of the 4-phenolic group.

With the isodityrosine derivative **39** in hand, selective halogenation was investigated. However, all efforts toward iodination of the isodityrosine derivative **39** by treatment with iodine and silver(I) salts were unsuccessful. No explanation for the lack of success of this reaction in light of the successful iodinations of other tyrosine derivatives is currently forthcoming. Attention was therefore turned toward bromination of isodityrosine derivative **39**, and it was found that treatment of **39** with 1.5

SCHEME 9



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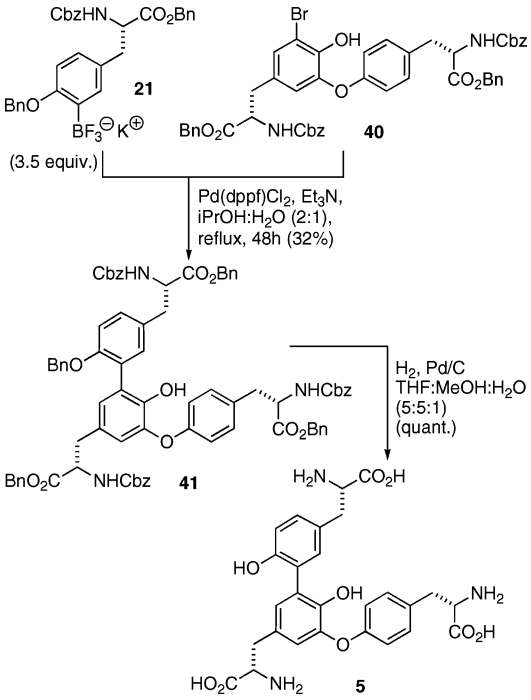

equiv of *N*-bromosuccinimide afforded the aryl bromide **40** selectively in 70% yield.

It was envisaged that the Suzuki coupling procedure previously utilized in the synthesis of trityrosine derivative **23** could be adopted for the preparation of protected pulcherosine **41**. Treatment of bromo-isodityrosine derivative **40** with excess tyrosine trifluoroborate **21**, potassium carbonate, and Pd(dppf)Cl_2·CH_2Cl_2 in a THF/water solvent mixture afforded the coupled product **41** in only 7% yield. Unreacted starting material **40** and protodeborylated product **14** were isolated in 67% and 26% yield, respectively. Following Molander's investigations,[24] the use of a 2-propanol/water solvent mixture and 6 equiv of triethylamine were then examined and found to give the optimum yield of the coupled product to date, affording the pulcherosine derivative **41** in 32% yield (Scheme 10).

With the protected pulcherosine derivative **41** in hand, a global deprotection was required to furnish pulcherosine **5**. Hydrogenolysis of pulcherosine derivative **41** employing the conditions previously optimized for deprotection of the trityrosine derivative **23** (H_2, Pd/C, THF/MeOH/water) afforded the deprotected pulcherosine **5** in quantitative yield (Scheme 10).

Conclusion

An efficient synthesis of dityrosine and the first syntheses of the tyrosine trimers trityrosine and pulcherosine have been achieved. Dityrosine was prepared in 53% overall yield in four steps from 3-iodo-L-tyrosine, employing a tandem Miyaura borylation−Suzuki coupling strategy. Preparation of trityrosine was most efficient through Suzuki coupling of a tyrosine-3-trifluoroborate with a 3,5-diiodotyrosine derivative. Access to pulcherosine was achieved through copper-catalyzed coupling of phenylalanine-4-boronic acid and 4-*O*-protected dopa derivatives to give an isodityrosine derivative. Selective halogenation followed by Suzuki coupling with the potassium tyrosine-3-trifluoroborate gave protected pulcherosine. One-step global deprotection of the protected trityrosine and pulcherosine derivatives completed the first syntheses of the corresponding tris-α-amino acids.

Tyrosine-3-boronic acid derivatives have been shown to be highly useful precursors to cross-linked tyrosines as these organoboron compounds are suitable for the preparation of both biaryl-linked tyrosines, through Suzuki coupling, and biaryl ether-linked tyrosines, through copper(II)-catalyzed coupling with tyrosine derivatives. Additionally, tyrosine-3-boronic acid derivatives can be converted directly to differentially protected dopa derivatives, which are alternative precursors to biaryl ether-linked tyrosine oligomers. These general procedures should allow for the preparation of a wide range of cross-linked tyrosine oligomers present in naturally occurring peptides and proteins, as well as unnatural oligomers.

Experimental Section

General procedures are available in Supporting Information.

***N*-Cbz-4-*O*-Benzyl-3-iodo-l-tyrosine Benzyl Ester 7.** To an ice-cold solution of potassium carbonate (6.75 g, 48.8 mmol) in water (60 mL) was added 3-iodo-L-tyrosine **6** (5.00 g, 16.3 mmol). A solution of 50% benzylchloroformate in toluene (8.35 mL, 25.0 mmol) was added over 30 min at 0 °C. The mixture was stirred at room temperature for 21 h. The resulting mixture was acidified to pH 4 with 3 M HCl and extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with saturated sodium chloride solution (2 × 100 mL), dried ($MgSO_4$), and concentrated in vacuo to give Cbz-3-iodo-L-tyrosine (7.2 g) as a white powder. The crude product was added to a solution of potassium carbonate (6.80 g, 49.2 mmol) and tetrabutylammonium iodide (40 mg) in dry acetone (200 mL). Nitrogen was bubbled through the mixture for 15 min. Benzyl bromide (4.27 mL, 35.9 mmol) was added and the mixture was heated at reflux in the dark for 20 h. The resulting mixture was cooled and concentrated in vacuo. To the residue was added water (100 mL) and the mixture was extracted with DCM (2 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to give a pale yellow oil. The oil was chromatographed on silica eluting with EtOAc/hexane (1:2−1:1 gradient) to give the dibenzylated product **7** (7.63 g, 76%) as a white solid: mp 88.0−88.5 °C; $[\alpha]_D$ +11.3 (*c* 2.0, $CHCl_3$); IR (Nujol) υ_{max} (cm^{-1}) 2922, 2853, 1735, 1460, 1377, 721; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (1H, d, J = 2.1 Hz), 7.49−7.29 (15H, m), 6.91 (1H, dd, J = 2.1, 8.4 Hz), 6.65 (1H, d, J = 8.4 Hz), 5.25 (1H, br d, J = 8.1 Hz), 5.13−5.07 (6H, m), 4.64 (1H, m), 3.02−3.00 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1 (s), 156.4 (s), 155.5 (s), 140.2 (d), 136.4 (s), 134.9 (s), 130.3 (d), 130.2 (d), 130.1 (s), 128.6 (d), 128.6 (d), 128.5 (s), 128.5 (d), 128.4 (d), 128.1 (d), 128.0 (d), 127.9 (d), 127.4 (d), 112.5 (d), 86.8 (s), 70.8 (t), 67.3 (t), 67.0 (t), 54.9 (d), 36.9 (t); MS (ESI, +ve) *m/z* 644 (M + Na^+, 100%); HRMS (ESI, +ve) *m/z* calcd for (M + Na)$^+$ 644.0905, found 644.0906.

