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Regioselective Ring Cleavage of Chiral β-Trichloromethyl-β-propiolactone with Organoaluminum Compounds for the Synthesis of Optically Active Intermediates

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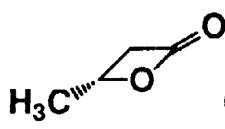
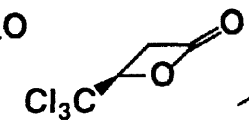
Abstract: A novel alkylating ring cleavage reaction of enantiomerically pure β-trichloromethyl-β-propiolactone as a chiral building block with organoaluminum compounds provided ring-opened products with a chiral trichloromethyl carbinol moiety. A product was demonstrated to be used as an effective chiral synthon for the synthesis of chiral bioactive derivatives such as ipsdienol and sodium cilastatin.

Keywords: lactones; asymmetric; cleavage reaction; aluminum reagents; pheromone & drugs

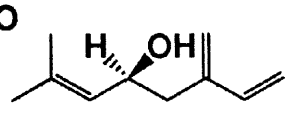
Optically active β-methyl-β-propiolactone (**1**) can serve as an excellent chiral synthon for natural product synthesis because the lactone is cleaved completely with cuprate in an S_N2-type fashion by the oxygen-alkyl bond fission [1]. Further, enantiomerically pure β-trichloromethyl-β-propiolactone (**2**) has been reported to be easily prepared from chloral and ketene in the presence of quinidine [2]. Since a trichloromethyl group is easily transformed into another functional group, the lactone **2** is a very interesting compound as a chiral synthon for natural product synthesis; however, reports on the carbon-carbon bond formation reaction using lactone **2** are limited to only two from our laboratory [3,4]. In this paper we wish to report some novel findings that reveal a reactive affinity of (*R*)-**2** with organoaluminum compounds to afford convenient ring-opened products. Although the lactone **2** does not react with organocuprates, and organolithium compounds and Grignard reagents gave acylated products in low yields, a Friedel-Craft type reaction of **2** with aromatic compounds in the presence of Lewis acids gave aromatic ketones with a chiral trichloromethylcarbinol moiety [3]. This cleavage occurs regioselectively between the acyl carbon and oxygen, in spite of the fact that β-methyl-β-propiolactone opens by the bond cleavage between an oxygen-alkyl bond. The acyl carbon is a rather hard base compared with the alkyl carbon in the lactone **2** [5]. Accordingly, next we aimed for a hard acid [6] of organoaluminum reagents as a nucleophile on the regioselective ring cleavage of β-trichloromethyl-β-propiolactone. This means that an



(*R*)-**1**



(*R*)-**2**



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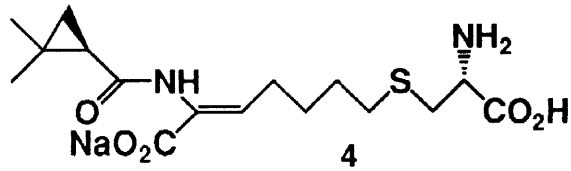

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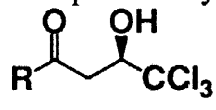
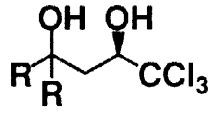
easy oxygen-acyl bond fission would occur rather than the oxygen-alkyl counterpart in the ring cleavage of β-lactone **2** by the hard acid of organoaluminum compounds, and that chiral β-trichloromethyl-β-propiolactone **2** would serve as an excellent chiral precursor of biologically active derivatives such as ipsdienol **3** [7], an aggregation pheromone of the bark beetle, and sodium cilastatin **4** [8], an inhibitor of dehydropeptidase.

