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SYNTHESIS OF L,L-ISODITYROSINE

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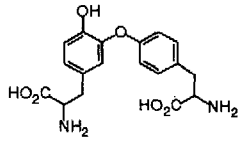
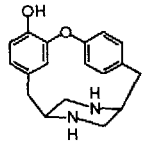
Abstract: *A study of the development of reaction conditions for implementation of an activated Ullmann diaryl ether condensation reaction that may be conducted without amino acid racemization and that has proven suitable for incorporation of a selectively-protected catechol is described and its application to the synthesis of* L,L-*isodityrosine (**1**) is detailed.*

The highly insoluble, hydroxyproline-rich glycoprotein extensin characteristic of plant cell walls undergoing extension growth has been shown to contain the crosslinking amino acid isodityrosine (**1**)[2] in which the function of isodityrosine is to provide structural stability to the polypeptide. The structure of isodityrosine was established as an amino acid dimer, isomeric with dityrosine,[2] in which two tyrosine units are linked through an unsymmetrical diphenyl ether bond. Additional recent efforts have established the natural occurrence of the antifungal agent piperazinomycin (**2**),[3a] the aminopeptidase B inhibitors OF4949-I - OF4949-IV (**3a-3d**),[3b] the angiotensin converting enzyme (ACE) inhibitor K-13 (**4**),[3c] and a class of antitumor agents including bouvardin (**5a**),[4a] deoxybouvardin (**5b**),[4a] RA-I - RA-V (**5c-g**)[4b] bearing structural subunits presumably derived from isodityrosine. In the instances tested, the isodityrosine-derived unit present in the agents has proven to be of fundamental importance to their properties, e.g., *O-seco*-deoxybouvardin (**6**),[5a,b] and has been characterized by the failure of synthetic efforts to effect diaryl ether formation on a fully assembled peptide precursor[3a,5a,c] suggesting the direct incorporation of isodityrosine into the cyclic peptides.

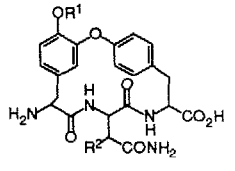
Herein we detail the synthesis of L,L-isodityrosine [**1**, *S*-4-hydroxy-3-(*S*-4-(2-amino-2-carboxy)ethyl)phenoxy)phenylalanine] suitable for the incorporation into the total synthesis of **2-5** based on the development of reaction conditions for implementation of an Ullmann diaryl ether condensation reaction



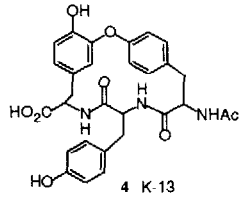
1 isodityrosine



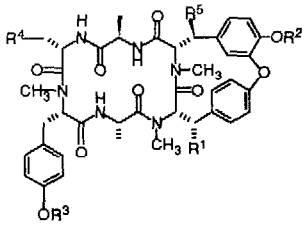
2 piperazinomycin



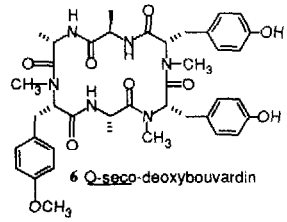
3a R^1=H R^2=H OF4949-IV
3b R^1=H R^2=OH OF4949-II
3c R^1=CH_3 R^2=H OF4949-I
3d R^1=CH_3 R^2=OH OF4949-III



4 K-13

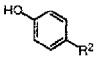
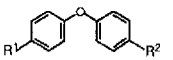
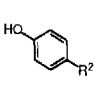
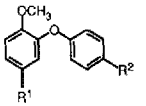
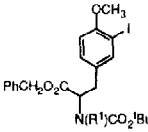
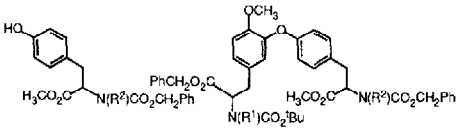
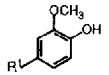
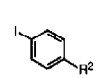
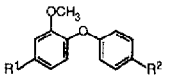
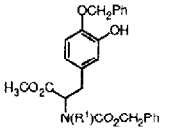
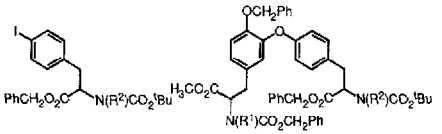
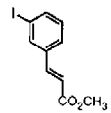
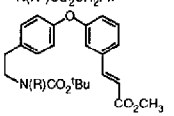
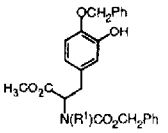
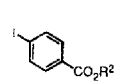
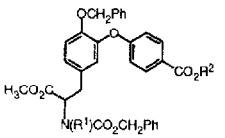


