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TOTAL SYNTHESIS OF OF4949-III AND OF4949-IV: UNUSUAL EFFECTS OF REMOTE SUBSTITUENTS ON THE RATE OF MACROCYCLIZATION REACTIONS.

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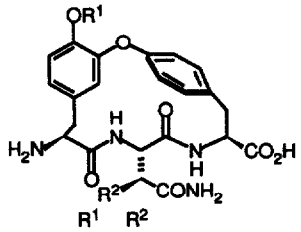
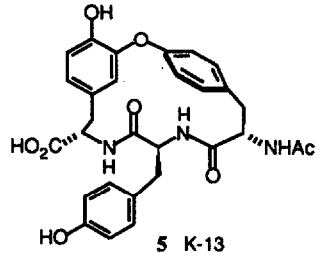
Summary: The total syntheses of OF4949-III and OF4949-IV are detailed and a study of the unusual effects remote substituents may have on the rate of the key macrocyclization reaction leading to 17-membered cyclic tripeptides incorporating a diaryl ether linked meta- and paracyclophane structural subunit is described.

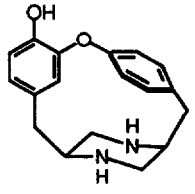
OF4949-I - OF4949-IV (**1-4**), isodityrosine-derived cyclic tripeptides isolated from *Penicillium rugulosum*[2] and identified in spectroscopic and chemical degradative studies,[3] have been shown to exhibit potent aminopeptidase B inhibitory activity, immunopotentiating activity, and confirmed antitumor activity.[4] Since the agents *lack* cytotoxic activity but possess confirmed antitumor activity against solid IMC carcinoma and antimetastatic activity against the pulmonary metastases of Lewis lung carcinoma, the agents constitute a new class of potentially useful antitumor agents that act as immunopotentiators and that may not display host antigenicity or toxicity.[4] Thus, OF4949-I - OF4949-IV constitute unique additions to a growing class of important biologically active isodityrosine-derived[5] cyclic peptides now including K-13 (**5**),[6,7] piperazinomycin (**7**),[6,8] and a series of bicyclic hexapeptide antitumor-antibiotics RA-I-VII (**7-14**).[6,9] Herein we detail a total synthesis of OF4949-III (**1**) and OF4949-IV (**2**) based on our recently disclosed Ullmann condensation that may be conducted under reaction conditions that permit incorporation of a selectively-protected



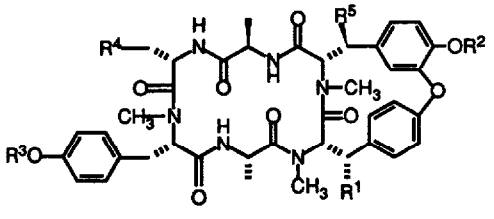
	R^1	R^2	
1	CH_3	H	OF4949-III
2	H	H	OF4949-IV
3	CH_3	OH	OF4949-I
4	H	OH	OF4949-II



