Tetrahedron Letters, Vol.32, No.35, pp 4503-4504, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

A New Enantioselective Synthesis of (4*S*, 5*S*)-5-(*N*-Boc)-Amino-6-cyclohexyl-4-hydroxy-hexanoic Acid Lactone, a Hydroxyethylene Dipeptide Isostere Precursor

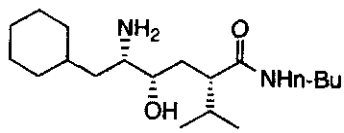
Hiyoshizo Kotsuki,* Aya Miyazaki, and Masamitsu Ochi

Department of Chemistry, Faculty of Science, Kochi University, Akebono-cho, Kochi 780, Japan

Key Words: Renin inhibitor; Hydroxyethylene dipeptide isostere; Chiral triflates; Coupling reaction; Enantioselective synthesis

Abstract: A new enantioselective synthesis of a valuable hydroxyethylene dipeptide isostere precursor, (4*S*, 5*S*)-5-(*N*-Boc)-amino-6-cyclohexyl-4-hydroxy-hexanoic acid lactone, has been developed by using coupling reaction of chiral triflates as a key step.

The enzyme renin, an aspartic proteinase, is an important constituent of the renin-angiotensin system for the regulation of blood pressure and currently much efforts have been directed toward the development of inhibitors of human renin such as peptide mimics containing an isostere of the scissible Leu-Val dipeptide bond.[1] As one of these candidates Bühlmayer et al. have recently disclosed the preparation of the hydroxyethylene dipeptide isostere **1**.[2] Herein we wish to describe an alternative flexible approach to the precursor of **1**, the lactone **2**,[3] by applying our chiral triflate technology.[4]

