Pergamon

Tetrahedron Letters, Vol. 38, No. 47, pp. 8189-8192, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10217-9

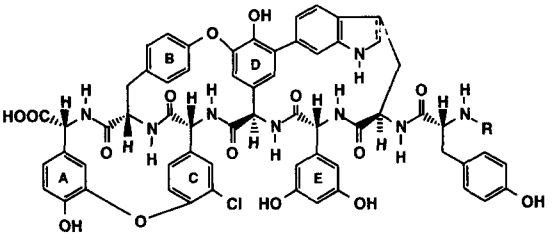
The First Synthesis of 16+15-Membered Bicyclic Polypeptide Model of A-O-C-B-O-D Rings of Kistamicin

René Beugelmans, Eduardo González Zamora and Georges Roussi*

Institut de Chimie des Substances Naturelles, CNRS, 91198, Gif-sur-Yvette, France

Abstract : A 16+15 membered bicyclic polypeptide containing biaryl ether bonds, model of A-O-C-B-O-D rings of kistamicin has been synthesized by sequential intramolecular SN_{Ar} reactions.

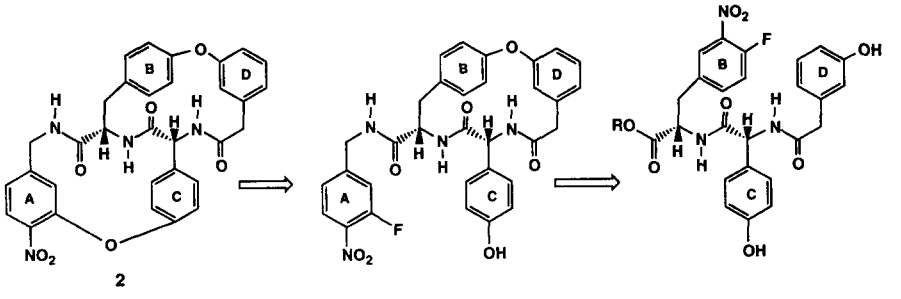
The recently isolated Kistamicins A and B **1a,b** are produced by *Microtetraspora parvasaeta* subsp. *kistnae* and were found to exibit type A influenza virus inhibition, and moderate *in vitro* antibacterial activity against Gram-positive bacteria.[1] Structurally, these polypeptidic compounds are characterized by a 16-membered **B-O-D** ring fused to a 15-membered **A-O-C** one each containing a biaryl ether bond, and by a 17-membered ring linked to the central amino acid **D** by a carbon-carbon bond. In our continuing effort toward the synthesis of these compounds,[2] we describe here the first synthesis of a model of the bicyclic left part **A-O-C-B-O-D** which is common to kistamicins A and B (Figure 1).



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

Figure 1

The synthesis of the bicyclic ring system **2** was planned by a strategy based upon a sequence of intramolecular SN_{Ar} reactions for ring closure of the 16-membered **B-O-D** ring [3,4] and then of the fused 15-membered one **A-O-C** (Scheme 1).