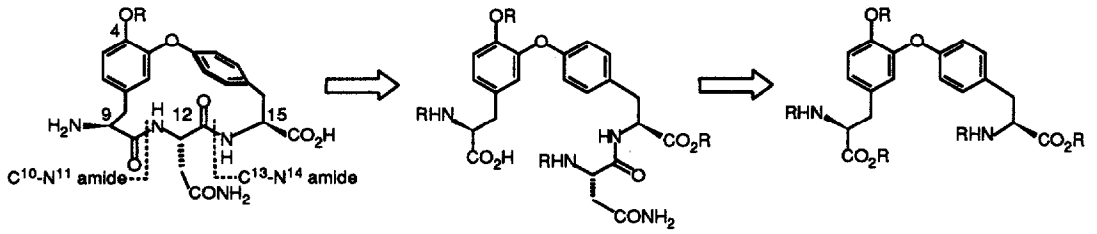
5 K-13



6 piperazinomycin



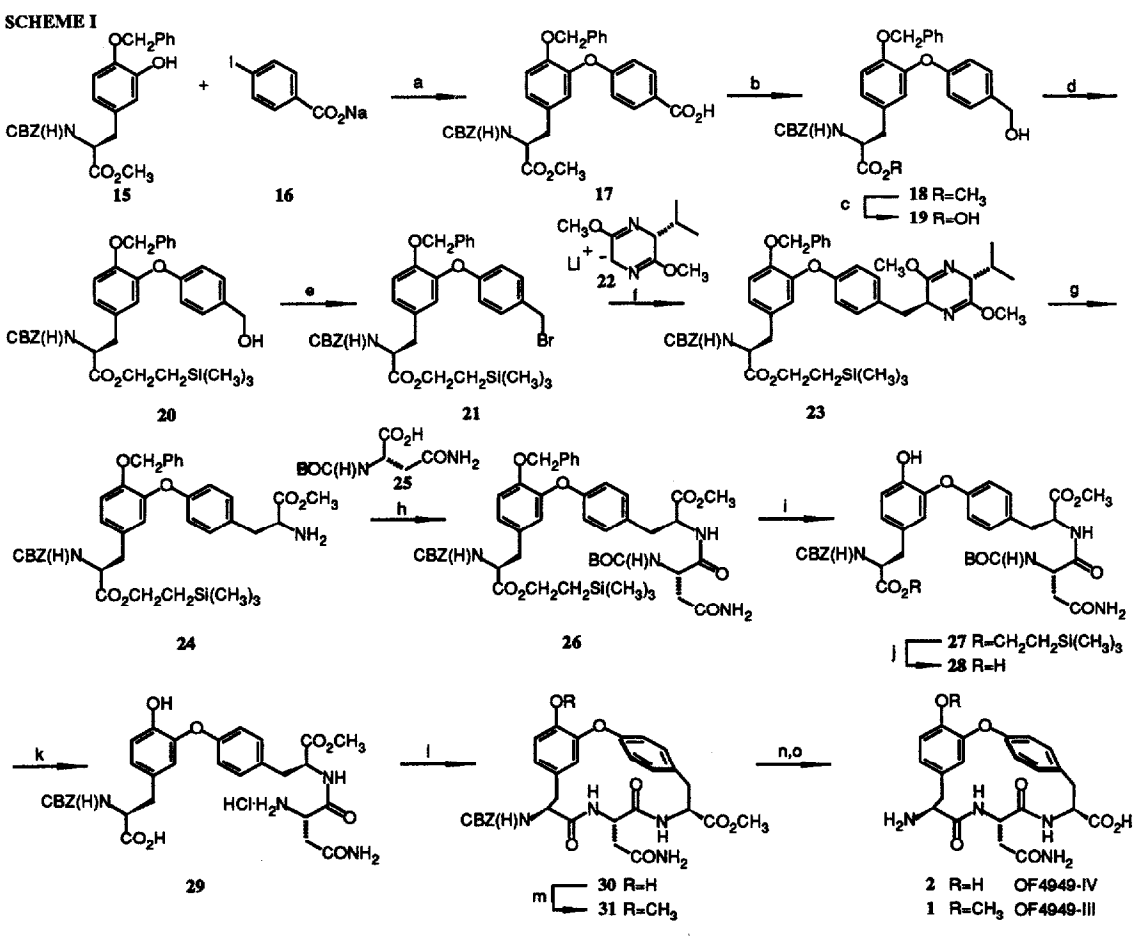
	R^1	R^2	R^3	R^4	R^5	
7	OH	H	CH_3	H	H	bouvardin
8	H	H	CH_3	H	H	deoxybouvardin, (RA-V)
9	H	H	CH_3	OH	H	RA-I
10	H	CH_3	H	H	H	RA-II
11	H	CH_3	CH_3	OH	H	RA-III
12	H	CH_3	CH_3	H	OH	RA-IV
13	H	CH_3	CH_3	H	H	O-methyl deoxybouvardin
14	OH	CH_3	CH_3	H	H	O-methyl bouvardin



catechol including L-Dopa derivatives without amino acid racemization.[10] Additional studies of the key macrocyclization reaction leading to 17-membered cyclic tripeptides incorporating a diaryl ether linked meta- and paracyclophane structural subunit are detailed and illustrate unanticipated effects that remote substituents have on the reaction rate of the ring closure.

