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Novel Lactonization of Ethenetricarboxylate Derivatives: Intermolecular Trapping of Alkenes

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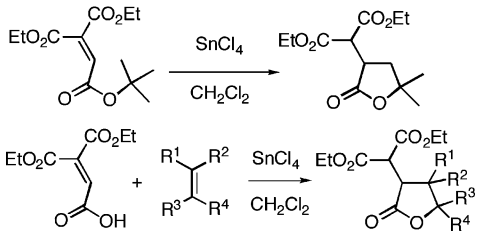
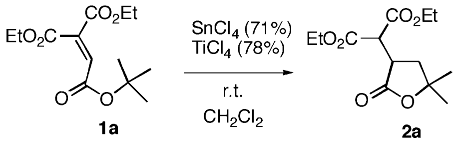
ABSTRACT



A novel cyclization of 1,1-diethyl 2-*tert*-butyl ethenetricarboxylate (1a) in the presence of a Lewis acid afforded a 5,5-dimethyl-γ-lactone derivative 2a. The reaction process has been shown to arise from formation by trapping of isobutylene generated in situ. Lewis acid-promoted intermolecular reactions of 1,1-diethyl 2-hydrogen ethenetricarboxylate (5) and various alkenes to afford highly functionalized γ-lactones were also developed.

Ethenetricarboxylate derivatives have been employed as highly electrophilic C2 components in Lewis acid-promoted [2 + 2] and [2 + 1] cycloadditions.[1,2] In addition, Lewis acid-promoted intramolecular cyclizations of ethenetricarboxylate esters bearing nucleophilic C═C and C≡C bonds and aromatic rings have been studied.[3] As part of our efforts to demonstrate the utility of Lewis acid-promoted reaction of highly electrophilic ethenetricarboxylates, a highly unusual γ-lactone formation by trapping of isobutylene generated in situ was discovered (eq 1). Furthermore, Lewis acid-promoted intermolecular reactions of 1,1-diethyl 2-hydrogen ethenetricarboxylate (**5**) and alkenes to highly functionalized γ-lactones were also developed.



(eq 1)

1,1-Diethyl 2-*tert*-butyl ethenetricarboxylate (**1a**) was used as an electrophile in Lewis acid-promoted [2 + 1] cycloadditions with the nucleophilic olefin 1-(phenylseleno)-2-(trimethylsilyl)ethene.[2] The reactivity of **1a** in the absence of a nucleophile and in the presence of a Lewis acid is of interest. The reaction of **1a** in the presence of SnCl$_4$ or TiCl$_4$ (1.2 equiv) in CH$_2$Cl$_2$ at room temperature for 3 h gave the γ-lactone **2a** in 71−78% yield (eq 1). The reaction of **1a** at −40 °C for 3 h also gave **2a** in 75% yield. The reaction at −78 °C for 3 h did not proceed, and starting material **1a** was recovered. The structure of **2a** was suggested by the presence of two differentiated methyl groups (^{1}H δ 1.39 and 1.48 ppm) and the disappearance of C═C*H* (^{1}H δ 6.80) and the *tert*-butyl group (^{1}H δ 1.49) in **1a**. ^{1}H, ^{13}C, ^{1}H/^{1}H−COSY, ^{1}H/^{13}C−HSQC, HMBC, and NOESY spectra and IR spectra

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(1) Srisiri, W.; Padias, A. B.; Hall, H. K., Jr. *J. Org. Chem.* **1994**, *59*, 5424.

(2) Yamazaki, S.; Kumagai, H.; Takada, T.; Yamabe, S. *J. Org. Chem.* **1997**, *62*, 2968.

(3) (a) Snider, B. B.; Roush, D. M. *J. Org. Chem.* **1979**, *44*, 4229. (b) Yamazaki, S.; Yamada, K.; Yamabe, S.; Yamamoto, K. *J. Org. Chem.* **2002**, *67*, 2889. (c) Yamazaki, S.; Yamada, K.; Yamamoto, K. *Org. Biomol. Chem.* **2004**, *2*, 257. (d) Yamazaki, S.; Morikawa, S.; Iwata, Y.; Yamamoto, M.; Kuramoto, K. *Org. Biomol. Chem.* **2004**, *2*, 3134.