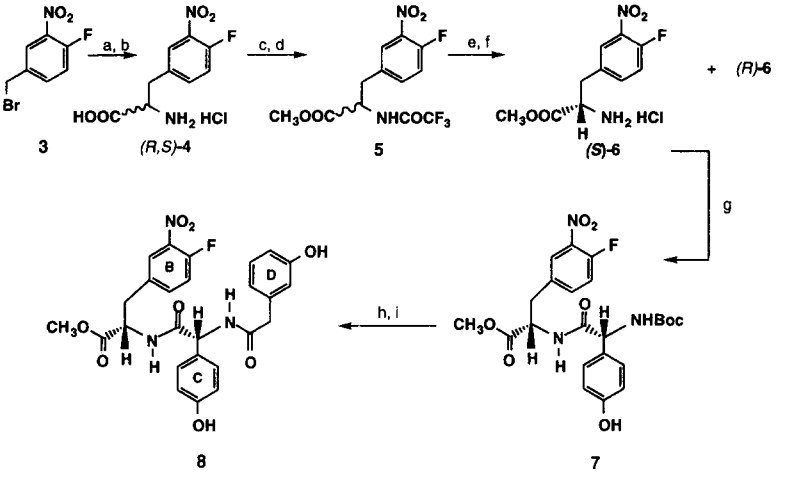
2

Scheme 1

Fax:{33} (01) 69 07 72 47. E-mail: Georges.Roussi@icsn.cnrs-gif.fr

For the synthesis of the 16-membered **B**-O-**D** ring **9**, the non proteinogenic *(S)*-4-fluoro-3-nitrophenylalanine amino acid **6** was required. It was obtained in enantiomerically pure form as the methyl ester *via* enzymatic resolution of the corresponding trifluoroacetates **5** [5], prepared in quantitative yield by conventional procedure from 4-fluoro-3-nitro-benzylbromide **3** treated with diethyl acetamidomalonate in the presence of sodium hydride and then with HCl. Coupling of *(S)*-**6** with *(R)*-4-hydroxyphenylglycine protected as a NHBoc derivative afforded the peptide **7** [6] (77%). Deprotection under mild acidic conditions followed by coupling with 3-hydroxyphenylacetic acid provided **8** in high yield (89%), (Scheme 2).

The phenol group of amino acid **C** was not protected, based upon a computational simulation which revealed that for the minimal activation energy (-202 KJ/mol), the active sites C_F and OH_{para} involved in ring closure of the linear precursor **8** leading to the 16-membered ring **9** were situated at 4.55 Å, while C_F and OH_{meta} which could react competitively to give the 14-membered ring compound **12** were at 6.62 Å (Scheme 3).

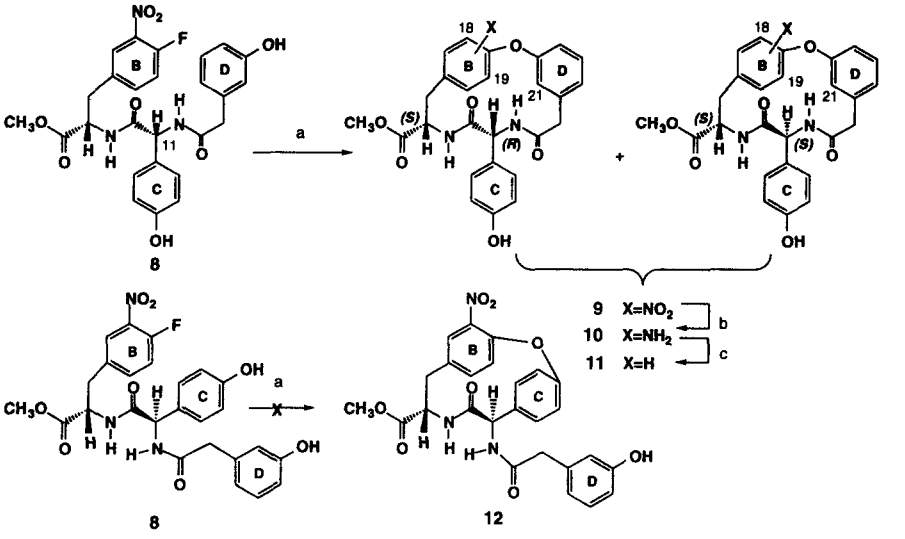


Reagents and conditions: a) $C_2H_5OOCCH(NHAc)COOC_2H_5$/NaH/DMF, 98 %; b) HCl, 96 %; c) $SOCl_2$/MeOH, 97 %; d) NEt_3/CH_2Cl_2 $(CF_3CO)_2O$, 97 %; e) Protease type VIII-A from *Bacillus Licheniformis*/phosphate phosphate buffer pH=7.5/CH_2Cl_2; f) $SOCl_2$/MeOH, 0°C, 42 % ; g) NEt_3/CH_2Cl_2, *p*-hydroxyphenylglycine-NHBoc/EDC/HOBt, 77 %; h) TFA/CH_2Cl_2; i) NEt_3/CH_2Cl_2 3-hydroxyphenylacetic acid/EDC/HOBt, 89 %