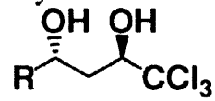
Thus, the reaction of (*R*)-**2** with organoaluminum compounds was investigated. A typical procedure is described as follows: To a solution of (*R*)-**2** (8.0 mmol) in CH_2Cl_2 (8 ml) was added a hexane solution (0.9M) of trimethylaluminum (24 mmol) at 0 °C. The reaction mixture was allowed to stand at room temperature and stirred for 10 h at the same temperature, and then quenched with 2N HCl. After usual work-up, the crude product was purified on silica gel TLC to afford (*R*)-4-methyl-1,1,1-trichloro-2,4-pentanediol **6** in 94% yield as white crystals (mp 95~8°C). Table 1 shows the results using some organoaluminum compounds. Although the use of an equimolar amount of trimethylaluminum afforded the monoalkylated product **5** in small quantity (Entry 1), the use of 3 equivalents of trimethylaluminum gave exclusively the dialkylated adduct **6** in high yield (Entry 2). On the other hand, the reaction of (*R*)-**2** with triethylaluminum gave mainly keto compound (*R*)-**5** along with the reduced product (*2R,4S*)-**7** [9] in low yield (Entry 5). The reduced product (*2R,4S*)-**7** may be obtained by first attack of hydride from ethyl aluminum reagents, then the ethyl group was incorporated by the attack to aldehyde group initially formed.



(*R*)-**5**



(*R*)-**6**

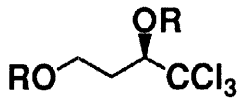


(*2R,4S*)-**7**

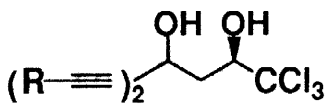
Table 1. Reaction of (*R*)-2 with some organoaluminum reagents[a]

Entry	Reagent	(eq)	Temp (°C)	Yield 5, 6 and 7 (%)[b]		
1	Me_3Al	(1.0)	0~rt	9	13	0
2	Me_3Al	(3.0)	0~rt	0	94	0
3	$MeAlCl_2$	(3.0)	0~rt	13	72	0
4	Me_2AlCl	(3.0)	0~rt	15	68	0
5	Et_3Al	(3.0)	0~rt	63	0	21
6	Et_2AlCl	(3.0)	0~rt	65	0	17
7	Et_2AlCl	(5.0)	0~rt	71	0	0
8	$EtAlCl_2$	(3.0)	reflux	63	0	16

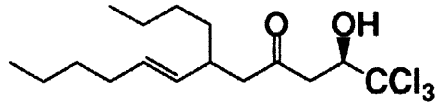
a) The reaction was carried out according to the typical experimental procedure. b) Isolated yield.



(*R*)-**8** : R = H
(*R*)-**9** : R = Ac



(*R*)-**10** : R = n-$C_{11}H_{23}$
(*R*)-**11** : R = Ph



(*R*)-**12**

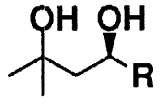
Diisobutylaluminum hydride also reacted with (*R*)-**2** at 0 °C to give diol (*R*)-**8** in a yield of 96%. In the same way, aluminum acetylide compounds containing tridecyne and phenyl-acetylene reacted with (*R*)-**2** at 0 °C to afford diacetylenated compounds (*R*)-**10** and (*R*)-**11** in yields of 31 and 74%, respectively. Further, sp^2 carbon nucleophile of

hexenylaluminum compounds gave (*R*)-**12** in a yield of 34%, which may be obtained by the Michael addition of the second nucleophile toward α,β-unsaturated ketone initially formed.

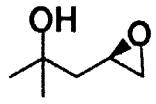
Since the present alkylation proceeded by the oxygen-acyl bond fission of **2**, the stereochemical integrity of the hydroxy carbon in the alkylated products **6** (R = Me) $[\alpha]_D^{23}$ +5.7 (c 0.28, $CHCl_3$), **5** (R = Et) $[\alpha]_D^{23}$ +22.4 (c 0.25, $CHCl_3$), and **7** (R = Et) $[\alpha]_D^{23}$ +35.6 (c 0.55, $CHCl_3$) should be retained, which was confirmed as a single product by GLC analysis using a chiral column (Daicel OJ). The ratios of enantiomers in (*S*)-**8** $[\alpha]_D^{23}$ +23.8 (c 0.22, $CHCl_3$), after derivatization into the corresponding acetate (*R*)-**9**, (*S*)-**10** $[\alpha]_D^{23}$ +3.1 (c 0.12, $CHCl_3$), (*S*)-**11** $[\alpha]_D^{23}$ +7.5 (c 0.93, $CHCl_3$), and (*S*)-**12** $[\alpha]_D^{23}$ +34.7 (c 0.15, $CHCl_3$) were also confirmed by GLC as single for the carbon at the hydroxy group. The absolute configuration of the carbinols was assigned by comparison of the optical rotation value of the allylic alcohol derivative **16** with that in literature (vide infra) [10].

