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A Convenient Synthesis of γ-Alkyl-α-hydroxy-γ-lactones as a Food Intake-Control Substance

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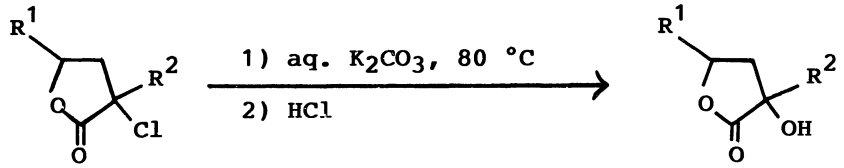
A series of new γ-alkyl-α-hydroxy-γ-lactones which are promising as excellent food intake-control substances was synthesized in high yields by the hydrolysis of γ-alkyl-α-chloro-γ-lactones.

Recently, much interest has been focused on α-hydroxy-γ-lactones such as (2S)-α-hydroxy-γ-lactone and (2S,4S)-α-hydroxy-γ-hydroxymethyl-γ-lactone, because they act much effectively as a food intake-control substance upon the ventromedial nucleus of the hypothalamus (VMH), which is referred to the satiety center in the hypothalamus, a part of brain.[1] However, unfortunately, these lactones have such disadvantage that the lipid solubility is so low that the injection of the α-hydroxylactone to Male Wister strain rats through the jugular vein requires at least 100-fold dose based on the effective quantities in the hypothalamus.[2] Therefore, the synthesis of new α-hydroxy-γ-lactones with good to high lipid solubility has been highly desired. In view of the circumstances, it is of great value to investigate a convenient synthesis of α-hydroxy-γ-lactones having an alkyl group which may be expected to increase the lipid solubility. However, to date, no reports have been published for the convenient synthesis of such α-hydroxy-γ-lactones.

Now, we have successfully synthesized a series of γ-alkyl-α-hydroxy-γ-lactones by the hydrolysis of the corresponding α-chloro-γ-lactones, which are easily prepared by the Ru(II)-catalyzed reaction of α-polychlorinated carboxylic acids with terminal alkenes under mild conditions.[3] We wish to report herein our preliminary results.



A typical procedure is as follows: A mixture of α-chloro-γ-hexyl-γ-lactone (3.0 g, 15 mmol, a 1:1 mixture of cis and trans γ-lactone) and aqueous K_2CO_3(1 mol dm^{-3}, 17 ml) was stirred at 80 °C for 32 h. The resulting mixture was allowed to cool to room temperature and then poured slowly into aqueous HCl(12 mol dm^{-3}, 10 ml). Ethereal extracts from the resulting solution were dried over magnesium sulfate, concentrated, and distilled, giving 2.55 g(91%) of a stereoisomeric mixture of α-hydroxy-γ-hexyl-γ-lactones: bp 121 °C/1.5 mmHg;[4] IR(neat); 3400(O-H),

1770 (C=O), and 1190cm^{-1}(C-O-C); ^{1}H NMR(CCl_4) δ= 4.83-3.87(3H, m), 3.00-1.90 (2H, m), 1.77-1.10 (10H, m), and 0.88(3H, t, J=5 Hz); MS(CI, iso-butane) m/e 187(M^++1); Found: C, 64.07; H, 9.7%; Calcd for $C_{10}H_{18}O_3$: C, 64.49, H, 9.74%.

Table 1. Synthesis of γ-Alkyl-α-Hydroxy-γ-Lactones[a)]

Run	R^1	R^2	Product No.	Yield[b)] %	Bp/°C(mmHg)[4)]	IR[c)] ν_{O-H}/cm^{-1}	IR[c)] $\nu_{C=O}$/cm^{-1}	MS[d)] (M^++1)
1	C_4H_9	H	1	96	98-99(1.5)	3400	1770	159
2	i-C_4H_9	H	2	99	120(3)	3435	1785	159
3	C_5H_{11}	H	3	89	105-120(4)	3400	1760	173
4	C_6H_{13}	H	4	91	121(1.5)	3400	1770	187
5	C_7H_{15}	H	5	95	118-120(1.5)	3400	1770	201
6	C_8H_{17}	H	6	100	132-135(0.5)	3400	1770	215
7	$C_{10}H_{21}$	H	7	98	——— e)	3450[f)]	1765[f)]	243
8	$C_{12}H_{25}$	H	8	95	——— e)	3450[f)]	1760[f)]	271
9	C_4H_9	CH_3	9	97	93-95(2)	3450	1760	173
10	C_7H_{15}	CH_3	10	97	149.5(5.5)	3450	1760	215

a) The hydrolysis was carried out under conditions at 80 °C for 30-40 h stirring. Each product is a stereoisomeric mixture. Satisfactory elementary analyses and spectral data(IR, ^{1}H NMR, and MS) were obained for all new lactones (1-10). b) Isolated yields. c) Liquid film. d) MS was measured by CI method using iso-butane. e) The pasty liquid, which was isolated by means of evaporation under vacuum, the purity of which was enough for elemental analysis as it is. f) Nujol mull.

Other results are summarized in Table 1. In summary, the present hydrolysis of α-chloro-γ-lactones proceeded under milder conditions than did the previously reported that of α-bromo-γ-lactone[5)] and has advantages of the high yields of the products as well as the simplicity of the reaction procedure. Finally, it should be emphasized that α-hydroxy-γ-lactones thus prepared 4 and 6 were found to act efficiently as a food intake-control substance.[6)]

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References
1) N. Shimizu, Y. Oomura, and T. Sakata, Am. J. Physiol., 246, 542 (1984); K. Puthuraya, Y. Oomura, and N. Shimizu, Brain Research, 332, 165 (1985).
2) Y. Oomura, Yuki Gosei Kagaku Kyokaishi, 44, 33 (1986); Kagaku, 42, 440 (1987).
3) T. Nakano, K. Ohkawa, S. Ikemori, R. Hasegawa, R. Sako, H. Matsumoto, and Y. Nagai, Nippon Kagaku Kaishi, 1983, 1770.
4) Boiling points are uncorrected. 1 mmHg≈133.3 Pa.
5) A. C. J. Opfermann, Brit., 688253 (1953), Chem. Abstr., 48, 3996i (1954).
6) A private communication from Professor Oomura of Faculty of Medicine, Kyushu University: Some α-hydroxylactones so prepared were sent to Professor Oomura to examine food intake-control activity using Male Wister strain rats. γ-Alkyl-α-hydroxy-γ-lactones were found to show excellent food intake-control activity even by intragastric administration. Especially, the adminitration of 4 or 6 in physiological saline into the rats made the food intake dramatically decrease. The details will be reported elsewhere by Oomura et al.

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