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IMPROVED SYNTHESIS OF L,L-CYCLOISODITYROSINE SUBUNIT OF ANTITUMOR AGENTS DEOXYBOUVARDIN AND RA-VII

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A facile synthesis of the core cycloisodityrosine 14-membered ring system is detailed from commercially available L-tyrosine through a novel synthetic approach to aryl boronic acid* 12 *via intramolecular cyclization.

Keywords: Aryl boronate; cycloisodityrosin; deoxybouvardin; palladium catalyst; ring closure

INTRODUCTION

Deoxybouvardin1 and RA-VII **2** constitute representative members of a growing class of naturally occurring antitumor agents (Chart 1).[1,2] The molecular architecture and interesting biological activity make these compounds attractive synthetic targets.[3] Although several synthetic strategies could be envisaged, only three primary routes have been exploited, namely (1) transannulation,[4] (2) bottom-up route, and (3) top-down route.[4–6] Although the first two strategies failed to give the target molecules, the top-down approach was more rewarding. Because ring closure of the bottom 18-membered macrocycle from secoacid **3** (bond disconnection a) is relatively easy,[7] all synthetic efforts have thus far concentrated on synthesis of the key subunit, L,L-cycloisodityrosine **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,[8,9] whereas preparation of cycloisodityrosines via degradation of natural RA-VII **2** into cycloisodityrosine requires a large quantity of **2** as the starting material.[10] Such difficulty in the formation of the cycloisodityrosine unit has hampered the synthesis of the analogs of those important peptides.

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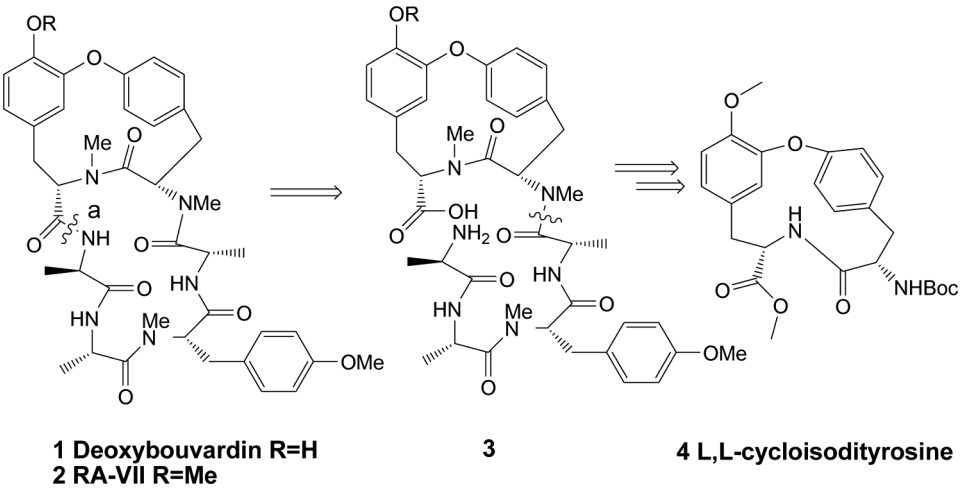


Chart 1. Preparation of the cycloisodityrosine subunit.

