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A convenient preparation of dityrosine via Miyaura borylation–Suzuki coupling of iodotyrosine derivatives

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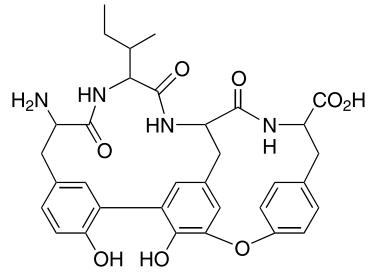
Abstract—Dityrosine has been prepared from 3-iodo-L-tyrosine derivatives by sequential Miyaura borylation and Suzuki coupling reactions. A tandem borylation–coupling protocol results in improved yields of the dityrosine derivatives. Suitable protecting group strategies are employed to allow for global deprotection as the final step.

Examples of tyrosine–tyrosine cross-links (Fig. 1) occur in a plethora of living organisms. Dityrosine (**1**),[1] a tyrosine dimer formed by 3,3′-biaryl bond formation, occurs naturally in fungal cell wall proteins,[2] insect egg[3] and sea-urchin envelopes,[4] and vertebrate proteins such as elastin and collagen.[5] In these examples the formation of dityrosine is believed to accord a strengthening and/or defensive role to the proteins.[6] Dimerisation of proteins through dityrosine linkages is also necessary for the proper functioning of proteins such as thyroglobulin, the precursor to the thyroid hormone, thyroxine.[7] 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.[8]

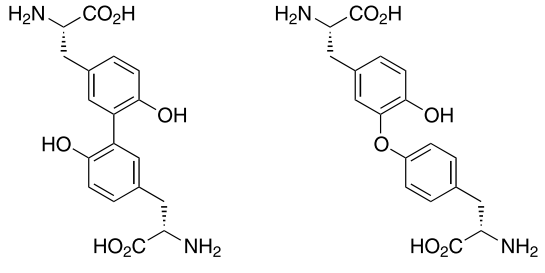
Formation of tyrosine cross-links in proteins has also been associated with Alzheimer's and Parkinson's diseases,[9] cystic fibrosis,[10] atherosclerosis,[11] and cataract formation.[12] Dityrosine and isodityrosine units also occur in the biologically active cyclic peptide RP 66453 (**3**).[13]



3 RP 66453

While much effort has been directed towards the synthesis of isodityrosine derivatives, there are few efficient procedures for the preparation of dityrosine. Malencik[1] has reported an enzyme-catalysed oxidative-coupling of tyrosine to provide dityrosine, albeit in low yield. Nishiyama and co-workers[14] have prepared dityrosine via electrolysis of a 3,5-diiodotyrosine derivative, again in low yield. Lygo[15] has prepared dityrosine via an elegant double asymmetric alkylation of a biphenyl derivative. Zhu and co-workers[16] have employed a related asymmetric alkylation of an arylated tyrosine derivative to prepare a dityrosine derivative.

The recent development of procedures for the preparation of biaryl compounds via the Pd-catalysed coupling of arylboron compounds and aryl halides has enabled the efficient preparation of biaryls.[17] Additionally, the preparation of arylboronate esters via the coupling of aryl halides with bis(diol)diboron reagents has enabled



1 **2**

Figure 1.

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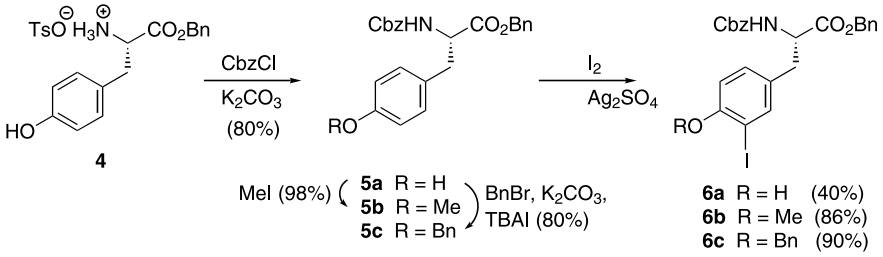


Scheme 1.

