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# Macrocyclization by TTN Oxidation for the Synthesis of Chloropeptin Left-hand Segment

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**Abstract:** Cyclic tripeptides containing a diphenylether bond of the Chloropeptin left-hand segment were synthesized with the use of TTN phenolic oxidation in high yield. They were found to exist as equilibrium mixtures of two stable conformers caused by a rotation of the amide bond in solution. 

*Key words:* macrocyclization, TTN oxidation, Chloropeptin, cyclic tripeptide

Chloropeptin (**1**) is a peptide antibiotic isolated from *Streptomyces* sp. WK-3419 as a potent inhibitor against gp120–CD4 binding.[1] The structure of **1** was estimated by NMR experiment, chemical degradation and molecular dynamic calculation.[2, 3]

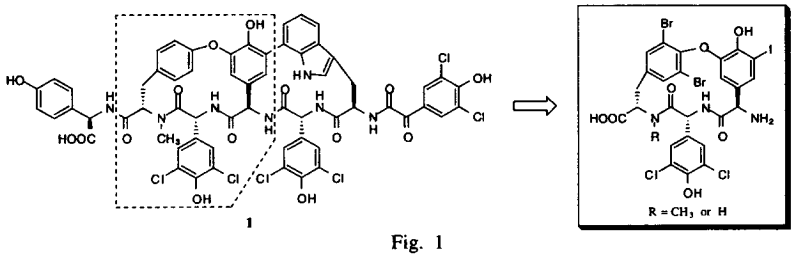


Fig. 1

Against this background, we began to work on the total synthesis of **1** for the purpose of establishing a synthetic route of the derivative to determine the configuration and biological active part of **1**. This time we succeeded in the facile synthesis of a cyclic tripeptide containing a diphenylether bond with the use of TTN (thallium trinitrate) in high yield, and discussed the influence that the *N*-methyl amide bond of the cyclic tripeptide had on the conformation. The key step for the synthesis of Chloropeptin left-hand segment was the formation of a diphenylether bond. Several methods are known for the formation of the diphenylether bond.[4–7] We employed TTN phenolic oxidation by Yamamura *et al.*,[6] because although the yield of this oxidation by TTN was generally 30 – 50%, the synthesis of natural products could be performed under

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relatively mild conditions.

For the synthesis of the cyclic tripeptide, five kinds of amino acid subunits (**2**, **3**, **4**, **5** and **6**) were required. These were prepared by conventional procedure in 48%, 65%, 51%, 46% and 78%, respectively, from commercially available D-4-hydroxyphenylglycine, *O*-benzyl-*N*-Boc-L-tyrosine and L-tyrosine. Coupling of **2** with **5** proceeded under BOP-Cl in THF to give the dipeptide in quantitative yield. Deprotection by trifluoroacetic acid followed by coupling with **3** or **4** under EDCI / HOBt in $CH_2Cl_2$ – THF provided the corresponding tripeptides **7** and **8** in 74% and 54% yield, respectively. By the same method performed under EDCI / HOBt in THF with **2**, **3**, **4** and **6**, the corresponding tripeptides **9** and **10** were given in 49% and 46% yield, respectively, from the starting material (Fig. 2).

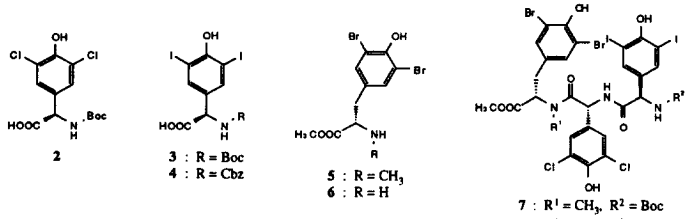
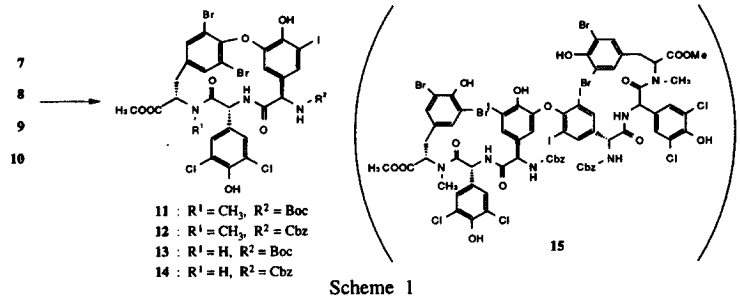



