Pergamon

Tetrahedron Letters, Vol. 38, No. 25, pp. 4405-4406, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00941-6

The First Synthesis of a 15-Membered Macrocycle. Model of Ring I of Kistamycin

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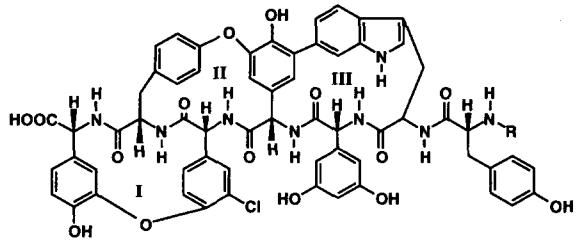
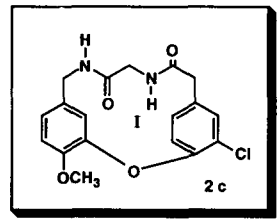
Abstract : The intramolecular S_NAr reaction of a linear peptid precursor, whose termini carry respectively an ortho fluoro-nitro group and a phenol function, gives the 15-membered ring compound in good yield, under mild conditions.

Kistamicins A and B **1** are produced by *Microtetraspora parvasata* subsp. *kistanae*. They exibit moderate *in vitro* antibactarial activity against Gram-positive bacteria, and antiviral activity against type A influenza virus.[1]



1a Kistamicine A R=H
1b Kistamicine B R=CO-NH-CH_2-CH_2-C_6H_5



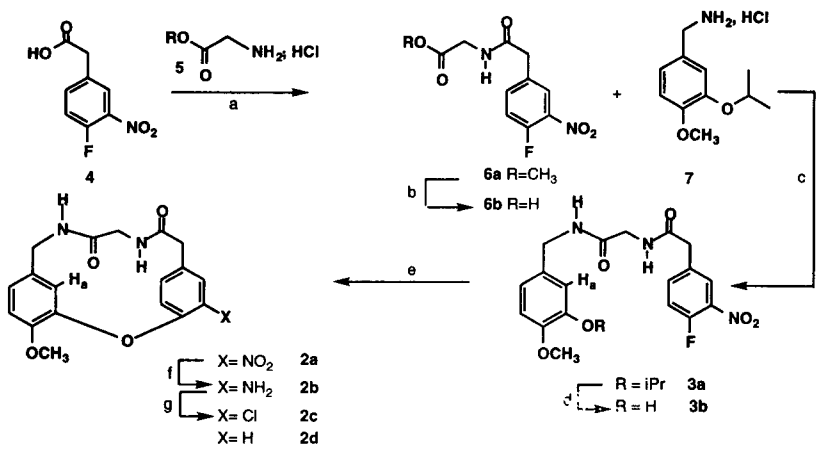
2c

There is in the literature no report on the synthesis of this compound whose left part of the structure is characterised by a 15-membered ring I, fused to a 16-membered one II, each containing a biaryl ether bond.

We describe now the first synthesis of a model 15- membered ring **2c**, by an extension of the S_NAr based macrocyclisation *via* biaryl ether formation.[2]

The synthesis of the linear precursor **3b**, whose nucleophilic phenol function bears a methoxy group in *ortho* position, was effected as follows. 4-Fluoro-3-nitrophenylacetic acid **4** was prepared from *p*-fluoro benzaldehyde by nitration, borohydride reduction, bromation, cyanation and hydroysis of the resulting nitrile. Coupling with glycine methyl ester hydrochloride **5**, in the presence of DCC, gave **6b** (93%) after hydrolysis of the corresponding methyl ester **6a**. 3-Isopropoxy-4-methoxy-benzylamine hydrochloride **7**, was prepared in three steps by standard methods from commercially available isovaniline protected as isopropyl ether, conversion of the aldehyde into nitrile by sodium azide in the presence of aluminium chloride,[3] BH_3 reduction, and hydrochloride formation. Coupling of **6b** with **7** in the presence of DCC gave the peptidic chain **3a** whose phenol function was deprotected by BCl_3 to give the precursor **3b**, ready for macrocyclisation (Scheme 1).

Submitted to well established cyclization conditions (0.01M in DMF, K_2CO_3, r.t.) **3b** gave the 15-membered nitro-macrocycle **2a** (86%) in pure form. Compared with previously reported macrocyclisation this intramolecular S_NAr reaction was slow (24h) and, as reported in other cases,[2b] the reaction time became significantly shorter (8h) by addition of 18-crown-6-ether, to give **2a** in 91% yield (Mass spectrum: m/z 378 [M+Li]; ^1H NMR: characteristic H_a upfield shift, δ=5.30 ppm in the cyclised compound, compared with δ= 6.69 ppm in the open chain precursor **3b**.



a: DCC, HOBT/DMF, 93%; b: K_2CO_3 / MeOH, 94%; c: DCC, HOBT, NEt_3 / DMF, 80%; d: BCl_3 / CH_2Cl_2, 0 °C, 92%; e: K_2CO_3 / DMF 24 h, 86%; f: H_2, Pd/C / MeOH, 94%; g: $NaNO_2$, HCl, CuCl/$CuCl_2$, / CH_3COOH, 57%

Scheme 1

The high yields observed resulted from a favorable conformation of **3b**, in accordance with a computational simulation which revealed that the two active sites (OH and C_F) involved in the intramolecular biaryl ether formation, are within 4.86 Å resulting in low activation energy (-187.5 KJ/mol) and favorable entropy for cyclisation.

Catalytic hydrogenation of **2a** gave the corresponding amino derivative **2b** (94%), deamination of which in degassed solvent under modified Sandmeyer conditions[4] led to the expected chloro compound **2c** (57%), easily separated from the reduction product **2d** (37%).

Conclusion

The first synthesis of a 15-membered ring compound, model of ring I of kistamycin, has been achieved, demonstrating the usefulness and the generality of the S_NAr methodology for the synthesis of polypeptidic macrocycles containing a biaryl ether linkage.

Acknowledgement : A doctoral fellowship to E. González Zamora from UAM-I, (Universidad Autonoma Metropolitana-Iztapalapa, Mexico-City), is gratefully acknowledged.

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(*Received in France* 10 *March* 1997; *accepted* 7 *May* 1997)