Pergamon

Tetrahedron Letters, Vol. 37, No. 48, pp. 8791-8794, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)02033-3

TTN Oxidation of Mixed Halogenated Phenols: Synthesis of Vancomycin Model Diaryl Ether Possessing a Chlorine Atom

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Abstract: The diaryl ether possessing a chlorine atom has been synthesized as a model study on a synthesis of vancomycin class glycopeptide antibiotics. Thallium (III) oxidation of the bisphenol derivative followed by selective reduction provided the corresponding cyclic product in moderate overall yield. Conformation of the products is also discussed. Copyright © 1996 Elsevier Science Ltd

One of the most crucial points in the synthesis of isodityrosine natural products involving vancomycin-class glycopeptide antibiotics,[1] may be the construction of diaryl ether moieties, which generally play an important role in the biological activity. In this context, we have developed the biomimetic phenol coupling methodology by electrolytic and thallium (III) oxidations of *o,o'*-dihalogenated phenols as substrates.[1b] From our accumulated investigation, it appears that the former method is effective for dimerization, and the latter for intramolecular cyclization. Although related approaches have employed Ullmann or S_NAr reactions, the thallium (III) oxidation has been recognized as a standard procedure to produce cyclic isodityrosines. This method requires halogen substituents at both *ortho*-positions of the phenol group, and a complex mixture was obtained in the case of phenols carrying a mono halogen substituent such as the vancomycin core.[1b] As Rao pointed out,[2] specific introduction of a chlorine atom to the desired position of the diaryl ether moieties would be a problem to be solved for completion of the vancomycin synthesis. In addition to his method by coupling

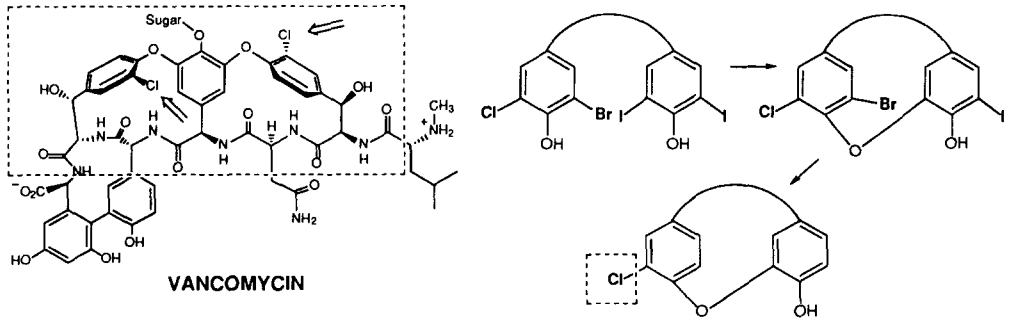
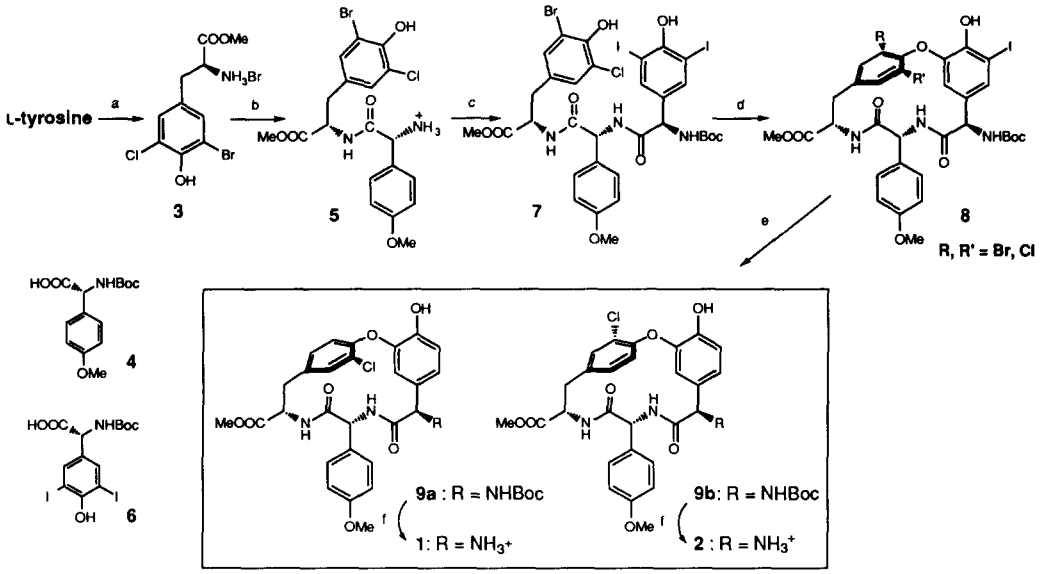


