Pergamon

Tetrahedron Letters, Vol. 36, No. 48, pp. 8787-8790, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01876-X

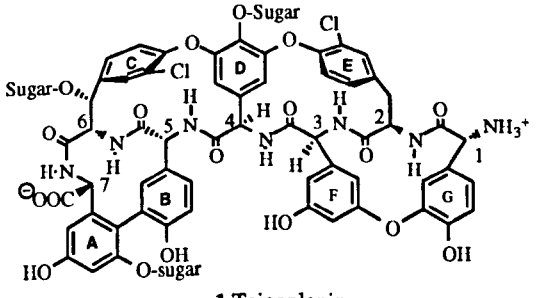
The First Synthesis of a Model Bicyclic D-O-E-F-O-G Ring of Teicoplanin *via* Sequential Intramolecular S_NAr Reactions

René Beugelmans, Luc Neuville, Michèle Bois-Choussy, Jieping Zhu*

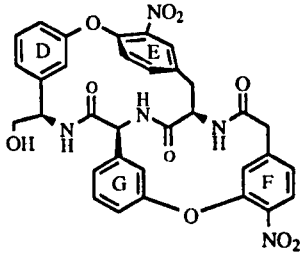
Institut de Chimie des Substances Naturelles, 91198 Gif-sur-Yvette, France

Abstract: A model bicyclic D-O-E-F-O-G ring (**2**) of teicoplanin (**1**) has been efficiently synthesized *via* sequential intramolecular S_NAr reactions.

Teicoplanin **1**,[1] a glycopeptide related to vancomycin and ristocetine,[2] is an antibiotic produced by *Actinoplanes teichomyceticus*. This compound has recently been introduced into clinical practice for treatment of infections caused by methicillin-resistant *Staphylococcus aureus* and gram positive organisms. The antibacterial activity of this family of antibiotics arises from specific binding of the glycopeptide to bacterial cell wall precursors terminating in the sequence D-Ala-D-Ala.[3] *In vitro* and *in vivo* studies[4] have shown that teicoplanin is superior to vancomycin, having lower toxicity and higher activity.



1 Teicoplanin



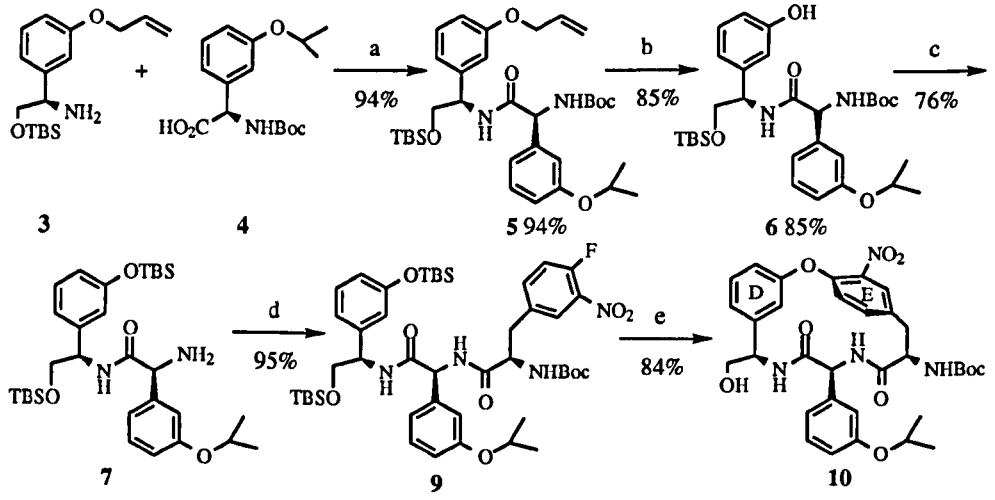
2

Figure 1

Structurally, teicoplanin is very similar to vancomycin but has an extra 14-membered macrocycle comprising an ether bond between the aryl moieties of amino acid 1 and 3. Despite considerable research efforts,[5] no total synthesis of vancomycin and related antibiotics has been achieved to date, principally because the difficulties involved in obtaining polymacrocyclic ring system. We have recently developed an efficient macrocyclization procedure based on intramolecular S_NAr reactions which has been applied to the synthesis of 14-, 16- and 17-membered macrocycles.[6] We report here the first successful synthesis of model bicyclic **D-O-E-F-O-G** ring of teicoplanin **2**[7] *via* sequential application of this technique.

