Tetrahedron Letters,Vol.27,No.33,pp 3889-3890,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

PREPARATION OF MEDIUM- AND LARGE-RING LACTONES. SmI_2-INDUCED CYCLIZATION OF ω-(α-BROMOACYLOXY) ALDEHYDES[1)]

Takanori Tabuchi, Kisa Kawamura, Junji Inanaga,* and Masaru Yamaguchi
Department of Chemistry, Kyushu University 33,
Hakozaki, Higashi-ku, Fukuoka 812, Japan

Summary: ω-Bromoacetoxy- and ω-(α-bromopropionyloxy) aldehydes were cyclized by SmI_2 giving 8- to 14-membered ring β-hydroxy lactones in excellent yields.

Recent synthetic elaborations in the field of macrolides have prompted the development of numerous useful lactonization methods.[2)] However, few of them are effective for the formation of medium-ring lactones, especially for 8- and 9-membered rings.[3)] Therefore, indirect ring expansion methods such as Baeyer-Villiger oxidation of cyclic ketones[4)] or oxidative cleavage of C-C double bond of bicyclic enol ethers[5)] have so far been adopted to get such strained lactones and the formation of medium-ring lactones by direct cyclization in good yields has still remained as a challengeable problem in organic synthesis.

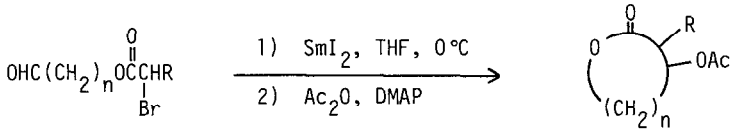
Here, we wish to report a very effective method for the formation of medium- as well as large-ring lactones by utilizing an intramolecular Reformatsky-type reaction[6)] with the aid of SmI_2. It has already been reported by Kagan et al. that a reaction of (+)-ethyl α-bromopropionate with cyclohexanone by SmI_2 produced Reformatsky product in 51 % yield, in which the optical purity of starting α-bromo ester was completely lost in the product indicating that the reaction proceeds through radical process.[7)] We assumed that C-C bond formation by radical reaction was much effective for the formation of medium-rings, since it might be possible to activate both the carbon atoms to be coupled, at the same time.[8)] Based on the idea, Kagan's method was applied to the cyclization of ω-(α-bromoacyloxy) aldehydes.

The results were very satisfactory as can be seen in the Table. Since medium-ring β-hydroxy lactones tended to be hydrolyzed in work-up stage, the products were isolated as acetates (entry 3, footnote e). Yields were not much affected by the concentration of the reactants (cf. entries 3~5). It is noteworthy that regardless of the difference of ring-size, uniformly very high yields were obtained. However, in cases of α-methyl-β-acetoxy lactones, stereoselectivity was not satisfactory (3:7~4:6).

In a typical experiment, to a cold (~0°C) THF solution of SmI_2 (0.1 mol dm^{-3}, 12 ml) was added dropwise a solution of 5-oxopentyl bromoacetate (45 mg, 0.2 mmol) in THF (100 ml) under nitrogen over 3~4 h. Excess SmI_2 was quenched by exposing the mixture to air and the crude product was directly acetylated with excess Ac_2O and DMAP. Usual work-up followed by chromatographic purification (SiO_2) gave 3-acetoxy-7-heptanolide (28.5 mg, 76 %) as an oil (entry 1).

β-Hydroxy lactone structure is frequently encountered in macrolide antibiotics. A study on the synthesis of some such macrolides by utilizing the present cyclization method is under way.

Table. Preparation of Medium- and Large-ring Lactones[a)]



Entry	Ring size (n + 4)	Yield (%) of lactones[b)] R = H	R = CH_3 [Isomeric ratio][c)]
1[d)]	8	76	82 [38:62]
2[d)]	9	92	90 [31:69]
3	10	82	88 (75)[e)] [35:65]
4[f)]	10	82	
5[g)]	10	75	
6	11	86	80 [30:70]
7	12	85	82 [30:70]
8	13	80 ((35))[h)]	91 [38:62] ((48))[h)]
9	14	84	

a) The reactions were carried out at 2 mmol dm^{-3} concentration in 0.1 mmol scale, unless otherwise stated. b) Isolated yield after acetylation. All products gave satisfactory ^1H NMR and mass spectral data. c) Relative ratio obtained from ^1H NMR spectrum. Configuration was not determined. d) The reaction was performed in 0.2 mmol scale. e) Isolated yield of β-hydroxy lactone without O-acetylation. f) At 10 mmol dm^{-3} concentration. g) At 50 mmol dm^{-3} concentration. h) The yield reported in reference 6 is given in double parentheses.

References and Notes

1) Presented at the 52th National Meeting of the Chemical Society of Japan, Kyoto, Apr 1986. 2) For reviews: K.C.Nicolaou, Tetrahedron, **33**, 683 (1977) and I.Paterson and M.M.Mansuri, ibid., **41**, 3569 (1985). 3) It was reported that sodium 8-bromooctanoate (ca. 0.1 mol dm^{-3} solution in 99 % DMSO at 50°C) was lactonized to give nonanolide in 93 % yield (GLC), though the isolation of the product was not described: C.Galli, G.Illuminati, and L.Mandolini, J. Am. Chem. Soc., **95**, 8374 (1973). A mixed anhydride method has also been known to produce 36 % yield of nonanolide: J.Inanaga, K.Hirata, H.Saeki, T.Katsuki, and M.Yamaguchi, Bull. Chem. Soc. Jpn., **52**, 1989 (1979). 4) For example, see E.J.Corey, D.J.Brunelle, and K.C.Nicolaou, J. Am. Chem. Soc., **99**, 7359 (1977). 5) For example, see T.Wakamatsu, K.Akasaka, and Y.Ban, J. Org. Chem., **44**, 2008 (1979) and references cited therein. 6) An intramolecular Reformatsky-type reaction by Zn-Ag and Et_2AlCl has already been reported to give large-ring lactones in 35-68 % yield, where an aluminum enolate intermediate is proposed: K.Maruoka, S.Hashimoto, Y.Kitagawa, H.Yamamoto, and H.Nozaki, J. Am. Chem. Soc., **99**, 7705 (1977). 7) P.Girard, J.L.Namy, and H.B.Kagan, J. Am. Chem. Soc., **102**, 2693 (1980). 8) Some radical reactions have been known to be effective for the formation of medium-ring compounds: For example, acyloin condensation [J.J.Bloomfield, D.C.Owsley, and J.M.Nelke, Org. Reactions, **23**, 259 (1976)] or titanium-induced dicarbonyl-coupling reaction [J.E.McMurry, Acc. Chem. Res., **16**, 405 (1983)].

(Received in Japan 10 May 1986)