***N*-Cbz-4-*O*-Benzyl-3-pinacolatoborono-l-tyrosine Benzyl Ester 8.** To a solution of bis(pinacolato)diboron (2.46 g, 9.66 mmol), Pd(dppf)Cl_2·CH_2Cl_2 (0.24 g), and potassium acetate (1.90 g, 19.3 mmol) in DMSO (30 mL) was added 3-iodotyrosine derivative **7** (3.00 g, 4.83 mmol). The mixture was stirred under nitrogen at 80 °C for 24 h. A 50% saturated

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sodium chloride solution (50 mL) was added, and the resulting mixture was extracted with EtOAc (2 × 100 mL). The combined organic extracts were washed with 50% saturated sodium chloride solution (3 × 100 mL), dried ($MgSO_4$), and concentrated in vacuo to give a dark brown oil. The oil was chromatographed on alumina eluting with EtOAc/hexane (1:3−1:2 gradient) to give the boronate derivative **8** (2.55 g, 85%) as a pale brown oil: $[\alpha]_D$ +5.31 (*c* 1.08, $CHCl_3$); IR (Nujol) υ_{max} (cm^{-1}) 2897, 1735, 1456, 1377, 1366, 1151, 721; ^1H NMR (300 MHz, $CDCl_3$) δ 7.60 (2H, dd, J = 1.4, 8.0 Hz), 7.48 (1H, d, J = 2.4 Hz), 7.41−7.28 (13H, m), 7.07 (1H, dd, J = 2.4, 8.4 Hz), 6.77 (1H, d, J = 8.4 Hz), 5.24 (1H, br d, J = 8.2 Hz), 5.12−5.07 (6H, m), 4.66 (1H, m), 3.07−3.04 (2H, m), 1.34 (12H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6 (s), 162.6 (s), 155.7 (s), 137.6 (d), 136.3 (s), 135.1 (s), 133.3 (d), 128.6 (d), 128.5(3) (d), 128.4(8) (d), 128.1(9) (d), 128.1(5) (s), 128.0(6) (d), 127.6 (d), 127.4(4) (s), 127.3(6) (d), 127.0 (d), 126,7 (d), 112.2 (d), 83.5 (s), 70.0 (t), 67.3 (t), 67.0 (t), 55.1 (d), 37.3 (t), 25.0 (q), 24.9 (q) (C−B not observed); MS (ESI, +ve) *m/z* 644 (M + Na^+, 100%); HRMS (ESI, +ve) *m/z* calcd for $(M + Na)^+$ 644.2798, found 644.2790.

Protected Dityrosine 9. Method 1. To a solution of iodotyrosine derivative **7** (52.9 mg, 0.09 mmol), Pd(dppf)Cl_2·CH_2Cl_2 (2.00 mg), and potassium carbonate (44.7 mg, 0.36 mmol) in DMSO (1.5 mL) was added bis(pinacolato)diboron (20.5 mg, 0.086 mmol). The mixture was stirred under nitrogen at 80 °C for 48 h. The resulting mixture was extracted with EtOAc (2 × 30 mL) and the combined organic extracts were washed with 50% saturated sodium chloride solution (2 × 30 mL), dried ($MgSO_4$), and concentrated in vacuo to give a dark brown oil. The oil was chromatographed on silica eluting with ether/DCM/hexane (1:2:3−1:2:2 gradient) to give dityrosine derivative **9** (29.3 mg, 70%) as a pale yellow oil: $[\alpha]_D$ +5.70 (*c* 3.14, $CHCl_3$); IR (Nujol) υ_{max} (cm^{-1}) 3339, 2926, 1713, 1499, 1454, 1344, 1217, 1053, 696; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36−7.11 (30H, m), 6.98 (2H, m), 6.92 (2H, dd, J = 1.9, 8.3 Hz), 6.78 (2H, d, J = 8.3 Hz), 5.23 (2H, br d, J = 7.9 Hz), 5.14−4.99 (8H, m), 4.90 (4H, s), 4.65 (2H, m), 3.05−3.03 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5 (s), 155.7 (s), 155.4 (s), 137.4 (s), 136.3 (s), 135.2 (s), 132.6 (d), 129.3 (d), 128.6 (d), 128.5 (d), 128.4 (d), 128.3 (d), 128.1 (d), 128.0 (d), 127.6 (s), 127.4 (d), 126.6 (d), 113.2 (d), 70.3 (t), 67.1 (t), 66.9 (t), 55.0 (d), 37.8 (t) (2 coincident C−H); MS (ESI, +ve) *m/z* 1011 (M + Na^+, 100%), 921 (32); HRMS (ESI, +ve) *m/z* calcd for $(M + Na)^+$ 1011.3828, found 1011.3865.

Method 2. To a solution of iodo-tyrosine derivative **7** (23.4 mg, 0.04 mmol), Pd(dppf)Cl_2·CH_2Cl_2 (1.00 mg), and potassium carbonate (10.4 mg, 0.08 mmol) in DMSO (3 mL) was added boronate derivative **8** (46.8 mg, 0.08 mmol). The mixture was stirred under nitrogen at 80 °C for 24 h. The resulting mixture was extracted with EtOAc (2 × 30 mL) and the combined organic extracts were washed with saturated sodium chloride solution (2 × 30 mL), dried ($MgSO_4$), and concentrated in vacuo to give a dark brown oil. The oil was chromatographed on silica, eluting with ether/DCM/hexane (1:2:3−1:1:1 gradient) to give dityrosine derivative **9** (21.3 mg, 56%) as a pale yellow oil.

Dityrosine 1.[4a] To a solution of protected dityrosine derivative **9** (0.29 g, 0.30 mmol) in MeOH (12 mL) was added 10% palladium on charcoal (0.03 g, 0.03 mmol). The reaction mixture was stirred under hydrogen at room temperature for 21 h. The resulting mixture was filtered through Celite, washed with HCl (1 M, 30 mL), and concentrated in vacuo to give dityrosine **1** in quantitative yield. For analytical purposes, the crude product was chromatographed on reverse-phase HPLC eluting with H_2O/CH_3CN/TFA (95:5:0.05) to give dityrosine **1** as an off-white solid: mp 136−140 °C; $[\alpha]_D$ −2.6 (*c* 0.08, 1 M HCl), (lit.[4a] $[\alpha]_D$ −7 (*c* 1.00, 1 M HCl)); ^1H NMR (400 MHz, 1 M DCl·D_2O) δ 7.12 (2H, d, J = 8.3 Hz), 7.02 (2H, s), 6.89 (2H, d, J = 8.3 Hz), 4.23 (2H, m), 3.21(2H, dd, J = 5.4, 14.5 Hz), 3.09 (2H, dd, J = 7.3, 14.5 Hz); ^{13}C NMR (100 MHz, 1 M DCl·D_2O) δ 171.1 (s), 152.6 (s), 132.2 (d), 130.4 (d), 125.8 (s), 120.0 (s), 116.4 (d), 54.0 (d), 38.7 (t); MS (ESI, +ve) *m/z* 361 (M + Na^+, 100%).

