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An Easy Access to Functionalized Diaryl Ethers: Formal Total Synthesis of K-13

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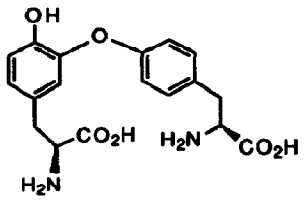
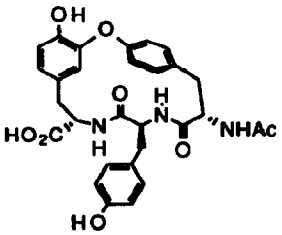
Abstract: As an alternative to the Ullmann ether synthesis, the S_NAr reaction led to an efficient one step synthesis of chiral bis-aminoacid diaryl ethers, important intermediates in the synthesis of K-13.

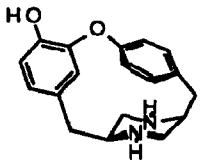
In numerous biological active metabolic products of fungi and bacteria, diamino dicarboxylic acids have been found as characteristic building blocks. Isodityrosine (**1**) (Figure 1),[1] in which two tyrosine units are linked through an unsymmetrical diphenyl ether bond, has been found in a number of natural products such as K-13 (**2**),[2] OF4949 I-IV,[3] piperazinomycin (**3**)[4] and a series of bicyclic hexapeptide antitumor-antibiotics RA I-XIV.[5] Different strategies have been developed for the synthesis of isodityrosine in studies related to the total synthesis of above mentioned macrocyclic peptides.[6] However, direct coupling of two tyrosine units to the isodityrosine has never been achieved[6c] due to the incompatibility of amino acid functionalities with the harsh reaction conditions required for constructing the diaryl ether bond.



1 Isodityrosine



2 K 13

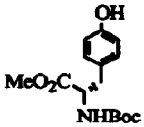
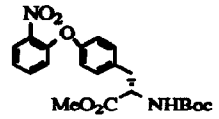
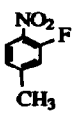
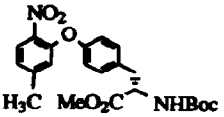
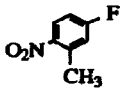
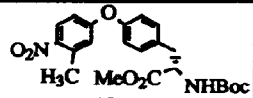
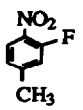
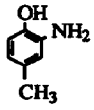
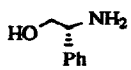
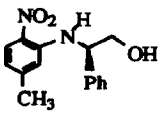
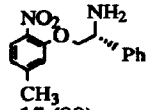


3 Piperazinomycin

Figure 1

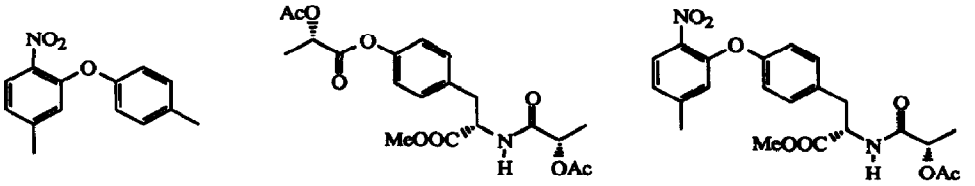
Recently, we reported a facile synthesis of triaryl diethers[7] based on the S_NAr reaction of methyl gallate with *ortho* nitro substituted aryl fluoride[8]. The nitro function was carefully selected because it can be used not only as an activating group but also as a surrogate of a range of functional groups. While the S_NAr reaction has been thoroughly studied, the application to the synthesis of optically active compounds is lacking. We feel that the mild conditions of this reaction may well be amenable to the synthesis of more complex diaryl ether compounds and in this letter, we wish to report an easy access to chiral diaryl ethers using this reaction and its application to the formal total synthesis of K-13.

Table1: Preparation of Diaryl Ethers

Entry	Electrophile	Nucleophile	Solvent	Base (eq.)	Time (h)	Products (yield%)
						
1	4	5	DMF	K_2CO_3	8	6 (70)
2			DMF	CsF	8	6 (70)
3			CH_3CN	K_2CO_3	48	6 (70)
						
4	7	5	DMF	K_2CO_3	8	8 (80)
						
5	9	5	DMF	K_2CO_3	8	10 (80)
						
6	7	11	DMF	K_2CO_3	168	12 (70)
7			DMF	NaH	2	12 (76)
						
8	7	13	DMF	K_2CO_3	24	14 (80)
						
9	7	13	DMF	NaH	24	15 (80)

