CHEMISTRY LETTERS, pp. 885-888 , 1978. Published by the Chemical Society of Japan

A USEFUL METHOD FOR THE SYNTHESIS OF MACROCYCLIC LACTONE

Koichi NARASAKA, Kazuo MARUYAMA, and Teruaki MUKAIYAMA

Department of Chemistry, Faculty of Science,

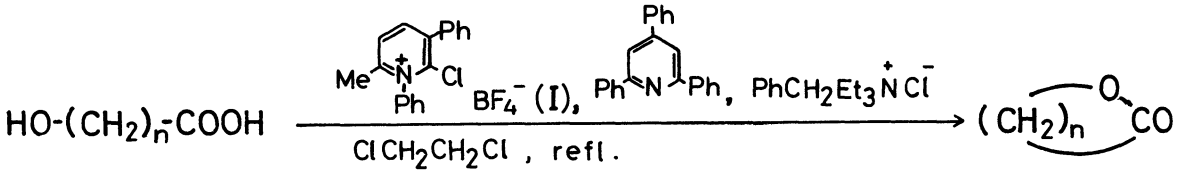
The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113

Long chain hydroxy acids were converted into macrocyclic lactones in high yields by the treatment with 2-chloro-6-methyl-1,3-diphenylpyridinium tetrafluoroborate, 2,6-dimethylpyridine (or 2,4,6-triphenylpyridine) and benzyltriethylammonium chloride. The lactonization reaction was successfully applied to the synthesis of (R)-(+)-ricinelaidic acid lactone, and prostaglandin $F_{2\alpha}$ 1,9- and 1,15-lactones.

Recently, we have reported an efficient method for cyclization of long chain hydroxy acids to macrocyclic lactones via 6-phenyl-2-pyridyl esters by two-steps procedure.[1] This method was successfully applied to the syntheses of recifeiolide and ricinelaidic acid lactone,[2] however, it was afraid that the use of p-toluenesulfonic acid in the second step for the cyclization of 6-phenyl-2-pyridyl ester would limit the application to the synthesis of more complex molecule. In order to develop a more promising method for lactonization of complex molecules, the previous method using 2-chloropyridinium salts[3] was reexamined. In this method, the treatment of hydroxy acids with 2-chloro-1-methylpyridinium salts and triethylamine afforded macrocyclic lactones in reasonable but not satisfactory yields. This result was mainly due to the decomposition of the pyridinium salts under the cyclization conditions by the attack of triethylamine to either 1-methyl group or 2-position of pyridinium ring to form 2-chloropyridine or 2-ammoniopyridinium salts.

In consideration of the above facts, a stable pyridinium salt, 2-chloro-6-methyl-1,3-diphenylpyridinium tetrafluoroborate (I),[4] was prepared according to the procedure developed in our laboratory,[5] and its applicability to the lactonization reaction was examined. When 15-hydroxypentadecanoic acid (IIa) was treated with I and

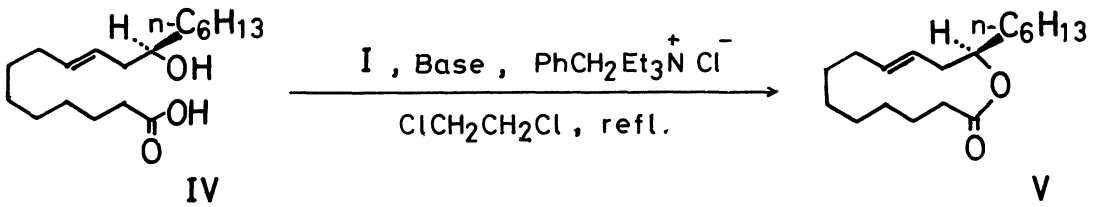
2,4,6-triphenylpyridine in refluxing dichloroethane by dilution method,[1] the pentadecanolide (IIIa) could not be obtained and the hydroxy acid (IIa) was recovered. On the other hand, the transformation of IIa to IIIa could be achieved effectively by the addition of benzyltriethylammonium chloride. For example, a dichloroethane (50 ml) solution of IIa (0.25 mmol) and 2,4,6-triphenylpyridine (1.0 mmol) was added during 7 h to a refluxing dichloroethane (30 ml) solution of I (0.5 mmol) and benzyltriethylammonium chloride (0.5 mmol) under argon. The reaction mixture was refluxed for an additional 1 h, and condensed under reduced pressure. After purification by column chromatography (silica gel), pentadecanolide (IIIa) was isolated in 99% yield. Similarly, 12-hydroxydodecanoic acid (IIb) was lactonized to dodecanolide (IIIb) in 85% yield.