The requisite non-proteinogenic amino acids were prepared using modified literature procedures. Diastereoselective electrophilic amination developed by Evans[8] was used as a key step for the syntheses of both D-(*R*)-aminoalcohol **3**[6c] and L-(*S*)-Boc-3-isopropyloxyphenylglycine (**4**), while diastereoselective alkylation of Schöllkopf's bislactim ether[9] was employed for the preparation of D-(*R*)-Boc-4-fluoro-3-nitrophenylalanine (**8**).[6c]

The macrocycle **10** was synthesized as disclosed previously (Scheme 1).[6c] Coupling of the aminoalcohol **3** with the racemization prone L-(*S*)-Boc-3-isopropyloxyphenylglycine (**4**) (EDC, HOBt) provided the dipeptide **5** in 94% yield. The presence of HOBt is essential to minimize racemization and other coupling conditions, including EDC-$CuCl_2$[10] and DPPA[11], did not give superior results in terms of diastereomeric purity. Reductive removal of the allyl protecting group under conditions developed in this laboratory[12] afforded compound **6** in 85% yield with less than 5% racemization as determined by NMR analysis. TBDMSOTf mediated removal of Boc[13] function provided the amine **7**, which was coupled with D-(*R*)-Boc-4-fluoro-3-nitrophenylalanine (**8**) to furnish the tripeptide (**9**) in excellent yield. The tiny amount of undesired diastereoisomer was readily removed by flash chromatography.



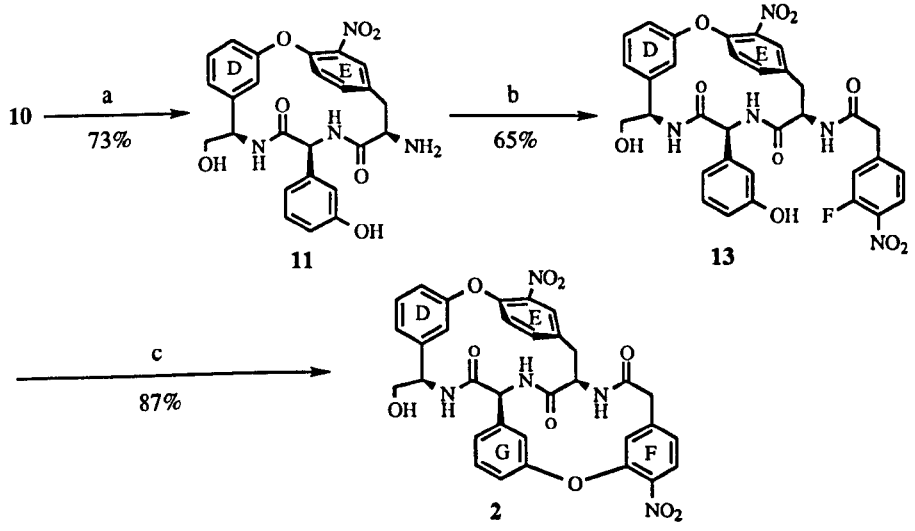
Reagents and Conditions: a) EDC, HOBt; b) $Pd(PPh_3)_4$, $NaBH_4$; c) TBDMSOTf, 2,6-lutidine; d) D-(*R*)-Boc-4-fluoro-3-nitro-Phenyl Ala (**8**), EDC, HOBt; e) CsF, DMF.

Scheme 1

Macrocyclization of diastereomerically pure **9** using dry CsF as promotor in DMF (0.01M) gave 84% yield of the desired macrocyclic **D-O-E** ring **10** as a single atropisomer with the "natural" configuration.[6b] To ascertain the absence of racemization in this key ring closure step, racemic amino acid (±)-**4** which was most likely to be racemized in all synthetic sequence involved was prepared *via* Strecker synthesis[14] and incorporated into the tripeptide **9** following the same synthetic scheme as described before. Flash chromatographic separation gave then the diastereomerically pure compounds **9** (*R, S, R*) and *epi*-**9** (*R, R, R*). Cyclization of the latter under the conditions identical to that used for **9** afforded the macrocycle *epi*-**10** which has R_f value and physical

data completely different from that of **10**. This result convincely shows that no racemization had occured under our macrocyclization conditions. It is interesting to note that CsF[15] plays a dual role in this cyclization reaction: it deprotects TBS ethers and promotes the cyclization in a one-pot fashion.