As previously detailed, Ullmann condensation of the selectively-protected L-Dopa derivative **15** (L:D 95:5)[10] with sodium *p*-iodobenzoate (**16**, $CuBr{\cdot}SMe_2$, $C_6H_5NO_2$, 130°C, 8 h, 51%) provided the diaryl ether **17** (L:D 94:6) under reaction conditions that permitted the coupling to proceed without amino acid racemization and that permitted the use of the selectively-protected catechol **15**, Scheme I.[11] Reduction of **17** ($BH_3{\cdot}THF$, THF, 0°C, 3 h, 89%) provided the primary alcohol **18** and ester exchange (LiOH, 92%; EDCI, HOBt, $Me_3SiCH_2CH_2OH$, CH_2Cl_2, 25°C, 12h, 86%) followed by

SCHEME I



a) NaH, $CuBr{\cdot}SMe_2$, $C_6H_5NO_2$, 130°C, 8h, 51%. b) $BH_3{\cdot}THF$, THF, 89%. c) LiOH, THF:H_2O:MeOH, 92%. d) $(CH_3)_3SiCH_2CH_2OH$, EDCI, 86%. e) Ph_3P, CBr_4, 70%. f) NaH, THF; **22**, THF, -78°C; g) 0.5N HCl/THF, 59% from **21**. h) EDCI, HOBt, **25**, DMF, 88%. i) H_2, Pd-C; $ClCO_2CH_2Ph$, THF, 86%. j) nBu$_4$NF, THF, 90%. k) 3.0M HCl/EtOAc. l) DPPA, $NaHCO_3$, DMF, 0.004M, 0°C, 58%. m) CH_2N_2, quant. n) LiOH, 88% for **30**, 92% for **31**. o) H_2, 10% Pd-C, 93% for **2**, for 95% **1**

treatment of the primary alcohol **20** with Appel's reagent[12] provided the primary bromide **21** (CBr_4, Ph_3P, Et_2O, 25°C, 12 h, 70%). Treatment of **21** with Schöllkopf's reagent **22**[13] (NaH, THF, 0°C, 20 min; 1.0 equiv **22**, THF, -78°C, 12 h) and subsequent acid-catalyzed hydrolysis of the cyclic imidate **23** (0.5 N aqueous HCl-THF, 1:1, 25°C, 14 h, 59% from **21**) provided **24**.[14]

As previously described,[6c] although two amide bonds potentially may be formed in a macrocyclization reaction leading to the OF4949 agents, it is only closure at the C^{10}-N^{11} amide bond that might be expected to productively provide the 17-membered cyclic tripeptides. Closure at the C^{13}-N^{14} amide bond can be anticipated to suffer competitive succinimide or iminosuccinic anhydride formation. Consequently, acylation of the free amine **24** with *N*-BOC-L-asparagine (**25**, EDCI, HOBt, DMF, 25°C, 12 h, 88%) provided **26**. As anticipated from our prior studies on K-13, the OF4949 macrocyclization reaction was expected and shown to be optimally conducted on substrates bearing a C-9 carbamate derivative and the *free C-4 phenol* with C^{10}-N^{11} amide bond closure.[6c] Consequently, *O*-debenzylation of **26** (H_2, 10% Pd-C, THF, 25°C, 3 h; $ClCO_2CH_2Ph$, $NaHCO_3$, THF, 25°C, 86%) followed by sequential deprotection of the 2-trimethylsilylethyl ester (nBu_4NF, DMF, 25°C, 4 h, 90%) and the asparagine C-2 terminal amine (3.0 M HCl/EtOAc, 25°C, 0.5 h) provided **29**. Diphenylphosphoroazidate-promoted cyclization of the liberated free amine employing the recently improved reaction conditions[15] (1.5 equiv DPPA, 5.0 equiv $NaHCO_3$, DMF, 0.008 M, pH 7, 0°C, 72 h, 58%) provided the cyclic tripeptide **30**. Final hydrolysis of the C-15 methyl ester (LiOH, THF:H_2O:MeOH, 25°C, 88%) followed by C-9 amine deprotection (H_2, 10% Pd-C, THF, 25°C, 93%) provided OF4949-IV[16] identical in all comparable respects to natural[3] material. Similarly, *O*-methylation of **30** (CH_2N_2, Et_2O, 0°C) followed by C-15 methyl ester hydrolysis (LiOH, THF:H_2O:MeOH, 25°C, 92%) and C-9 amine deprotection (H_2, 10% Pd-C, THF, 25°C, 95%) provided OF4949-III[17] identical in all comparable respects to natural[3] and synthetic[6] material.

