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Synthesis of Model Tricyclic C-O-D-O-E-F-O-G Ring of Teicoplanin

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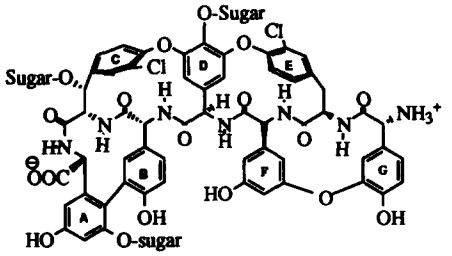
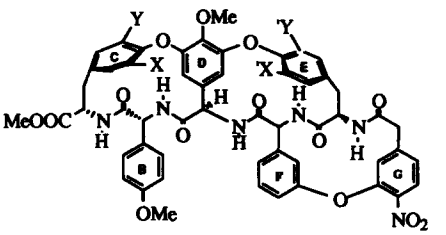
Key words: vancomycin, teicoplanin, antibiotics, S_NAr, macrocyclization

Abstract: Synthesis of model tricyclic C-O-D-O-E-F-O-G rings (2) of teicoplanin (1) by means of efficient S_NAr based cycloetherification methodology is reported. © 1997 Elsevier Science Ltd.

Teicoplanin[1] produced by *Actinoplanes teichomyceticus* is a tetracyclic glycopeptide structually related to vancomycin.[2] Both of them are widely used in hospital as the last resort for the treatment of infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and other Gram positive bacteria. As an important class of antibiotics, the family of glycopeptide has spurred multidisciplinary interest over the last several decades.[3]



1 teicoplanin



2a X = Y' = H, Y = X' = NO_2
2b X = X' = H, Y = Y' = NO_2

Figure 1

The architectural complexity and the therapeutical importance of these polymacrocyclic compounds have made them valuable synthetic targets and have provided synthetic chemists with the impetus for the development of new synthetic reactions.[4] The oxidative coupling methods developed by Yamamura,[5] Evans[6] and the intramolecular Ullmann reaction developed by Boger et.al.[7] are notable examples. Our contribution to this field is the discovery of an efficient cycloetherification methodology based on intramolecular S_NAr reaction.[8,9,10] Formation of biaryl ether bond with concomitant macrocyclic ring formation in high yield and under mild conditions caracterized this cyclization.[11] The reaction has been applied in the synthesis of 16-membered vancomycin model, 14-membered *m,m*-cyclophane, *m,p*-cyclophane found in teicoplanin and bouvardin, respectively, and in the total synthesis of 17-membered natural product K-13.[8] Very recently, it has been employed by Evans's group as a final concluding cyclization step in their brillant total synthesis of orienticin.[12] To illustrate further the power of this methodogy, we report herein the first synthesis of tricyclic C-O-D-O-E-F-O-G ring compounds (2) of teicoplanin (1) featuring a three-fold intramolecular S_NAr reaction for the construction of this poly-macrocyclic structure.

