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Tetrahedron Letters 44 (2003) 5901–5903

TETRAHEDRON LETTERS

Synthesis of L,L-cycloisodityrosines by copper(II) acetate-DMAP-mediated intramolecular O-arylation of phenols with phenylboronic acids

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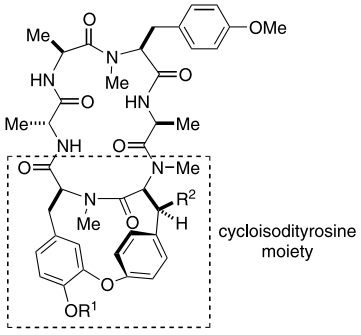
Received 30 April 2003; revised 29 May 2003; accepted 30 May 2003

Abstract—Two types of cycloisodityrosines, **11** and **13**, were synthesized from commercially available chiral tyrosine derivatives through the copper(II) acetate-DMAP-mediated diaryl ether formation of boronotyrosyltyrosines **8** and **10**, respectively.

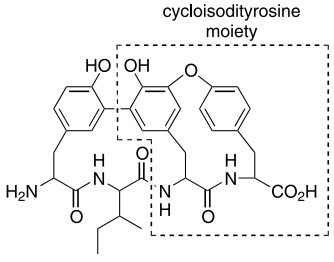
Cycloisodityrosines are tyrosyl-tyrosine dipeptide analogues in which one of the two phenoxy groups forms an ether linkage with the aromatic carbon at the ε position of the other tyrosine, and a few compounds of this type are known among natural products. There are two types of cycloisodityrosines. One type of the cycloisodityrosines, in which an ether linkage is formed between the hydroxyl oxygen at the ζ position of the N-terminus tyrosine and the carbon atom at the ε position of the C-terminus tyrosine, is found in bouvardin (**1**)[1] and RA-series antitumor bicyclic peptides[2,3] from Rubiaceous plants. The other type of cycloisodityrosine, in which the ether linkage is formed between the carbon atom at the ε position of the N-terminus tyrosine and the hydroxyl oxygen at the ζ position of the C-terminus tyrosine, is found in RP 66453 (**2**) from *Streptomyces* sp., possessing a specific binding affinity to the neurotensin receptor.[4]

Several synthetic routes to cycloisodityrosines are known. Total synthesis of cycloisodityrosines involves construction of a strained 14-membered macrocycle which requires elaborate work for the preparation of chiral phenylalanine or tyrosine derivatives and subsequent transformations,[5–8] whereas preparation of cycloisodityrosines via degradation of natural RA-VII (**3**) into cycloisodityrosine requires a large quantity of **3** as the starting material.[9] Such difficulty in the formation of the cycloisodityrosine unit has hampered the synthesis of the analogues of those important peptides.

In the present letter, we describe a practical and short synthetic route to cycloisodityrosines from commercially available tyrosine derivatives by a coupling reaction of arylboronic acids with phenols originally developed by Chan,[10] Evans,[11] and Lam.[12,13]



Bouvardin (**1**): R^1 = H, R^2 = OH
RA-VII (**3**): R^1 = Me, R^2 = H



RP 66453 (**2**)

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doi:10.1016/S0040-4039(03)01390-X

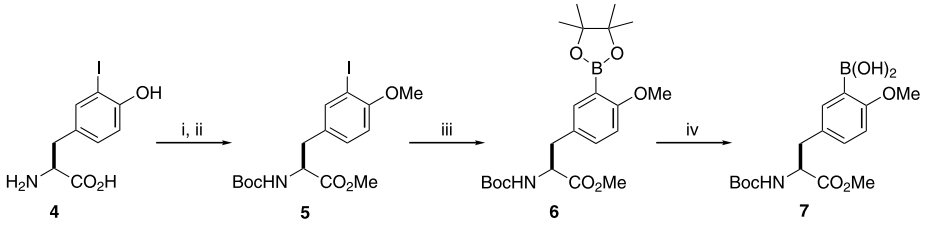
Commercially obtained 3-iodo-L-tyrosine (**4**) was N-protected with a Boc group, and then methylated with (trimethylsilyl)diazomethane[14] to afford protected iodotyrosine **5** in 96% yield from **4**. Reaction of **5** with bis(pinacolato)diboron using $PdCl_2$(dppf) as a catalyst afforded a mixture of cyclic arylboronate **6** and boronic acid **7**. After treating the mixture with sodium periodate to convert **6** to **7**,[15] **7** was obtained in 83% yield from **5** (Scheme 1). Compound **7** was N-deprotected and coupled with Boc-L-tyrosine to afford dipeptide **8** in 83% yield. When hydrolyzed, **7** afforded acid **9** in 90% yield, which by subsequent coupling reaction with L-tyrosine methyl ester gave dipeptide **10** in 85% yield (Scheme 2).