***N*-Cbz-3,5-Diiodo-L-tyrosine Benzyl Ester 11.** To a solution of silver sulfate (0.16 g, 0.50 mmol) and iodine (0.13 g, 0.50 mmol) in MeOH (5 mL) was added *N*-Cbz-L-tyrosine benzyl ester **20** (0.10 g, 0.25 mmol). The mixture was stirred under nitrogen in the dark at room temperature for 5 h. The yellow precipitate was removed by filtration, a 1:1 mixture of saturated sodium hydrogen carbonate solution and saturated sodium chloride solution (50 mL) was added to the filtrate, and the mixture was extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with a 1:1 mixture of saturated sodium hydrogen carbonate solution and saturated sodium chloride solution (50 mL), saturated sodium thiosulfate solution (50 mL), dried ($MgSO_4$), and concentrated in vacuo to give a yellow oil. The oil was chromatographed on silica, eluting with ether/DCM/hexane (1:2:3) to give the 3,5-diiodo-L-tyrosine derivative **11** (85.3 mg, 52%) as a yellow solid: mp 93.0−94.5 °C; $[\alpha]_D$ +17.3 (*c* 2.02, $CHCl_3$); IR (Nujol) υ_{max} (cm^{-1}) 2927, 2852, 1724, 1456, 1376, 1157, 724; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41−7.29 (12H, m), 5.74 (1H, br s), 5.37 (1H, br d, J = 7.8 Hz), 5.18−5.08 (4H, m), 4.62 (1H, br m), 3.00−2.91 (2H, br m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6 (s), 156.2 (s), 153.4 (s), 140.6 (d), 136.8 (s), 135.4 (s), 132.5 (s), 129.4 (d), 129.3 (d), 129.3 (d), 129.1 (d), 128.9 (d), 128.7 (d), 82.9 (s), 68.2 (t), 67.8 (t), 55.5 (d), 37.0 (t); MS (EI) *m/z* 522 ($M^{+\bullet}$ − CO_2Bn, 1%), 507 ($M^{+\bullet}$ − CbzNH, 18), 460 (5), 380 (25), 359 (8), 333 (4), 252 (10), 232 (3), 91 (100); HRMS (ESI, +ve) *m/z* calc. for $(M + Na)^+$ 679.9409, found 679.9415.

***N*-Cbz-4-*O*-Benzyl-3,5-diiodo-L-tyrosine Benzyl Ester 12.** To an ice-cold solution of potassium carbonate (2.06 g, 15.1 mmol) in water (20 mL) was added 3,5-diiodo-L-tyrosine **10** (2.00 g, 4.3 mmol). A solution of 50% benzyl chloroformate in toluene (3.04 mL, 9.09 mmol) was added over 30 min at 0 °C. The mixture was stirred at room temperature for 20 h. The resulting mixture was acidified to pH 4 with 3 M HCl and extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with saturated sodium chloride solution (50 mL), dried ($MgSO_4$), and concentrated in vacuo to give the crude Cbz-3,5-diiodo-L-tyrosine (2.46 g, 99%) as a pale yellow solid. To a solution of cesium carbonate (46.1 mg, 0.14 mmol) in MeOH (1 mL) was added *N*-Cbz-3,5-diiodo-tyrosine (80.2 mg, 0.14 mmol) and the mixture was concentrated in vacuo. The residue was dissolved in DMF (2 mL) then benzyl bromide (33.6 μL, 0.28 mmol) was added and the mixture stirred under nitrogen at room temperature for 20 h. The resulting mixture was cooled and concentrated in vacuo. To the residue was added water (30 mL) and the mixture was extracted with DCM (2 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to give a pale yellow oil. The oil was chromatographed on silica, eluting with ether/DCM/hexane (1:3:7−1:3:5 gradient) to give the dibenzylated product **12** (33.8 mg, 32%) as a white solid: mp 124−125 °C; $[\alpha]_D$ +8.00 (*c* 2.07, $CHCl_3$); IR (Nujol) υ_{max} (cm^{-1}) 2930, 1725, 1454, 1377, 1366, 1306, 1155, 721; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (2H, d, J = 7.0 Hz), 7.54 (2H, s), 7.44−7.30 (13H, m), 5.34 (1H, br d, J = 8.2 Hz), 5.20−5.08 (4H, m), 4.95 (2H, s), 4.64 (1H, m), 3.05−2.95 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8 (s), 156.5 (s), 155.6 (s), 140.7 (d), 136.2 (s), 136.0 (s), 134.7 (s), 128.8 (d), 128.8 (d), 128.7 (d), 128.5 (d), 128.5 (d), 128.5 (d), 128.4 (d), 128.3 (d), 128.1 (d), 91.1 (s), 74.4 (t), 67.6 (t), 67.2 (t), 54.8 (d), 36.5 (t) (1 coincident C−C); MS (ESI, +ve) *m/z* 770 (M + Na^+, 60%); HRMS (ESI, +ve) *m/z* calcd for (M + $Na)^+$ 769.9870, found 769.9887.

***N*-Cbz-4-*O*-Benzyl-3-(*N*-Cbz-4′-*O*-benzyl-L-3′-tyrosyl benzyl ester)-5-iodo-L-tyrosine Benzyl Ester 16.** To a solution of 3,5-diiodo-L-tyrosine derivative **12** (24.0 mg, 0.03 mmol), Pd(dppf)Cl_2·CH_2Cl_2 (2.36 mg), and potassium carbonate (22.2 mg, 0.15 mmol) in DMSO (1 mL) was added boronate derivative **8** (40.0 mg, 0.06 mmol). The mixture was stirred under nitrogen at 80 °C for 18 h. A further portion of boronate derivative **8** (40.0 mg, 0.06 mmol) was then added and the reaction mixture

stirred at 80 °C for 21 h. The resulting mixture was extracted with EtOAc (2 × 30 mL) and the combined organic extracts were washed with saturated sodium chloride solution (2 × 30 mL), dried ($MgSO_4$), and concentrated in vacuo to give a dark brown oil. The oil was chromatographed on silica, eluting with EtOAc/hexane (1:2−1:1 gradient) to give iodo-dityrosine derivative **16** (7.4 mg, 21%) as a pale yellow oil: $[\alpha]_D$ +15.6 (*c* 0.54, $CHCl_3$); IR (neat) υ_{max} (cm^{-1}) 3373, 2089, 1636, 1454, 1342, 1215, 1057, 694; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (1H, d, J = 1.2 Hz), 7.28−7.12 (30H, m), 6.99−6.94 (3H, m), 6.78 (1H, dd, J = 1.2, 5.8 Hz), 5.28 (1H, br d, J = 7.9 Hz), 5.23 (1H, br d, J = 9.7 Hz), 5.14−5.00 (8H, m), 4.90−4.89 (4H, m), 4.64 (1H, m), 4.37 (1H, m), 3.03−2.96 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4 (s), 171.2 (s), 155.6 (s), 155.3 (s), 155.0 (s), 139.1 (d), 137.4 (s), 137.0 (s), 136.5 (s), 136.2 (s), 134.9 (s), 133.2(8) (d), 133.1(6) (s), 132.6 (d), 132.3 (d), 130.0 (d), 129.2 (d), 128.6(6) (d), 128.5(8) (s), 128.5(4) (d), 128.4(8) (s), 128.4(1) (d), 128.3 (d), 128.1(4) (s), 128.1(0) (d), 127.9 (d), 127.6 (d), 127.4 (d), 126.9 (d), 126.6 (d), 113.0 (d), 92.9 (s), 74.9 (t), 70.3 (t), 67.3(7) (t), 67.2(6) (t), 67.1 (t), 67.0 (t), 54.8(7) (d), 54.8(0) (d), 37.3 (t), 37.0 (t) (2 coincident C−C and 6 C−H); MS (ESI, +ve) *m/z* 1137 ($M + Na^+$, 57%), 1011 ($M - I + Na^+$, 100%).

