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A New Access To 14-Membered Macrocycle: Synthesis of Model F-O-G ring of Teicoplanin

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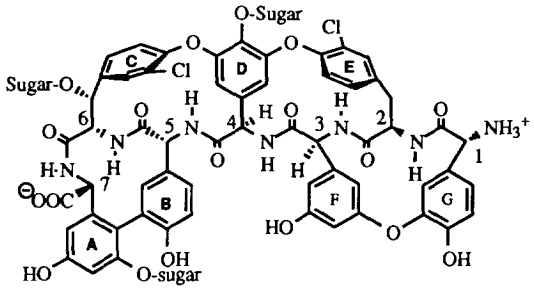
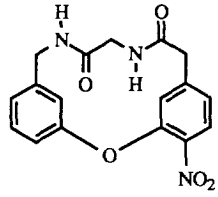
Abstract: A new strategy based upon the intramolecular S_NAr reaction was developped for the synthesis of 14-membered macrocycle. The reason for the easy macrocyclisation was advanced and supported by computational studies.

Since the first isolation of vancomycin from *Amycolatopsis oritentalis* in 1955,[1] well over 200 glycopeptides of this class have been isolated from 45 organisms.[2] All these glycopeptide antibiotics exert their antibiotic activity by binding specifically to cell wall precursors terminating with peptide D-alanyl-D-alanine.[3] While vancomycin has been marketed for 35 years as a human anti-infective agent, teicoplanin has only recently been introduced into clinical practice. *In vitro* and *in vivo* studies have shown the superiority of teicoplanin over vancomycin in view of its low toxicity and high activity.[4]



1 Teicoplanin



2

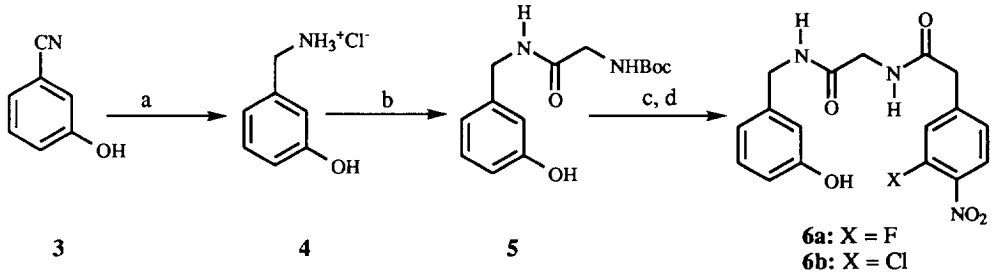
Figure 1

Structurally, teicoplanin is very similar to vancomycin, except for an extra 14-membered macrocycle comprising an ether bond between the aryl moieties of aminoacids 1 and 3. While the synthesis of 16-membered macrocycle related to C-O-D and D-O-E rings of vancomycin[5] has been the subject of intensive studies during the last ten years, only two recent reports[6] dealt with the construction of 14-membered F-O-G macrocycle found in teicoplanin, both employing the macrolactamisation as the key step.

Our interest in this area had led to an efficient synthesis of actinoidic acid[7a] and triaryl diethers,[7b] the degradation products of vancomycin family glycopeptides. More recently, we have developped an efficient macrocyclisation procedure for the construction of peptido aryl ethers based on the intramolecular S_NAr reaction and have applied it to the synthesis of 16-membered C-O-D and D-O-E rings of vancomycin models[8a,8b] as well as a naturally occuring 17-membered cyclic tripeptide: K-13.[8c,8d] In addition to high yields and absence of

racemisation, an important advantage of our approach is that the nitro group *ortho* to the diaryl ether linkage, after serving as an activator, allows the possibility to introduce the functional groups (H, Cl OH etc) found in the natural products. This useful synthetic method has recently been employed by RAO's group.[9] We report herein a successful extension of our method to the preparation of a 14-membered macrocycle **2** as a model of the F-O-G ring found in teicoplanin.

The appropriately functionalized precursors **6** needed for our macrocyclisation studies were prepared in a straightforward fashion as illustrated in Scheme 1. Coupling of 3-hydroxylbenzylamine (**4**), obtained by reduction of 3-hydroxybenzonitrile (**3**), with N-Bocglycine using the mixed anhydride method followed by basic hydrolysis afforded **5** in 54% yield. Removal of the Boc group and reaction with 3-fluoro-4-nitrophenylacetic acid employing EDCI as coupling reagent lead to the macrocyclisation precursor **6a** in 90% yield.