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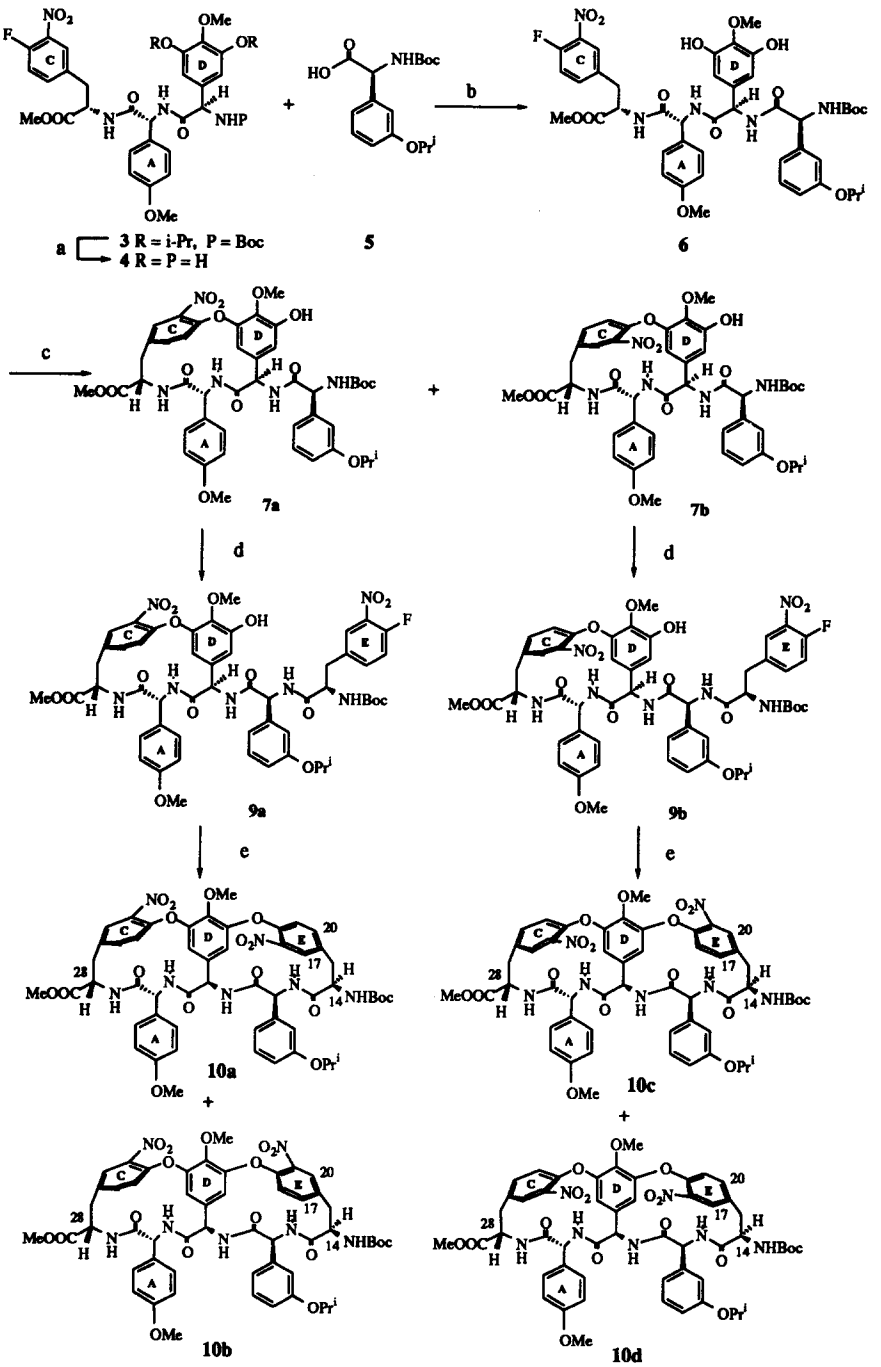
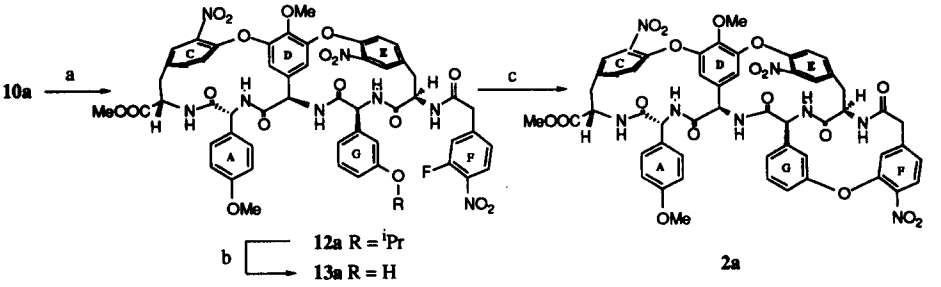


Reagents and Conditions: a) BCl_3, CH_2Cl_2, 0°C, 2 h, then MeOH; b) EDC, HOBt, CH_2Cl_2, 0°C, 3 h, 53%; c) CsF, DMF (0.01M), 5°C, 20 h, 60%; d) (i) HCl, MeCN, rt, 1 h; (ii) D-*N*-Boc-3-fluoro-4-nitrophenyl alanine pentafluorophenyl ester, 0°C, 5 h, 50-60%; e) the same conditions as c, 20 h, 60%.

Scheme 1

The bicyclic C-O-D-O-E ring compopunds **10a-d** were prepared by means of sequential S_NAr reactions in analogy with the synthesis of bicyclic vancomycin models (Scheme 1)[13]. Thus, simultaneous removal of isopropyl ether as well as *N*-Boc protecting group from known tripeptide **3**[14] was realized by treatment with excess of boron trichloride to give the hydrochloride salt of amino phenol **4**. Without purification, the crude product **4** was directly reacted with enantiomerically pure (L)-*N*-Boc-3-isopropyloxy phenylglycine (**5**)[15] employing conventional conditions [1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (EDC), 1-hydroxybenzotriazole (HOBt), triethylamine (TEA)] to afford the tetrapeptide **6** in 53% yield. This coupling reaction should be carried out at 0°C and carefully monitored by TLC as the (L)-*N*-Boc-3-isopropyl phenylglycine (**5**) is prone to racemization at room temperature and under prolonged period of time. Moreover, if the coupling was performed at room temperature, a significant amount of *O*-acylated by-product was formed. Cycloetherification of compound **6** under our standard conditions (CsF, DMF, 5°C)[16] proceeded smoothly to afford the 16-membered macrocycles as two separable atropisomers **7a** and **7b** (1/1) in 60% yield. The same ratio of atropdiastereoisomers was obtained at room temperature in contrast to what was observed in vancomycin series.[13] The atropdiastereoisomerism of two cyclic compounds were determined by detailed NMR studies (1D, 2D, DMSO-d_6 as solvent) as described earlier.[13,15] Thus, a NOE crosspeak between protons H-28 and $H_{para\ to\ nitro}$ was observed for P atropdiastereoisomer (**7a**), while that of H-28 and $H_{ortho\ to\ nitro}$ was observed for M diastereoisomer (**7b**).