Scheme 2

A 0.01 M solution of the linear tripeptide **8** in various solvents (DMF, THF, DMSO) was treated at room temperature in the presence of 18-crown-ether by K_2CO_3 or $KHCO_3$ as base. Under the best conditions ($KHCO_3$, DMF), the macrocyclisation was complete after 6-8 hours, yielding four cyclised products in 75% isolated yield. By preparative thin layer chromatography *(S,R)*-**9A**, *(S,R)*-**9B**, *(S,S)*-**9B** were obtained in pure form, while *(S,S)*-**9A** could not be separated from *(S,S)*-**9B**. All are 16-membered ring macrocycles, as evidenced by their ^1H NMR spectra.[7] The formation of this mixture of four products resulted from two distinct processes: i) epimerization at C_{11} the chiral center of amino acid **C** affording a mixture of diastereoisomers *(S,R/S,)*=60/40) even under the minimal basic conditions required for macrocyclisation, ii) creation of a chiral axial center leading to atropoisomers **A** (X=18-NO_2) and **B** (X=19-NO_2), (**A/B**= 1).

The lack of atroposelectivity is of no consequence, as chiral planarity will be destroyed by removal of the activating nitro group at the next stage of the synthesis. Reduction (Pd in MeOH) of pure *(S,R)*-**9A** or *(S,R)*-**9B** gave the corresponding amino derivatives *(S,R)*-**10A** or *(S,R)*-**10B** whose reductive deamination[8] afforded an identical compound *(S,R)*-**11** devoid of axial asymetry. By the same sequence, the atropomeric mixture *(S,S)*-**9A,B** or pure *(S,S)*-**9A** led to *(S,S)*-**11** (Scheme 3).

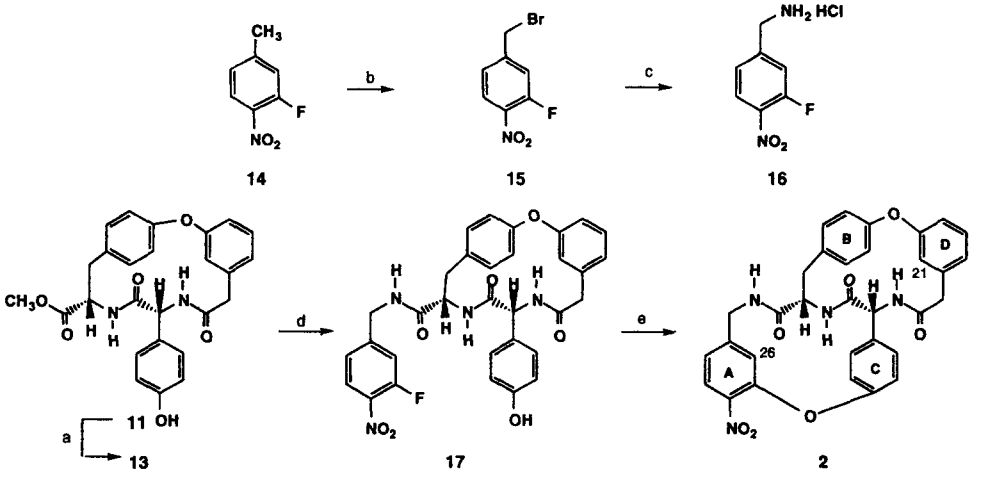


Reagents and conditions: a) $KHCO_3$/DMF/18-Crown-ether, 75 % ; b) Pd/C/MeOH 92 %; c) t-BuONO/DMF 40 %

Scheme 3

The product of natural configuration *(S,R)*-**11** required for the the next steps was obtained on a larger scale by chromatographic separation from the diastereomeric mixture *(S,R)*-**10**+*(S,S)*-**10** obtained by reduction of the crude outcome of the macrocyclisation reaction.

Construction of the 15-membered macrocycle fused to the 16-membered one was completed as follows. Alkaline treatment of the ester *(S,R)*-**11** (LiOH in THF/MeOH/H_2O) led to pure acid **13** with less than 15%, epimerization at C_{11}. The macrocyclisation precursor **17** was prepared in high yield (87%) by coupling of **13** (EDC/HOBt) with 3-fluoro-4-nitro-benzylamine hydrochloride **16** prepared from 3-fluoro-4-nitro-toluene **14** by successive bromination (NBS/CCl_4, 88%) to give **15** and amination (hexamethylenetetramine/CCl_4, HCl/EtOH, 87%).



