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Synthesis and properties of germa-γ-lactones

Norihiro Kakimoto *, **Tohru Yoshiwara,**
Asai Germanium Research Institute, 1-6-4, Izumihoncho, Komae-shi, Tokyo 201 (Japan)

Mitsuo Akiba * **and Yoshiharu Ishido**
Tokyo College of Pharmacy, 1432-1, Horinouchi, Hachioji-shi, Tokyo 192-03 (Japan)

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Abstract

Trialkylgermylpropanoic acids treated with 1 mole of bromine afford the monobromopropanoic acids, which are converted into the corresponding germa-γ-lactones in good yields by hydrolysis. The physical, chemical, and biological properties of these compounds are described.

Introduction

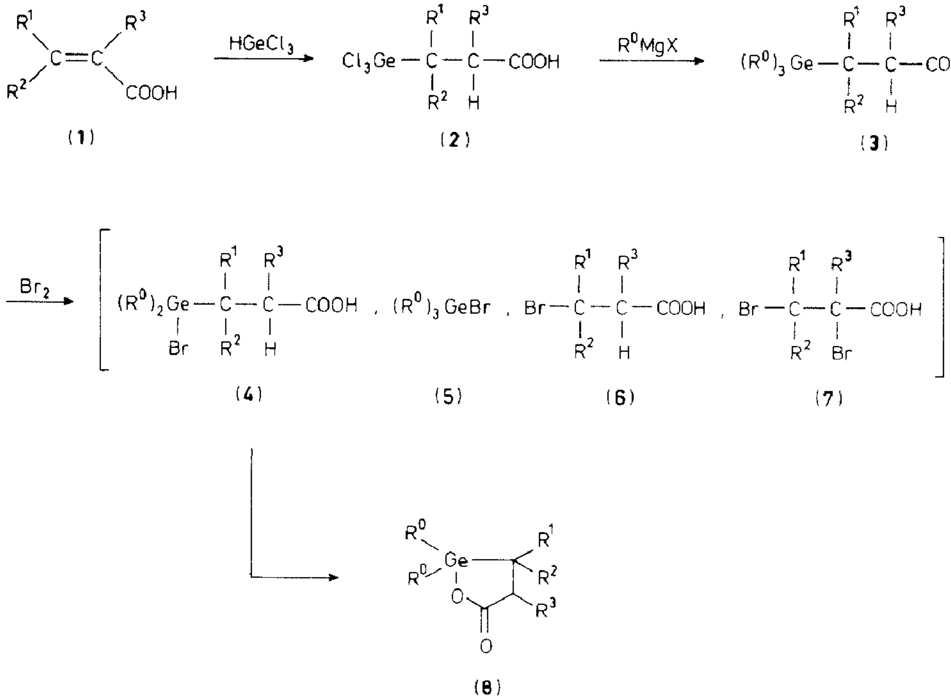
The 4-substituted butanolides (γ-lactones) occur in a number of natural products and insect sex pheromones [1]. Furthermore, these compounds are useful and versatile intermediates for the synthesis of biologically useful compounds [2].

As part of our study of synthetic biologically active organogermanium compounds, we herein report a simple method for the novel synthesis of germa-γ-lactones (**8**), whose physical and chemical properties, and bioactivity were compared with those of the γ-lactones.

Results and discussion

The synthetic route to **8** is shown in Scheme 1.

The α,β-unsaturated carboxylic acids (**1**) were treated with trichlorogermane to give the trichlorogermyl adducts (**2**) [3], which in turn were transformed into γ-trialkylgermylpropanoic acids (**3**) by Grignard reagents in 63–84% yields. The reaction of (**3a–e**) with 1 mole of bromine in chloroform at 0 °C afforded the monobrominated germylpropanoic acids (**4a–e**) in good yields except for **4d**. In the case of **3f,g** ($R^1 = C_6H_5$), **4f** or **4g** was not obtained but **6f** or **6g** was produced as a sole product isolated. The bromination of **3f** was monitored by ^{1}H NMR spectroscopy which revealed the signal of the trimethyl moiety due to trimethylgermyl