Figure 1



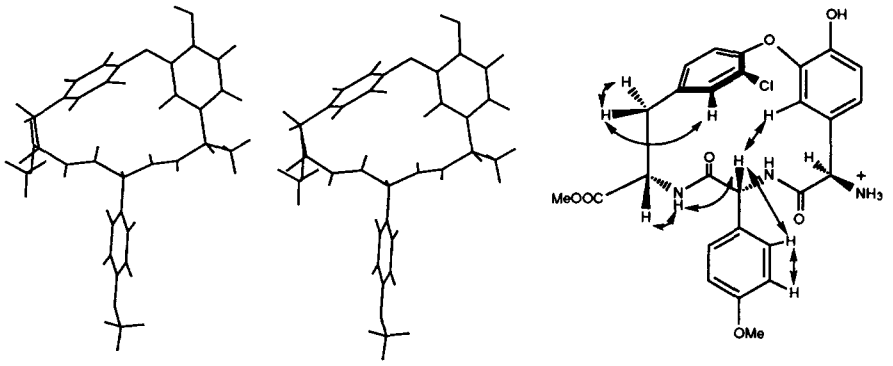
Scheme 1. *Reagents*: a. i). $SOCl_2$/MeOH, room temp.; ii) Cl_2/MeOH, 0 °C; iii) Br_2/dioxane, room temp. (81% in three steps). b. i) **4**, DCC, HOBt, NMM/DMF, room temp.; ii) TFA/CH_2Cl_2, room temp. (81% in two steps). c. **6**, DCC, HOBt, NMM/DMF, room temp. (76%). d. TTN (3 eq)/THF-MeOH (20:1), 0 °C (43%). e. H_2, Pd-black, NaOAc, EtOAc-MeOH→MeOH (82%). f. TFA/CH_2Cl_2, 0 °C (100%).

of a monochlorotyrosine derivative with dihaloquinone,[2] several groups have reported S_NAr approaches[3] involving conversion of a nitro group to a chlorine atom.[3h] Against this background, we planned an approach by the thallium (III) oxidation of a phenol derivative carrying selectively removable halogen substituents, as can be seen in Fig. 1. After the cyclization, removal of halogens operated as controllers of the oxidation potential, except for the most unreactive chlorine, would provide the desired products such as **9a** and **9b**. We disclose herein the synthesis of the vancomycin core model.

At the outset, L-tyrosine was derived in three steps to give bromochloro-L-tyrosine derivative **3** in 81% yield. Compound **3** was condensed with the N-Boc-phenylglycine derivative **4** under the DCC conditions, followed by removal of the N-protective group, leading to **5** in 81% yield. Subsequently, **5** was submitted to coupling with the diiodophenylglycine derivative **6** by essentially the same procedure as the case of **3** to afford the desired diphenol **7**[4] in 76% yield. TTN (thallium trinitrate) oxidation of **7** effected the desired cyclization to give **8** in 43% yield as a mixture of atropisomers. The yield was comparable to those of our previous oxidations (~40% yields) to construct vancomycin core models.[1b,5] At this stage, it should be mentioned that the thallium (III) oxidation is effective even with phenols possessing different halogens at both *ortho* positions. Subsequent catalytic hydrogenation effected selective removal of the bromine and iodine atoms to afford a 3:2 mixture of isomers (**9a** and **9b**)[6] in 82% yield, which were chromatographically separated. Interconversion of **9a** and **9b** was not spectroscopically observed even at 100 °C in DMSO-d_6 solution.