3 **4** **5** **6a: X = F** **6b: X = Cl**

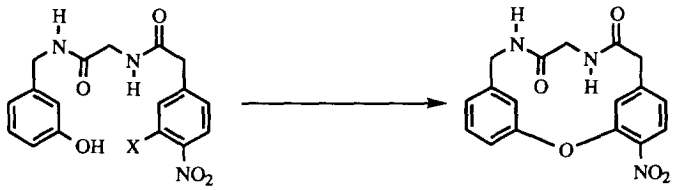
Reagents and conditions: a) BH_3-THF then MeOH-HCl; b) Et_3N, EtOCOCl, N-Bocglycine; c) TFA; d) EDCI, Et_3N, 3-fluoro-4-nitrophenylacetic acid or 3-chloro-4-nitrophenylacetic acid

Scheme 1

When **6a** was submitted to our previously established cyclisation conditions[8] (Table 1, entry 1), the 14-membered macrocycle **2** was obtained in 66% yield after simple extraction and recrystallisation. To further optimize the reaction conditions, macrocyclisation of **6a** to **2** was examined under a range of experimental conditions. As can be seen from Table 1, CsF is an excellent base to promote the desired intramolecular S_NAr reaction, while Li_2CO_3 and $NaHCO_3$ are ineffective in this regard due to their insufficient basicity. The effect of crown ether (entry 3) is significant: under standard conditions, the reaction in the presence of a catalytic amount of 18-crown-6[10] was much faster than the non-catalyzed one. This can be explained by the increased nucleophilicity of alkoxide due to the complexation of K^+ by crown ether leading to the more reactive "naked" anion.

In order to use chloride as a possible leaving group in intramolecular S_NAr reaction, compound **6b** was also prepared (Scheme 1). Unlike **6a**, no cyclisation reaction occured under standard conditions (entry 6) at room temperature, consistent with the low "leaving ability" of chloride. At 40°C, cyclisation did occur but the conversion was low. Longer reaction time at this temperature led to degradation, indicating that **2** was not fully stable to these reaction conditions. No beneficial effect was observed either when 18-crown-6 (entry 8) was added and the degradation of starting material was observed even at room temperature. The best conditions for the cyclisation of **6b** which afforded **2** in 80% yield is heating to 80°C for 6 hrs (entry 9).

Table 1: Representative results of the macrocyclisation reaction[a]



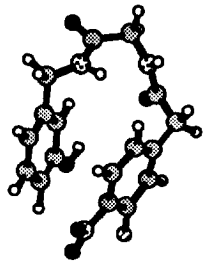
entry	base (eq)	additive	solvent	temperature, time	yield
		X = F			
1	K_2CO_3 (3)	no	DMF	r t, 20h	66%
2	CsF(5)	no	DMF	r t, 20h	62%
3	K_2CO_3 (3)	18-crown-6	DMF	r t, 6h	82%
4	Li_2CO_3 (30)	no	DMF	r t, 4 days	no reaction
5	$NaHCO_3$ (3)	no	DMF	r t, 2 days	trace
		X = Cl			
6	K_2CO_3 (3)	no	DMF	r t, 2 days	no reaction
7	K_2CO_3 (3)	no	DMF	40°C, 24h	degradation
8	K_2CO_3 (3)	18-crown-6	DMF	r t, 2 days	degradation
9	K_2CO_3 (3)	no	DMF	80°C, 6h	80%

[a]All reactions were run at the concentration of 0.01M

The easy formation of the 14-membered macrocycle **2** is rather spectacular considering the obvious strains in this system and the fact that there are only very few methods available at present. The success of our approach could possibly be explained by an electrostatic interaction between the electron-deficient fluoro-nitro substituted aromatic ring and an electron-rich phenoxide ring. As a consequence the two aromatic rings of the macrocyclisation precursor (**6a** or **6b**) came close to each other, resulting in a lower activation energy and favorable entropy for intramolecular cyclisation. Indeed, molecular modelling of macrocyclisation precursor **6a** indicated that the bent conformation as shown in figure 2 was the global energy minimum (E = -259.4 KJ/mol) and largely preferred over the linear one. The two reactive sites of this bent conformer were placed sufficiently close for cyclisation (O-C_F = 4.015 Å). We believe that this conformational effect adequately explained the easy cyclisation encountered in our studies and may be considered as an *intramolecular recognition phenomenon* which may provide a useful guide in designing novel approaches to other macrocycles of interest.[11]

In conclusion, we have demonstrated that the intramolecular S_NAr reaction is also efficient for the synthesis of 14-membered macrocycle. Both fluoro and chloro could be used as the leaving group, however, the

former is certainly preferred for the milder reaction conditions. *Intramolecular recognition phenomenon* may explain the successfull macrocyclisation reported here and in other related studies. Detailed mechanistic studies as well as the application of this cyclisation method will be reported in due course.



E = -259.44 KJ/mol
$O\text{-}C_F$ = 3.95 Å

Figure 2: Lowest energy conformation (macromodel, batchmin, version 3.5a, OPLSA force field[12])

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