When a dichloromethane solution of **8** (0.025 M) was treated with 1 equiv. of copper(II) acetate and 5 equiv. of pyridine[11] in the presence of powdered 4 Å molecular sieves for 48 h at room temperature, desired cycloisodityrosine **11**[6g] and the protodeborylated product **12** were obtained both in 29% yield (Table 1, entry 1). When 5 equiv. of triethylamine[10,11] was used as the base, the reaction gave **11** and **12** in 5 and 65% yield, respectively (entry 2). Production of the protodeborylated product is a known side reaction when the boronic acid possesses an *ortho*-hetero atom.[11] To suppress the formation of **12**, several related amines were examined for their effect on the reaction. The use of *N*,*N*-diisopropylethylamine gave a similar result as triethylamine (entry 3). The use of 3,5-dichloropyridine, a less basic pyridine derivative, or 2,2′-dipyridyl and 1,10-phenanthroline, common pyridine-based ligands for copper(II) ion, did not enhance the yield of **11**, either (entries 4–6). When more basic 4-picoline (entry 7) or 4-(dimethylamino)pyridine (DMAP) (entry 8) was employed, the yield of **11** was improved to 36 and 45%, respectively,

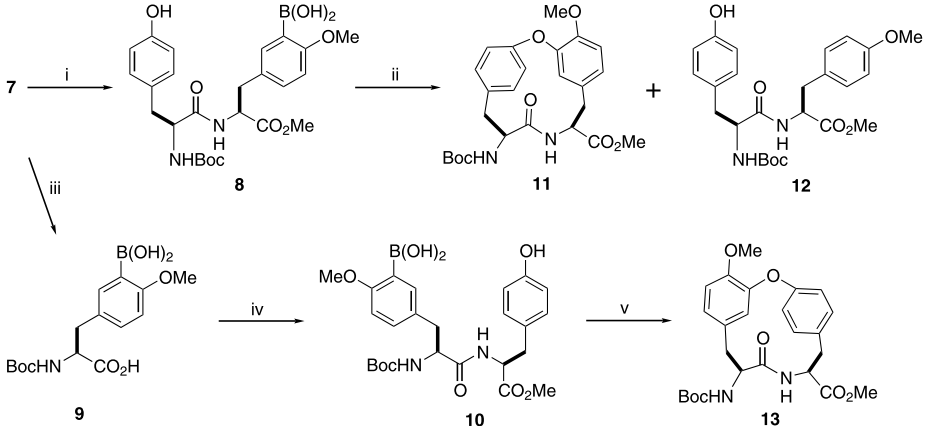
Table 1. Cyclization of dipeptide **8**[a]

Entry	Amine	Concentration (M)	Products (%)	
			11	**12**
1	Pyridine	0.025	29	29
2	Triethylamine	0.025	5	65
3	*N*,*N*-Diisopropylethyl amine	0.025	4	72
4	3,5-Dichloropyridine	0.025	6	33
5	2,2′-Dipyridyl	0.025	4	75
6	1,10-Phenanthroline	0.025	12	39
7	4-Picoline	0.025	36	28
8	4-(Dimethylamino)-pyridine	0.025	45	5
9	4-(Dimethylamino)-pyridine	0.013	56	6
10	4-(Dimethylamino)-pyridine	0.0063	55	4

[a] The reactions were carried out by using 1 equiv. of $Cu(OAc)_2$, 5 equiv. of amine and powdered 4 Å molecular sieves in CH_2Cl_2 for 48 h at room temperature.



Scheme 1. *Reagents and conditions*: (i) Boc_2O, Et_3N, H_2O, rt; (ii) (trimethylsilyl)diazomethane, MeCN–MeOH (9:1), rt; 96% (two steps); (iii) bis(pinacolato)diboron, KOAc, $PdCl_2$(dppf), DMSO, 80°C; (iv) $NaIO_4$, NH_4OAc, acetone–H_2O (1:1), 83% (two steps).