Fig. 2

Macrocyclization of the linear tripeptides **7**, **8** and **10** was first performed in $1.0 \times 10^{-3}$ M MeOH solution at 0 – -15 °C with various equivalents of TTN (1.0 – 3.0 eq.) (Scheme 1, Table 1). In 1.0 and 3.0 equivalent, most of **7** and **8** were remained unreacted. In 2.0 equivalent, cyclized products **11**, **12** and **14** were produced in 26%, 18% and 21% yields, respectively (runs 1 – 7). In THF solution, the reaction scarcely proceeded (runs 8 and 9). In the case of using THF–MeOH (4 : 1), the corresponding cyclized products **11**, **12** and **13** were given in excellent yield (76%, 74% and 76%), respectively (runs 10 – 12). On the other hand, when the cyclization reaction of **8** was performed in $CH_2Cl_2$ solution, a dimer of **8** (**15**) was produced as a main product (run 13). On adding 20% volume of MeOH or THF to the $CH_2Cl_2$ solution, formation of dimer **15** was controlled and the cyclized product **12** was slightly produced (runs 14 and 15). From this result, it was found that the TTN oxidation for the synthesis of the cyclic tripeptide in Chloropeptin was influenced by the reaction solvent in terms of the product and yield obtained. The structure of each cyclized product was elucidated by MS and NMR spectroscopy. The characteristic molecular ion peaks which indicated two atoms of bromine and those of chlorine were observed in mass spectra of cyclic tripeptides. This result implied that the direction of cyclization could be controlled by the reactivity of the halogen atom as Inoue *et al.* reported previously.[8] The signal at aromatic H-2 of the D-4-hydroxy-3, 5-diiodophenylglycine unit in cyclic tripeptide indicated the characteristic upfield shift (about 1.7 ppm) comparing with the corresponding linear tripeptide,




Scheme 1

Table 1. Reaction Conditions and Yields of Cyclic Tripeptides

| Run | Tripeptide | TTN (eq.) | Solvent | Product | Yield (%) |
|---|---|---|---|---|---|
| 1 | **7** | 1.0 | MeOH | **11** | trace |
| 2 | **8** | 1.0 | MeOH | **12** | trace |
| 3 | **7** | 2.0 | MeOH | **11** | 26 |
| 4 | **8** | 2.0 | MeOH | **12** | 18 |
| 5 | **10** | 2.0 | MeOH | **14** | 21 |
| 6 | **7** | 3.0 | MeOH | **11** | 9 |
| 7 | **8** | 3.0 | MeOH | **12** | 3 |
| 8 | **8** | 1.0 | THF | **8** | recovery |
| 9 | **8** | 2.0 | THF | **12** | trace |
| 10 | **7** | 2.0 | THF–MeOH (4 : 1) | **11** | 76 |
| 11 | **8** | 2.0 | THF–MeOH (4 : 1) | **12** | 74 |
| 12 | **9** | 2.0 | THF–MeOH (4 : 1) | **13** | 76 |
| 13 | **8** | 1.0 | $CH_2Cl_2$ | **15** | 28 |
| 14 | **8** | 1.0 | $CH_2Cl_2$–MeOH (4 : 1) | **12** | trace |
| 15 | **8** | 1.0 | $CH_2Cl_2$–THF (4 : 1) | **12** | trace |