Owing to the electron-withdrawing nature of a trichloromethyl group, the trichloromethyl carbinol moiety is very stable. In addition, the trichloromethyl group can be transformed into another functional group [11]. Thus, to explore the utility of the present method for a chiral synthon of physiologically active compounds, a further reaction using an addition product was next examined. The reduction of diol (*R*)-**13** with dibutyltin hydride gave monochlorinated derivative **14** $[\alpha]_D^{23}$ -123 (c 0.25, $CHCl_3$) in a yield of 91%, which was easily converted into the known precursor **15** [7] $[\alpha]_D^{23}$ +24.1 (c 0.52, $CHCl_3$) lit. $[\alpha]_D^{23}$ +21.9 (c 1.91, $CHCl_3$) of ipsdienol **3** by treatment with sodium hydroxide in 59% yield.

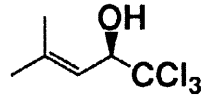
Furthermore, the reaction of (*R*)-**13** in the presence of $CuSO_4$ on SiO_2 [12] in refluxing toluene gave dehydrated product **16** $[\alpha]_D^{23}$ +12.5 (c 0.68, $CHCl_3$) in 53% yield, whereas low temperature in the same solvent provided **16** along with isomer **17** in 42% and 32% yields, respectively. Although the ratio of the regioisomers varied by the reaction conditions, the same treatment of **17** with $CuSO_4$ on SiO_2 in refluxing toluene afforded **16** in 58% yield. The product **16** (mp 106~108°C) known as a precursor of dichlorochrysanthemic acid [10,13] was confirmed to be a single product by HPLC analysis with a chiral column (Daicel OJ), which shows that the retention of the stereochemical integrity during the transformations as judged by the reported optical rotation data, lit.[8] $[\alpha]_D^{25}$ +12.0 (c 2, $CHCl_3$).



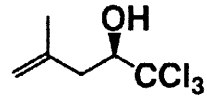
(*R*)-**13** : R = CCl_3
(*R*)-**14** : R = CH_2Cl



(*R*)-**15**



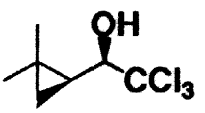
(*R*)-**16**



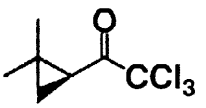
(*R*)-**17**

Chiral cyclopropanecarboxylic acid derivatives are known as important building blocks for many biologically active compounds. Among them, (**S**)-3,3-dimethylcyclopropane-carboxylic amide **20** is an important precursor [8] for the synthesis of an inhibitor for hydorase, *e.g.*, sodium cilastatin **4** which has attracted major therapeutic interest in the antibiotic field. The dehydroxylated chiral allylic alcohol **16** obtained in the present study could be easily converted into the precursor **18** $[\alpha]_D^{23}$ +25.7 (c 0.62, $CHCl_3$) of cilastatin in 74% yield by the diastereoselective Simmons-Smith reaction [14]. Oxidation of the hydroxy

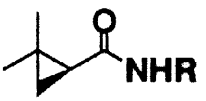
group of **18** with $Na_2Cr_2O_7$ - H_2SO_4 in AcOH [15] gave α-trichloromethyl ketone **19** $[\alpha]_D^{23}$ +40.0 (c 0.04, $CHCl_3$) in 72% yield. The subsequent hydrolysis of **19** under alkaline conditions like haloform reaction [16] failed to obtain the corresponding carboxylic acid; however, the corresponding amide **20** mp 135-8°C, $[\alpha]_D^{23}$ +78.3 (c 0.7, CH_3OH) (lit.[17] mp 135-8°C), and **21** mp 76-9°C $[\alpha]_D^{23}$ +39.3 (c 0.78, $CHCl_3$) were easily obtained in 72% and 94% yields, respectively, by aminolysis and confirmed to be enantiomerically pure by HPLC analysis using a chiral column (Daicel OJ). These absolute configurations were determined by comparison with the corresponding commercially available sample **20**, mp 135-8°C, $[\alpha]_D^{20}$ +82 (c 1, CH_3OH) [18].