	R^1	R^2	R^3	R^4	R^5	
5a	OH	H	CH_3	H	H	bouvardin
5b	H	H	CH_3	H	H	deoxybouvardin, (RA-V)
5c	H	H	CH_3	OH	H	RA-I
5d	H	CH_3	H	H	H	RA-II
5e	H	CH_3	CH_3	OH	H	RA-III
5f	H	CH_3	CH_3	H	OH	RA-IV
5g	H	CH_3	CH_3	H	H	O-methyl deoxybouvardin



6 O-seco-deoxybouvardin

TABLE I.

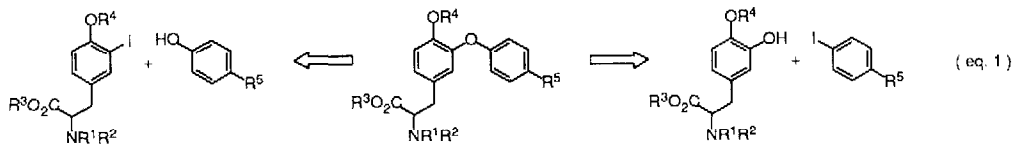
Entry	R^1	R^2	Iodide	Phenol	Diaryl Ether	Conditions[a]				Yield (%), (L:D ratio)
A. REACTIONS OF ELECTRON RICH ARYL IODIDES						NaH (eq)	CuBr (eq)	Time (h)		
1	H	H				2.0	2.0	18		82
2	CH_3	CH_3				2.0	2.0	20		77
3	CHO	CH_3				2.0	2.0	18		63
4	CO_2CH_3	CH_3				2.0	2.0	18		74
5	CH_3	$CH_2CH(CO_2CH_3)NHCO_2CH_2Ph$				2.0	2.0	18		47
6	CH_3	CH_3				2.0	2.0	20		44
7	CH_3	$CH_2CH(CO_2CH_3)NHCO_2CH_2Ph$				2.0	2.0	18		20
8	$CH_2CH(CO_2CH_2Ph)NHCO_2{}^tBu$	CH_3				2.0	2.0	12		14
9a	H	H				2.0	2.0	20		0
9b	CH_3	CH_3				1.2	1.2	18		0
B. REACTIONS OF ELECTRON RICH PHENOLS AND SELECTIVELY PROTECTED CATECHOLS										
10	H	H				1.2	1.2	18		65
11	H	CH_3				1.2	1.2	18		62
12	CH_3	CH_3				1.2	1.2	20		66
13	H	CO_2CH_3				2.0	2.0	20		75
14a	H	H				1.2	1.2	12		0
14b	CH_3	CH_3				1.2	1.2	12		0
15a	H					1.2	1.2	18		57
15b	CH_3					1.2	1.2	18		46
16a[b]	CH_3	$CO_2{}^tBu$				a. 1.0	1.0	18		32(56:44)
									solvent[c]	
16b[c]	CH_3	$CO_2{}^tBu$				b. 1.0	1.0	18	pyridine	36 (55:45)
16c	CH_3	$CO_2{}^tBu$				c. 1.0	1.0	18	chlorobenzene	22
16d	CH_3	$CO_2{}^tBu$				d. 1.0	1.0	18	diglyme	trace
16e	CH_3	$CO_2{}^tBu$				e. 1.0	1.0	18	xylene	trace
16f	CH_3	$CO_2{}^tBu$				f. 1.0	1.0	18	nitrobenzene	32 (65:35)
16g	CH_3	$CO_2{}^tBu$				g. 1.0	1.0	18	DMF	22
						h. 1.0	1.0	18	DMSO	33 (62:38)
16i[d]	CH_3	$CO_2{}^tBu$				i. 1.0	1.4	8	nitrobenzene	45 (94:6)
16j	H	$CO_2{}^tBu$				j. 1.0	1.4	8	nitrobenzene	46 (94:6)
16k	H	Na				k. 1.0	1.4	8	nitrobenzene	51 (94:6)