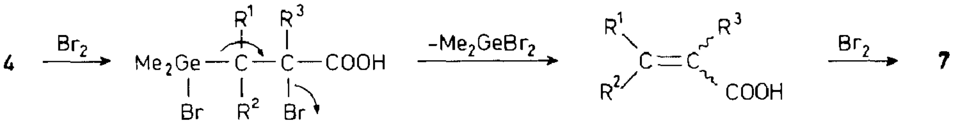
Scheme 1

bromide (**5**) at 0.83 ppm in addition to that of 3-bromo-3-phenylpropanoic acid (**6f**). The Ge–C bonds in germacyclobutanes and alkenylgermanes are readily cleaved by iodine at 0°C in the absence of catalyst [4]. Thus, bromine, being more reactive than iodine, readily and exclusively cleaves Ge–C (benzyl) bonds. On treatment with an excess of bromine, on the other hand, **3c** (or **3d**) did not give **4c** (**4d**) but **7c** (or **7d**) as the sole product. Thus, **7** should form via **4** during the bromination of **3**. Table 1 shows the results of the bromination of **3**. Compounds **4c** was treated with an excess of bromine and did indeed give the expected compound, **7c**. In light of the

Table 1

Reaction of trialkylgermylpropanoic acids (3) with bromine in chloroform

3	R^0	R^1	R^2	R^3	Reaction conditions			Product yield (%)		
					Br$_2$ (mol)	temp. (°C)	time (h)	**4**	**6**	**7**
a	CH$_3$	H	H	H	1	0	1	87	–	–
b	CH$_3$	CH$_3$	H	H	1	0	1	83	–	–
c	CH$_3$	H	H	CH$_3$	1	0	1	80	–	–
					3	0	5	–	–	80
d	CH$_3$	CH$_3$	H	CH$_3$	1	0	2	39	–	40
					3	0	5	–	–	72
e	CH$_3$	CH$_3$	CH$_3$	H	1	0	1	80	–	–
f	CH$_3$	C$_6$H$_5$	H	H	1	0	1	–	60	–
g	CH$_3$	C$_6$H$_5$	H	CH$_3$	1	0	1	–	70	–
h	C$_2$H$_5$	H	H	H	1	0	1	53	–	–



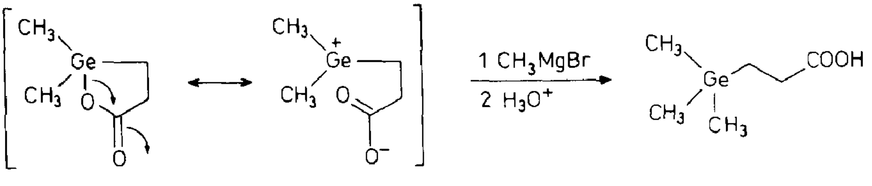
(9)

Scheme 2

above results, we propose a mechanism in which bromination of **4** gives the α-bromocarboxylic acid intermediate **9**, which undergoes β-elimination [5] to the α,β-unsaturated carboxylic acid followed by re-bromination to give **7** (Scheme 2).

Treatment of **4** with water in carbon tetrachloride at room temperature gives germa-γ-lactone (**8**) in good yields. The molecular structure of **8** thus obtained was determined by elemental analysis and spectral data. The results of the preparation of **8** are listed in Table 2.

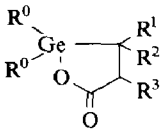
The IR spectrum of **8** generally shows an absorption band attributable to the carbonyl group of germa-γ-lactone at an much lower frequency (1620–1645 cm^{-1}) than that of the γ-lactone. This remarkable feature in the IR spectrum of **8** suggests the presence of σ–π conjugation [6] between the Ge–O bond and the C=O double bond in the structure of **8**. However, the cause is not clear. **8a** undergoes selective attack of methylmagnesium bromide at the γ-position to afford trimethylgermylpropanoic acid (**3a**) in 76% yield.



(8a) (3a)

Table 2

Preparation of 4,4-dialkyl-4-germa-γ-butyrolactones (**8**)



(**8**)

8	Molecular formula [a]	Yield (%)	M.p. (°C)	IR (cm^{-1})		MS (M^+ m/z)
				ν(C=O)	ν(Ge–C)	
a	$C_5H_{10}GeO_2$	74	174–175	1645	640	177
b	$C_6H_{12}GeO_2$	69	145–147	1640	640	191
c	$C_6H_{12}GeO_2$	68	150–152	1630	630	191
d	$C_7H_{14}GeO_2$	85	120	1620	635	205
e	$C_7H_{14}GeO_2$	85	141	1625	620	205
h	$C_7H_{14}GeO_2$	93	116–117	1623	602	205

[a] Elemental analyses of these compounds were within acceptable limits.