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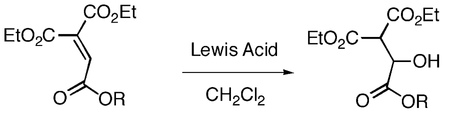
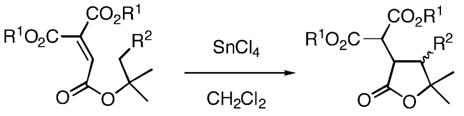
(C═O, 1770, 1750, 1735 cm^{-1}) were in accord with the lactone structure **2a**. The reaction of **1a** with other Lewis acids (1.2 equiv) also gave **2a** in somewhat lower yields ($FeCl_3$, 59%; $AlCl_3$, 34%; $GaCl_3$, 33%). The reaction also proceeded with a catalytic amount of $SnCl_4$ (0.2 equiv) at room-temperature overnight to give **2a** in 67% yield. The reaction of 1,1-diethyl 2-isopropyl and 1,1,2-triethyl ethenetricarboxylates **3a**,**b** in the presence of $SnCl_4$ or $FeCl_3$ (1.2 equiv) in CH_2Cl_2 at room temperature for 3 h was also examined; however, only hydrated products **4a**,**b** were obtained in 12−56% yield, along with starting material **3a**,**b** (eq 2). The formation of **4** presumably arises from participation of adventitious water in situ.[4]


(eq 2)

3a: R = iPr
3b: R = Et

4a: R = iPr
$SnCl_4$; (28%); $FeCl_3$; (50%)
4b: R = Et
$SnCl_4$; (12%); $FeCl_3$; (56%)

In addition to the 1,1-diethyl 2-*tert*-butyl ester, 1,1-isopropyl 2-*tert*-butyl ester **1b** afforded γ-lactone **2b** in 90% yield; however, the reaction of 1,1-dibenzyl 2-*tert*-butyl ester gave a complex, decomposed mixture using $SnCl_4$, $TiCl_4$, or $FeCl_3$. The reaction of tertiary esters (1,1-dimethylethyl) **1d**,**e** also gave γ-lactones **2d**,**e** in 61−78% yields regioselectively in 3:1−4:1 diastereomer ratios.


(eq 3)

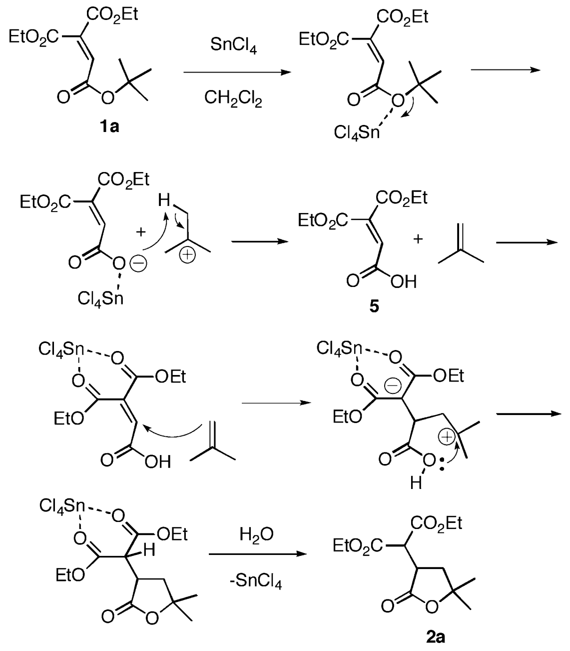
1b: R^1 = iPr, R^2 = H
1c: R^1 = CH_2Ph, R^2 = H
1d: R^1 = Et, R^2 = CH_3
1e: R^1 = iPr, R^2 = CH_3

2b: R^1 = iPr, R^2 = H (90%)
2c: R^1 = CH_2Ph, R^2 = H (0%)
2d: R^1 = Et, R^2 = CH_3
(78%, dr 3:1 trans/cis)
2e: R^1 = iPr, R^2 = CH_3
(61%, dr 4:1 trans/cis)