Scheme 2. *Reagents and conditions*: (i) 4 M HCl–dioxane, rt; Boc-Tyr, EDC, HOBt, Et_3N, $CHCl_3$, rt, 83%; (ii) $Cu(OAc)_2$, amine, powdered 4 Å MS, CH_2Cl_2, see Table 1; (iii) LiOH, THF–MeOH–H_2O (3:3:1), rt, 90%; (iv) Tyr-OMe·HCl, EDC, HOBt, Et_3N, $CHCl_3$, 85%; (v) $Cu(OAc)_2$, DMAP, powdered 4 Å MS, CH_2Cl_2, 0.013 M, 35%.

the production of **12** being effectively reduced in the latter. When the concentration of the starting dichloromethane solution of **8** was diluted to 0.013 M, the yield of **11** increased to 56% (entry 9). However, further dilution of the starting material (0.0063 M) did not give further increase in the yield of **11** (entry 10).[16] Although this type of cycloisodityrosine is known to readily epimerize at the C-terminus chiral center,[6e–g,7b] under these reaction conditions, apparently no epimerization took place: no epimerized cycloisodityrosine was separated.[17]

In the same manner, dipeptide **10** was cyclized by using its dichloromethane solution at 0.013 M to afford **13**[18] in a moderate yield of 35%, which constitutes the cycloisodityrosine moiety of RP 66453 (**2**) (Scheme 2).

Our methods described above provide shorter routes for the preparation of the two types of cycloisodityrosines from commercially available chiral tyrosine derivatives. Thus, it is now possible to obtain sufficient quantities of cycloisodityrosines, which will facilitate the analogue syntheses of bouvardin (**1**), RA-VII (**3**) and RP 66453 (**2**) for their structure–activity relationship studies and designing of more promising antitumor peptide analogues or of neurotensin antagonists.

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16. *Representative reaction procedure*—To a solution of dipeptide **8** (43.2 mg, 0.0837 mmol) in CH_2Cl_2 (6.7 mL) were added DMAP (51.0 mg, 0.417 mmol) and powdered 4 Å molecular sieves (200 mg), and the mixture was stirred at room temperature for 30 min. Copper(II) acetate (15.3 mg, 0.0842 mmol) was added to the mixture, and the mixture was stirred at room temperature for 48 h. The mixture was filtered, and the filtrate was diluted with $CHCl_3$ (30 mL). The $CHCl_3$ solution was washed successively with 5% aqueous $KHSO_4$ (10 mL) and brine (10 mL), dried over $MgSO_4$ and filtered. The solvent was removed in vacuo, and the residue was separated by HPLC (ODS, MeOH–H_2O, 55:45) to afford cycloisodityrosine **11** (21.9 mg, 56%, $[\alpha]_D^{21}$ +53°, *c* 0.25, $CHCl_3$; lit.[6g] $[\alpha]_D^{25}$ +57°, *c* 0.6, $CHCl_3$) and peptide **12** (2.2 mg, 6%).
17. The epimer of **11** is less polar than **11** and more polar than peptide **12** (the data not shown). Thus, if present, the epimer of **11** should have been separated by ODS-HPLC under the conditions described in Ref. 16.
18. Data for **13**: colorless prisms, mp 96–99°C (from isopropyl ether), $[\alpha]_D^{21}$ +145° (*c* 0.10, $CHCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$, 313 K) δ 7.43 (dd, 1H, J=8.3, 2.1 Hz), 7.22 (dd, 1H, J=8.3, 2.5 Hz), 7.08 (dd, 1H, J=8.3, 2.1 Hz), 6.88 (dd, 1H, J=8.3, 2.5 Hz), 6.78 (d, 1H, J=8.2 Hz), 6.58 (dd, 1H, J=8.2, 1.5 Hz), 6.52 (br s, 1H), 5.01 (m, 1H), 4.78 (d, 1H, J=1.5 Hz), 4.40 (br t, 1H, J=8 Hz), 4.06 (br s, 1H), 3.95 (s, 3H), 3.79 (s, 3H), 3.61 (d, 1H, J=15.6 Hz), 3.57 (dd, 1H, J=13.4, 5.1 Hz), 2.64 (dd, 1H, J=13.4, 12.3 Hz), 2.56 (dd, 1H, J=15.6, 6.8 Hz), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 313 K) δ 171.68 (s), 171.14 (s), 158.15 (s), 155.85 (s), 152.90 (s), 147.20 (s), 134.38 (s), 133.40 (d), 130.15 (d), 128.02 (s), 125.63 (d), 123.41 (d), 123.37 (d), 116.32 (d), 112.60 (d), 81.06 (s), 56.28 (q), 53.52 (d), 53.23 (d), 52.53 (q), 38.51 (t), 33.07 (t), 28.29 (q).