Both structures were confirmed as the corresponding ammonium salts (**1** and **2**)[7] by the ROESY experiments and molecular dynamics calculations. Conformation analysis was performed using the Biosym Insight & Discover modeling software[8] on a Indigo 2 work station of Silicon Graphics, Inc.. The starting

Compound 1



Compound 2

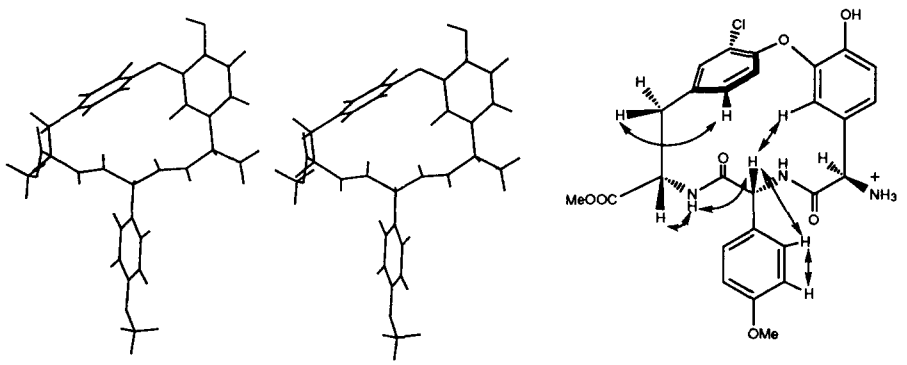


Figure 2. The Stereoview of the Calculated Structures (**1**and **2**), and the Selected ROESY Data.

structures were generated by Insight II,[8a] then the dynamics calculations were performed using the Discover program.[8b] After 30-ps equilibration period at 300 K, the dynamics simulation was performed for 300 ps at the same temperature. During this simulation period the structures were saved every 150 fs. Out of the 2000 structures thus obtained, 100 low-energy ones were selected. Then, the structure optimization was carried out using the CFF91 force field of the Discover program.[8b] The conformation energy of the most stable structures of **1** and **2** was 81.2580 Kcal and 81.7057 Kcal/mol, respectively. As depicted in Fig. 2, the calculated conformation is compatible with the results of the ROESY experiments. Although no pronounced difference in the stereochemistry of the two molecules was generated by the positions of a chlorine substituent, natural-type atropisomer **1** was obtained in ca. 1.5-fold higher yield than the other. This observation accommodates a possibility of the regiospecific introduction of a chlorine substituent by arranging a substitution pattern.

In conclusion, the phenolic oxidation methodology has included mixed halogenated tyrosine derivatives as substrates, which made it possible to introduce a chlorine atom into the vancomycin core model by selective removal of the other halogens. Further synthetic investigation toward vancomycin-class natural products is in progress.

This research was financially supported by a Grant-in-Aid from the Ministry of Education, Science and Culture, and the Takeda Foundation, which are gratefully acknowledged.