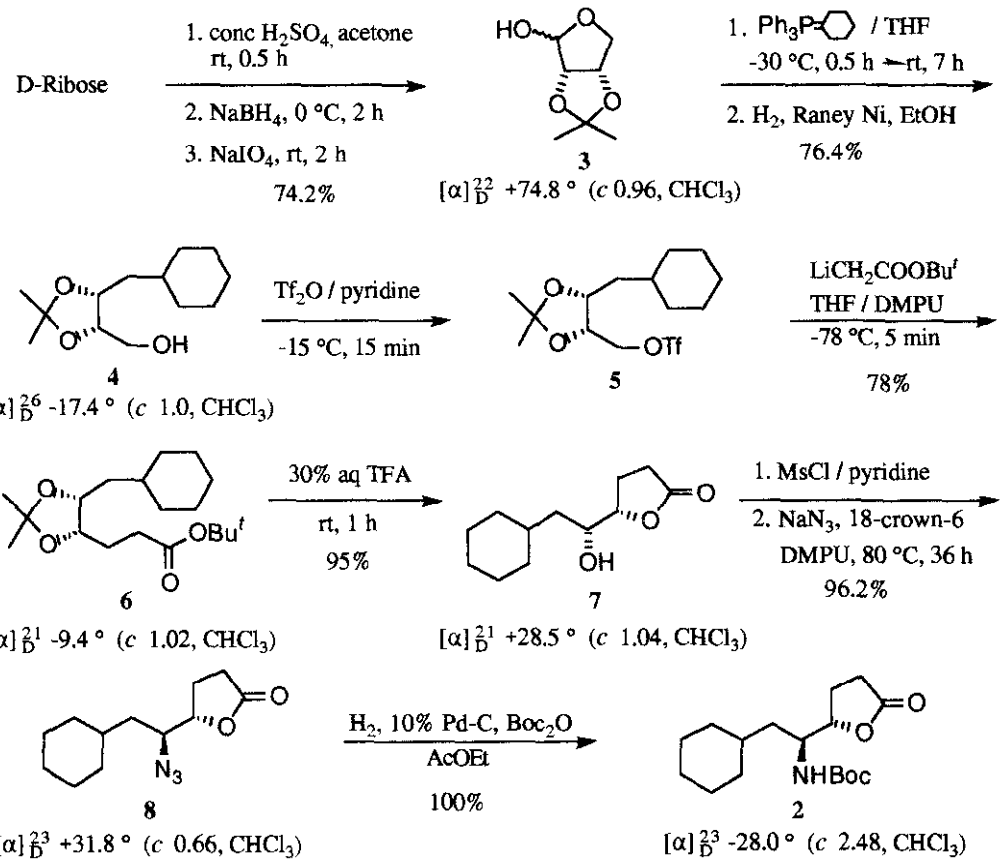


1

As outlined in Scheme 1, the lactone **2** was assembled from D-ribose. The requiste chiral building block, the lactol **3** [lit.[5] $[\alpha]^{25}_{D}$ +75° (*c* 1.0, MeOH)], was readily accessible from D-ribose in large amount. The introduction of a cyclohexyl side chain onto **3** was accomplished smoothly by the Wittig olefination followed by catalytic hydrogenation. Similarly as reported in our previous papers,[4d,f] we have initially examined the synthesis of hydroxylactone **7** from alcohol **4** through the coupling reaction of triflate **5** with allylmagnesium bromide. Unexpectedly, however, we found that the reaction was extremely slow and a considerable amount of the halogen-substituted byproduct was formed.[6] After numerous trials to perform the desired carbon chain functionalization, we observed that the alkylation of **5** with lithio t-butyl acetate inTHF-DMPU (6:1) was most satisfactory for this purpose. Thus, the reaction proceeded very fast even at -78 °C to afford **6** in 78% yield. The usual treatment of **6** under acidic conditions gave hydroxylactone **7**, mp 68.0-69.0 °C, which was, after conversion to the corresponding mesylate, reacted with NaN_3 to provide azide **8** in high yield. The complete S_N2 inversion in this step was confirmed by comparing with the literature data [lit.[3a] $[\alpha]_D$ +31.8° ($CHCl_3$)]. Finally, **8** was successfully transformed into the target molecule **2**, a precursor of the hydroxyethylene isostere.[3]

In conclusion, we have succeeded in exploring a new expeditious synthetic route to **2** in an enantiomerically pure form. The synthetic utility of this procedure is apparent from the easiness for deriving analogs by using several kinds of Wittig reagent. In this study we could also reconfirm the powerful tool of chiral triflate methodology for constructing chiral molecules with the correct stereochemistry.

Acknowledgement. The present work was partially supported by Central Glass Co., Ltd.



Scheme 1

References

1. W. J. Greenlee, *Pharm. Res.*, **4**, 364 (1987); C. S. J. Walpole and R. Wrigglesworth, *Nat. Prod. Rep.*, **1989**, 311.
2. P. Bühlmayer, A. Caselli, W. Fuhrer, R. Göschke, V. Rasetti, H. Rüeger, J. L. Stanton, L. Criscione, and J. M. Wood, *J. Med. Chem.*, **31**, 1839 (1988).
3. a) H. Yanagisawa, T. Kanazaki, and T. Nishi, *Chem. Lett.*, **1989**, 687. b) T. Nishi, M. Kataoka, and Y. Morisawa, *ibid.*, **1989**, 1993. c) P. K. Chakravarty, S. E. de Laszlo, C. S. Sarnella, J. P. Springer, and P. F. Schuda, *Tetrahedron Lett.*, **30**, 415 (1989). d) R. H. Bradbury, J. M. Revill, J. E. Rivett, and D. Waterson, *ibid.*, **30**, 3845 (1989). e) P. Herold, R. Duthaler, G. Rihs, and C. Angst, *J. Org. Chem.*, **54**, 1178 (1989).
4. a) H. Kotsuki, I. Kadota, and M. Ochi, *Tetrahedron Lett.*, **30**, 1281 (1989). b) *Idem, ibid.*, **30**, 3999 (1989). c) H. Kotsuki, Y. Ushio, I. Kadota, and M. Ochi, *J. Org. Chem.*, **54**, 5153 (1989). d) H. Kotsuki, I. Kadota, and M. Ochi, *ibid.*, **55**, 4417 (1990). e) *Idem, Tetrahedron Lett.*, **31**, 4609 (1990). f) H. Kotsuki, A. Miyazaki, M. Ochi, and J. J. Sims, *Bull. Chem. Soc. Jpn.*, **64**, 721 (1991). g) H. Kotsuki, in "Research Trends-Organic Chemistry," Council of Scientific Research Integration, Trivandrum, India; in press.
5. T. Hudlicky, H. Luna, J. D. Price, and F. Rulin, *J. Org. Chem.*, **55**, 4683 (1990).
6. The details will be reported elsewhere.

(Received in Japan 18 April 1991)