Potassium *N*-Cbz-4-*O*-Benzyl-L-tyrosyl-3-trifluoroborate Benzyl Ester 21. To a solution of tyrosine boronate derivative **8** (50.0 mg, 0.08 mmol) in MeOH (1 mL) was added potassium hydrogen fluoride (4.5 M, 0.13 mL). The mixture was stirred at room temperature for 2 h. The resulting mixture was filtered and the solid washed with DCM and hot acetone. The filtrate was concentrated in vacuo to give the potassium trifluoroborate derivative **21** (48.0 mg, 100%) as white crystals; $[\alpha]_D$ +10.4 (*c* 0.95, $CHCl_3$); IR (Neat) υ_{max} (cm^{-1}) 3416, 2359, 1717, 1645, 1452, 1211, 1018, 737, 696; ^1H NMR (400 MHz, CD_3CN) δ 7.52−7.50 (3H, m), 7.38−7.28 (13H, m), 6.86 (1H, dd, J = 2.5, 8.3 Hz), 6.68 (1H, d, J = 8.3 Hz), 6.05 (1H, br d, J = 8.1 Hz), 5.15−4.98 (6H, m), 4.45 (1H, m), 3.05 (1H, dd, J = 5.5, 13.8 Hz), 2.86 (1H, dd, J = 8.5, 13.8 Hz); ^{13}C NMR (100 MHz, CD_3CN) δ 173.1 (s), 161.5 (s), 157.1 (s), 139.7 (s), 138.0 (s), 136.9 (s), 135.4 (d), 129.5(2) (d), 129.4(7) (d), 129.4(1) (d), 129.2 (d), 129.0 (d), 128.9 (d), 128.7 (d), 112.8 (d), 75.4 (d), 70.4 (t), 67.6 (t), 67.2 (t), 57.0 (d), 41.0 (d), 37.8 (t), 25.2 (d) (1 coincident C−C) (C−B not observed); MS (ESI, −ve) *m/z* 563 ($[M - K]^-$, 100%), 1163 ($[M_2 - K]^-$, 20%); HRMS (ESI, −ve) *m/z* calcd for $(M - K)^-$ 562.2010, found 562.1970.

Protected Trityrosine 23. To a solution of diiodo-tyrosine derivative **11** (50.1 mg, 0.08 mmol) and tyrosyl-3-trifluoroborate derivative **21** (91.7 mg, 0.15 mmol) in H_2O:THF (1:10, 3 mL) was added potassium carbonate (31.6 mg, 0.23 mmol) and $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (5.50 mg). The reaction mixture was stirred under nitrogen at reflux for 26 h. The resulting mixture was filtered through Celite, washed with DCM (3 × 20 mL), and concentrated in vacuo to give a brown oil. The oil was chromatographed on silica eluting with EtOAc/hexane (1:2−1:1 gradient) to give protected trityrosine derivative **23** (70.8 mg, 67%) as an off-white solid: mp 55.5−58 °C; $[\alpha]_D$ +5.78 (*c* 1.98, $CHCl_3$); IR (Nujol) υ_{max} (cm^{-1}) 3346, 3032, 1720, 1499, 1456, 1340, 1213, 1057, 1026, 696; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.16 (40H, m), 6.97−6.93 (6H, m), 6.82−6.79 (2H, m), 6.23 (1H, br s), 5.29−5.25 (3H, br m), 5.14−4.89 (16H, m), 4.68−4.65 (3H, m), 3.07−2.97 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4 (s), 162.9 (s), 155.6 (s), 154.7 (s), 150.2 (s), 136.7 (s), 136.2 (s), 135.9 (s), 135.1 (s), 133.5 (d), 133.1 (d), 132.1 (d), 131.8 (d), 129.5 (d), 128.9 (d), 128.7 (d), 128.5 (d), 128.4(2) (s), 128.3(8) (d), 128.2 (d), 128.1 (d), 128.0(3) (d), 127.9(6) (d), 127.8 (d), 127.7 (d), 126.9 (d), 126.6 (s), 120.8 (d), 114.0 (d), 111.4 (d), 71.0 (t), 67.3 (t), 67.2 (t), 67.0 (t), 66.9 (t), 55.7 (d), 55.0 (d), 37.9 (t), 37.4 (t) (4 coincident C−C); MS (ESI, +ve) *m/z* 1415 ($M + Na^+$, 100%); HRMS (ESI, +ve) *m/z* calcd for $(M + Na)^+$, 1414.525, found 1414.526. Further elution gave the iododityrosine derivative **22** (17.2 mg, 22%) as an off-white solid: mp 59−61 °C; $[\alpha]_D$ +7.04 (*c* 1.95, $CHCl_3$); IR (Nujol) υ_{max} (cm^{-1}) 3346, 3032, 1720, 1499, 1456, 1340, 1213, 1059, 1026, 696; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46−7.10 (25H, m), 6.97−6.69 (5H, m), 6.43 (1H, s), 5.24−5.19 (2H, br m), 5.04−4.81 (10H, m), 4.59−4.57 (2H, m), 3.01−2.85 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3 (s), 171.2 (s), 155.6 (s), 154.8 (s), 154.3 (s), 151.8 (s), 139.2 (d), 136.2 (s), 135.0 (s), 132.9 (d), 132.7 (d), 130.5 (d), 129.5 (d), 129.4 (s), 128.6 (d), 128.5 (d), 128.4 (d), 128.3 (d), 128.1 (d), 128.0 (d), 127.1 (d), 127.0 (d), 126.9 (s), 125.6 (s), 114.1 (d), 86.1 (s), 71.1 (t), 67.3 (t), 67.2 (t), 67.0 (t), 66.4 (t), 55.8 (d), 55.0 (d), 37.7 (t), 36.9 (t) (4 coincident C−C and 6 C−H); MS (ESI, +ve) *m/z* 1048 ($M + Na^+$, 44%); HRMS (ESI, +ve) *m/z* calcd for $(M + Na)^+$ 1047.2325, found 1047.2314.