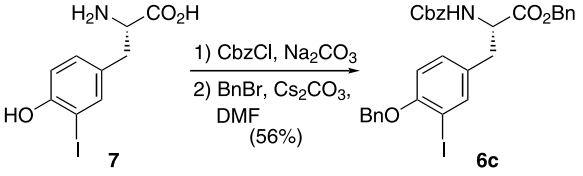
the mild preparation of many arylboronic acid derivatives under mild conditions.[18]

In their work towards the total synthesis of macrocyclic peptides, Zhu and co-workers[19] have prepared a dityrosine-containing cyclic peptide via an intramolecular borylation–Suzuki coupling, though only under precise conditions and in moderate yield. Suzuki couplings of tyrosine-3-boronic acid derivatives have also been used in the synthesis of the TMC-95 peptides.[20] Herein, we present an efficient preparation of dityrosine via a Miyaura borylation–Suzuki coupling of 3-iodotyrosine derivatives.

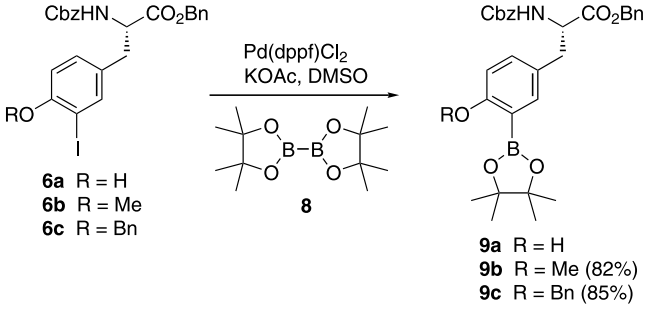
Iodotyrosine derivatives **6a–c** were prepared as shown in Scheme 1. L-Tyrosine benzyl ester *p*-toluenesulfonate **4** (commercially available or easily prepared from L-tyrosine[21]) was *N*-protected by treatment with Cbz-Cl. Treatment of **5a** with iodomethane or benzyl bromide gave the *O*-methyl and *O*-benzyl derivatives, **5b** and **5c**, respectively, in excellent yields. Iodination of **5a–c** with iodine/silver sulfate then gave the iodotyrosine derivatives **6a–c**. Alternatively, 4-*O*-benzyl iodotyrosine derivative **6c** could be prepared from 3-iodo-L-tyrosine (**7**) as shown in Scheme 2.

Conversion of the iodotyrosine derivatives **6a–c** to the corresponding pinacolboronates **9a–c** was performed under standard Miyaura conditions (bis(pinacolato)diboron (**8**), $Pd(dppf)Cl_2$, KOAc, DMSO, 80°C, 24 h, Scheme 3). All reactions proceeded to 100% conversion, giving the pinacol boronates as the only detectable products. Purification of the *O*-Me and *O*-Bn derivatives **9b** and **9c** was achieved by chromatography on silica, furnishing the pure boronates in 82% and 85% isolated yield. Purification of the phenol **9a** by chromatography on silica gave low to moderate yields of the boronate, together with variable amounts of the corresponding boronic acid, indicating that partial hydrolysis of the pinacol boronate was occurring on silica. Accordingly, the crude boronate **9a** was used directly in the following step without purification.

Suzuki coupling of iodotyrosine derivative **6a** with the corresponding tyrosine-3-boronate **9a** required triethylamine as the base (use of K_2CO_3 gave no coupled product), and gave the protected dityrosine derivative **10a** in only low yield. Employing a 1:1 ratio of iodide **6a** and boronate **9a** gave the dityrosine derivative **10a** in only 19% yield, with the tyrosine derivative **5a**



Scheme 2.

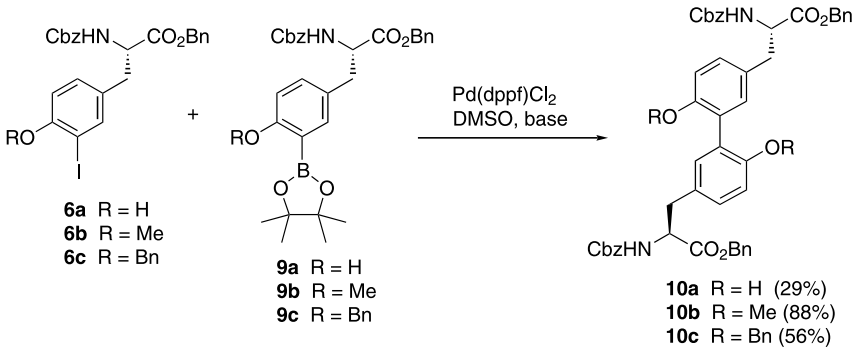


Scheme 3.

isolated in 23% yield and iodotyrosine **6a** recovered in 23% yield. This result indicates that protodeborylation of the tyrosine-3-boronate **9a** to give **5a** is competitive with the Suzuki coupling reaction. Accordingly, optimum conditions employed an excess (2 equiv.) of boronate **9a** with respect to the aryl iodide **6a**, yielding the dityrosine derivative **10a** in 29% yield.

