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An efficient total synthesis of K-13, a non-competitive inhibitor of ACE I

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Abstract

An efficient synthesis of K-13, a non-competitive inhibitor of ACE I, with an *endo* biaryl ether bond is described. The key cycloetherification reaction of linear tripeptide **10** gave 17-membered macrocycle in quantitative yield.

K-13 (**1**, Fig. 1), a 17-membered cyclopeptide with an *endo* aryl–aryl ether bond, has been isolated from *Micromonospora halophytica ssp. exilisia K-13*.[1] It is a non-competitive inhibitor of angiotensin I converting enzyme and weak inhibitor of aminopeptidase B.[2] The characteristic feature of this cyclopeptide is the presence of the isodityrosine unit (**2**) which has been found in several other biologically important natural products such as OF4949 I–IV,[3] piperazinomycin[4] and a series of bicyclic hexapeptide antitumor-antibiotics RA I–XIV.[5] Total synthesis of K-13 has been reported by a number of research groups, most of them employing a macrolactamization strategy through the preparation of a key isodityrosine intermediate (**2**).[6] The synthesis of (**2**) is nevertheless troublesome and requires linear multistep sequence since direct coupling of two tyrosine unit proved to be difficult.[7] On the other hand, synthesis of K-13 via cycloetherification reaction has also been developed which appears to be more convergent as the cyclization precursor can be prepared in only two conventional peptide coupling steps.[8] Indeed, three such syntheses have been accomplished using thallium trinitrate promoted oxidative cyclization and intramolecular S_NAr reaction, respectively.[9–11]

The nitro group played a pivotal role in our S_NAr based cycloetherification methodology.[12] Its dual role as an activator for the cyclization and as a handle for post-manipulation has been fully demonstrated. In our previous synthesis of K-13 based on this strategy,[10] the nitro was used as a surrogate of hydroxy function (Scheme 1, route a). Although the cyclization worked efficiently, its conversion to hydroxylated derivative via amino intermediate was less than satisfactory in terms of reproducibility. Based on the consideration that hydro-dediazoniation works better than

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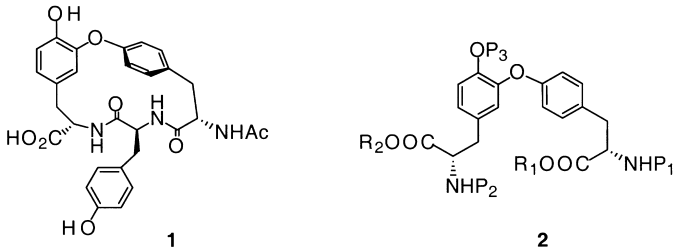
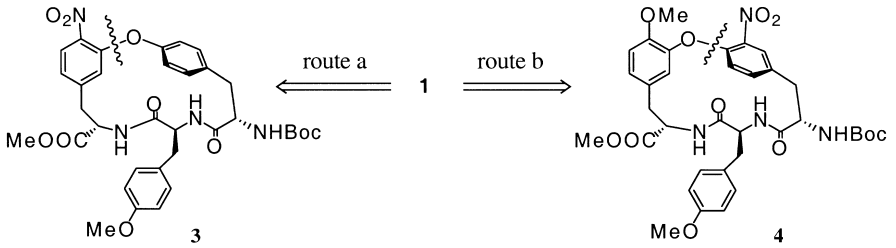