Trityrosine 3. To a solution of protected trityrosine derivative **23** (90.3 mg, 0.06 mmol) in H_2O/MeOH/THF (1:5:5, 10 mL) was added 10% palladium on charcoal (7.0 mg). The reaction mixture was stirred under hydrogen at room temperature for 7 d. The resulting mixture was filtered through Celite, washed with $NH_{3(aq)}$/MeOH/$CHCl_3$ (2:18:80, 3 × 20 mL), and concentrated in vacuo to give the deprotected trityrosine in quantitative yield. For analytical purposes, the crude product was chromatographed on reverse-phase HPLC using H_2O/CH_3CN/TFA (95:5:0.05) as eluent to give pure trityrosine **3** as an off-white solid: mp 152.5−154 °C; $[\alpha]_D$ −15.7 (*c* 0.30, 1 M HCl); ^1H NMR (400 MHz, D_2O) δ 7.17 (2H, dd, J = 2.2, 8.3 Hz), 7.13 (2H, d, J = 2.2 Hz), 7.12 (2H, s), 6.95 (2H, d, J = 8.3 Hz), 4.09−4.03 (3H, m, αH's), 3.24−3.08 (6H, m, βH's);[33] ^{13}C NMR (100 MHz, D_2O) δ 173.1 (s), 173.0 (s), 152.6 (s), 149.9 (s), 132.5 (d), 132.0 (d), 130.7 (d), 127.1 (s), 126.8 (s), 126.5 (s), 125.3 (s), 117.8 (d), 55.4(0) (d), 55.3(9) (d), 35.1(2) (t), 35.0(6) (t); MS (ESI, +ve) *m/z* 540 ($M + H^+$, 90%).

***N*-Cbz-3-Iodo-L-tyrosine Benzyl Ester 30.** To a solution of silver sulfate (0.77 g, 2.47 mmol) and iodine (0.63 g, 2.47 mmol) in MeOH (60 mL) was added *N*-Cbz-L-tyrosine benzyl ester **20** (1.00 g, 2.47 mmol). The mixture was stirred under nitrogen in the dark at room temperature for 5 h. The yellow precipitate was removed by filtration, a 1:1 mixture of saturated sodium hydrogen carbonate solution and saturated sodium chloride solution (100 mL) were added to the filtrate, and the mixture was extracted with EtOAc (2 × 100 mL). The combined organic extracts were washed with 50% saturated sodium chloride solution (100 mL) and saturated sodium thiosulfate solution (100 mL), dried ($MgSO_4$), and concentrated in vacuo to give a dark brown oil. The oil was chromatographed on silica, eluting with ether/DCM/hexane (1:3:4) to give the diiodo-tyrosine derivative **11** (0.21 g, 13%) and the iodotyrosine derivative **30** (0.57 g, 43%) as a yellow solid: mp 131.5−133.0 °C; $[\alpha]_D$ +11.9 (*c* 2.06, $CHCl_3$); IR (Nujol) υ_{max} (cm^{-1}) 3354, 1765, 1725, 1498, 1223, 1027, 697; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39−7.27 (11H, m), 6.85 (1H, dd, J = 2.0, 8.3 Hz), 6.76 (1H, d, J = 8.3 Hz), 5.76 (1H, br s, OH), 5.35 (1H, br d, J = 8.0 Hz), 5.19−5.07 (4H, m), 4.65 (1H, m, αH), 3.04−2.94 (2H, m, βH's);[34] ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2 (s), 155.6 (s), 154.1 (s), 138.9 (d), 136.0 (s), 134.8 (s), 131.0 (d), 129.5 (s), 128.6 (d), 128.6 (d), 128.5 (d), 128.5 (d), 128.2 (d), 128.0 (d), 115.0 (d), 85.4 (q), 67.4 (t), 67.1 (t), 54.9 (d), 36.8 (t); MS (EI) *m/z* 380 ($M^{+\bullet}$ − CbzNH, 59%), 335 (13), 334 (21), 253 (53), 233 ($M^{+\bullet}$ − $CbzNHCHCO_2Bn$, 29), 207 (19), 91 (100).

N-Cbz-4-*O*-*p*-Methoxybenzyl-3-iodo-L-tyrosine Benzyl Ester 31. To a solution of potassium carbonate (2.65 g, 19.2 mmol) and tetrabutylammonium iodide (0.18 g) in dry acetone (100 mL) was added iodotyrosine derivative **30** (2.55 g, 4.80 mmol). The mixture was stirred under nitrogen at room temperature for 30 min. *p*-Methoxybenzyl chloride (2.61 mL, 19.2 mmol) was added and the mixture was heated at reflux in the dark for 24 h. The resulting mixture was cooled and concentrated in vacuo. To the residue was added water (100 mL) and the mixture was extracted with DCM (3 × 200 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to give a brown/maroon oil. The oil was

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chromatographed on silica, eluting with EtOAc/hexane (1:4−1:2 gradient) to give the protected iodo-tyrosine derivative **31** (2.39 g, 76%) as a pale yellow oil: $[\alpha]_D$ +11.7 (*c* 0.78, $CHCl_3$); IR (Neat) υ_{max} (cm^{-1}) 3317, 2955, 2359, 1734, 1489, 1456, 1240, 1173, 1026, 694; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (1H, d, J = 1.8 Hz), 7.29 (2H, d, J = 8.5 Hz), 7.26−7.14 (10H, m), 6.82 (2H, d, J = 8.5 Hz), 6.78 (1H, br d, J = 8.4 Hz), 6.55 (1H, d, J = 8.4 Hz), 5.24 (1H, br d, J = 7.9 Hz), 5.25−4.99 (4H, m), 4.89 (2H, s), 4.54 (1H, m), 3.70 (3H, s), 2.94−2.84 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2 (s), 159.4 (s), 156.5 (s), 155.6 (s), 136.3 (s), 135.0 (s), 130.3 (d), 130.1 (s), 128.7 (d), 128.6 (d), 128.2 (d), 128.1 (d), 127.6 (s), 127.0 (d), 114.0 (d), 112.7 (d), 87.0 (s), 70.8 (t), 67.4 (t), 67.1 (t), 55.3 (q), 55.0 (d), 36.9 (t) (3 coincident C−H); MS (ESI, +ve) *m/z* 674 (M + Na^+, 100%); HRMS (ESI, +ve) *m/z* calcd for $(M + Na)^+$ 674.1010, found 674.1017.