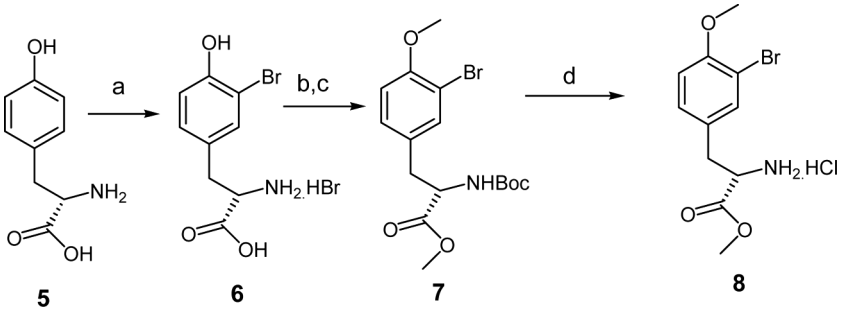
DISCUSSION

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

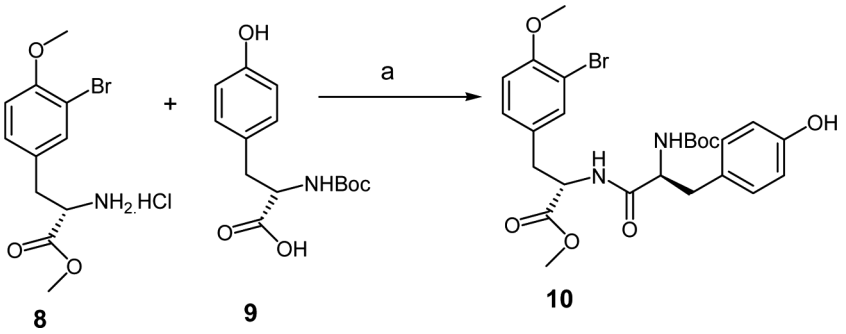
Commercially available L-tyrosine **5** was brominated at the 3-position with bromine in acetic acid and hydrobromic acid in acetic acid at 25 °C to afford 3-bromo-L-tyrosine hydrobromide **6** in 95% yield from **5**. Compound **6** was N-protected with a Boc group and methylated with dimethyl sulfate in the presence of potassium carbonate in acetone to afford protected bromotyrosine **7** in 96% yield from **6**. The methylation step was initially conducted using methyl iodide and potassium carbonate as a base, but the reaction ended with the formation of many impurities. The reaction was optimized with dimethyl sulfate (2.5 equiv) and potassium carbonate (3 equiv) in acetone at 25 °C in 96% yield. Compound **7** was N-deprotected using 2 N HCl in ethyl acetate at 25 °C for 30 min to afford compound **8** in 96% yield (Scheme 1).

Compound **8** was coupled with compound **9** using EDCI and HOBt in the presence of diisopropyl ethyl amine in CH_2Cl_2 at 25 °C to afford dipeptide **10** in 90% yield (Scheme 2).

When compound **10** was treated with bis(pinacolato)diboron (1.3 equiv) and potassium acetate (3 equiv) in dimethylsulfoxide (DMSO) using $Pd(PPh_3)_4$ as a catalyst for 18 h at 90 °C, no desired product **11** observed (Table 1, entry 1). When the same reaction was performed using dimethylformamide (DMF) as a solvent under the same condition, only 5% of product **11** was observed (entry 2). More reactions were performed under the same conditions with different bases such as sodium acetate and sodium carbonate, but no product **11** was observed (entries 3 and 4). We thought that perhaps the catalyst was the culprit, and we conducted a few more reactions using $PdCl_2$[1,1′-bis(diphenylphosphino)ferrocene](dppf) as a catalyst. When compound **10**



Scheme 1. Reagents and conditions: (a) Br_2/AcOH, HBr/AcOH, 25 °C, 6 h, 95%; (b) $(Boc)_2O$, $NaHCO_3$, MeOH, EtOAc, 25 °C, 4 h; (c) Me_2SO_4, K_2CO_3, acetone, 25 °C, 12 h, 96% (from 6 to 7); and (d) 2 N HCl, EtOAc, 25 °C, 30 min, 96%.