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4. **7**: $[\alpha]_D^{22}$ -42.4° (*c* 1.00, MeOH); IR (nujor) 3300, 1740, 1640, 1515 cm^{-1}; δ_H (CD_3OD) 2.67-2.76 (1H, complex), 2.98-3.05 (1H, complex), 3.68 (3H, s), 3.78 (3H, s), 4.69 (1H, q, J= 5 Hz), 5.09 (1H, s), 5.39 (1H, s), 6.80 (2H, d, J= 9Hz), 6.96 (1H, d, J= 1.98 Hz), 7.11 (2H, d, J= 9 Hz, overlapped with 1H), 7.71 (2H, s).
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6. **9a**: $[\alpha]_D^{22}$ -87° (*c* 1.00, MeOH); IR (film) 3350, 1735, 1680, 1645, 1510 cm^{-1}; δ_H (DMSO-d_6) 1,37 (9H, s), 2.85 (1H, dd, J= 13.4, 7.6 Hz), 3.57 (3H, s), 3.71 (3H, s), 4.31 (1H, broad s), 5.21 (1H, d, J= 9.3 Hz), 5.25 (1H, d, J= 8.8 Hz), 6.19 (1H, s), 6.62 (1H, d, J= 8.3 Hz), 6.73 (1H, m), 6.84 (4H, complex), 7.06 (1H, d, J= 8.8 Hz), 7.21 (2H, d, J= 8.8 Hz), 7.58 (1H, s), 8.40 (1H, broad d, J= 5.9 Hz), 8.97 (1H, d, J= 8.3 Hz), 9.46 (1H, s). **9b**: $[\alpha]_D^{21}$ -101.4° (*c* 1.00, MeOH); IR (film) 3250, 1750, 1680, 1640, 1515 cm^{-1}; δ_H (DMSO-d_6) 1.37 (9H, s), 2.99 (1H, dd, J= 13.4, 7.9 Hz), 3.42 (1H, dd, J= dd, J= 13.4, 5.5 Hz), 3.56 (3H, s), 3.71 (3H, s), 4.35 (1H, broad s), 5.24 (1H, broad d, J= 9.2 Hz), 5.34 (1H, m), 5.98 (1H, s), 6.71 (1H, d, J= 8.4 Hz), 6.76 (1H, broad d, J= 8.8 Hz), 6.82 (1H, d, J= 8.4 Hz), 6.84 (2H, d, J= 8.8 Hz), 7.07 (1H, broad d, J= 8.1 Hz), 7.23 (2H, d, J= 8.8 Hz), 7.34 (1H, s), 7.38 (1H, d, J= 8.1 Hz), 8.51 (1H, broad d, J= 5.9 Hz), 8.86 (1H, d, J= 8.8 Hz), 9.40 (1H, s).
7. **1**: δ_H (DMSO-d_6) 2.81 (1H, dd, J= 7.3, 14 Hz), 3.39 (1H, dd, J= 4.7, 14 Hz), 3.55 (3H, s), 3.72 (3H, s), 4.26 (1H, m), 4.41 (1H, s), 5.24 (1H, d, J= 8.4 Hz), 6.16 (1H, d, J= 1.8 Hz), 6.78 (1H, d, J= 8.1 Hz), 6.83 (1H, d, J= 8.4 Hz), 6.86 (2H, complex), 7.04 (2H, complex), 7.21 (2H, d, J= 8.8 Hz), 7.67 (1H, d, J= 1.8 Hz), 8.45 (1H, d, J= 6.6 HZ), 8.71 (1H, d, J= 8.4 Hz), 9.39 (1H, s). **2**: δ_H (DMSO-d_6) 2.97 (1H, dd, J= 7.7, 14 Hz), 3.43 (1H, dd, J= 5.9, 14 Hz), 3.56 (3H, s), 3.73 (3H, s), 4.30 (1H, s), 4.35 (1H, dd, J= 6.5, 14 Hz), 5.32 (1H, d, J= 8.8 Hz), 5.93 (1H, d, J= 1.8 Hz), 6.80 (1H, d, J= 8.4 Hz), 6.85 (3H, complex), 7.05 (1H, broad d, J= 9.9 Hz), 7.08 (1H, d, J= 8.1 Hz), 7.22 (1H, d, J= 8.8 Hz), 7.35 (2H, complex), 8.52 (2H, complex), 9.27 (1H, s).
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(*Received in Japan* 18 *September* 1996; *revised* 9 *October* 1996; *accepted* 14 *October* 1996)