a) all reactions were performed in pyridine at 125°C (bath temp.) unless otherwise specified, using an excess of phenol corresponding to equivalents of NaH

b) all reactions in entry 16 were performed using 2.0 equiv of aryl iodide

c) reactions in entries 16b-h were performed in their respective solvents at 130°C (bath temp) in the presence of tris[2-(2-methoxyethoxy)ethyl]amine[6b] (1.0 equiv)

d) reactions in entries 16i-k were performed employing the dimethylsulfide complex of cuprous bromide ($CuBrSMe_2$) as the copper (I) source

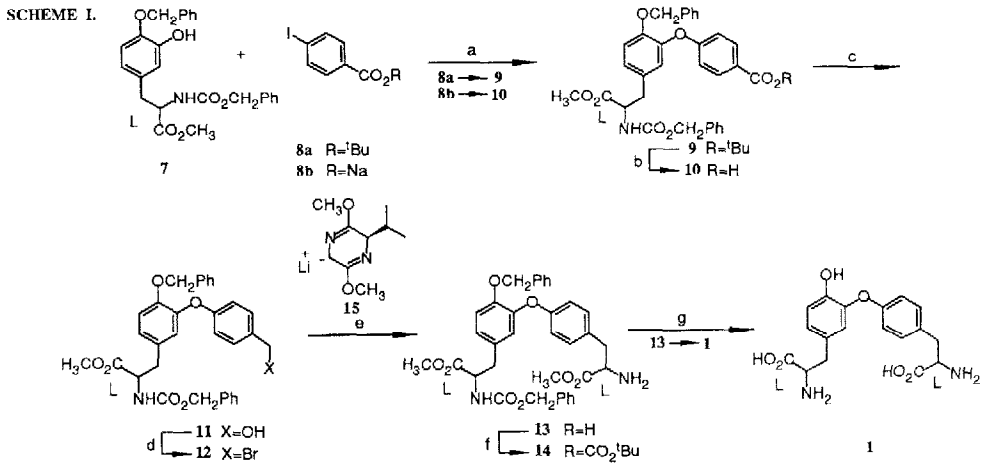


(eq. 1)

that may proceed without amino acid racemization and that have proven applicable to phenols constituting part of a selectively-protected catechol. Although the availability of L-3-iodotyrosine[6a] initially directed our and related[3a,5c] investigations toward studies of the Ullmann condensation of suitably protected derivatives of this amino acid with a protected tyrosine derivative, equation 1, the results of such studies have proven unsuccessful. As illustrated in Table I, although the Ullmann condensation of electron-rich aryl iodides with unactivated phenols has proven successful for simple substrates (entries 1,2,5),[7] and modestly successful for simple electron-rich aryl iodides bearing an ortho alkoxy substituent and/or for reactions of a single functionalized tyrosine derivative (entries 6-8), such an Ullmann condensation has failed when applied to the fully functionalized tyrosine derivatives (entry 9a,b). Presumably this may be attributed to the recognized steric and electronic deceleration of the Ullmann condensation due to the aryl iodide ortho electron donating substituent[7] and the sensitivity of the protected amino acid to the standard reaction conditions. However, the alternative combination of promoting an Ullmann condensation of a selectively-protected catechol (entries 10-13) including Dopa derivatives such as 7 has proven successful, equation 1.[8] In contrast to the unsuccessful direct Ullmann condensation of 7 with a protected *p*-iodophenylalanine (entry 14a,b) and the modestly successful couplings of 7 with simple aryl iodides, the accelerated Ullmann condensation of **7** with the activated aryl iodide **8a**, *t*-butyl *p*-iodobenzoate, proved viable. In addition, a study of the Ullmann condensation of **7** and **8a** revealed suitably mild reaction conditions (130°C, nitrobenzene) that permitted the coupling to proceed without amino acid racemization *and* that this Ullmann condensation could be extended to the productive use of sodium *p*-iodobenzoate (**8b**). Representative results of the optimization of the chemical conversion with minimization of the extent of racemization for the Ullmann condensation of 7 with **8a** are detailed in Table I, entry 16.[8]