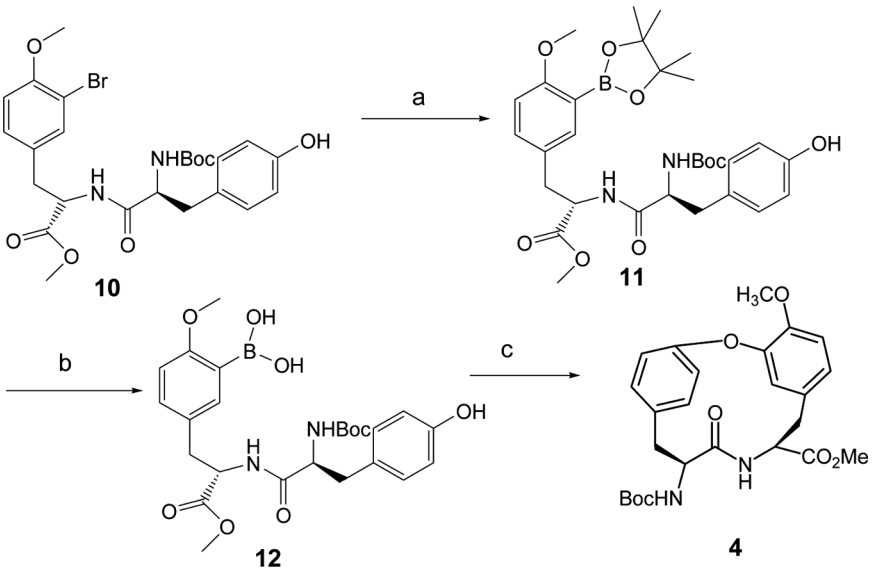


Scheme 2. Reagents and conditions: (a) EDCI, HOBt, DIPEA, CH_2Cl_2, 25 °C, 1 h, 90%.

was treated with bis(pinacolato)diboron (1.3 equiv) and potassium acetate (3 equiv) in DMSO using $PdCl_2$(dppf) as a catalyst for 18 h at 90 °C, only 20% of desired product **11** was observed (entry 5). When the same reaction was performed using DMF as a solvent under the same condition, only 30% of product **11** was observed (entry 6). The most favorable yield was obtained using potassium acetate as a base (3 equiv) and $PdCl_2$(dppf) as a catalyst (0.05 equiv) in 1,2-dimethoxyethane (DME) as a solvent at 110 °C for 16 h. The yield was 90% (entry 7).

Table 1. Reaction conditions for conversion of **10** to **11**

Entry	Base	Solvent	Catalyst	Temp. (°C)	Time (h)	Yield (%)
1	KOAc	DMSO	$Pd(PPh_3)_4$	90	18	Nil
2	KOAc	DMF	$Pd(PPh_3)_4$	90	18	<5
3	NaOAc	DMF	$Pd(PPh_3)_4$	90	18	Nil
4	Na_2C0_3	DMF	$Pd(PPh_3)_4$	90	18	Nil
5	KOAc	DMSO	PdCl2(dppf)	90	18	20
6	KOAc	DMF	$PdCI_2$(dppf)	90	18	30
7	KOAc	DME	$PdCI_2$(dppf)	110	18	90



Scheme 3. Reagents and conditions: (a) bis(pinacolato)diboron, KOAc, $PdCl_2$(dppf), DME, 110 °C, 18 h, 90%; (b) $NaIO_4$, acetone, 0.1 N aq. NH_4OAc, 25 °C, 16 h, 90%; (c) $Cu(OAc)_2$, DMAP, CH_2Cl_2, powdered 4-Å^0 molecular sieves, 48 h, 60%.

This aryl boronate **11** was converted into aryl boronic acid **12** using $NaIO_4$ in acetone in the presence of 0.1 N NH_4OAc aq. solutions at 25 °C for 16 h in 90% yield. The key ring closure of **12** to **4**[14] via the intramolecular *O*-arylation of phenols with aryl boronic acid **12** reaction smoothly proceeded using $Cu(OAc)_2$ (1.3 equiv) and dimethylaminopyridine (DMAP; 5 equiv) in CH_2Cl_2 in the presence of powered 4-Å molecular sieves for 48 h at 25 °C in 60% yield (Scheme 3).