IIa n=14
IIb n=11

IIIa 99 %
IIIb 85 %

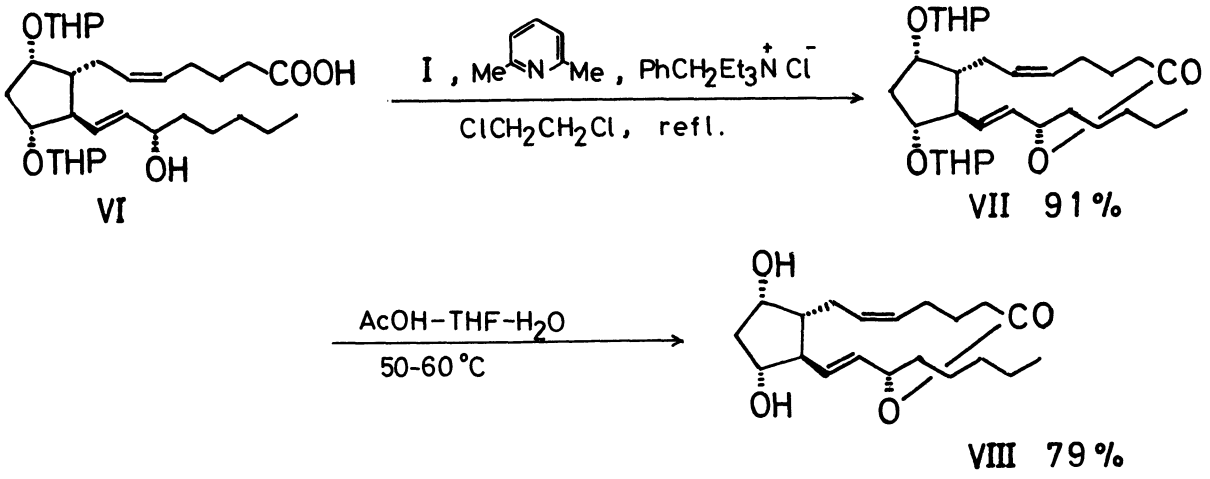
The use of 2-chloropyridinium salt (I) for the lactonization of optically active hydroxy acid is illustrated by the lactonization of (R)-(+)-ricinelaidic aid (IV). (R)-(+)-Lactone (V)[6] was obtained in 91% yield without epimerization[7] upon treatment of IV with I, 2,4,6-triphenylpyridine and benzyltriethylammonium chloride in refluxing dichloroethane. Similarly, when 2,6-dimethylpyridine was employed as a base instead of 2,4,6-triphenylpyridine in the above reaction, the lactone (V) was obtained in 86% yield.