The completion of synthesis of the bicyclic **D-O-E-F-O-G** ring model **2** is shown in Scheme 2. Deprotection of Boc group and isopropyl ether was realized in one single step by treatment with BCl_3 followed by acidic work-up leading to pure amino compound **11** in 73% yield by simple acid-base extraction. To minimize the competitive O-acylation process, DPPA was used as coupling reagent for the reaction between **11** and 3-fluoro-4-nitrophenylacetic acid (**12**), prepared from 3-fluorophenylacetic acid,[6f] to provide the desired macrocyclization precursor **13** in 65% yield.



Reagents and Conditions: a) BCl_3; b) MeCN-HCl; c) 3-fluoro-4-nitrophenylacetic acid (**12**), DPPA, DMF; d) K_2CO_3, 18-crown-6, THF.

Scheme 2

After searching for different reaction parameters, the optimized conditions for the cyclization of **13** were found to be 10 eq. of K_2CO_3 in THF in the presence of crown ether 18-C-6. Under these conditions, the bicyclic **D-O-E-F-O-G** ring **2**[16] was isolated in 87% yield. Given that this bicyclic system is obviously strained, the high yield obtained under mild conditions in the second macrocyclization is remarkable.

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. Furthermore, the sequential cyclization reported in this letter allows differentiation of the two nitro groups and consequently introduction of the different functionalities (Cl, OH in ring **E** and **F**, respectively) found in natural products. The bicyclic **D-O-E-F-O-G** ring model **2**, obtained in 19% overall yield, is the most advanced synthetic intermediate to date on the way to the total synthesis of teicoplanin and related antibiotics.

References and Notes

1 (a) Hunt, A. H.; Molloy, R. M.; Occolowitz, J. L.; Marconi, G. G.; Debono, M. *J. Am. Chem. Soc.* **1984**, *106*, 4891-4895; (b) Barna, J. C. J.; Williams, D. H.; Stone, D. J. M.; Leung, T. W. C.; Doddrell, D. M. *J. Am. Chem. Soc.* **1984**, *106*, 4895-4902.

2 (a) Williamson, M. P.; Williams, D. H. *J. Am. Chem. Soc.* **1981**, *103*, 6580-6585; (b) Harris, C. M.; Kopecka, H.; Harris, T. M. *J. Am. Chem. Soc.* **1983**, *105*, 6915-6922; (c) Gerhard, U.; Mackay, J. P.; Maplestone, R. A.; Williams, D. H. *J. Am. Chem. Soc.* **1993**, *115*, 232-237 and references cited therein; (d) Nagarajan, R. *J. Antiobiot.* **1993**, *46*, 1181-1195.

3 (a) Sheldrick, G. M.; Jones, P. G.; Kennard, O.; Williams, D. H.; Smith, G. A. *Nature* **1978**, *271*, 223-225; (b) Williams, D. H. *Acc. Chem. Res.* **1984**, *17*, 364-369; (c) Williamson, M. P.; Williams, D. H.; Hammond, S. J. *Tetrahedron* **1984**, *40*, 569-577; (d) Popieniek, P. H.; Pratt, R. F. *J. Am. Chem. Soc.* **1991**, *113*, 2264-2270; (e) Batta, G.; Kövér, K. E.; Székely, Z.; Sztaricskai, F. *J. Am. Chem. Soc.* **1992**, *114*, 2757-2758; (f) Wright, G. D.; Walsh, C. T. *Acc. Chem. Res.* **1992**, *25*, 468-473.

4 (a) Parenti, F.; Beretta, G.; Berti, M.; Arioli, V. *J. Antibiot.* **1978**, *31*, 276-283; (b) Varaldo, P. E.; Debbia, E.; Schito, G. C. *Antimicrob. Agents Chemother.* **1983**, *23*, 402-406.

