Pergamon

Tetrahedron Letters, Vol. 35, No. 42, pp. 7809-7812, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01684-4

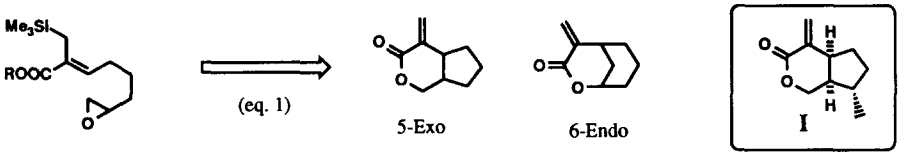
Intramolecular Reaction of β-(Alkoxycarbonyl)allylsilane with Epoxide into α-Methylene-δ-lactones Fused to Carbocycles[1]

Kiyoshi Nishitani, Yasuko Harada, Yukitaka Nakamura, Kumiko Yokoo and Koji Yamakawa*

Faculty of Pharmaceutical Sciences, Science University of Tokyo, Ichigaya-Funagawara, Shinjuku-ku, Tokyo 162, Japan

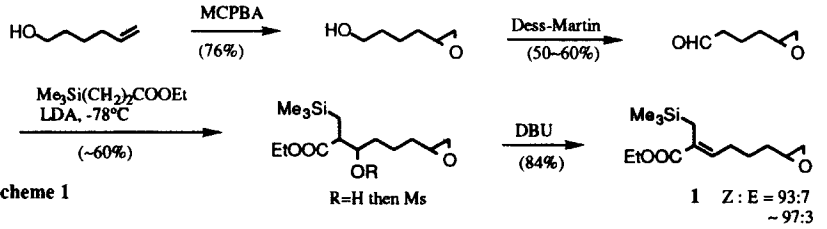
Abstract: Intramolecular cyclization of ω-epoxy-β-ethoxycarbonylallylsilane (**1**) was effected with Lewis acids to give a good yield of 5-*exo*-cyclization products (**5** and **6**), and a small amounts of 6-*endo*-product (**7**). The 5-*exo*-products were converted into α-methylene-δ-butyrolactone (**6La** and **b**) fused to cyclopentane.

We have reported a facile synthesis of α-methylene-γ-lactones fused to five or six-membered carbocycles employing the intramolecular Sakurai-Hosomi reaction of ω-formyl-β-alkoxycarbonylallylsilanes.[2] We also reported the synthesis of optically active terpenoid lactones utilizing our cyclization method.[3] Intramolecular reaction of β-alkoxycarbonylallylsilane with epoxide was expected to be a good method for a synthesis of α-methylene-δ-lactone fused to carbocycles. Some intramolecular cyclization reaction of allylsilanes with epoxide using Lewis acids were reported.[4a-e] However, Lewis acid-promoted reaction of β-alkoxycarbonylallylsilane with epoxide - the ester function would destabilize the cation intermediate - have not been reported. We wish to report the intramolecular reaction of β-ethoxycarbonylallylsilane with epoxide into α-methylene-δ-lactone fused to carbocycles. (Eq.1)



Proctor *et al.* reported the titanium tetrachloride-promoted intramolecular cyclization of 7,8-epoxyallylsilane giving 5-exo-cyclization products (*cis* and *trans* mixture) in 55% yield.[4a] We investigate the 7,8-epoxy-2-ethoxycarbonylallylsilane (**1**) into α-methylene-δ-lactone fused to cyclopentane which was found in the structure of iridoid monoterpene, teucriumlactone (**I**), isolated from *Teucrium marum*.[5]

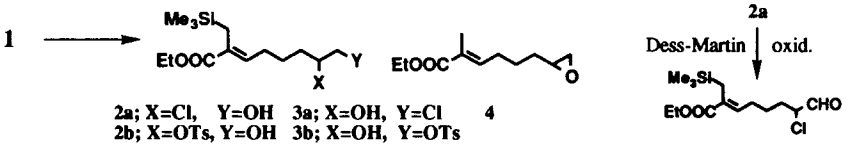
The epoxyallylsilane (**1**) was synthesized starting from 5-hexenol in several steps as shown in scheme 1. The resulting allylic silane was a mixture of the *Z*- and *E*-isomers in a ratio of 93:7~97:3. The ^{1}H-NMR spectrum of the mixture exhibited the olefinic proton signals at δ 6.55 (t, *J*=7 Hz) for *Z*-isomer and δ 5.62 (t, *J*=7 Hz) for *E*-isomer.