because of a shielding effect based on the aromatic ring of the *N*-methyl-L-tyrosine or L-tyrosine unit. Two peaks which have different chemical shift values were observed about aromatic H-2 and H-6 of the tyrosine unit. In dimer **15**, the molecular ion peaks which indicated four atoms of bromine and those of chlorine were observed in mass spectrum, and two couples of peaks based on the tripeptide **8** were observed in $^1H$ and $^{13}C$ NMR. The characteristic four strong peaks based on two couples of bromine and chlorine atoms and three weak peaks based on iodine atoms bound to the aromatic ring were observed in $^{13}C$ NMR, so it was concluded that the binding position of **15** was between aromatic H-3 and the phenolic hydroxy group of each D-4-hydroxy-3, 5-diiodophenylglycine unit. Further, in detailed NMR analysis, it was found that each spectrum of **11**, **12**, **13** and **14** indicated a mixture of two kinds of different peaks. Ratios of major and minor

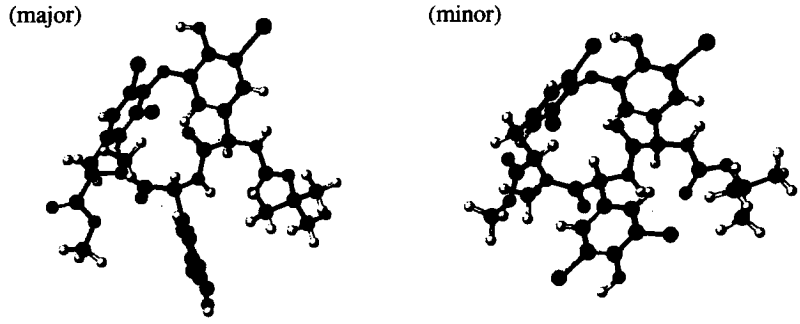



Fig. 3

peaks were 3 : 1 (**11** and **12**) and 7 : 1 (**13** and **14**), respectively. In the major peak of **11**, an NOE was observed between the methine proton of the D-4-hydroxy-3, 5-dichlorophenylglycine unit and the *N*-methyl proton of the *N*-methyl-L-tyrosine unit, so we presumed that the major peak was originated in the *trans* isomer of the *N*-methylamide bond. The lowest energy conformations for **11** were shown in Fig. 3. In the major peak of **13**, an NOE was also observed in a similar way.

From these results, it became obvious that the cyclic tripeptides existed as equilibrium mixtures of two stable conformers caused by a rotation of the amide bond in solution. It seems that the *N*-methyl amide group makes the ratio of the *cis* isomer increase, because the ratio of *cis* isomer of **11** and **12** was larger than that of **13** and **14**.

## References

1. H. Tanaka, K. Matsuzaki, H. Nakashima, T. Ogino, A. Matsumoto, H. Ikeda, H. B. Woodruff, and S. Ōmura, *J. Antibiot.*, **50**, 58–65 (1997).
2. K. Matsuzaki, T. Ogino, T. Sunazuka, H. Tanaka, and S. Ōmura, *J. Antibiot.*, **50**, 66–69 (1997).
3. H. Gouda, K. Matsuzaki, H. Tanaka, S. Hirono, and S. Ōmura, *J. Am. Chem. Soc.*, **118**, 13087–13088 (1996).
4. D. L. Boger, Y. Nomoto, and B. R. Teegarden, *J. Org. Chem.*, **58**, 1425–1433 (1993).
5. J. Zhu, *SYNLETT*, **1997**, 133–144.
6. S. Yamamura and S. Nishiyama, *Studies in Natural Products Chemistry*, **10**, 629–669 (1992).
7. K. C. Nicolau, C. N. C. Boddy, S. Natarajan, T.-Y. Yue, H. Li, S. Bräse, and J. M. Ramanjulu, *J. Am. Chem. Soc.*, **119**, 3421–3422 (1997).
8. T. Inoue, T. Inaba, I. Umezawa, M. Yuasa, H. Itokawa, K. Ogura, K. Komatsu, H. Hara, and O. Hoshino, *Chem. Pharm. Bull.*, **43**, 1325–1335 (1995).