(*R,S*)-18



(*S*)-19



(*S*)-20 : R = H
(*S*)-21 : R = Bn

In summary, a novel alkylating reaction using the hard acid of organoaluminum compounds is demonstrated where chiral β-trichloromethyl-β-propiolactone **2** is used as a convenient chiral synthon of bioactive cyclopropanecarboxylic acid derivatives via the some transformation. The easy availability of chiral β-trichloromethyl-β-propiolactone makes the present reaction of high value. The alkylated products retain completely the stereochemical integrity of the starting β-trichloromethyl-β-propiolactone. Accordingly, chiral β-trichloromethyl-β-propiolactone **2** can be used as an effective chiral synthon for the synthesis of chiral bioactive compounds as demonstrated in the synthesis of an important precursor of ipsdienol and sodium cilastatin.

References and Notes

† Present address: Osaka Municipal Technical Research Institute.
[1] Fujisawa T. Shimizu M. β-Methyl-β-propiolactone, Encyclopedia of Reagents for Organic Syntheses, 1995;5:3574-3576. Fujisawa T. Sato T. J. Synth. Org. Chem. Jpn., 1982;40: 618-628. Sato T. Kawara T. Nishizawa A. Fujisawa T. Tetrahedron Lett., 1980;21:3377-3380. Fujisawa T. Sato T. Kawara T. Ohhashi K. Tetrahedron Lett. 1981;22:4823-4826. Sato T. Itoh T. Hattori C. Fujisawa T. Chem. Lett. 1983: 1391-1394.
[2] Wynberg H. Staring E. G. J. J. Am. Chem. Soc. 1982;104:166-168. Wynberg H. Staring E. G. J. J. Org. Chem. 1985;50: 1977-1979. Song C. E. Ryu T. H. Roh E. J. Kim I. O. Ha H. J. Tetrahedron Asymm. 1994;5:1215-1218.
[3] Fujisawa T. Ito T. Fujimoto K. Shimizu M. Wynberg H. Staring E. G. J. Tetrahedron Lett. 1997;38:1593-1596.
[4] Shimizu M. Ishii K. Fujisawa T. Chem. Lett. 1997:765-766.
[5] Fujisawa T. Sato T. Takeuchi M. Chem. Lett. 1982:71-74.
[6] Ho T-L. Hard and Soft Acids and Bases Principle in Organic Chemistry, Academic Press 1977.
[7] Mori K. Tetrahedron Lett. 1976:1609-1976.
[8] Kahan F. M. Kropp H. Sundelof J. G. Birrnbaum J. J. Antimicrob. Chemother. 1983;12 (Suppl.D):1-35.
[9] The *anti*-configuration was assigned by comparison of NMR after derivatization to the corresponding acetonide derivative. cf. Dondoni A. Merino P. Synthesis 1993:903-908.
[10] Muljiani Z. Gadre S . R. Modak S. Pathan N. Mitra R. B. Tetrahedron Asymm, 1991;2:239-242.
[11] Wynberg H. Staring E. G. J. J. Chem. Soc. Chem. Commun. 1984: 1181-1182; Song C. E. Lee J. K. Lee, S. Tetrahedron Asymm. 1995;6:1063-11066.
[12] Nishiguchi T. Machida N.Yamamoto E. Tetrahedron Lett. 1987;28:4565-4568.
[13] Hatch III C. E. Baum J. S. Takashima T. Kondo K. J. Org. Chem. 1980;45:3281-3285.
[14] Arai I. Mori A. Yamamoto H. J. Am. Chem. Soc. 1985;107:8254-8256.
[15] Gallina C. Giordano C. Synthesis, 1989:466-468.
[16] Donohoe T. J. Guyo P. M. J. Org. Chem. 1996;61:7664-7665.
[17] Graham D. W. Japanese Patent, Tokkaisho 1980-40669.
[18] Aldrich Catalog, Handbook of Fine Chemicals 1996-1997;582.