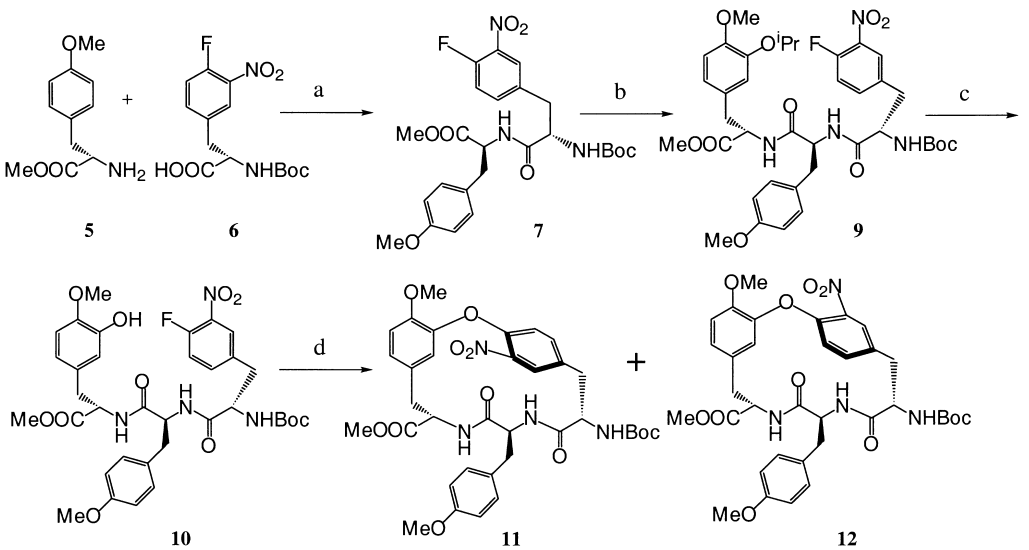
Figure 1.

hydroxylation of diazonium salt,[13] an alternative synthesis of K-13 using NO_2 as proton surrogate (Scheme 1, route b) was investigated and is the subject of the present communication.

Coupling of L-methyl 4-methoxyphenyl alanate (**5**) with L-*N*-Boc 4-fluoro-3-nitrophenylalanine (**6**)[14] gave the dipeptide **7** which after hydrolysis of methyl ester, was reacted with L-methyl 4-methoxy-3-isopropyloxyphenyl alanate (**8**)[13] to afford the tripeptide **9** (Scheme 2). Deprotection of isopropyloxy ether with BCl_3 caused partial removal of the *N*-Boc moiety. However, treatment



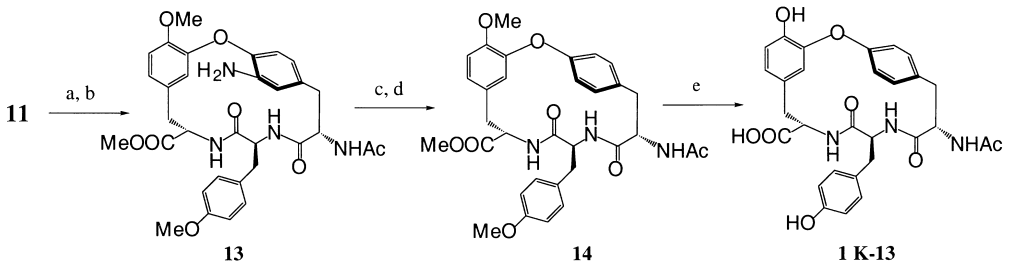
Scheme 1.



Scheme 2. *Reagents and conditions*: (a) EDC, HOBt, 85%; (b) (i) LiOH, THF–H_2O; (ii) EDC, HOBt, methyl 3-methoxy-4-isopropyloxyphenyl alanate (**8**), 90%; (c) (i) BCl_3, (ii) Boc_2O, 95%; (d) K_2CO_3 (3 equiv.), DMSO, 0.01 M, rt, 99%

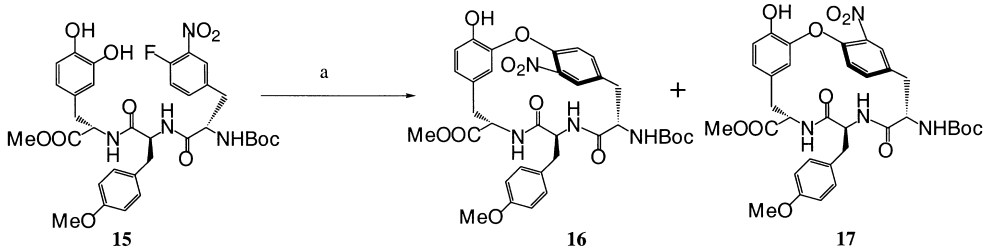
of the crude product with Boc_2O under standard conditions reinstalled the *N*-Boc function, providing **10** in excellent yield. Treatment of tripeptide **10** with K_2CO_3 in DMF at room temperature for 24 h did not afford any cyclic compound and only starting material was recovered. However, by simply switching to the more polar solvent DMSO,[13,15] the cyclization occurred smoothly to provide the 17-membered macrocycle as a mixture of two atropoisomers **11** and **12** (ratio: 1:1) in quantitative yield.