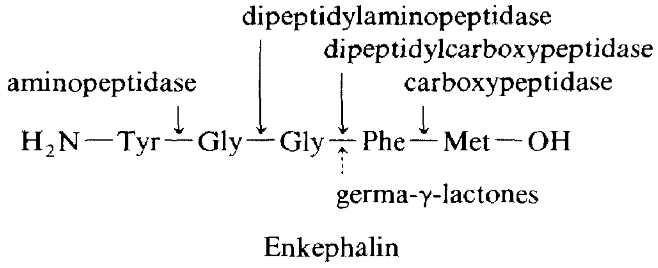
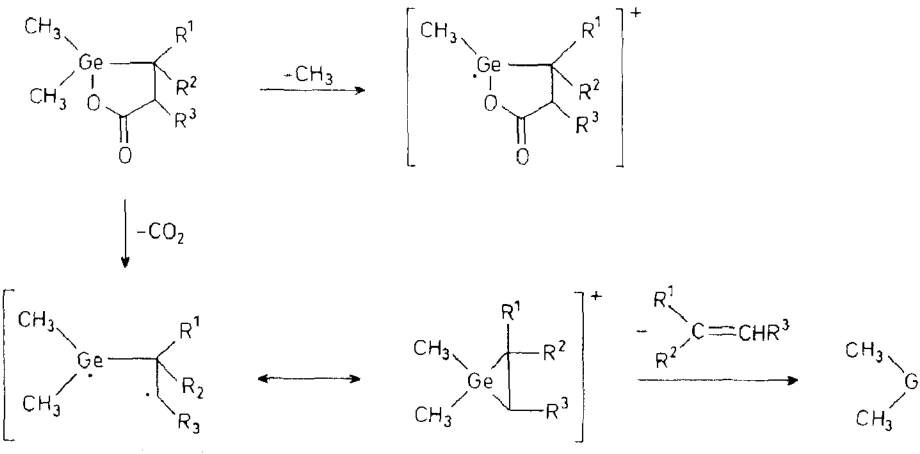


Fig. 1. Enkephalin degrading enzymes and germa-γ-lactones as their inhibitors.



Scheme 3

The mass spectra of **8a–e** generally show the typical peaks of $[M^+ - CH_3]$, $[M^+ - CO_2]$, $(CH_3)_2Ge$, in addition to those of the molecular ion, M^+ (Scheme 3). Notably, the very strong peak of $(CH_3)_2Ge$ was observed as a base peak, and suggests the existence of the germylene [7] as an reaction intermediate in the pyrolysis of **8**.

Of these compounds, 4,4-dimethyl-4-germa-γ-butyrolactone (**8a**) strongly inhibits dipeptidylcarboxypeptidase degradation of enkephalins – compounds which show morphine-like activity. This result suggests that **8a** may be as effective in the physiological pain-regulation system in vivo. Investigation of other biological activities of these compounds is now being carried out.

Experimental

All the melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. IR spectra were recorded with a Hitachi 260-10. ^{1}H-NMR spectra were determined with a Varian EM-390 spectrometer using tetramethylsilane as an internal standard. Mass spectra were recorded with a Hitachi M-80 mass spectrometer.

General procedure for the formation of trialkylgermylpropanoic acids (3). To a solution of trichlorogermylpropanoic acid (0.04 mol) in absolute ether (50 ml) was gradually added a solution of methylmagnesium iodide (0.18 mol) in absolute ether (50 ml) at 0 °C under nitrogen with stirring. The reaction mixture was refluxed for 30 min, then cooled, and poured into a dilute hydrochloric acid solution. The ether layer was separated, washed with water, dried over anhydrous $MgSO_4$, and evaporated to dryness in vacuo. The residue was purified by distillation to give the expected product **3** in 68–80% yields.

*3-(Trimethylgermyl)propanoic acid (**3a**)*

B.p. 100 °C/18 Torr. ^1H NMR($CDCl_3$, δ ppm): 0.13 (s, 9H, $(CH_3)_3Ge$), 1.03 (t, 2H, J 8.1 Hz, $GeCH_2$), 2.43(t, 2H, J 8.1 Hz. CH_2CO), 11.00(s, 1H, COOH). mass spectrum (EI, 70 eV) m/z 192 (M^+). Anal. Found: C, 37.57; H, 7.37; Ge, 37.82. $C_6H_{14}GeO_2$ calcd.: C, 37.78; H, 7.40; Ge, 38.05%.