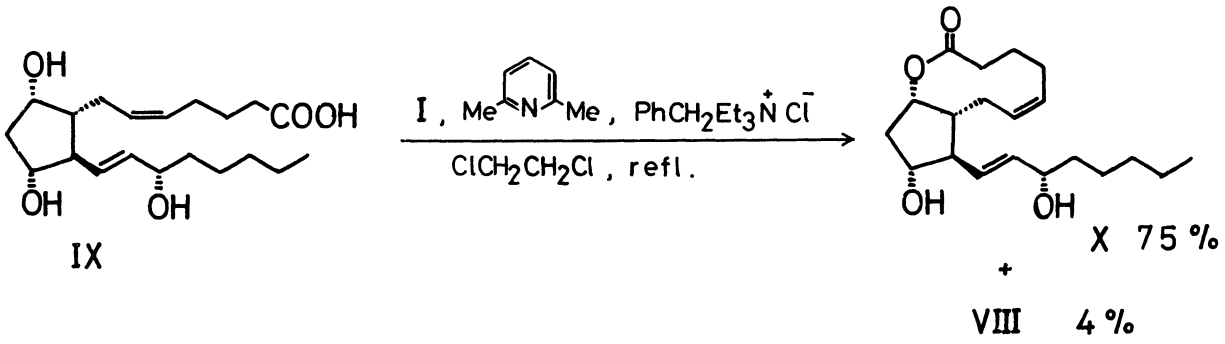
IV V

Base		
	2,4,6-Triphenylpyridine	91%
	2,6-Dimethylpyridine	86%

To demonstrate the applicability of this macrolactonization process to more complex hydroxy acids, the cyclizations of prostaglandin $F_{2\alpha}$ and prostaglandin $F_{2\alpha}$ 9,11-bis(tetrahydropyranyl) (THP) ether were now examined. A dichloroethane (20 ml) solution of prostaglandin $F_{2\alpha}$ 9,11-bis(THP) ether (VI, 0.14 mmol) was added to a dichloroethane (25 ml) solution of I (0.44 mmol), 2,6-dimethylpyridine (0.96 mmol) and benzyltriethylammonium chloride (0.42 mmol) under reflux during 4.25 h, and was further refluxed for additional 1 h. The protected 1,15-lactone of prostaglandin $F_{2\alpha}$ (VII, IR 1730 cm^{-1}) was isolated in 91% yield. Removal of the protecting group (AcOH-THF-H_2O,3:1:1; 50-60°C, 8 h) gave prostaglandin $F_{2\alpha}$ 1,15-lactone (VIII, 79%)[8] as crystals.



The lactonization of prostaglandin $F_{2\alpha}$ (IX) was carried out according to the same procedure and prostaglandin $F_{2\alpha}$ 1,9-lactone (X, 75%, R_f=0.1 (silica gel) 15% acetone in methylene chloride) was obtained along with a small amount of prostaglandin $F_{2\alpha}$ 1,15-lactone (VIII, 4%, R_f=0.2 (silica gel) 15% acetone in methylene chloride).



The successful synthesis of lactones V, VIII, and X described above demonstrates the utility of the present macrolactonization process.

Acknowledgment. We wish to express our hearty thanks to Professor Dr. Hans Gerlach, Eidgenössische Technische Hochschule Zürich, for his kind gift of (R)-(+)-ricinelaidic acid and Ono Pharmaceutical Co., LTD. for the kind gift of prostaglandins.

References and Notes

1) T. Mukaiyama, K. Narasaka, and K. Kikuchi, Chem. Lett., 1977, 441.

2) K. Narasaka, M. Yamaguchi, and T. Mukaiyama, Chem. Lett., 1977, 959.

3) T. Mukaiyama, M. Usui, and K. Saigo, Chem. Lett., 1976, 49; K. Narasaka, T. Masui, and T. Mukaiyama, ibid, 1977, 763.

4) NMR($CDCl_3$) δ 2.43 (3H. s), 7.47 (5H, s), 7.61 (5H, s) 7.94 (1H, d , J=8Hz), 8.27 (1H, d , J=8Hz).

5) M. Shiono, T. Shibanuma, and T. Mukaiyama, Chem Lett., 1976, 1041.

6) Ricinelaidic acid lactone (V) was identified by the comparison with the authentic sample (IR, NMR and TLC);[2] $[\alpha]_D^{25}$ +46° (c=1 in $CHCl_3$).

7) H. Gerlach, K. Oertle, and A. Thalmann, Helv. Chim. Acta, 59, 755 (1976).

8) Physical properties of 1,15-lactone (VIII) were well agreed with the literature;[10] mp 109-110°C, mp 110-111°C (after recrystallization from ether-hexane); IR(neat) 1730 cm^{-1}; $[\alpha]_D^{26}$ -92° (c=1.0 in $CHCl_3$); MS 336 (M^+), 318 (M^+-H_2O), 300 (M^+-2H_2O).

9) 1.9-Lactone (X) solidified gradually on standing in a few days; IR(neat) 1740 cm^{-1}; $[\alpha]_D^{26}$+95° (c=3.17 in $CHCl_3$); MS 318 (M^+-H_2O), 300 (M^+-2H_2O).

10) E. J. Corey, K. C. Nicolaou, and L. S. Melvin, Jr., J. Am. Chem. Soc., 97, 653, (1975).

11) The NMR spectra of these lactones (VIII and X) were well agreed with the NMR data of authentic samples;[10] personal communication from Dr. K. C. Nicolaou.

(Received June 15, 1978)