Mild acid hydrolysis of the *tert*-butyloxycarbonyl carbamate (Boc) followed by acetylation and reduction of the nitro group (Pd/C, H_2, MeOH, HBF_4) provided the amine **13** (Scheme 3). Hydrogenolysis must be carried out in an acidic media in order to avoid decomposition of **13** and HBF_4 was selected in order to keep the same counterion as in the subsequent diazotization step. The diazonium salt, generated in organic solvent under Cohen's conditions ($BF_3{\cdot}OEt_2$, ^{t}BuONO),[16] was then reduced with $FeSO_4$ in DMF[17] to afford the known compound **14**[6b] in 85% overall yield. Demethylation of **14** with $AlBr_3$ in the presence of EtSH[6b,18] afforded K-13 (**1**). The same synthetic sequence applied to compound **12** also afforded K-13 identical with that obtained from **11** with equal efficiency, thus firmly establishing the atropoisomerism of compounds **11** and **12**. The physical and spectroscopic data of our synthetic material are identical with those of the natural product.[19]



Scheme 3. *Reagents and conditions*: (a) (i) TFA, rt; (ii) Ac_2O, $NaHCO_3$, THF, 100%; (b) Pd/C, H_2, MeOH, few drops of HBF_4, 85%; (c) ^{t}BuONO, $BF_3{\cdot}OEt_2$, CH_2Cl_2, –10 to 0°C; (d) $FeSO_4$, degassed DMF, 85%; (e) $AlBr_3$, EtSH, 65%

Finally, cyclization of **15** containing two potentially nucleophilic hydroxy functions gave only the 17-membered *m*,*p*-cyclophane as a mixture of two atropoisomers without the concomitant formation of 18-membered *p*,*p*-cyclophane (Scheme 4).[20] A similar ring size selective cyclization has been observed in our synthesis of cycloisodityrosine.[13] The merit of this approach is that commercially available L-dopamine can be used instead of a side chain selectively protected dopamine derivative **8** whose synthesis requires five steps in the, until now, shortest synthesis.[21]



Scheme 4. [a]K_2CO_3 (4 equiv.), DMSO, 0.002 M, rt, molecular seive 3 Å, 45%

The total synthesis of K-13 reported herein is one of the most efficient syntheses known to date in terms of the overall yield and the convergency.

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19. Synthetic K-13 (**1**): mp: 265–270°C dec. (Ref. 2 265–270°C dec.); $[\alpha]_D = -6.0°$ (*c* 0.40, MeOH; Ref. 6b $[\alpha]_D = -6.5°$, *c* 0.46, MeOH; natural:[2] $[\alpha]_D = -3.4°$, *c* 0.60, MeOH; MS (FAB thioglycerol): 548 (M+H); ^{1}H NMR (300 MHz, CD_3OD) δ 2.03 (s, 3H), 2.78 (t, $J = 12.1$ Hz, 2H), 2.82–2.98 (m, 2H), 3.01 (dd, $J = 5.1$, 12.3 Hz, 1H), 3.18 (m, 1H), 4.10–4.20 (m, 2H), 4.44 (dd, $J = 5.0$, 11.6 Hz, 1H), 6.35 (d, $J = 1.9$ Hz, 1H), 6.59 (d, $J = 8.4$ Hz, 2H), 6.64 (dd, $J = 2.5$, 8.3 Hz, 1H), 6.73 (dd, $J = 1.9$, 8.2 Hz, 1H), 6.81 (d, $J = 8.2$ Hz, 1H), 6.95 (m, 3H), 7.03 (dd, $J = 2.5$, 8.3 Hz,

1H), 7.29 (dd, $J = 2.1$, 8.2 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 22.4, 37.3, 38.7, 39.1, 56.0, 56.1, 57.4, 115.9 (2C), 117.3, 119.1, 121.1, 122.3, 125.5, 128.3, 131.2, 131.4, 132.0 (2C), 132.1, 132.9, 147.2, 147.9, 157.0, 158.1, 171.1, 172.2, 172.9, 178.1.

20. No acyclic or cyclic dimer was isolable which nevertheless did not exclude the possible formation of oligomers.
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