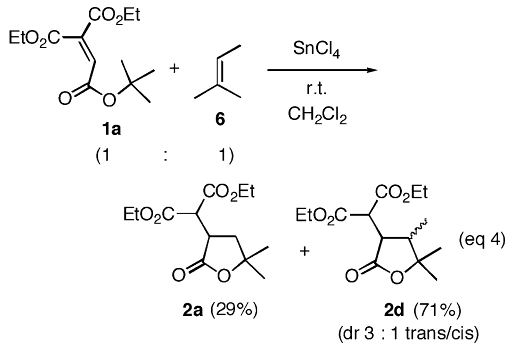
It was suggested that the formation of γ-lactone **2a** probably proceeds by Lewis acid-catalyzed generation of isobutylene driven by activation of the *tert*-butyl ester, followed by elimination. Addition of isobutylene to the double bond of ethenetricarboxylate **5** (activated by Lewis acid chelation to two carboxyl ester groups), followed by ring closure of carboxyl group to the stable tertiary carbocation thus generated, delivers product **2a** (Scheme 1).

To obtain information on the mechanism, the reaction of **1a** with 2-methyl-2-butene (1.0 equiv for **1a**) with $SnCl_4$ (1.2 equiv for **1a**) in CH_2Cl_2 was examined. The reaction gave a mixture of **2d** (3:1 diastereomer mixture, 71%) and **2a** (29%) (eq 4).[5] Furthermore, the reaction of a 1:1 mixture of **1d** and **1b** with $SnCl_4$ gave **2a** (17%), **2b** (21%), **2d** (30%), and **2e** (21%), respectively.[6] These results demonstrate that the reaction of carboxylic acids and alkenes generated in situ proceeds not in an intramolecular but rather in an intermolecular manner.

Scheme 1



Since it was discovered that the γ-lactone formation reaction proceeds intermolecularly, reactions of carboxylic acid **5** (prepared by treatment of **1a** with CF_3COOH)[7] with various alkenes were examined (eq 6, Table 1).[8] Alkene substrates giving cation intermediates stabilized by *tertiary*-alkyl, phenyl, and β-silyl groups were investigated. At first,



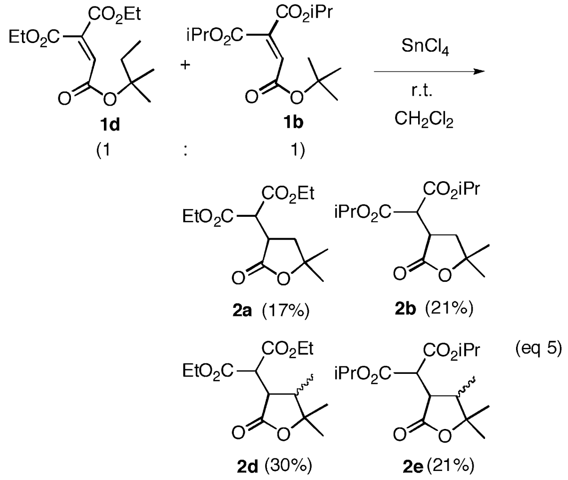
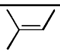
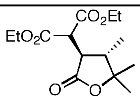
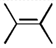
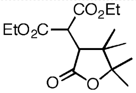
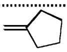
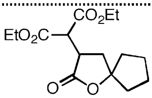
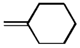
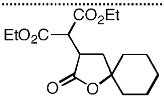
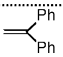
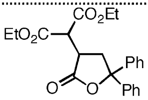
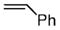
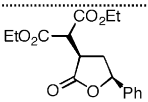
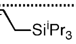
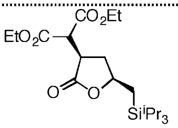
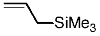
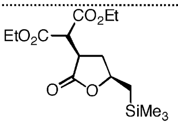
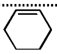
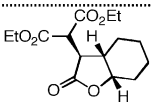


