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A Novel Synthesis of K-13

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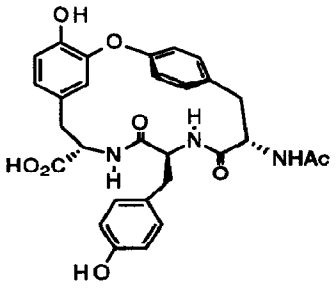
Abstract: A new and concise synthesis of 17-membered macrocyclic tripeptide K-13 is achieved featuring intramolecular S_NAr reaction as a key step.

K-13 (**1**), a potent, non competitive inhibitor of angiotensin I converting enzyme and weak inhibitor of aminopeptidase B,[1] has been isolated from *Micromonospora halophytica ssp. exilisia K-13* .[2] The characteristic feature of this cyclopeptide is the presence of the isodityrosine unit which has been found in several other biologically important natural products such as OF4949 I-IV (**2**),[3] piperazinomycin [4] and a series of bicyclic hexapeptide antitumor-antibiotics RA I-XIV.[5] Total synthesis of K-13 and OF4949 have been reported by several groups following a common linear synthetic strategy *i.e.*: Ullmann biaryl ether synthesis, elaboration of the biaryl ether side chain and ultimate macrolactamisation.[6] The only exception is the thallium trinitrate promoted two-step sequence, developed by Yamamura *et.al*,[7] for achieving the intramolecular oxidative phenol coupling. However, the yield of the cyclisation step is lower than 15%.



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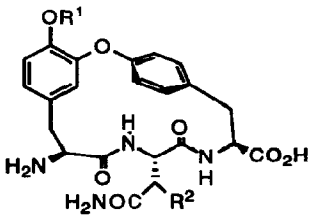
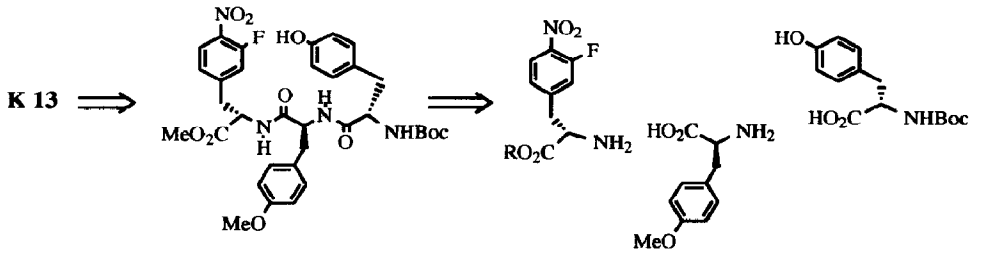


2

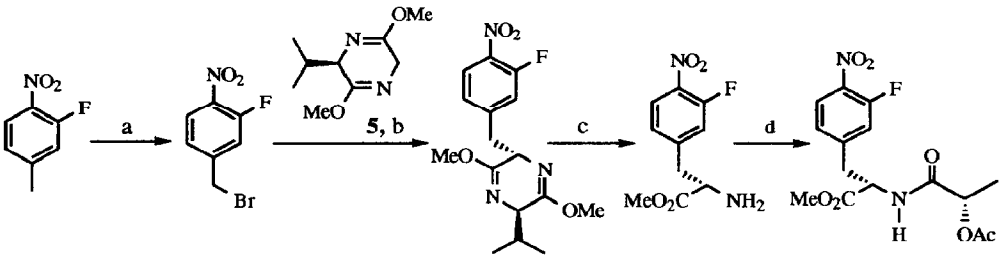
OF4949-I, R^1 = Me, R^2 = OH
OF4949-II, R^1 = H, R^2 = OH
OF4949-III, R^1 = Me, R^2 = H
OF4949-IV, R^1 = H, R^2 = H

Recently, we have reported an easy access to highly functionalized diaryl ethers using an *intermolecular* S_NAr reaction.[8] In connection with our efforts towards the synthesis of vancomycin and related antibiotics,[9] we have devised an efficient method for the preparation of a 16-membered macrocycle based on the *intramolecular* S_NAr reaction.[10] As further extension of this work, we report herein a successful implementation of this method to the preparation of a *17-membered macrocycle* and its application to the synthesis of K-13 (**1**) as outlined in the retro-synthetic scheme.