Scheme 1

The epoxyallylsilane was treated with titanium tetrachloride at -95 ~ -70 °C to give regioisomeric chlorohydrines (**2a** and **3a**) in 71.6% yield. The major component was determined to be primary alcohol (**2a**), because the Dess-Martin oxidation[6] of **2a** gave α-chloroaldehyde. *p*-Toluenesulfonic acid also selectively reacted with the epoxy function to give diol-monotosylate (**2b** and **3b**) in an excellent yield. Fluoride ion, tetrabutylammonium fluoride, was reacted with the trimethylsilyl function of **1** to give detrimethylsilyl compound (**4**) in 78 % yield. (Table 1)

Table 1. Some Unsuccessful Results of Intramolecular Cyclization Reaction of **1**



2a; X=Cl, Y=OH **3a**; X=OH, Y=Cl **4**
2b; X=OTs, Y=OH **3b**; X=OH, Y=OTs

Reagent(eq)	Solv.	Temp (°C)	Time (h)	Product yield (%)		
				2a,b	**3a,b**	**4**
$TiCl_4$ (2.2)	CH_2Cl_2	-95~ -70	2.0	63.0	8.6	
p-TsOH (1.2)	benzene	r.t.	3.0	66.0	33.0	
Bu_4NF (1.2)	THF	r.t.	0.3			78.0

On the contrary, boron trifluoride etherate, trimethylsilyl trifrate and chlorotitanium triisopropoxide[7] were effective on the intramolecular cyclization of **1** in moderate to good yield. The 5-*exo*-cyclization was much preferable to the 6-*endo*-cyclization. (Table 2)[8] The stereochemistry of the 6-*endo*-product (**7**) was determined to be *cis* from the *J*-value of the two methine proton signals [δ 3.70 (tt, *J*=11.5, 4.5 Hz,1-H), 2.54 (tt, *J*=11.5, 2.5 Hz, 3-H)]. Treatment of **7** with *p*-TsOH gave an α-methylene-δ-butyrolactone (**7L**) quantitatively. The 5-*exo*-cyclization products were composed of the *cis*-fused tetrahydrofuran derivatives (**5a** and **5b**), *cis*- and *trans*-hydroxyl esters (**6a** and **6b**), and a small amount of the corresponding α-methylene-δ-lactones (**6La** and **6Lb**). The 2-oxabicyclo[3.3.0]octane structure of **5a** and **5b** was determined from the mass (m/z 270 M^+), IR (1745, 1750 cm^{-1}) and the ^{1}H-NMR data, but the stereostructure could not be determined from these spectral data. The stereoisomeric hydroxy esters (**6a** and **b**) were not separable, but their ratios were estimated by the intensity of both the olefinic and the low field methylene proton signals. The mixture of the hydroxy esters was treated with *p*-TsOH to yield the mixture of the fused δ-lactones (**6La** and **b**) quantitatively. It is not easy to determine the stereochemistry of the lactones (*cis* or *trans*) because the *J*-values of the methine and methylene protons are depending on the conformation. The cyclization reactions

were smoothly proceeded with BF_3•OEt_2 above -60 °C, or with up to 1.1 eq. of TMSOTf at -78 °C. The yield of the 2-oxabicyclo[3.3.0]octane derivatives (**5**) was decreased with a rise in temperature, and that of the hydroxy esters (**6**) was increased. The ratio of *cis* - to *trans* -isomer in the total yield of the 5-*exo*-cyclization products is between 1.2:1 and 1.5:1. The 2-oxabicyclo[3.3.0]octane derivative (**5b**) was treated with BF_3•OEt_2 at 0 °C to give **6b** in excellent yield within a few min. On the other hand, treatment of the isomer **5a** with BF_3•OEt_2 at 0 °C for 2 d gave **6a** in 39 % yield together with the starting material in 33 % yield, and at room temperature for 7 h gave quantitative yield of **6a**. The rate of the conversion reaction of **5b** into **6b** was much faster than that of the corresponding isomer **5a**. These results indicate that the minor isomer **5b** is less stable than **5a**, therefore, **5b** and **5a** should have *trans* and *cis* configuration with the ring junction, respectively. Therefore, the hydroxy ester **6a** and the corresponding lactone (**6La**), and **6b** and **6Lb** should have *cis* and *trans* configuration, respectively. These 5-*exo*-cyclization products were formed *via* the intermediate (**A**) shown in scheme 2. When the reaction was carried out at room temperature with an excess of BF_3•OEt_2, the 5-*exo*-cyclization products (**5a** and **6a,b**) were obtained in 86% yield.