Suzuki coupling of the *O*-methyl and *O*-benzyl boronates **9b** and **9c** with the corresponding iodides **6b** and **6c** was more successful, giving the protected dityrosine derivatives **10b** and **10c** in 88% and 56% yield, respectively (Scheme 4). Optimum conditions again employed 2 equiv. of the boronate with respect to the iodide, with K_2CO_3 as the base.

As the dityrosine derivatives **10a–c** are symmetrical biaryls, we also investigated the direct conversion of iodotyrosine derivatives **6a–c** to dityrosine derivatives in a one-pot borylation–coupling procedure. In theory, treatment of an aryl iodide with 0.5 equiv. of bis(pinacolato)diboron (**8**) 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, optimisation of the amount of the diboron reagent is required for each

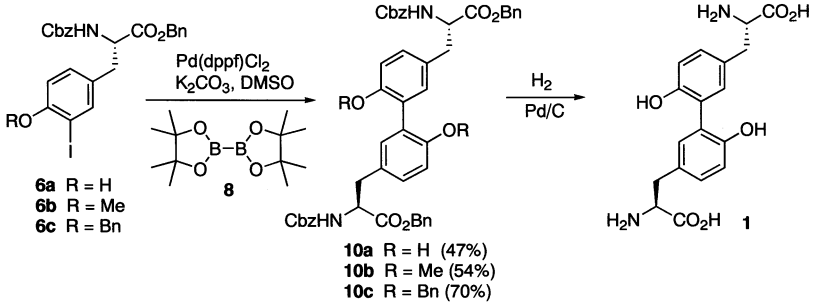


Scheme 4.

iodide due to the differing relative rates of conversion of the iodide to the boronate intermediate, protodeborylation, and Suzuki coupling (Table 1).

Treatment of iodophenol **6a** with 0.5 equiv. of diboron reagent **8** gave dityrosine derivative **10a** (Scheme 5) in 47% yield (entry 1). Increasing the amount of the diboron reagent **8** did not greatly affect the yield (entries 2, 3), indicating that the increase in available boronate intermediate is offset by a decrease in the amount of iodide remaining. Again, coupling of the phenol **6a** required triethylamine as the base for the Suzuki coupling to proceed—use of K_2CO_3 gave a 1:1 mixture of iodide **6a** and boronate **9a** (entry 4).

Direct conversion of the *O*-methyl iodotyrosine derivative **6b** to the corresponding dityrosine derivative **10b** was most efficient with 0.75 equiv. of the diboron reagent **8** (entry 6), providing a 54% yield of **10b**. Conversion of the *O*-benzyl iodotyrosine derivative **6c** to dityrosine derivative **10c** was achieved in 70% yield using 0.95 e2quiv. of the diboron reagent **8** (entry 10).[22] In most cases low yields of the tyrosine derivatives **5a–c** were isolated as a result of protodeborylation of the intermediate boronates **9a–c**. The requirement of increasing amounts of diboron reagent **8** in the optimised one-pot couplings of the iodotyrosine derivatives **6a**, **6b** and **6c**, respectively, suggests that the steric bulk of the *ortho*-substituent affects the relative rate of the borylation step to a greater extent than the Suzuki coupling step.



Scheme 5.

Table 1. One-step conversion of iodotyrosine derivatives to dityrosine derivatives[a]

Entry	R	Equivalents of bis(pinacolato)diboron (**8**)	Recovered iodide **6** (%)	Yield of tyrosine derivative **5** (%)	Yield of dityrosine derivative **10** (%)
1[b]	H	0.5	15	10	47
2[b]	H	0.6	8	5	45
3[b]	H	0.75	3	8	38
4	H	0.75	50	0	0
5	Me	0.5	53	0	16
6	Me	0.75	7	11	54
7	Me	0.85	0	14	21
8	Bn	0.75	11	14	35
9	Bn	0.85	7	15	41
10	Bn	0.95	0	20	70

[a] Conditions: iodide (**6**), bis(pinacolato)diboron (**8**), Pd(dppf)Cl_2·CH_2Cl_2 (0.03 equiv.), K_2CO_3 (4 equiv.), DMSO, 80°C, 48 h.
[b] NEt_3 (4 equiv.) added after 24 h.