Retro-synthetic scheme

According to our synthetic plan, the unknown L-(*S*)-3-fluoro-4-nitro-phenylalanine (**7**) was required and it was thought to prepare it by alkylation of Schöllkopf's bislactim ether **5** with 3-fluoro-4-nitro-benzylbromide (**4**).[11] The reaction of **4** with the lithium azaenolate of **5** gave only a poor yield (<10%) of alkylated product mainly due to the high acidity of benzylic protons.[12] Attempts to switch the reaction course from the S_N2 to the radical anion mechanism[13] failed to give the coupled product **6**. However, when the lithium anion of **5** was transmetalated into a higher order organocuprate,[14] compound **6** could be reproducibly isolated in 40-50% yield. This is quite satisfactory considering the poor reactivity of *p*-nitrobenzyl halides towards nucleophiles under S_N2 condition.[15] Hydrolysis of **6** under acidic conditions afforded the desired amino acid **7**[16] in 91% yield. The *S* configuration of **7** was taken for granted from the known alkylation mechanism.[11] The optical purity of **7** was probed by conversion to the corresponding (*S*)-lactate **8**, the ^1H NMR and GC/Ms spectra of which showed that the optical purity of **7** was higher than 95%.

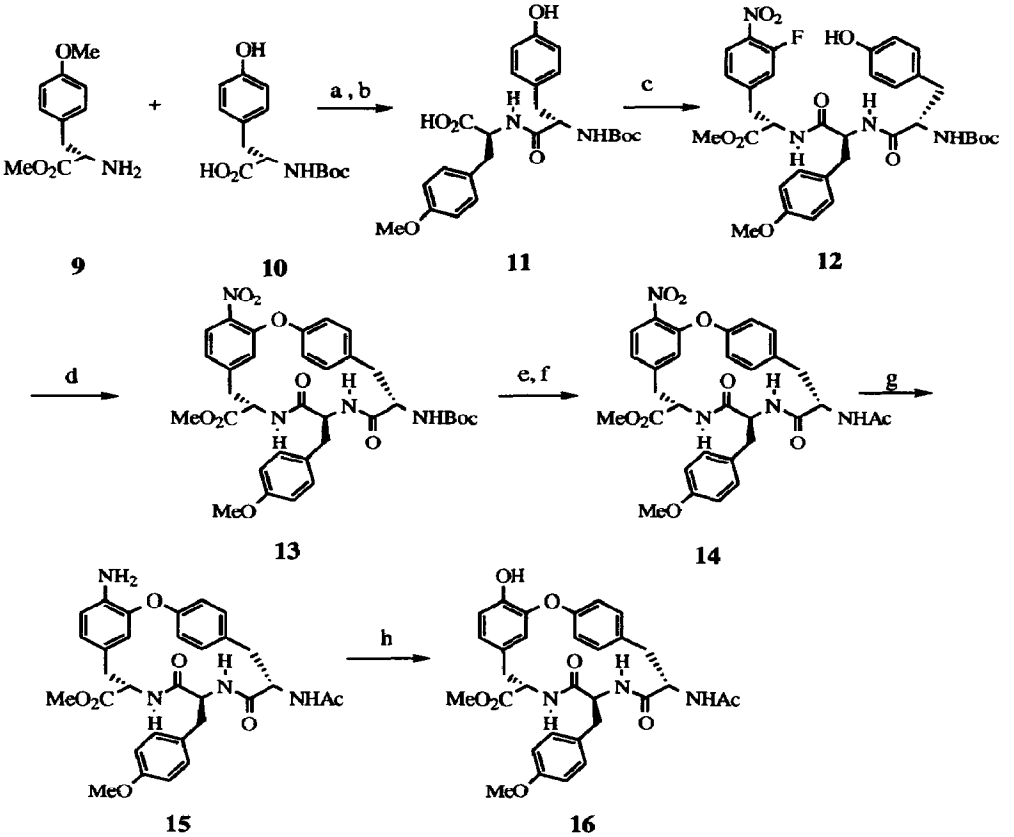


3 **4** **6** **7** **8**

Reagents and conditions: a) NBS, $(PhCOO)_2$, CCl_4, reflux, 54%; b) ^nBuLi, CuCN, THF, -20°C, 50%; c) HCl, 0.25N, THF-MeCN, rt, 91%; d) (*S*)-Me(MeCOO)CHCOCl, Et_3N, DMAP, CH_2Cl_2, rt, 100%

The other two fragments **9** and **10** were prepared from L-(*S*)-tyrosine following standard group protection procedures. Having the required building blocks in hand, the tripeptide **12** was easily prepared. Coupling of the dipeptide **11**, obtained by condensation of **9** and **10**, with amino acid **7**, using 1-[3'-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC) and hydroxybenzotriazole (HOBt), furnished the macrocycle precursor **12** in 80% isolated yield. It is worth noting that the fluoro containing tripeptide **12**, prepared here as a precursor for the macrocyclisation studies, is of interest on its own right for its potential biological activity.[17]