5 For the synthesis of 16-membered macrocycles: (a) Pant, N.; Hamilton, A. D. *J. Am. Chem. Soc.* **1988**, *110*, 2002-2003; (b) Suzuki, Y.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1989**, *30*, 6043-6046; (c) Evans, D. A.; Elleman, J. A.; Devries, K. M. *J. Am. Chem. Soc.* **1989**, *111*, 8912-8914; (d) Crimmin, M. J.; Brown, A. G. *Tetrahedron Lett.* **1990**, *31*, 2021-2024; (e) Stone, M. J.; Van Dyk, M. S.; Booth, P. M.; Williams, D. H. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1629-1635; (f) Pearson, A. J.; Park, J. G. *J. Org. Chem.* **1992**, *57*, 1744-1752; (g) Boger, D. L.; Nomoto, Y.; Teegarden, B. R. *J. Org. Chem.* **1993**, *58*, 1425-1433; for the synthesis of 14-membered macrocycles: (a) Chakraborty, T. K.; Reddy, G. V. *J. Org. Chem.* **1992**, *57*, 5462-5469; (b) Pearson, A. J.; Shin, H. *J. Org. Chem.* **1994**, *59*, 2314-2323; for the synthesis of 12-membered macrocycles: (a) Brown, A. G.; Crimmin, M. J.; Edwards, P. D. *J. Chem. Soc., Perkin Trans. 1* **1992**, 123-130; (b) Evans, D. A.; Dinsmore, C. J.; Evrard, D. A.; Devries, K. M. *J. Am. Chem. Soc.* **1993**, *115*, 6426-6427; (c) Evans, D. A.; Dinsmore, C. J. *Tetrahedron Lett.* **1993**, *34*, 6029-6032.

6 For the synthesis of 16-membered macrocycles: (a) Beugelmans, R.; Zhu, J.; Husson, N.; Bois-Choussy, M.; Singh, G. P. *J. Chem. Soc., Chem. Commun.* **1994**, 439; (b) Beugelmans, R.; Singh, G. P.; Bois-Choussy, M.; Chastanet, J.; Zhu, J. *J. Org. Chem.* **1994**, *59*, 5535-5542; (c) Bois-Choussy, M.; Beugelmans, R.; Bouillon, J. P.; Zhu, J. *Tetrahedron Lett.* **1995**, *36*, 4781-4784; (d) Rama Rao, A. V.; Reddy, K. L.; Rao, A. S. *Tetrahedron Lett.* **1994**, *35*, 8465-8468. For the synthesis of 14-membered macrocycles: (e) Beugelmans, R.; Bourdet, S.; Zhu, J. *Tetrahedron Lett.* **1995**, *36*, 1279-1282; For the synthesis of 17-membered macrocycles: (f) Beugelmans, R.; Bigot, A.; Zhu, J. *Tetrahedron Lett.* **1994**, *35*, 7391-7394.

7 The presence of primary hydroxy group instead of a carboxyl function was for the purpose of reversing drug resistance phenomenon, for detailed discussion see ref 6c and (a) Courvalin, P. *Antimicrob. Agents Chemother.* **1990**, *34*, 2291-2296; (b) Walsh, C. T. *Science* **1993**, *261*, 308-309. Moreover, it has been demonstrated that the loss of terminal amino group of teicoplanin reduces the *in vitro* activity to only one-half that of natural product, see: a Trani, A.; Ferrari, P.; Pallanza, R.; Tarzia, G. *J. Med. Chem.* **1989**, *32*, 310-314.

8 (a) Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L.; *J. Am. Chem. Soc.* **1990**, *112*, 4011-4030; (b) Evans, D. A.; Evrard, D. A.; Rychnovsky, S. D.; Früh, T.; Whittingham, W. G.; Devries, K. M. *Tetrahedron Lett.* **1992**, *33*, 1189-1192.

9 Schöllkopf, U.; Groth, U.; Deng, C. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 798-799.

10 Miyazawa, T.; Otomatsu, T.; Fukui, Y.; Yamada, T.; Kuwata, S. *Int. J. Peptide Protein Res.* **1992**, *39*, 237-244.

11 Shioiri, T.; Ninomiya, K.; Yamada, S.-I. *J. Am. Chem. Soc.* **1972**, *94*, 6203-6205.

12 (a) Beugelmans, R.; Bourdet, S.; Bigot, A.; Zhu, J. *Tetrahedron Lett.* **1994**, *35*, 4349-4350; (b) Beugelmans, R.; Neuville, L.; Bois-Choussy, M.; Chastanet, J.; Zhu, J. *Tetrahedron Lett.* **1995**, *36*, 3129-3132.

13 Sakaitani, M.; Ohfune, Y. *J. Org. Chem.* **1990**, *55*, 870-876.

14 Zhu, J.; Beugelmans, R.; Bigot, A.; Singh, G. P.; Bois-Choussy, M. *Tetrahedron Lett.* **1993**, *34*, 7401-7404.

15 Clark J. H. *Chem. Rev.* **1980**, *80*, 429-452.

16 All new compounds described gave spectral data consistent with the assigned structures.

(*Received in France* 8 *September* 1995; *accepted* 29 *September* 1995)