Scheme 2

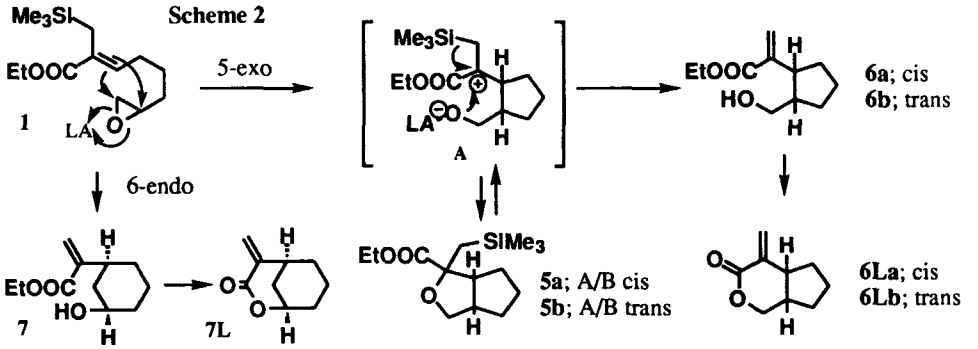


Table 2. Intramolecular Cyclization Reaction of **1** with Lewis Acids

Run	Reaction conditions[a] Reagent (eq)	Temp °C	Time (h)	Products Yield (%) (a; cis, b; trans) 5a[b]	5b[b]	(5a+b)	6(L)	(a:b)[c]	5+6	(a:b)	7
1	BF_3•Et_2O (1.1)	-60	0.5	30.1	12.0	**(42.1)**	**19.6**	(1:3)	**[62]**	(1.3:1)	4.5
2	BF_3•Et_2O (2.1)	-60	1.0	32.3	6.9	**(39.2)**	**35.0**	(1:3)	**[74]**	(1.3:1)	6.0
3	BF_3•Et_2O (6.0)	-15	0.1	30.3	trace	**(30.3)**	**40.0**	(1:4)	**[70]**	(1.2:1)	4.0
4	BF_3•Et_2O (4.4)	r.t.	25.0	8.7	-	**(8.7)**	**77.5**	(1.1:1)	**[86]**	(1.3:1)	6.2
5	BF_3•Et_2O (4.4)[d]	r.t.	20.0	-	-	-	**76.3**	(1:1.1)	**[76]**	(1:1.1)	9.4
6	TMSOTf (1.1)	-78	<0.3	23.8	trace	**(23.8)**	**32.0**	(1:2.5)	**[56]**	(1.4:1)	1.0
7	TMSOTf (2.2)	-78	<0.2	36.0	-	**(36.0)**	**~40**[e]	(2:1)	**[76]**	(6:1)	1.0
8	$ClTi(OiPr)_3$ (2.2)	0	17.0	2.6	trace	**(2.6)**	**66.1**	(1.1:1)	**[69]**	(1.2:1)	-[f]

a) The reactions were carried out in CH_2Cl_2 solution at 0.001M concentration of the substrate. b) The complete stereochemistry has not been determined. c) The ratio of the stereoisomer was evidenced by ^{1}H-NMR spectroscopy. d) The reaction was carried out at 0.01M concentration of the substrate. e) A small amount of unknown inpurities was contained. f) About 7% of the chlorohydrine (**3a**) was obtained.

Thus, the Lewis acid-promoted intramolecular cyclization reaction of the epoxyallylsilane (**1**) is one of the useful methods preparing α-methylene-δ-lactones fused to cyclopentane system. We are now synthesizing (-)-teucriumlactone (**I**) utilizing this cyclization procedure. And also, we are investigating the regio- and stereoselectivities of this cyclization depending on both the number of alkyl substituent of the epoxy function and that of the carbon between the allylsilane moiety and the epoxy function.

Acknowledgments. We thank Miss N.Sawabe and Mrs. F.Hasegawa of this laboratory for NMR and mass spectral measurements.