***N*-Cbz-4-*O*-*p*-Methoxybenzyl-L-tyrosyl-3-boronic Acid Benzyl Ester 33.** To a solution of bis(neopentylglycolato)-diboron (1.55 g, 6.85 mmol), Pd(dppf)Cl_2·CH_2Cl_2 (84.0 mg), and potassium acetate (1.35 g, 13.7 mmol) in DMSO (100 mL) was added 3-iodotyrosine derivative **31** (2.23 g, 3.43 mmol). The mixture was stirred under nitrogen at 80 °C for 6 h. Water (100 mL) was added and the resulting mixture was extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with saturated sodium chloride solution (3 × 100 mL), dried (Na_2SO_4), and concentrated in vacuo to give a dark brown oil. The oil was chromatographed on silica, eluting with EtOAc/hexane (1:2−1:1 gradient) to give a mixture of neopentylglycolyl boronate **32** and boronic acid **33** (1.71 g) as a pale yellow oil. To a solution of the above mixture (1.71 g) in EtOAc (100 mL) was added water (250 mL). The biphasic reaction was stirred at room temperature for 20 h. The organic extract was washed with water (4 × 100 mL), dried (Na_2SO_4), and concentrated in vacuo to give tyrosine boronic acid derivative **33** (1.73 g, 89%) as a pale yellow oil: IR (Neat) υ_{max} (cm^{-1}) 3408, 2955, 1713, 1610, 1516, 1339, 1251, 1034, 698; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (1H, d, J = 2.2 Hz), 7.37−7.28 (12H, m), 7.12 (1H, dd, J = 2.2, 8.4 Hz), 6.95 (2H, d, J = 8.5 Hz), 6.85 (1H, d, J = 8.4 Hz), 6.18 (2H, br s), 5.38 (1H, br d, J = 8.2 Hz), 5.18 (2H, m), 5.12 (2H, s), 5.02 (2H, s), 4.72 (1H, m), 3.84 (3H, s), 3.16−3.06 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5 (s), 163.1 (s), 159.9 (s), 155.7 (s), 137.8 (s), 136.3 (d), 135.1 (d), 133.5 (s), 129.6 (d), 129.5 (d), 128.6(0) (d), 128.5(8) (s), 128.5(1) (d), 128.3 (s), 128.1(4) (d), 128.0(7) (d), 127.9(4) (d), 114.4 (d), 111.5 (d), 70.5 (t), 67.3 (t), 67.0 (t), 55.3 (d), 55.2 (q), 37.4 (t) (C−B not observed); MS (ESI, +ve) *m/z* 592 (M + Na^+, 100%); HRMS (ESI, +ve) *m/z* calcd for $(M + Na)^+$ 592.2131, found 592.2134.

***N*-Cbz-4-*O*-*p*-Methoxybenzyl-L-dopa Benzyl Ester 34.** To a solution of tyrosine boronic acid derivative **33** (1.66 g, 2.91 mmol) in MeOH (35 mL) was added a solution of 30% hydrogen peroxide in water (33 mL). The mixture was stirred at room temperature for 30 min. The resulting mixture was concentrated in vacuo. To the residue was added water (50 mL) and the mixture was extracted with DCM (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to give a pale yellow oil. The oil was chromatographed on silica, eluting with EtOAc/hexane (2:3) to give dopa derivative **34** (1.28 g, 81%) as a pale yellow oil: $[\alpha]_D$ +4.88 (*c* 2.85, $CHCl_3$); IR (Neat) υ_{max} (cm^{-1}) 3416, 1705, 1636, 1514, 1250, 1028, 696; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34−7.28 (12H, m), 6.91 (2H, d, J = 8.5 Hz), 6.74 (1H, d, J = 8.2 Hz), 6.65 (1H, d, J = 2.1 Hz), 6.47 (1H, dd, J = 2.1, 8.2 Hz), 5.61 (1H, br s), 5.24 (1H, br d, J = 8.6 Hz), 5.13−5.08 (4H, m), 4.96 (2H, s), 4.65 (1H, m), 3.81 (3H, s), 3.02−2.99 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7 (s), 159.8 (s), 155.9 (s), 146.2 (s), 145.3 (s), 136.5 (s), 135.4 (s), 129.6 (d), 129.3 (s), 128.6(9) (d), 128.6(1) (d), 128.5(3) (d), 128.1(9) (d), 128.1(5) (d), 127.5 (d), 120.8 (d), 116.1 (d), 114.2 (d), 112.7 (d), 71.0 (t), 67.2 (t), 67.0 (t), 55.3 (q), 55.2 (d), 37.6 (t) (1 coincident C−C); MS (ESI, +ve) *m/z* 564 (M + Na^+, 100%); HRMS (ESI, +ve) *m/z* calcd for $(M + Na)^+$ 564.1993, found 564.1995.

***N*-Cbz-4-Iodo-L-phenylalanine Benzyl Ester 36.** To an ice-cold solution of potassium carbonate (3.33 g, 24.1 mmol) in water (30 mL) was added 4-iodo-L-phenylalanine **35** (2.00 g, 6.88 mmol). A solution of 50% benzyl chloroformate in toluene (2.36 mL, 7.06 mmol) was added over 30 min. The mixture was stirred at room temperature for 6 h. The resulting mixture was acidified to pH 4 with 3 M HCl, extracted with *i*-PrOH/$CHCl_3$ (1:3, 3 × 300 mL), dried (Na_2SO_4), and concentrated in vacuo to give Cbz-4-iodophenylalanine (2.77 g, 95%) as an off-white solid. To a solution of potassium carbonate (1.31 g, 9.45 mmol) and tetrabutylammonium iodide (0.11 g) in dry acetone (100 mL) was added Cbz-iodo-phenylalanine (2.68 g, 6.30 mmol). The mixture was stirred under nitrogen in the dark at room temperature for 30 min. Benzyl bromide (1.50 mL, 12.6 mmol) was added and the mixture was heated at reflux for 2 h. The resulting mixture was cooled and concentrated in vacuo. To the residue was added water (100 mL) and the mixture was extracted with DCM (3 × 200 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to give a pale yellow oil. The oil was chromatographed on silica, eluting with EtOAc/hexane (1:4−1:3 gradient) to give protected iodophenylalanine derivative **36** (2.86 g, 86%) as a white solid: mp 89.3−90.1 °C; $[\alpha]_D$ +4.00 (*c* 1.20, $CHCl_3$); IR (Neat) υ_{max} (cm^{-1}) 3408, 2359, 1718, 1498, 1340, 1256, 1211, 1059, 1007, 696; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (2H, d, J = 8.2 Hz), 7.38−7.24 (10H, m), 6.70 (2H, d, J = 8.2 Hz), 5.28 (1H, br d, J = 8.0 Hz), 5.17−5.04 (4H, m), 4.66 (1H, m, αH), 3.07−2.97 (2H, m, βH's);[35] ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1 (s), 155.5 (s), 137.6 (d), 136.2 (s), 135.3 (s), 134.9 (s), 131.3 (d), 128.7(1) (d), 128.7(0) (d), 128.6 (d), 128.3 (d), 128.1 (d), 92.6 (s), 67.4 (t), 67.1 (t), 54.6 (d), 37.8 (t) (1 coincident C−H); MS (ESI, +ve) *m/z* 538 (M + Na^+, 100%).

***N*-Cbz-4-Neopentylglycolylborono-L-phenylalanine Benzyl Ester 37.** To a solution of bis(neopentylglycolato)diboron (2.18 g, 9.64 mmol), Pd(dppf)Cl_2·CH_2Cl_2 (0.12 g) and potassium acetate (1.89 g, 19.3 mmol) in DMSO (100 mL) was added *N*-Cbz-4-iodo-L-phenylalanine benzyl ester **36** (2.48 g, 4.82 mmol). The mixture was stirred under nitrogen at 80 °C for 4.5 h. Water (100 mL) was added and the resulting mixture extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with saturated sodium chloride solution (3 × 100 mL), dried (Na_2SO_4), and concentrated in vacuo to give a dark brown oil. The oil was chromatographed on silica, eluting with EtOAc/hexane (1:3−1:1 gradient) to give neopentylglycolyl boronate derivative **37** (2.21 g, 92%) as a white solid: mp 118−119 °C; $[\alpha]_D$ +8.22 (*c* 1.11, $CHCl_3$); IR (Neat) υ_{max} (cm^{-1}) 3343, 2961, 1720, 1610, 1498, 1420, 1317, 1248, 1132, 1057, 698; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (2H, d, J = 7.7 Hz), 7.31−7.23 (10H, m), 7.01 (2H, d, J = 7.7 Hz), 5.35 (1H, br d, J = 8.2 Hz), 5.19−5.02 (4H, m), 4.69 (1H, m), 3.72 (4H, s) 3.13−3.03 (2H, m), 0.97 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4 (s), 155.7 (s), 138.2 (s), 136.4 (s), 135.2 (s), 134.3 (d), 128.7 (d), 128.6 (d), 128.2 (d), 128.1 (d), 72.3 (t), 67.3 (t), 67.0 (t), 55.1 (d), 38.3 (t), 31.9 (s), 22.0 (q) (2 coincident C−H) (C−B not observed); MS (ESI, +ve) *m/z* 524 (M + Na^+, 59%), 457 (100%); HRMS (ESI, +ve) *m/z* calcd for $(M + Na)^+$ 524.2220, found 524.2210.