In conclusion, we have developed a practical method for the synthesis of L,L-cycloisodityrosine from commercially available L-tyrosine. Thus, it is possible to get sufficient quantities of cycloisodityrosine to facilitate the analog synthesis of deoxybouvardin **1** and RA-VII **2** for structure–activity relationship studies and design of more promising antitumor peptide analogs.

EXPERIMENTAL

Materials and Instruments

All solvents and reagents were purchased from the suppliers and used without further purification. All nonaqueous reactions were performed in dry glassware under a dry nitrogen atmosphere. Organic solutions were concentrated under reduced pressure. Thin-layer chromatography (TLC) was performed on Merck pre-coated silica-gel 60 F_{254} plates. ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini 400-MHz Fourier transform (FT) NMR spectrometer using DMSO-d_6 and $CDCl_3$ as a solvent. The chemical shifts were reported in δ ppm relative to tetramethylsilane (TMS). The mass spectra (MS) were recorded on Shimadzu

LCMS-QP 800 LC-MS and AB-4000 Q-trap LC-MS/MS instruments. Melting points were obtained using the open capillary method and are uncorrected.

(S)-2-Amino-3-(3-bromo-4-hydroxyphenyl) propanoic acid hydrobromide (6)

A solution of HBr in glacial acetic acid (33% w/v) (15 ml, 61 mmol) was added to a vigorously stirred suspension of (S)-tyrosine (5.54 g, 30.6 mmol) in glacial acetic acid (25 ml). A solution of bromine (1.7 ml, 33.2 mmol) in glacial acetic acid (11.3 ml) was added dropwise over 3 h, and the resulting mixture was stirred at rt for 24 h. The precipitate was filtered and washed with glacial acetic acid (3×5 ml) and Et_2O (5×5 ml) to furnish **6** as a white solid (10.03 g, 95%); mp 210–215 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.10 (br s, 1H), 10.16 (s, 1H), 8.13 (br s, 2H), 7.33 (s, 1H), 7.01 (m, 1H), 6.86 (d, $J = 8$ Hz, 1H), 4.10 (t, 1H), 2.99 (m, 2H), 1.86 (s, 1H); ESIMS: m/z calcd. [M +]: 260; found: 261.94 [M+H+].

(S)-Methyl 3-(3-bromo-4-methoxyphenyl)-2-(tert-butoxycarbonyl) propanoate (7)

$NaHCO_3$ (2.45 g, 29.32 mmol) and H_2O (20 mL) were added, followed by $(Boc)_2O$ (4.8 g, 22 mmol), to a solution of compound **6** (5.0 g, 14.66 mmol) in MeOH (30 mL) and EtOAc (30 mL) at 25 °C. The reaction mixture was stirred at the same temperature for 4 h. Heptane (50 mL) was added to the reaction mixture, and it was diluted with water (20 mL). The organic layer was separated, and aqueous layer was washed with heptane (40 mL) one more time. Then the aqueous layer was acidified with 10% aqueous citric acid solution (20 mL) to make the pH ~ 4–5. The aqueous layer was extracted with EtOAc (2×50 mL) and concentrated under vacuum to afford the corresponding Boc-protected compound (5.2 g). K_2CO_3 (6 g, 43.33 mmol) and Me_2SO_4 (4.5 g, 36.11 mmol) were added to a solution of Boc-protected compound (5.2 g, 14.44 mmol) in acetone (50 mL) at 25 °C. The reaction mixture was stirred at the same temperature for 12 h. The reaction mixture was filtered through a pad of Celite and washed with acetone (50 mL). The acetone layer was concentrated under vacuum. Purification by column chromatography (silica, 7:3 hexane/EtOAc) provided arylbromide **7** as an off-white solid (on storage at rt, it slowly became solid) (5.5 g, 96% yield), $R_f = 0.6$ (7:3; heptanes/EtOAc), mp 66–70 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.40 (s, 1H), 7.25 (d, $J = 8.4$ Hz, 1H), 7.18 (dd, 1H), 6.99 (d, $J = 8.4$ Hz, 1H), 4.08 (m, 1H), 3.76 (s, 3H), 3.57 (s, 3H), 2.89 (m, 1H), 2.75 (m, 1H), 1.28 (s, 9H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 170.9, 158.9, 155.1, 134.2, 131.0, 130.6, 114.5, 113.1, 79.9, 56.7, 53.5, 53.3, 35.4, 34.8; ESIMS: m/z calcd [M+]: 388; found: 287.94 [M+].