Table 1. Reaction of **5** with Various Alkenes

entry	alkene		Lewis acid	reaction conditions	product		yield (%)[a]
1	**6**		$SnCl_4$ (1.2 eq)	r.t. 3 h	**2d**		89 (dr 3:1)[b]
2	**7**		$SnCl_4$ (1.2 eq)	-78 °C, 3 h	**8**		82
			$SnCl_4$ (0.2 eq)	-78 °C, 3 h			60
3	**9a**		$SnCl_4$ (1.2 eq)	-78 °C, 3 h	**10a**		77
4	**9b**		$SnCl_4$ (1.2 eq)	-78 °C, 3 h	**10b**		75
			$SnCl_4$ (0.2 eq)	-78 °C, 3 h			64
5	**11a**		$SnCl_4$ (1.2 eq)	-78 °C, 3 h	**12a**		92
			$SnCl_4$ (0.2 eq)	-78 °C, 3 h			91
			$ZnBr_2$ (1.2 eq)	-40 °C, 17 h			33
6	**11b**		$SnCl_4$ (1.2 eq)	-78 °C, 3 h	**12b**		49 (dr 3:1)[b]
			$ZnBr_2$ (1.2 eq)	-40 °C, 17 h			20 (dr 2:1)[b]
7	**13a**		$SnCl_4$ (1.2 eq)	-40 °C, 3 h	**14a**		83 (dr 6:1)[b]
			$SnCl_4$ (0.2 eq)	-40 °C, 3 h			66 (dr 5:1)[b]
			$SnCl_4$ (1.2 eq)	-78 °C, 3 h			65 (dr 12:1)[b]
			$TiCl_4$ (1.2 eq)	-78 °C, 3 h			48 (dr 17:1)[b]
			$ZnBr_2$ (1.2 eq)	-40 °C, 17 h			37 (dr 2:1)[b]
8	**13b**		$SnCl_4$ (1.2 eq)	-78 °C, 3 h	**14b**		48 (dr 11:1)[b,c]
9	**15**		$SnCl_4$ (1.2 eq)	-78 °C, 6 h	**16**		16

[a] Yields are based on compound **1a**. [b] Structure shows a major diastereomer. [c] Compound **14b** is somewhat volatile.

the reaction of **1a** with 2-methyl-2-butene **6** with $SnCl_4$ at room temperature in CH_2Cl_2 gave a 3:1 (trans/cis) diastereomer mixture of **2d** (Table 1, entry 1), as expected by the result obtained in eq 4. Compound **5** also reacted with tetrasubstitued alkene **7** to give γ-lactone **8** in high yield (entry 2). The reaction of **5** with methylenecycloalkenes **9** in the presence of $SnCl_4$ at −78 °C for 3 h in CH_2Cl_2 gave **10** as major products (entries 3 and 4).[9] The reaction of **5** with 1,1-diphenylethene (**11a**) and styrene (**11b**) in the presence of $SnCl_4$ at −78 °C for 3 h in CH_2Cl_2 gave **12** (entries 5 and 6). The reaction of **5** with allylsilanes **13** in the presence of $SnCl_4$ or $TiCl_4$ at −78 °C gave **14** with high diastereoselectivity (entries 7 and 8). On the other hand, reaction of **5** with cyclohexene (**15**) gave γ-lactone **16** in

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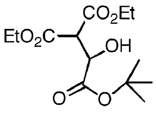
(4) Reaction of **1a** with $FeCl_3$ at −40 °C for 3 h also gave hydrated product **17** in 42% yield.



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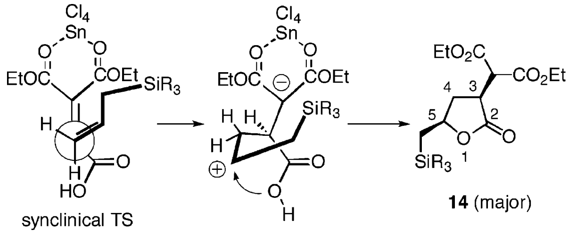
(5) Yields were determined by ^{1}HNMR of the product mixture.

(6) Product mixture was separated into two fractions (R_f = 0.4 and 0.5 (hexane−ether = 1: 1)) by column chromatography, and the yields were estimated by ^{1}H NMR of the fractions. The diastereomer ratios of **2d** and **2e** were not precisely determined.