***N*-Cbz-L-Phenylalanyl-4-boronic Acid Benzyl Ester 27.** To a solution of neopentylglycolyl boronate derivative **37** (2.00 g, 3.99 mmol) in EtOAc (60 mL) was added water (120 mL). The biphasic reaction was stirred at room temperature for 3 d. The organic extract was washed with water (4 × 100 mL), dried (Na_2SO_4), and concentrated in vacuo to give phenylalanine boronic acid derivative **27** (accompanied by varying amounts of boroxine) as a pale yellow oil (0.87 g, 50%): IR (Neat) υ_{max} (cm^{-1}) 3337, 1723, 1609, 1551, 1344, 1213, 1057, 696; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (2H, d, J = 7.9 Hz), 7.38−7.24 (10H, m), 7.02 (2H, d, J = 7.9 Hz), 5.33 (1H, br d, J = 8.0 Hz), 5.16−5.07 (4H, m), 4.72 (1H, m), 3.29−3.09 (2H,

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m); MS (ESI, +ve) *m/z* 456 (M + Na^+, 15%), 872 (2M − OH + Na^+, 100%); HRMS (ESI, +ve) *m/z* calcd for $(M + Na)^+$ 456.1605, found 456.1598. Starting material **37** (0.53 g, 27%) was also recovered.

PMB-Protected Isodityrosine 38. To a solution of copper(II) acetate (0.32 g, 1.77 mmol), pyridine (0.71 mL, 8.85 mmol), and 4 Å molecular sieves (5.00 g) in DCM (35 mL) was added dopa derivative **34** (0.96 g, 1.77 mmol) and phenylalanine boronic acid derivative **27** (1.09 g, 2.48 mmol). The mixture was stirred under nitrogen at room temperature for 48 h. The resulting mixture was filtered and the solid washed with DCM (2 × 30 mL). The filtrate was concentrated in vacuo to give a green oil. The oil was chromatographed on silica, eluting with EtOAc/hexane (1:2−1:1 gradient) to give the protected isodityrosine derivative **38** (1.31 g, 80%) as a yellow oil: $[\alpha]_D$ +7.48 (*c* 1.23, $CHCl_3$); IR (Neat) υ_{max} (cm^{-1}) 3354, 1720, 1506, 1250, 1028, 696; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31−7.21 (20H, m), 7.10 (2H, d, J = 8.5 Hz), 6.89−6.78 (5H, m), 6.75−6.70 (4H, m), 5.26−5.21 (2H, m), 5.16−5.00 (8H, m), 4.93 (2H, s), 4.69−4.61 (2H, m), 3.74 (3H, s), 3.04−2.93 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3(4) (s), 171.2(6) (s), 159.4 (s), 157.4 (s), 155.6(8) (s), 155.6(3) (s), 149.7(8) (s), 149.7(5) (s), 145.2 (s), 136.3 (s), 135.1 (s), 135.0 (s), 130.4 (d), 129.3 (s), 129.1 (s), 128.8(6) (s), 128.8(0) (d), 128.6(7) (d), 128.6(4) (d), 128.6(1) (d), 128.5(7) (d), 128.5(5) (d), 128.5(0) (d), 128.4(0) (d), 128.2(2) (d), 128.2(0) (d), 128.1(1) (d), 125.8 (d), 122.8 (d), 116.9 (d), 115.5 (d), 113.9 (d), 70.8 (t), 67.3(6) (t), 67.2(9) (t), 67.2(6) (t), 67.0 (t), 55.3 (q), 54.9(5) (d), 54.9(2) (d), 37.4(8) (t), 37.4(0) (t) (2 coincident C−H); MS (ESI, +ve) *m/z* 951 (M + Na^+, 100%); HRMS (ESI, +ve) *m/z* calcd for $(M + Na)^+$ 951.3464, found 951.3467.

Protected Isodityrosine 39. To a solution of PMB-protected isodityrosine derivative **38** (43.2 mg, 0.05 mmol) in H_2O/DCM (1:10, 2 mL) was added DDQ (12.7 mg, 0.06 mmol). The mixture was stirred at reflux for 24 h. Saturated sodium hydrogen carbonate solution (30 mL) was added and the resulting mixture extracted with DCM (3 × 30 mL). The combined organic extracts were washed with saturated sodium hydrogen carbonate solution (30 mL) and saturated sodium chloride solution (30 mL), dried (Na_2SO_4), and concentrated in vacuo to give a yellow oil. The oil was chromatographed on silica, eluting with EtOAc/hexane (1:2−2:3 gradient) to give the deprotected product **39** (29.5 mg, 78%) as an off-white solid: mp 50−51 °C; $[\alpha]_D$ +6.02 (*c* 1.05, $CHCl_3$); IR (Neat) υ_{max} (cm^{-1}) 3346, 1718, 1506, 1437, 1217, 1057, 696; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25−7.10 (20H, m), 6.81−6.78 (3H, m), 6.66 (2H, d, J = 8.5 Hz), 6.60 (1H, dd, J = 1.8, 8.2 Hz), 6.47 (1H, d, J = 1.8 Hz), 5.54 (1H, br s), 5.18−5.16 (2H, br m), 5.09−4.90 (8H, m), 4.57−4.48 (2H, m), 2.96−2.82 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2 (s), 171.0 (s), 155.9 (s), 155.6(4) (s), 155.5(9) (s), 146.8 (s), 143.1 (s), 136.2 (s), 135.1 (s), 135.0 (s), 130.8 (d), 128.7(7) (d), 128.6(7) (d), 128.6(4) (d), 128.5(6) (d), 128.4(6) (d), 128.2(5) (d), 128.2(1) (d), 128.1(4) (d), 128.0(6) (d), 128.0(0) (s), 125.9 (d), 120.1 (d), 117.7 (d), 116.4 (d), 113.9 (d), 67.3(3) (t), 67.2(6) (t), 67.0(3) (t), 67.0(0) (t), 55.2 (d), 54.9 (d), 37.5 (t), 37.3 (t) (2 coincident C−H and 2 C−C); MS (ESI, +ve) *m/z* 831 (M + Na^+, 100%); HRMS (ESI, +ve) *m/z* calcd for (M + $Na)^+$ 831.2889, found 831.2915.