*3-(Trimethylgermyl)butanoic acid (**3b**)*

B.p. 116 °C/4 Torr. ^1H NMR($CDCl_3$, δ ppm): 0.12(s, 9H, $(CH_3)_3Ge$), 1.08(d, 3H, J 6.6 Hz, $CHCH_3$), 1.47 (m, 1H, GeCH), 2.33(m, 2H, CH_2CO), 12.13(s, 1H, COOH). mass spectrum m/z 206 (M^+).

*2-Methyl-3-(trimethylgermyl)propanoic acid (**3c**)*

B.p. 99 °C/4Torr. ^1H NMR($CDCl_3$, δ ppm): 0.15(s, 9H, $(CH_3)_3Ge$), 1.00(m, 2H, CH_2), 1.23(d, 3H, J 6.9 Hz, $CHCH_3$), 2.58(m, 1H, $CHCH_3$), 12.25(s, 1H, COOH). mass spectrum m/z 206 (M^+).

*2-Methyl-3-(trimethylgermyl)propanoic acid (**3d**)*

B.p. 125 °C/10 Torr. ^1H NMR($CDCl_3$, δ ppm): 0.15(s, 9H, $(CH_3)_3Ge$), 1.07(d, 3H, J 6.4 Hz, $CHCH_3$), 1.20(d, 3H, J 6.4 Hz, $CHCH_3$), 1.18(m. 1H, $CHCH_3$), 2.55(m, 1H, $CHCH_3$), 12.32(s, 1H, COOH). mass spectrum m/z 220 (M^+).

*3-Methyl-3-(trimethylgermyl)butanoic acid (**3e**)*

B.p. 130 °C/15 Torr. ^1H NMR($CDCl_3$, δ ppm): 0.10(s, 9H, $(CH_3)_3Ge$), 1.08(s, 6H, $2 \times CH_3$), 2.22(s, 2H, CH_2), 11.70(s, 1H, COOH). mass spectrum m/z 220 (M^+).

*3-Phenyl-3-(trimethylgermyl)propanoic acid (**3f**)*

M.p. 89–91 °C. ^1H NMR($CDCl_3$, δ ppm): 0.06(s, 9H, $(CH_3)_3Ge$), 2.77(s, 1H, CHph), 2.77(s, 2H, CH_2), 7.10(m, 5H, ph), 12.02(s, 1H, COOH). mass spectrum m/z 268 (M^+). Anal. Found: C, 54.01; H, 6.80. $C_{12}H_{18}GeO_2$ calcd.: C, 53.97; H, 6.64%.

*2-Methyl-3-phenyl-3-(trimethylgermyl)propanoic acid (**3g**)*

M.p. 94–95 °C. ^1H NMR($CDCl_3$, δ ppm): 0.08(s, 9H, $(CH_3)_3Ge$), 1.27(d, 3H, J 7.1 Hz, $CHCH_3$), 2.47(d, 1H, J 10.6 Hz, CHPh), 2.97(m, 1H, $CHCH_3$), 11.68(s, 1H, COOH). mass spectrum m/z 282 (M^+). Anal. Found: C, 55.39; H, 6.95. $C_{13}H_{20}GeO_2$ calcd.: C, 55.59; H, 7.18%.

*3-(Triethylgermyl)propanoic acid (**3h**)*

B.p. 135–137 °C/4 Torr. ^{1}H NMR($CDCl_3$, δ ppm): 0.50–1.20(m, 17H, 3 × $C_2H_5 + GeCH_2$), 2.37(t, 2H, *J* 8.1 Hz, CH_2CO), 11.81(s, 1H, COOH). Anal. Found: C, 46.33; H, 8.99. $C_9H_{20}GeO_2$ calcd.: C, 46.41; H, 8.66%.

Reaction of trialkylgermylpropanoic acids (3) with bromine

Method A: Bromine (0.1 mol) in carbon tetrachloride (100 ml) was added dropwise to a stirred solution of trialkylgermylpropanoic acid (**3a–e**, and **3h**) (0.1 mol) in carbon tetrachloride (50 ml) at 0 °C under nitrogen. The mixture was stirred for 1 or 2 h and then allowed to warm to room temperature. The mixture was evaporated to dryness to afford a crude product. Purification by recrystallization from hexane or by medium pressure liquid chromatography using a hexane/ethyl acetate mixture as the developing solvent gave 3-(bromodialkylgermyl)propanoic acid (**4a–e**, and **4h**) or **4d** and 2,3-dibromopropanoic acid (**7d**). In the case of **3f** or **3g**, 3-bromocinnamic acid **6f** or **6g** was obtained as the sole product.