Thus, the synthesis of L,L-isodityrosine (**1**) was initiated with the incorporation of a selectively-protected L-Dopa derivative **7**[9] (chiral phase HPLC[10a] L:D ratio 95:5) in an Ullmann condensation with *t*-butyl *p*-iodobenzoate (**8a**, NaH, CuBr·SMe$_2$, $C_6H_5NO_2$, 130°C, 8 h, 46%) to afford diaryl ether **9** (chiral phase HPLC[10a]

SCHEME I.



a) 1.0 Equiv NaH, 1.4 equiv CuBrSMe$_2$, $C_6H_5NO_2$, 130°C, 8 h; 46% for **9**, 51% for **10**. b) 3.0 M HCl/EtOAc, 25°C, 1.5 h, 95%. c) 1.0 Equiv BH_3·THF, THF, 0°C, 3 h, 89%. d) 2.0 Equiv CBr_4, 2.0 equiv Ph_3P, Et_2O, 25°C, 72%. e) 1.0 Equiv NaH, THF, 0°C, 5 min; 1.0 equiv **15**, THF, -78°C, 14 h; 0.5 N aq. HCl/THF (1:1), 25°C, 15 h, 57% from **12**. f) 1.0 Equiv di-*t*-butyldicarbonate, THF, 25°C, 1.5 h. g) 6.0 N HCl, 65°C, 6 h, 100%.

L:D ratio 94:6), Scheme I. Conversion of the *tert*-butyl ester **9** to the carboxylic acid **10** (3.0 M HCl/EtOAc, 25°C, 1.5 h, 95%) and subsequent reduction (BH_3·THF, THF, 0°C, 3h, 89%) provided the primary alcohol **11** which was converted to primary bromide **12** (CBr_4, Ph_3P, Et_2O, 25°C, 72%). Alternatively, the carboxylic acid **10** could be obtained directly from the Ullmann condensation reaction of **7** with sodium *p*-iodobenzoate (**8b**, NaH, CuBr·SMe_2, $C_6H_5NO_2$, 130°C, 8 h, 51%). Treatment of benzyl bromide **12** with Schöllkopf's reagent **15**[11] (NaH, THF, 0°C, 5 min; **15**, THF, -78°C, 14 h) and subsequent acid-catalyzed hydrolysis of the cyclic imidate (0.5 N aqueous HCl/THF, 25°C, 15 h, 57% from **12**) provided **13**.[10b] Exhaustive removal of protecting groups from **13** (6.0 N HCl, 65°C, 6 h, 100%) afforded L,L-isodityrosine (**1**) as the bishydrochloride salt[12] [**1**·2HCl, $[\alpha]_D^{22}$ -28.2° (c 1.0, MeOH)] thus completing a five-step synthesis of optically active **1**.

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10. (a) Chiral phase HPLC analysis was performed on a Gilson Model 320 dual pump chromatograph equipped with an ISCO V[4] variable wavelength absorbance detector employing a J.T. Baker Bakerbond DNPG (covalent) chiral column. (b) Normal phase HPLC analysis, performed on the same system employing an Altech Econosil silica (10μ) column, of the N-BOC derivative **14** revealed a 90:4.5:4.5:<1 ratio of diastereomers indicating the alkylation proceeded with 95% de.
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12. A sample of authentic, naturally occurring isodityrosine was not available for direct comparison. For **1**·2HCl: ^{1}H NMR (D_2O, 200 MHz, ppm) 7.28 (d, 2H, J = 8.7 Hz, C2′,C6′-H), 7.07 (bs, 2H, Ar-H), 6.89 (d, 2H, J = 8.7 Hz, C3′,C5′-H), 6.89 (bs, 1H, Ar-H), 4.14 (dd, 1H, J = 7.3 Hz, 4.9 Hz, CH_2CHNH), 4.11 (dd, 1H, J = 7.0 Hz, 5.5 Hz, CH_2CHNH), 3.35-3.02 (m, 4H, two CH_2CHN); HRMS, *m/e* 360.3656 ($C_{18}H_{20}N_2O_6$ requires 360.3658).

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