Bromoisodityrosine Derivative 40. To a solution of *N*-bromosuccinimide (54.0 mg, 0.30 mmol) in DMF (4 mL) was added isodityrosine derivative **39** (0.16 g, 0.20 mmol). The mixture was stirred under nitrogen at 80 °C for 19 h. Ether (30 mL) was added and the organic extract washed with saturated sodium thiosulfate solution (30 mL), water (30 mL), dried (Na_2SO_4), and concentrated in vacuo to give a yellow oil. The oil was chromatographed on silica, eluting with EtOAc/hexane (1:2−2:3 gradient) to give the brominated product **40** (0.13 g, 70%) as a pale yellow oil: $[\alpha]_D$ +11.3 (*c* 0.87, $CHCl_3$); IR (Neat) υ_{max} (cm^{-1}) 3354, 2916, 2849, 1718, 1497, 1213, 1059, 696; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.26 (18H, m), 7.21−7.18 (2H, m), 7.00 (1H, d, J = 1.6 Hz), 6.90 (2H, d, J = 8.4 Hz), 6.73 (2H, d, J = 8.4 Hz), 6.51 (1H, d, J = 1.6 Hz), 5.77 (1H, br s), 5.30−5.25 (2H, m), 5.14−4.98 (8H, m), 4.66−4.56 (2H, m), 3.06−2.87 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2 (s), 171.0 (s), 155.7 (s), 144.3 (s), 143.9 (s), 136.2 (s), 135.1 (s), 134.8 (s), 131.1 (s), 130.9 (d), 129.0 (s), 128.7 (s), 128.6(9) (d), 128.6(5) (d), 128.6(0) (d), 128.5(6) (d), 128.4 (d), 128.2 (d), 128.1 (d), 128.0 (d), 119.4 (d), 117.9 (d), 109.9 (s), 67.4 (t), 67.3 (t), 67.0(7) (t), 67.0(1) (t), 55.7 (d), 54.9 (d), 37.3 (t), 37.1 (t) (5 coincident C−H and 2 C−C); MS (ESI, +ve) *m/z* 909 (^{79}Br M + Na^+, 85%), 911 ($^{81}BrM + Na^+$, 100%); HRMS (ESI, +ve) *m/z* calcd for $(M + Na)^+$ 909.1993, found 909.1988.

Protected Pulcherosine 41. To a solution of tyrosine trifluoroborate derivative **21** (0.13 g, 0.21 mmol), triethylamine (52.0 μL, 0.36 mmol), and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (5.00 mg) was added bromoisodityrosine derivative **40** (55.2 mg, 0.06 mmol) in H_2O/*i*-PrOH (1:2, 4 mL). The mixture was stirred at reflux for 48 h. The resulting mixture was filtered through Celite and the solid washed with DCM (3 × 30 mL). The filtrate was concentrated in vacuo to give a dark brown oil. The oil was chromatographed on silica, eluting with EtOAc/hexane (1:2−2:3 gradient) to give pulcherosine derivative **41** (26.1 mg, 32%) as a pale yellow oil: $[\alpha]_D$ +8.25 (*c* 1.63, $CHCl_3$); IR (Neat) υ_{max} (cm^{-1}) 3356, 2922, 1734, 1498, 1215, 1057, 696; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24−7.07 (35H, m), 6.98 (1H, s), 6.90 (1H, d, J = 8.0 Hz), 6.80−6.78 (3H, m), 6.72−6.67 (3H, m), 6.54 (1H, s), 5.82 (1H, br s), 5.24 (1H, br d, J = 7.9 Hz), 5.15−5.13 (2H, m), 5.05−4.90 (14H, m), 4.58−4.54 (3H, m), 3.00−2.80 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4 (s), 171.3 (s), 156.5 (s), 155.6 (s), 154.7 (s), 144.7 (s), 143.9 (s), 136.7 (s), 136.2 (s), 135.1 (s), 132.8 (d), 130.6 (d), 130.1 (d), 130.0 (d), 128.7 (d), 128.6 (d), 128.5(3) (d), 128.4(9) (d), 128.4 (s), 128.3 (d), 128.2 (d), 128.1(3) (d), 128.0(5) (d), 127.9(7) (d), 127.8(5) (d), 126.9 (d), 119.9 (d), 117.7 (d), 113.8 (d), 71.0 (t), 67.3 (t), 67.2 (t), 67.0 (t), 54.9 (d), 37.5 (t), 37.3 (t) (27 coincident carbons; 1 C=O, 20 aryl, 6 aliphatic); MS (ESI, +ve) *m/z* 1325 (M + Na^+, 100%); HRMS (ESI, +ve) *m/z* calcd for $(M + Na)^+$ 1324.4778, found 1324.4824.

Pulcherosine 5. To a solution of protected pulcherosine derivative **41** (51.8 mg, 0.04 mmol) in H_2O/MeOH/THF (1:5:5, 5 mL) was added 10% palladium on charcoal (5.0 mg). The reaction mixture was stirred under hydrogen at room temperature for 7 d. The resulting mixture was filtered through Celite, washed with $NH_{3(aq)}$/MeOH/$CHCl_3$ (2:18:80, 3 × 20 mL), and concentrated in vacuo to give pulcherosine **5** in quantitative yield. For analytical purposes, the crude product was chromatographed on reverse-phase HPLC using H_2O/CH_3CN/TFA (95:5:0.05) as eluent to give pure pulcherosine **5** as an off-white solid: mp 170−172 °C; $[\alpha]_D$ +19.9 (*c* 0.33, 1 M HCl); ^1H NMR (400 MHz, D_2O) δ 7.17 (2H, d, J = 8.6 Hz), 7.11 (1H, dd, J = 2.2, 8.3 Hz), 7.05 (1H, d, J = 2.2 Hz), 6.92 (2H, d, J = 8.6 Hz), 6.88 (1H, d, J = 8.3 Hz), 6.86 (1H, d, J = 2.1 Hz), 6.84 (1H, d, J = 2.1 Hz), 3.95−3.87 (3H, m), 3.16−2.93 (6H, m);[33] ^{13}C NMR (100 MHz, D_2O) δ 173.2 (s), 173.0 (s), 156.6 (s), 152.5 (s), 144.5 (s), 144.1 (s), 132.2 (d), 130.9 (d), 130.7 (d), 129.6 (d), 127.8 (s), 127.6 (s), 127.4 (s), 126.8 (s), 124.9 (s), 121.0 (d), 117.8 (d), 116.3 (d), 55.7 (d), 55.6 (d), 35.4 (t), 35.3 (t), 35.2 (t); MS (ESI, +ve) *m/z* 562 (M + Na^+, 100%).

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Supporting Information Available: General procedures and experimental methods for compounds **13**, **15**, **18**, **19**, **24** and **29**; ^1H and ^{13}C NMR spectra for compounds **1**, **3**, **5**, **7**−**9**, **11**, **12**, **16**, **21**, **23**, **27**, **31**, **33**, **34**, and **36**−**41**; ^{13}C DEPT NMR spectra for compounds **9**, **23**, **41**. This material is available free of charge via the Internet at http://pubs.acs.org.

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