References and Notes

1. Studies on the Terpenoids and Related Alicyclic Compounds XLVII. Part XLVI: K. Nishitani, J. Suzuki, H. Ishibashi, Y. Saitoh, S. Kariya and K. Yamakawa, *Heterocycles*, **1995**, in press.
2. K. Nishitani and K. Yamakawa, *Tetrahedron Lett.*, **1987**, *28*, 655; **1991**, *32*, 387; K. Nishitani, Y. Nakamura, R. Orii, C. Arai, and K. Yamakawa, *Chem. Pharm. Bull.*, **1993**, *41*, 822.
3. K. Nishitani, H. Fukuda and K. Yamakawa, *Heterocycles*, **1992**, *33*, 97.
4. a) G. Proctor, A. T. Russell, P. J. Murphy, T. S. Tan and A. N. Mather, *Tetrahedron*, **1988**, *44*, 3953. b) I. Fleming and I. Paterson, *Synthesis*, **1979**, 446. c) D. Wang and T. -H. Chan, *J. Chem. Soc., Chem. Commun.*, **1984**, 1273. d) R. J. Armstrong and L. Weiler, *Can. J. Chem.*, **1986**, *64*, 584. e) G. A. Molander and S. W. Andrews, *J. Org. Chem.*, **1989**, *54*, 3114.
5. U. M. Pagnoni, A. Pinetti, R. Trave and L. Garanti, *Aust. J. Chem.*, **1976**, *29*, 1375.
6. D. B. Dess and J. C. Martin, *J. Org. Chem.*, **1983**, *48*, 4156.
7. T. Mukaiyama, *Angew. Chem. Int. Ed. Engl.*, **1977**, *16*, 817; M. T. Reez and R. Peter, *Tetrahedron Lett.*, **1981**, *22*, 4691.
8. Representative data: **5a**: oil, ^{1}H-NMR (500 MHz, in $CDCl_3$): δ 0.0 (9H,s), 1.29 (3H,t, *J*=7 Hz), 1.17,1.19 (each 1H, d, *J*=12 Hz), 1.86 (1H, m), 2.66 (1H, m), 2.84 (1H, q, *J*=8 Hz), 3.49 (1H, dd, *J*=8.5, 4.0 Hz), 3.96 (1H, t, *J*=8.5 Hz), 4.14 (2H, q, *J*=7 Hz), IR (neat); 1745, 1730, 850 cm^{-1}, MS; m/z 255 (M^+-Me). **5b**: oil, ^{1}H-NMR (500 MHz, in $CDCl_3$): δ 0.0 (9H, s), 0.92 (3H, t, *J*=7 Hz), 0.92,1.22 (each 1H, d, *J*=14.5 Hz), 1.58 (1H, m), 1.69 (1H, m), 2.15-2.33 (4H, m), 3.46 (1H, dd, *J*=10, 7 Hz), 3.89 (1H, dd, *J*=7, 6 Hz), 4.19 (2H, m), IR (neat); 1750, 1730, 850 cm^{-1}, MS; m/z 270 (M^+), 255 (M^+-Me). **6a**: oil, ^{1}H-NMR (500 MHz, in $CDCl_3$): δ 1.32 (3H, t, *J*=7 Hz), 1.58 (1H, OH), 2.03 (1H, dd, *J*=7.6, 4.9 Hz), 2.41 (1H, m), 3.13 (1H, q, *J*=7.6 Hz), 3.26-3.36 (2H, m), 4.23 (2H, q, *J*=7 Hz), 5.54 (1H, t, *J*=1.2 Hz), 6.28 (1H, br s). IR (neat); 3426, 1716, 1627 cm^{-1}, MS; m/z 198 (M^+). **6b**: oil, ^{1}H-NMR (500 MHz, in $CDCl_3$): δ 1.32 (3H, t, *J*=7 Hz), 1.57 (1H, OH), 2.03 (1H, dd, *J*=7.6, 4.9 Hz), 2.41 (1H, m), 2.72 (1H, q, *J*=8.0 Hz), 3.55 (2H, dm, *J*=15.5, 5.2 Hz), 4.21 (2H, q, *J*=7 Hz), 5.64 (1H, br s), 6.21 (1H, br s). IR (neat); 3413, 1716, 1626 cm^{-1}, MS; m/z 198 (M^+). **6La**: oil, ^{1}H-NMR (500 MHz, in $CDCl_3$): δ 1.76 (1H, m), 1.93 (1H, m), 2.12 (1H, m), 2.53 (1H, m), 3.04 (1H, br q, *J*=8.2 Hz), 3.97 (1H, dd, *J*=11.3, 7.5 Hz), 4.18 (1H, dd, *J*=11.3, 4.3 Hz), 5.52 (1H, t, *J*=1.8 Hz), 6.14 (1H, t, *J*=1.5 Hz). IR (neat); 1736, 1626 cm^{-1}, MS; m/z 152 (M^+). **6Lb**: oil, ^{1}H-NMR (500 MHz, in $CDCl_3$): δ 1.9 (4H, m), 2.11 (1H, m), 2.31 (1H, m), 4.18 (1H, t, *J*=11 Hz), 4.61 (1H, dd, *J*=11, 5 Hz), 5.44 (1H, dd, *J*=2.0, 1.0 Hz), 6.35 (1H, dd, *J*=2.0, 1.0 Hz). IR (neat); 1725, 1635 cm^{-1}, MS; m/z 152 (M^+). **7L**; oil, ^{1}H-NMR (270 MHz, in $CDCl_3$): δ 2.92 (1H, br s), 4.77 (1H, m), 5.54 (1H, dd, *J*=1.3, 0,7 Hz), 6.48 (1H, d, *J*=1.4 Hz).

(*Received in Japan* 19 *May* 1994; *accepted* 22 *July* 1994)