As a consequence of the unanticipated effect an aryl C-4 alkoxy substituent had on the rate of the K-13 macrocyclization,[6c] a series of OF4949-related substrates **32-35** were prepared. The relative rates of macrocyclization of **29**, **32-35** were compared experimentally with the intent of defining the C^{10}-N^{11} macrocyclization rate effects due to the presence and nature of the aryl C-4 substituent, the C-9 substituent, and the C-15 substituent. Consistent with our prior observations,[6c] the presence of a C-4 free phenol as well as the nature and presence of a C-9 and C-15 substituent had *no* substantial effect on the rate of the macrocyclization reaction with C^{10}-N^{11} amide bond closure [k_{rel}: **32** (1.0), **33** (0.98), **29** (0.92), Figure 1].

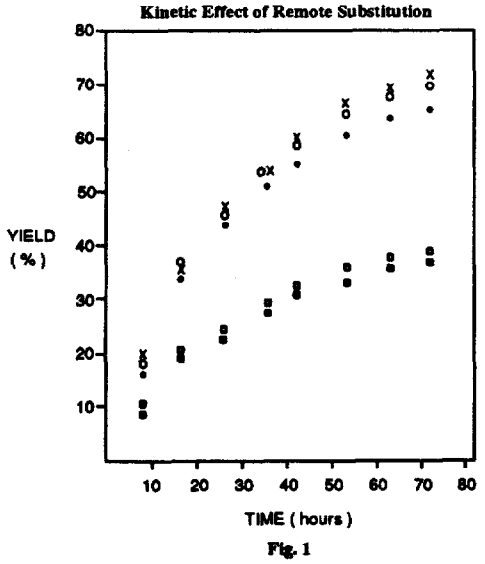
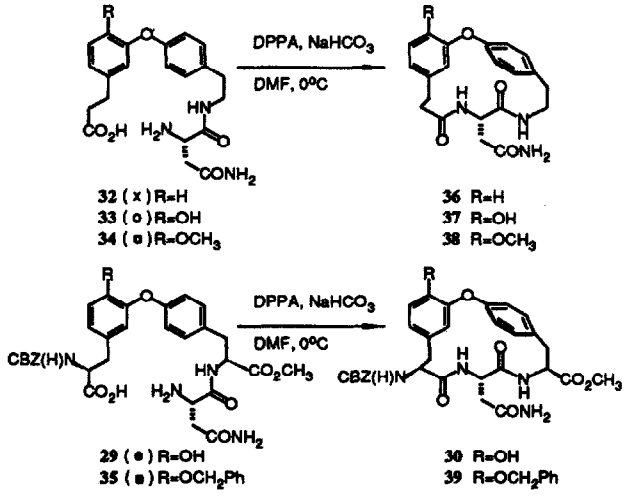


Fig. 1



In addition and as anticipated, the presence of a C-4 benzyloxy substituent in substrates lacking or possessing both a C-9 and C-15 substituent exhibited a substantial rate deceleration of the macrocyclization reaction that may be attributed exclusively to the presence of the aryl C-4 alkoxy substituent [k_{rel}: **34** (0.54), **35** (0.51), Figure 1].

Studies to unambiguously establish the conformational origin of the aryl C-4 alkoxy substituent rate deceleration of the OF4949 macrocyclization and the related K-13 macrocyclization reactions,[6c] the application of these observations in the total syntheses of functional analogs of OF4949-I - OF4949-IV, and their extension to the total syntheses of piperazinomycin and deoxybourvardin are in progress and will be reported in due course.