(S)-Methyl 3-(3-bromo-4-methoxyphenyl)-2-((S)-2-(tert-butoxycarbonyl)-3-(4-hydroxyphenyl)propanamido) propanoate (10)

Compound **9** (2.60 g, 9.25 mmol), EDCI (2.65 g, 13.87 mmol), HOBt (1.25 g, 9.25 mmol), and DIPEA (3.57 g 27.75 mmol) were added to a suspension of **8**

(3.0 g, 9.25 mmol) in dry CH_2Cl_2 (50 mL) at 25 °C. The resulting mixture was stirred at 25 °C for 2 h. The reaction mixture was quenched with water and neutralized with 10% aq. citric acid solution, and CH_2Cl_2 layer was separated and concentrated to get a residue. The residue was purified by column chromatography (silica, 5:5; heptanes/EtOAc) to afford compound **10** as an off-white solid (4.6 g, 90% yield), $R_f = 0.2$ (5:5; heptane/EtOAc), mp 90–95 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.25 (s, 1H), 8.20 (d, $J = 8$ Hz, 1H), 7.39 (s, 1H), 7.16 (d, $J = 8.4$ Hz, 1H), 6.97 (m, 3H), 6.67 (m, 3H), 4.40 (m, 1H), 4.09 (m, 1H), 3.75 (s, 3H), 3.66 (s, 3H), 2.94–2.83 (m, 4H), 1.28 (s, 9H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 172.5, 172.1, 156.0, 155.5, 155.0, 154.5 133.9, 131.0, 130.4, 130.1, 128.3, 115.2, 112.8, 110.6, 78.6, 56.5, 55.5, 53.8, 52.4, 39.0, 37.1, 28.5; ESIMS: m/z calcd [M+]: 551; found: 452.77 [M+H+].

(S)-Methyl 2-((S)-2-(*tert*-butoxycarbonyl)-3-(4-hydroxyphenyl)-propanamido)-3-(4-methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl) propanoate (11)

Aryl bromide **10** (5.0 g, 9.06 mmol), bis(pinacolato)diboron (2.95 g, 11.78 mmol), KOAc (2.66 g, 27.2 mmol), and $PdCl_2$(dppf) (0.369 g, 0.453 mmol) were suspended in dry 1,2-dimethoxyethane (50 mL, degassed by sparging with N_2) and heated to 110 °C for 18 h. Water (30 ml) and EtOAc (30 ml) were added. The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 50). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuum. Purification by column chromatography (silica, 5:5 hexane/EtOAc) provided aryl boronate **11** as an off-white solid (4.8 g, 90% yield), mp 80–83 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.13 (s, 1H), 8.22 (d, $J = 7.44$ Hz, 1H), 7.36–6.61 (m, 8H), 4.40 (q, 1H), 4.05 (q, 1H), 3.69 (s, 3H), 3.58 (s, 3H), 2.94–2.75 (m, 4H), 1.33 (s,12H), 1.26 (s, 9H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 171.9, 171.8, 162.7, 155.7, 155.0, 137.0, 133.3, 130.0, 129.6, 128.5, 128.0, 114.7, 110.7, 82.9, 77.9, 56.0, 55.3, 53.8, 51.7, 36.7, 35.8, 28.0, 24.9, 24.5. ESIMS: m/z calcd. [M+]: 598; found: 598.93 [M +H+], 621.86 [M+ +Na]. HRMS (ESI): m/z calcd. [M+]: 598.4921; found: 598.4935 [M+].