As a starting point, we first examined the condensation of N-Boc-L-(*S*)-tyrosine-methyl ester (**5**) with 1-fluoro-2-nitrobenzene (**4**)[9] (Table 1, entry 1). In DMF at room temperature in the presence of two equivalents of K_2CO_3, diaryl ether **6** was obtained in 70% isolated yield after a 8 hrs reaction time. Comparable result was obtained when CsF[10] was used as base (entry 2) instead of K_2CO_3. While the coupling proceeded in acetonitrile (entry 3), the time required to complete the reaction was lengthened significantly (48 hrs). Thus, DMF-K_2CO_3 (2 eq) were used as a standard conditions for other coupling reactions. As can be seen from table 1, both *ortho* or *para* nitro substituted fluorotoluene participate in the coupling reactions with **5** to give desired product **8** or **10** in good yields (entries 4, 5).

Variations on the nucleophilic component further demonstrated the versatility of this reaction. The reaction of 3-fluoro-4-nitrotoluene (**7**) with 2-amino-*p*-cresol (**11**) afforded exclusively O-arylated product **12** regardless of the base (K_2CO_3 or NaH) used (entries 6 and 7), in accordance with the more facile deprotonation of phenolic OH to give the nucleophilic aryloxide. That the coupling product obtained is O- rather than N-arylated is readily proved by converting it into **16** via standard dediazonization[11] (Figure 2). With aliphatic amino alcohol, either O- or N-arylated products could be prepared depending on the strength of the base used. Thus, coupling of **7** with D-(*R*)-phenylglycinol (**13**) gave exclusively N-arylated product **14** in the presence of K_2CO_3 (entry 8) and O-arylated product **15** when a strong base such as NaH was employed (entry 9) . This chemoselectivity is consistent with the greater nucleophilicity of amine *vs* alcohol and the alkoxide *vs* amine.



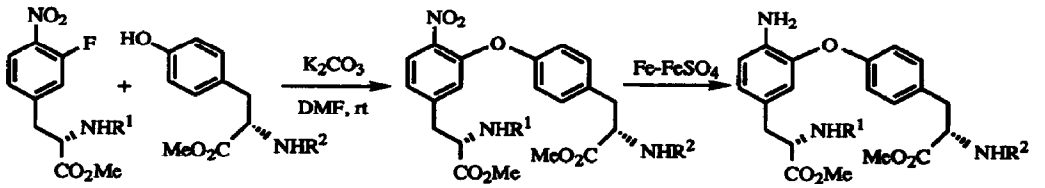
16 **17** **18**

Figure 2

To address the racemisation problem, both **5** and **6** were transformed into (*S*)-lactamides **17** and **18** (Figure 2) *via* a two step sequence [*i*: TFA ; *ii*: (*S*)-Me(OAc)CHCOCl, Et_3N, DMAP]. In order to facilitate the identification of diastereoisomeric peak, (±)-**5** and (±)-**6** were also prepared and transformed into the corresponding (*S*)-lactamides. ^1H NMR as well as GC analysis of these derivatives revealed that no detectable racemisation occured (**17**: ee 92% and **18** ee: 92%) within experimental errors.

The reaction conditions thus established were applied to the synthesis of K-13 (Scheme 1). We first prepared the unknown L-(*S*)-3-fluoro-4-nitro-phenylalanine derivatives **19a-c**[12] by alkylation of Schöllkopf's bislactim ether[13] with 3-fluoro-4-nitro-benzylbromide followed by hydrolysis and standard protection procedure. Much to our delight, coupling of **19** with L-tyrosine derivatives **5** and **20** smoothly gave the desired products **21a-d** in high yield. The presence of free amino group in **19a** did not alter the reaction course, consistently with the above observation (*vide supra*). Reduction of nitro to amine with Fe-$FeSO_4$[7] gave amino compounds **22**. Since this type of biaryl ether has been converted into K-13 (**1**) by Rama Rao's group,[6d] our work constitutes a formal total synthesis of this natural product.

In summary, an efficient alternative to the Ullmann ether synthesis has been developed. The mild conditions allowed for the first time a one step synthesis of L,L-isodityrosine unit **21**. Conditions leading either to O-arylation or N-arylation of amino alcohol have also been delineated and may find application in the synthesis of new chiral ligands.



19a R^1 = H **19b** R^1 = Boc **19c** R^1 = Ac

5 R^2 = Boc **20** R^2 = Ac

21a R^1 = H, R^2 = Boc, 80%
21b R^1 = R^2 = Boc, 80%
21c R^1 = Ac, R^2 = Boc, 80%
21d R^1 = R^2 = Ac, 80%

22 d → ref 6d → **K-13**

Scheme 1

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