Method B: Bromine (0.3 mol) in carbon tetrachloride (100 ml) was added dropwise to a stirred solution of trialkylgermylpropanoic acid (**3c** or **3d**) (0.1 mol) in carbon tetrachloride (50 ml) at 0 °C under nitrogen. The mixture was stirred for 5 h and worked up as described above, to give **7c** or **7d** as the sole product. The results are listed in Table 1.

*3-(Bromodimethylgermyl)propanoic acid (**4a**)*

M.p. 42–43 °C. ^{1}H NMR($CDCl_3$, δ ppm): 0.86(s, 6H, $(CH_3)_2Ge$), 2.68(t, 2H, *J* 7.5 Hz, CH_2), 10.70(s, 1H, COOH), 15.20(t, 2H, CH_2). mass spectrum *m/z* 177(M^+ − Br). Anal. Found: C, 23.63; H, 4.47; Br, 31.23. $C_5H_{11}BrGeO_2$ calcd.: C, 23.49; H, 4.33; Br, 31.26%.

*3-(Bromodimethylgermyl)butanoic acid (**4b**)*

M.p. 66–68 °C. ^{1}H NMR($CDCl_3$, δ ppm): 0.82(s, 6H. $(CH_3)_2Ge$), 1.22(d, 3H, J 7.2 Hz, CH_3), 1.78(m, 1H, CH), 2.57(m, 2H, CH_2), 12.07(s, 1H, COOH); mass spectrum *m/z* 191 (M^+ − Br). Anal. Found: C, 26.58, H, 4.97; Br, 29.40. $C_6H_{13}BrGeO_2$ calcd.: C, 26.72; H, 4.82; Br, 29.64%.

*2-Methyl-3-(bromodimethylgermyl)propanoic acid (**4c**)*

B.p. 150 °C/18 Torr. ^{1}H NMR($CDCl_3$, δ ppm); 0.85(s, 6H, $(CH_3)_2Ge$), 1.33(d, 3H, *J* 7.2 Hz, CH_3), 1.55 (d, 2H, *J* 7.2 Hz, CH_2), 2.83(m, 1H, CH), 12.00(s, 1H, COOH). mass spectrum *m/z* 191 (M^+ − Br). Anal. Found: C, 26.58; H, 4.92; Br, 29.36. $C_6H_{13}BrGeO_2$ calcd.: C, 26.72; H, 4.82; Br, 29.64%.

*2-Methyl-3-(bromodimethylgermyl)butanoic acid (**4d**)*

M.p. 120 °C; ^{1}H NMR($CDCl_3$, δ ppm): 0.87(s, 6H, $(CH_3)_2Ge$), 1.13(d, 3H, *J* 7.3 Hz, CH_3), 1.25(d, 3H, *J* 7.2 Hz, CH_3), 1.80(m, 1H, CH), 2.90(m, 1H, CH), 11.80(s, 1H, COOH). mass spectrum *m/z* 205(M^+ − Br). Anal. Found: C, 29.77; H, 5.39; Br, 27.91. $C_7H_{15}BrGeO_2$ calcd.: C, 29.64; H, 5.33; Br, 28.17%.

*3-Methyl-3-(bromodimethylgermyl)butanoic acid (**4e**)*

M.p. 91–93 °C. ^{1}H NMR($CDCl_3$, δ ppm): 0.80(s, 6H, $(CH_3)_2Ge$), 1.23(s, 6H,

$C(CH_3)_2$. 2.47(s, 2H, CH_2), 11.97(s, 1H, COOH). mass spectrum m/z 205 ($M^+ -$ Br). Anal. Found: C, 29.67; H, 5.30; Br, 27.92. $C_7H_{15}BrGeO_2$ calcd.: C, 29.64; H, 5.33; Br, 28.17%.

*3-(Bromodiethylgermyl)propanoic acid (**4h**)*

B.p. 165–168° C/5 Torr.. ^1H NMR($CDCl_3$, δ ppm): 1.22(s, 10H, $GeCH_2CH_3$), 1.50(t, 2H, J 8.0 Hz, $GeCH_2$), 2.64(t, 2H, J 8.0 Hz, CH_2), 12.01(s, 1H, COOH). mass spectrum m/z 205 ($M^+ -$ Br).