Reagents and conditions: a) LiOH/THF/MeOH/H_2O, 95 %; b) NBS/CCl_4/$(C_6H_5CO)_2O_2$, 88%; c) hexamethylenetetramine/CCl_4, HCl/EtOH, 87%; d) **16**, NEt_3/CH_2Cl_2, EDC/HOBt, 87 %; e) $KHCO_3$/DMF/18-crown-ether, 80%

Scheme 4

In order to minimize racemisation at the chiral center of amino acid **C**, the base was $KHCO_3$ (at difference with K_2CO_3 used in our synthesis of the simple 15-membered macrocycle[2]). The optimized conditions (0.01M in DMF, $KHCO_3$, 18-crown ether, r.t. 2 hours) led thus to the bicyclic (16+15) **A-O-B-O-D** ring system [9] in 80% yield (Scheme 4).

Conclusion

The target bicyclic compound **2**, synthesized for the first time, was obtained by two sequential intramolecular S_NAr reactions. It represents the most advanced intermediate on the way of the total synthesis of kistamycins A, B, demonstrating the usefulness of the intramolecular SN_{Ar} based methodology [4] for the synthesis of complex macrocycles containing aryl ether bonds.

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

References and Notes

1. a) Naruse, N.; Tenmyo, O.; Kobaru, S.; Hatori, M.; Tomita, K.; Hamagishi, Y.; Oki T.; *J. Antibiotics* **1993**, 1804-1811; b) Naruse, N.; Oka, M.; Konishi, M.; Oki, T.; *J. Antibiotics* **1993**, 1812-1818.
2. Roussi, G.; González Zamora, E.; Carbonnelle, A. C.; Beugelmans, R.; *Tetrahedron Lett.* **1997**, *38*, 4405-4406.
3. Zhu, J.; Bouillon, J.P.; Singh, G.P.; Chastanet, J.; Beugelmans, R. *Tetrahedron Lett.* **1995** *36*, 7081-7084; Beugelmans, R.; Singh, G.P.; Bois-Choussy, M.; Chastanet, J.; Zhu, J.; *J. Org. Chem.*, **1994**, *59*, 5535-5542.
4. For reviews see: Zhu, J.; *Synlett*, **1997**, 133-143; Rao, A. V. R.; Gurjar, M. K.; Reddy, K. L.; Rao, A. S.; *Chem. Rev.* **1995**, *95*, 2135-2167.
5. Vergne, C.; Bois-Choussy, M.; Ouazzani, J.; Beugelmans, R.; Zhu, J.; *Tetrahedron Asymetry* **1997**, *8*, 391-398.
6. Beugelmans, R.; Bois-Choussy M., Vergne, C.; Bouillon, J.P.; Zhu, J.; *J. Chem. Soc., Chem. Com.* **1996**, 1030-1031.
7. All new compounds have spectral data in accord with their structure. The cyclic structure of 16-membered ring compounds **9** were established on the basis of mass spectra, m/z 506 $[M+H]^+$ and ^1H NMR spectra: characteristic upfield shift of H_{21} (b.s.), compared with that of the same proton in the open chain compound **8,** as previously described (Roussi, G.; González Zamora, E.; Carbonnelle, A. C.; Beugelmans, R.; *Tetrahedron Lett.* **1997**, *38*, 4401-4404; see also ref 4).
8. Galli, C. *J. Chem. Soc., Perkin Trans. I* **1981**, 1459-1461.
9. In the ^1H NMR spectrum of **2** an upfield shift (H_{26}) characteristic of a 15-membred macrocycle (ref 2) was observed in addition to that of H_{21}. The complete NMR analysis does not allow, at the moment, a definitive attribution of the axial configuration to be made.

(*Received in France* 5 *August* 1997; *accepted* 23 *September* 1997)