Removal of *N*-Boc function from compound **7a** was achieved with concentrated HCl in MeCN (8%, v/v). When trifluoroacetic acid (TFA-anisole) was employed, the deprotection was less clean probably due to the interference between the *tert*-butyl cation generated *in situ* and the electron rich aromatic rings presented in compound **7a**. Coupling of the crude amine with (D)-*N*-Boc-4-fluoro-3-nitro phenylalanine **8** was carried out under various conditions including: i) TEA, EDC, HOBt, 0°C; ii) Diphenylphosphoryl azide (DPPA), DMF and iii) pentafluorophenyl ester of **8**, THF, 0°C to give the pentapeptide **9a** in 50-60% yield. In terms of product purification, the last method is preferred as the side product (pentafluorophenol) is easily removed by filtration. Cycloetherification of compound **9a** using CsF as promoter in dry DMF provided the two separable bicyclic compounds **10a** and **10b**[17] (1/1) in 60% overall yield. The stereochemistry of the newly created planar chirality of **10a** and **10b** was once again determined from careful NMR studies. Starting from monocyclic compound **7b** and employing the same synthetic sequence, two bicyclic compounds **10c** and **10d** (1/1.4) were separated and obtained in 59% overall yield (Scheme 1).



Reagents and Conditions: a) (i) 8% HCl-MeCN, room temperature, 1 h; (ii) DPPA, DMF, Et_3N, 3-fluoro-4-nitrophenylacetic acid (**11**), 0°C then room temperature, 6 h; b) BCl_3, CH_2Cl_2, 0°C, 7 h; c) CsF, DMF, molecular sieve, room temperature, 3 h.

Scheme 2

The synthesis of tricyclic teicoplanin models **2a** and **2b** was accomplished as shown in Scheme 2. Removal of *N*-Boc group from bicyclic compound **10a** (HCl-MeCN) followed by coupling to 3-fluoro-4-nitro phenylacetic acid (**11**)[18] gave the compound **12a** from which the isopropyl group was chemoselectively removed by treatment with BCl_3 in dichloromethane to afford compound **13a**. The cycloetherification conditions (K_2CO_3, THF, 18-crown-6)[15,18] established previously in the related synthesis of D-O-E-F-O-G model did promote the cyclization of **13a**, but only with low yield of desired tricyclic compound. After many trials varying the base, the solvent and the temperature, we found that the most important parameter was in fact the reaction time. The cyclization proceeded, to our surprise, extremely fast. Under optimized conditions (CsF-DMF, room temperature, 3 hrs), the C-O-D-O-E-F-O-G model of teicoplanin **2a**[19] was obtained in 45-50% overall yield from bicyclic compound **10a**. If, however, the reaction was allowed to stir overnight, the yield was significantly diminished indicating the instability of **2** under the reaction conditions. This is also in accord with our previous observation in teicoplanin series.[15,18] The efficient macrocyclization of **13a** could be explained on the basis of its conformational properties. We hypothesized that the entropic cost associated with

preorganizing the two reactive sites on ring F and ring G for macrocyclization have been paid for by the fact that two electronically reversed aromatic rings (F and G) were holded by a rigid bicyclic C-O-D-O-E ring leading to a reduced conformational mobility of compound **13a**. Application of the same synthetic scheme to compound **10b** led to the tricyclic compound **2b** with similar efficiency. The transformation of nitro groups to chlorine atoms of atropdiastereoisomer **10c** and **10d** and further elaboration to tricyclic teicoplanin model will be reported elsewhere.

In conclusion, these studies have further demonstrated the remarkable efficiency of intramolecular S_NAr reactions in the synthesis of polypeptidic macrocycles containing a biaryl ether bridge. The structure-activity relationship (SAR)[20] studies of compounds **10a-d**, **12a-b**, **13a-b**, and **2a-2b**, which were previously unavailable neither synthetically nor chemoenzymatically from natural sources, will be reported in due course. Furthermore, in conjuction with Evans's oxidative coupling methodology for the ring closure of biaryl A-B macroclycle,[6] we may expect a total synthesis of teicoplanin in the near future.

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