With the formation of the protected dityrosine derivatives optimised, deprotection was required to furnish dityrosine. Hydrogenolysis of compounds **10a** and **10c** would provide a one-step global deprotection, whereas deprotection of **10b** would require a further step to remove the methyl ether groups. Hence, deprotection of **10b** was not investigated. Additionally, compound **10c** was prepared in 58% yield from **4** (or 56% from iodotyrosine **7**), whereas preparation of **10a** was less efficient (32% yield from **4**). Accordingly, dityrosine (**1**) was prepared by treatment of **10c** with palladium-on-charcoal under an atmosphere of hydrogen. Dityrosine (**1**) was isolated in quantitative yield, and was purified by reverse-phase HPLC for characterisation purposes.[23]

In summary, we have developed an efficient preparation of dityrosine that employs a mild, one-pot Miyaura-borylation–Suzuki-coupling reaction. The optimum procedure furnishes dityrosine in four steps and 39% yield from 3-iodo-L-tyrosine. The methods developed should be extendable to the preparation of higher oligomers of tyrosine and work in this area is currently underway in our laboratories.

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22. Representative procedure: To a solution of **6c** (200 mg, 0.32 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8 mg, 0.01 mmol) and K_2CO_3 (178 mg, 1.29 mmol) in DMSO (5 mL) was added **8** (78 mg, 0.31 mmol). The mixture was stirred under N_2 at 80°C for 48 h. The mixture was diluted with water (30 mL), extracted with ethyl acetate (2×30 mL) and the combined extracts were washed with 20% aq. NaCl (2×30 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed on silica eluting with 1:2:2 ether/DCM/hexanes to give the protected dityrosine **10c** (111 mg, 70%): ^{1}H 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), 3.05–3.02 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 155.7, 155.4, 137.4, 136.3, 135.2, 132.6, 129.3, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 127.6, 127.4, 126.6, 113.2, 70.3, 67.1, 66.9, 55.0, 37.8; MS (ESI) m/z 1011 ($M+Na^+$, 100%), 921 (32%).
Data for **10b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.25 (20H, m), 6.97–6.93 (4H, m), 6.78 (2H, d, $J=8.2$ Hz), 5.28 (2H, br d, $J=8.0$ Hz), 5.12–5.09 (8H, m), 4.68 (2H, m), 3.65 (6H, m, OMe), 3.06–3.01 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 156.7, 156.4, 136.9, 135.8, 133.3, 129.9, 129.3, 129.2, 129.1, 129.0, 128.8, 128.7, 127.8, 127.6, 112.0, 67.8, 67.6, 56.3, 55.6, 37.9; MS (ESI) m/z 859 ($M+Na^+$, 100%).
Data for **10a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.23 (20H, m), 6.94–6.92 (4H, m), 6.85 (2H, d, $J=8.2$ Hz), 6.03 (2H, br s), 5.32 (2H, br d, $J=8.2$ Hz), 5.17 (2H, d, $J=12.2$ Hz), 5.13 (2H, d, $J=12.2$ Hz), 5.03 (2H, d, $J=12.2$ Hz), 4.97 (2H, d, $J=12.2$ Hz), 4.70 (2H, m), 3.14 (2H, dd, $J=4.5$, 13.7 Hz), 2.84 (2H, dd, $J=7.6$, 13.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 155.7, 152.8, 136.0, 134.9, 131.5, 131.1, 128.6, 128.6, 128.5, 128.4, 128.2, 128.0, 127.9, 122.9, 116.8, 67.4, 67.0, 55.1, 38.2; MS (ESI) m/z 831 ($M+Na^+$, 100%).
23. Data for **1**: ^{1}H NMR (300 MHz, D_2O/DCl) δ 7.02 (2H, br d, $J=8.3$ Hz), 6.92 (2H, br s), 6.79 (2H, d, $J=8.3$ Hz), 4.13 (2H, m), 3.11 (2H, dd, $J=5.6$, 14.7 Hz), 2.98 (2H, dd, $J=7.4$, 14.7 Hz), in accordance with literature values (Refs. 14 and 15).