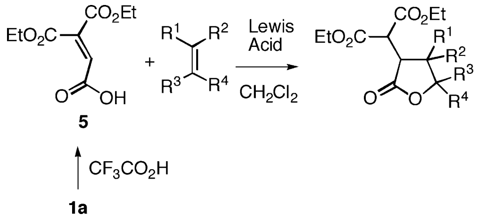
(7) Kelly, T. R. *Tetrahedron Lett.* **1973**, 437.

(8) **Typical Procedure (Table 1, Entry 5).** To **1a** (272 mg, 1.0 mmol) was added trifluoroacetic acid (4 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 1.5 h. The mixture was evaporated in vacuo to give **5** quantitatively. **5:** colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.33 (t, J = 7.1 Hz, 3H), 1.34 (t, J = 7.1 Hz, 3H), 4.32 (q, J = 7.1 Hz, 2H), 4.37 (q, J = 7.1 Hz, 2H), 6.89 (s, 1H), 11.31 (bs, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.72 (q), 13.88 (q), 62.34 (q), 62.79 (q), 128.97 (d), 140.59 (s), 161.97 (s), 164.07 (s), 168.37 (s); IR (neat) 3200 (broad), 2987, 1737, 1652, 1374, 1338, 1253, 1067 cm^{-1}; MS (FAB) m/z 217 ($(M + H)^+$); exact mass $(M + H)^+$ 217.0715 (calcd for $C_9H_{13}O_6$ 217.0712). To a solution of **5** (1.0 mmol) prepared above in dichloromethane (1.8 mL) was added 1,1-diphenylethene (**11a**) (180 mg, 1.0 mmol), followed by $SnCl_4$ (301 mg, 0.135 mL, 1.2 mmol) at −78 °C. The mixture was stirred for 3 h. The reaction mixture was quenched by water. The mixture was extracted with dichloromethane, and the organic phase was washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography over silica gel eluting with hexane−ether (1:1) to give **12a** (417 mg, 92%).

Scheme 2



low yield (16%) (entry 9). Alkenes such as **15**, which give a secondary alkyl carbocation, seem to be insufficient to stabilize the intermediate in these reaction conditions.



(eq 6)

The stereochemistry of the γ-lactone products was determined by NOESY spectra. The observed 3,5-cis-selective stereochemistry for reaction with allylsilanes can be explained by a synclinical transition state,[10] possibly arising from the secondary orbital interaction between ester carbonyl and CH_2SiR_3 groups[11] and subsequent γ-lactone ring closure (Scheme 2).

In summary, an unprecedented cyclization of a 1,1-diester of 2-*tert*-butyl ethenetricarboxylate by trapping of alkenes generated in situ in the presence of a Lewis acid such as $SnCl_4$ and $TiCl_4$ gave γ-lactone products in high yields. The reaction of predeprotected carboxylic acid 1,1-diethyl 2-hydrogen ethenetricarboxylate (**5**) and various alkenes in the presence of Lewis acid gave cycloadduct γ-lactones. Because the obtained highly functionalized γ-lactones can be synthetic intermediates for biologically interesting compounds,[12] further transformation of the products is ongoing.

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Supporting Information Available: Experimental procedures, spectral data, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Reaction of **5** and **9b** at room temperature or at −40 °C for 3 h gave a complex mixture containing **10b** and possibly compounds arising from rearranged alkenes.

(10) (a) Seebach, D.; Golinski, J. *Helv. Chim. Acta* **1981**, *64*, 1413. (b) Panek, J. S.; Jain, N. F. *J. Org. Chem.* **1993**, *58*, 2345.

(11) Pan, L.-R.; Tokoroyama, T. *Tetrahedron Lett.* **1992**, *33*, 1469.

(12) For examples, (a) Johnson, C. R.; Elliot, R. C.; Meanwell, N. A. *Tetrahedron Lett.* **1982**, *23*, 5005. (b) Jackson, R. F. W.; Raphael, R. A. *Tetrahedron Lett.* **1983**, *24*, 2117. (c) Sakurai, K.; Takahashi, K.; Yoshida, T. *Agric. Biol. Chem.* **1983**, *47*, 1249. (d) Kaiser, R. *Helv. Chim. Acta* **1984**, *67*, 1198.