When the linear tripeptide **12** was submitted to our previously established macrocyclisation conditions (K_2CO_3, DMF, 0.02M, rt, 4hrs),[10] the 17-membered cyclic peptide **13** was obtained in 87% isolated yield. Spectral data of **13**[18] were consistent with the macrocyclic compound. Its chiral homogenity was readily proven by GC analysis. The high dilution technique was not needed and possible side products derived from dimerisation or from O- and N-transacylation[19] were not observed. Mild acid hydrolysis of the *tert*-butyloxycarbonyl carbamate (Boc) followed by conventional acetylation and reduction of the nitro group provided the amine **15** in 60% overall yield. Diazotization (HBF_4, ^{t}BuONO, MeOH) and subsequent oxidative hydrolysis of the diazonium salt using $Cu(NO_3)_2.3H_2O$ and Cu_2O afforded the protected K-13 **16** [$[\alpha]_D$ = -14 (*c* 0.16, MeOH)] in 74% yield. The structure of **16** was unequivocally determined on the basis of ^{1}H NMR, ^{13}C NMR as well as HRMS (calc. for $C_{31}H_{33}N_3O_8$: 575.2268; found: 575.2305) spectra. Demethylation of **16** to natural K-13 (**1**) has already been reported by Evans' group[6b].



Reagents and conditions: a) DCC, HOBt, CH_2Cl_2-THF, rt, 60%; b) K_2CO_3, MeOH-H_2O, 100%; c) **7**, DCC, HOBt, CH_2Cl_2-THF, 82%; d) K_2CO_3, 0.02M in DMF, rt, 87%; e) TFA, rt; f) $NaHCO_3$, Ac_2O, CH_2Cl_2, rt, 83%; g) H_2, Pd/C, MeOH, HCl, 85%; h) HBF_4, ^{t}BuONO, MeOH,0°C then $Cu(NO_3)_2.3H_2O$, Cu_2O, H_2O, rt, 74%.

In conclusion, we have developed a concise synthesis of K-13 and demonstrated the usefulness of the intramolecular S_NAr reaction to the synthesis of 17 membered macrocycle. Further extension of this work to the syntheses of other structurally related natural products is in progress.

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(18) **13**. mp: 224-225; $[\alpha]_D$ = -8 (*c* 0.64, $CHCl_3$); IR (ν_{max}): 1744, 1706, 1613, 1594, 1512, 1500 cm^{-1}; ms (m/z): 662, 546; ^1H NMR ($CDCl_3$, 200 Hz): δ 1.45 (9H, s, ^tBu), 2.67 (1H, dd, *J* = 9.6 and 13.1 Hz), 2.82 (1H, t, *J* = 8 Hz), 2.98 (1H, dd, *J* = 4.5 and 13.1 Hz), 3.17 (1H, dd, *J* = 5.1 and 11.9 Hz), 3.26 (1H, dd, *J* = 3.8 and 13.9 Hz), 3.43 (1H, dd, *J* = 4.8 and 14.5 Hz), 3.7 (3H, s, OMe), 3.74 (3H, s, OMe), 3.93 (1H, m), 4.2 (1H, m), 4.36 (1H, dd, *J* = 4.3 and 4.6 Hz), 5.32 (1H, d, *J* = 7.9 Hz, NH), 5.4 (1H, d, *J* = 4.7 Hz), 6.2 (1H, d, *J* = 5.3 Hz, NH), 6.28 (1H, s), 6.63 (1H, d, *J* = 8.3 Hz), 6.75 (2H, d, *J* = 8.5 Hz), 6.81 (1H, dd, *J* = 8.3 and 2.41 Hz), 7.02 (2H, d, *J* = 8.5 Hz), 7.15 (2H, d, *J* = 8.07 Hz), 7.33 (1H, d, *J* = 8.3 Hz), 7.77 (1H, d, *J* = 8.3 Hz) ^{13}C NMR ($CDCl_3$, 50.03 MHz): δ 28.5, 34.1, 35.9, 38.9, 39.6, 49.3, 52.8, 53.3, 55.3, 56.3, 80.2, 114.2, 119.9, 121.0, 122.3, 122.8, 125.6, 130.2, 132.0, 134.0, 142.9, 154.2, 158.9, 170.0, 170.6
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