5-((S)-2-((S)-2-(*tert*-Butoxycarbonyl)-3-(4-hydroxyphenyl)-propanamido)-3-methoxy-3-oxopropyl)-2-methoxyphenylboronic acid (12)

NH_4OAc (aq) (50 mL, 0.1 N) and $NaIO_4$ (3.21 g, 15.04 mmol) were added to a stirred solution of the boronate ester **11** (3.0 g, 5.01 mmol) in acetone (60 mL). The mixture was stirred at 25 °C for 24 h. The reaction was monitored by TLC, and no starting material was left. Ethyl acetate (50 ml) was added to the reaction mixture, and the ethyl acetate layer was separated and concentrated to afford the product **12**. This was purified by column chromatography using silica (5:5 hexane/EtOAc) to provide aryl boronate **12** as an off-white solid (2.32 g, 90% yield), mp 98–102 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.13 (s, 1H), 8.23 (d, $J = 7.48$ Hz, 1H), 7.65 (m, 10H), 4.41 (q, 1H), 4.04 (q, 1H), 3.69 (s, 3H), 3.57 (s, 3H), 2.96–2.75 (m, 4H), 1.25 (s, 9H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 171.7, 171.6, 162.6, 155.6, 154.9, 136.2, 132.0, 129.9, 128.4, 128.0, 127.8, 114.9, 110.2, 77.9, 55.7, 55.2, 53.7, 51.6,

36.6, 36.0, 28.8. ESIMS: m/z calcd. [M+]: 516; found: 516.90 [M+H+], 538.89 [M+ +Na]. HRMS (ESI): m/z calcd. [M+]: 516.3485; found: 516.3935 [M+].

12-*tert*-Butoxycarbonylamino-4-methoxy-11-oxo-2-oxa-10-aza-tricyclo[12.2.2.1*3,7*]nonadecA-1(17),3(19),4,6,14(18),15-hexaene-9-carboxylic acid methyl ester (4)

DMAP (2.36 g, 19.36 mmol) and powdered 4-Å molecular sieves (4 g) were added to a solution of compound **12** (2.0 g, 3.87 mmol) in CH_2Cl_2 (200 mL), and the mixture was stirred at 25 °C for 30 min. Copper(II) acetate (0.91 g, 5.034 mmol) was added to the mixture, and the mixture was stirred at 25 °C for 48 h. The mixture was filtered, washed successively with 5% aqueous $KHSO_4$(50 mL) and brine (50 mL), and dried over $MgSO_4$. The solvent was removed in vacco, and the residue was purified by column chromatography using silica (7:3 hexane/EtOAc) to provide compound **4**[14] as an off-white solid (1.00 g, 60% yield); $[\alpha]^{25}{}_D + 57$ (c 0.6, $CHCl_3$), mp 84–88 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.14 (s, 1H), 7.77 (s, 1H), 7.10 (m, $J = 8.8$ Hz, 8.4 Hz, 2H), 6.96 (m, $J = 8.8$ Hz, 9.6 Hz, 2H), 6.82 (d, $J = 6.8$ Hz, 1H), 6.60 (d, $J = 8$ Hz, 1H), 4.94 (s, 1H), 4.40 (m, 1H), 4.21 (m, 1H), 3.77 (m, 3H), 3.49 (m, 3H), 3.07 (m, 4H), 1.25 (s, 9H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 174.4, 173.7, 160.6, 158.3, 154.3, 136.8, 134.7, 133.0, 132.7, 129.6, 123.9, 116.3, 114.4, 80.6, 57.5, 56.9, 56.3, 54.4, 35.7, 33.9, 30.9. ESIMS: m/z calcd. [M+]: 470; found: 471.12 [M+H+]. HRMS (ESI): m/z calcd [M+]: 470.5149; found: 470.5135 [M+].

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