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16. For **2**: mp 209-212°C dec (MeOH); $[\alpha]_D$ -43° (c 1.1, 0.1 N HCl); ^{1}H NMR (D_2O, 300 MHz, ppm) 7.34 (dd, 1H, J = 1.5, 8 Hz, aryl C-H), 7.21 (dd, 1H, J = 1.5, 8 Hz, aryl C-H), 7.09 (dd, 1H, J = 1, 8 Hz, aryl C-H), 6.86 (dd, 1H, J = 1, 8 Hz, aryl C-H), 6.78 (dd, 1H, J = 1, 8 Hz, aryl C-H), 6.69 (d, 1H, J = 8 Hz, aryl C-H), 5.80 (s, 1H, C_{5a}-H), 4.73-4.30 (m, 3H, $C_2^{Asn,1,2}$-H), 3.40 (dd, 1H, J = 3, 12 Hz, C_3^1-HH), 2.96 (d, 1H, J = 14 Hz, C_3^2-HH), 2.90 (dd, 1H, J = 5, 14 Hz, C_3^2-HH), 2.84 (dd, 1H, J = 3.5, 15 Hz, C_3^{Asn}-H), 2.70 (t, 1H, J = 12 Hz, C_3^1-HH); IR (KBr) ν_{max} 3577-2500, 3396, 1671, 1587, 1512, 1503, 1401, 1270, 1233, 1204, 1128, 1110, 922, 820 cm^{-1}; FABMS (glycerol-0.1 M HCl) m/e 479 (M^+ + Na), 457 (M^+ + H); HRFABMS, 456.4545 ($C_{22}H_{24}N_4O_7$ requires 456.4542).
17. Synthetic (mp 217-222°C dec) and natural OF4949-III (mp 217-225°C dec) proved indistinguishable by ^{1}H NMR (D_2O, 300 MHz), IR, and thin-layer chromatography (R_f 0.40 in 30% ammonium hydroxide/n-propanol, R_f 0.37 in EtOAc/HOAc/H_2O/n-Butanol, 1:1:1:1); for **1**: mp 217-222°C (MeOH); $[\alpha]_D$ -34° (c 1.0, 0.1N HCl); literature $[\alpha]_D$ -35° (c 1.14, 0.1N HCl)[6c] and $[\alpha]_D$ -38.2° (c 1.06, 0.1N HCl)[6a]; ^{1}H NMR (D_2O, 300 MHz, ppm) 7.40 (dd, 1H, J = 1.4, 8 Hz, aryl CH), 7.22 (dd, 1H, J = 1.4, 8 Hz, aryl CH), 7.10 (dd, 1H, J = 1, 8 Hz, aryl CH), 6.90 (dd, 1H, J = 1, 8 Hz, aryl CH), 6.79 (dd, 1H, J = 1, 8 Hz, aryl CH), 6.72 (d, 1H, J = 8 Hz, aryl CH), 5.81 (s, 1H, C_{5a}-H), 4.7-4.3 (m, 3H, $C_2^{Asn,1,2}$-H), 3.81 (s, 3H, OCH_3), 3.40 (dd, 1H, J = 3, 12 Hz, C_3^1-HH), 2.98 (d, 1H, J = 14 Hz, C_3^2-HH), 2.90 (dd, 1H, J = 5, 14 Hz, C_3^2-HH), 2.85 (dd, 1H, J = 3.5, 15 Hz, C_3^{Asn}-H), 2.70 (t, 1H, J = 12 Hz, C_3^1-HH); IR (KBr) ν_{max} 3580-2500, 3398, 1670, 1589, 1507, 1500, 1405, 1266, 1233, 1201, 1130, 1112, 925, 805 cm^{-1}; FABMS (glycerol-0.1M HCl) m/e 493 (M^+ + Na), 471 (M^+ + H); HRFABMS 470.4812 ($C_{23}H_{26}N_4O_7$ requires 470.4810).

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