*General procedure for the formation of germa-γ-lactones (**8**)*

To a solution of bromodialkylpropanoic acid (0.01 mol) in carbon tetrachloride (50 ml), was added water (25 ml). The mixture was allowed to stand for 1 h, neutralized with 5% Na_2CO_3 solution and ethyl acetate was added. The combined organic layer was separated, washed with water, dried over anhydrous $MgSO_4$, and evaporated to dryness in vacuo. The resulting solid was recrystallized from benzene to give the expected product 8 in 68–93% yields. The results are shown in Table 2.

*4,4-Dimethyl-4-germa-γ-butyrolactone (**8a**)*

^1H NMR(methanol-d_4, δ ppm): 0.79(s, 6H, $(CH_3)_2Ge$), 1.48(t, 2H, J 8.1 Hz, $GeCH_2$), 2.70(t, 2H, J 8.1 Hz, CH_2CO). Anal. Found: C, 34.14; H, 5.79; Ge, 41.75. $C_5H_{10}GeO_2$ calcd.: C, 34.37; H, 5.77; Ge, 41.55%.

*3,4,4-Trimethyl-4-germa-γ-butyrolactone (**8b**)*

^1H NMR(methanol-d_4, δ ppm): 0.63(s, 6H, $(CH_3)_2Ge$), 1.20(d, 3H, J 7.5 Hz, CH_3), 1.90(m, 1H, CH), 2.23(d,d, 1H, J 3.0, 8.1 Hz, CH), 2.82(d,d, 1H, J 3.0 8.1 Hz, CH). Anal. Found: C, 38.29; H, 6.38. $C_6H_{12}GeO_2$ calcd.: C, 38.18; H, 6.41%.

*2.4.4.-Trimethyl-4-germa-γ-butyrolactone (**8c**)*

^1H NMR(methanol-d_4, δ ppm): 0.67(s, 6H, $(CH_3)_2Ge$), 1.21(d,d, 1H, J 2.0 Hz, 8.1Hz, C^3-H), 1.27(d, 3H, J 7.5 Hz, CH_3), 2.70(m, 1H, C^2-H). Anal. Found: C, 38.09; H, 6.48. $C_6H_{12}GeO_2$ calcd.: C, 38.18; H, 6.41%.

*2,3,4,4-Tetramethyl-4-germa-γ-butyrolactone (**8d**)*

^1H NMR(methanol-d_4, δ ppm): 0.67(s, 6H, $(CH_3)_2Ge$), 1.10(d, 3H, J 7.6 Hz, C^3-CH_3), 1.22(d, 3H, J 7.3 Hz, C^2-CH_3), 1.92(m, 1H, C^3-H), 2.80(m, 1H, C^2-H). Anal. Found: C, 41.50; H, 7.11. $C_7H_{14}GeO_2$ calcd.: C, 41.46; H, 6.96%.

*3,3,4,4-Tetramethyl-4-germa-γ-butyrolactone (**8e**)*

^1H NMR(methanol-d_4, δ ppm): 0.67(s, 6H, $(CH_3)_2Ge$), 1.25(s, 6H, $C^3(CH_3)_2$), 2.47(s, 2H, CH_2CO). Anal. Found: C, 41.36; H, 7.08. $C_7H_{14}GeO_2$ calcd.: C, 41.46; H, 6.96%.

*4,4-Diethyl-4-germa-γ-butyloractone (**8h**)*

^1H NMR(methanol-d_4, δ ppm): 1.18(s, 10H, CH_3CH_2Ge), 1.48(t, 2H, J 7.0 Hz, $GeCH_2$), 2.61(t, 2H, J 7.0 Hz, CH_2CO). Anal. Found: C, 41.18; H, 7.10. $C_7H_{14}GeO_2$ calcd.: C, 41.46; H, 6.96%.

*Reaction of 4,4-dimethyl-4-germa-γ-butyrolactone (**8a**) with methylmagnesium bromide*

To a solution of 4,4-dimethyl-4-germa-γ-buthyrolactone (**8a**) (3.49 g, 0.02 mol) in absolute ether (50 ml) was gradually added a solution of methylmagnesium bromide (0.02 mol) in absolute THF (30 ml) at 0 °C under nitrogen with stirring. The reaction mixture was allowed to stand for 1 h under stirring, and then poured into a dilute hydrochloric acid solution (30 ml). The ether layer was separated, washed with water, dried over anhydrous $MgSO_4$ and evaporated to dryness in vacuo. The residue was purified by distillation to give 2.9 g (76%) of trimethylgermylpropanoic acid (**3a**) which was found to be identical with an authentic sample.

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