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SYNTHESIS OF 3-DPA LACTONE VIA TANDEM CYCLIZATION REACTION OF ACETONIDE PROTECTED METHYL 4,5-DIHYDROXY-2-CHLOROGLYCIDATE

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Abstract - The novel synthesis of 3-DPA lactone, which is known as a potent food intake-control substance, via tandem cyclization reaction of acetonide protected methyl 4,5-dihydroxy-2-chloroglycidate is described.

The 2-hydroxylated butyrolactone moiety is an important component of large number of natural compounds which demonstrate a wide range of biological activity.[1] For example, some 4-alkyl-2-hydroxybutyrolactones are known as food intake-control substances.[1a,b] Among them, (*2S*, *4S*)-2-hydroxy-4-hydroxymethylbutyrolactone (**1**) (3-DPA lactone) is a natural food intake-control substance.[2]

On the other hand, our group has reported the novel and effective method for the synthesis of 3-hydroxy-2-pyrones from acetonide protected 4,5-dihydroxy-2-chloroglycidic esters by the reaction with magnesium halides in aprotic solvent.[3] With our more profound investigation of this field, we found that isotetronic acid (**3**) was obtained when this reaction was carried out in the protic solvent such as H_2O, MeOH and EtOH (Figure 1).

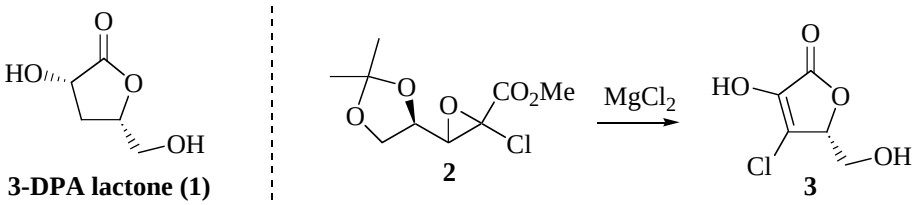
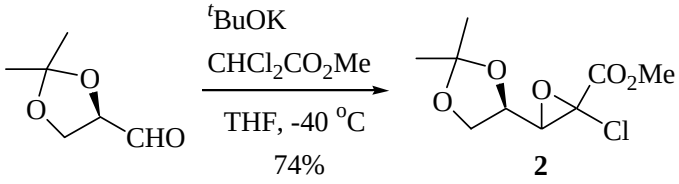


Figure 1.

There are various reported methods for the synthesis of isotetronic acid.[4] But concerning with the

synthesis of halogen substituted isotetronic acid, only a few methods are reported.[5] Furthermore this kind of one pot rearrangement-cyclization reaction is very unique. Here, we report the novel synthesis of 3-DPA lactone *via* acetonide protected methyl 4,5-dihydroxy-2-chloroglycidate with magnesium chloride.

Methyl 2-chloroglycidate (**2**) was prepared from acetonide protected glyceraldehyde[6] *via* the Darzens condensation reaction of dichloroacetate.[7] Treatment of acetonide protected glyceraldehyde and methyl dichloroacetate with ^{t}BuOK in THF provided **2** as two diastereomeric mixture in 74% yield after purification by silica gel flash chromatography (Scheme 1).

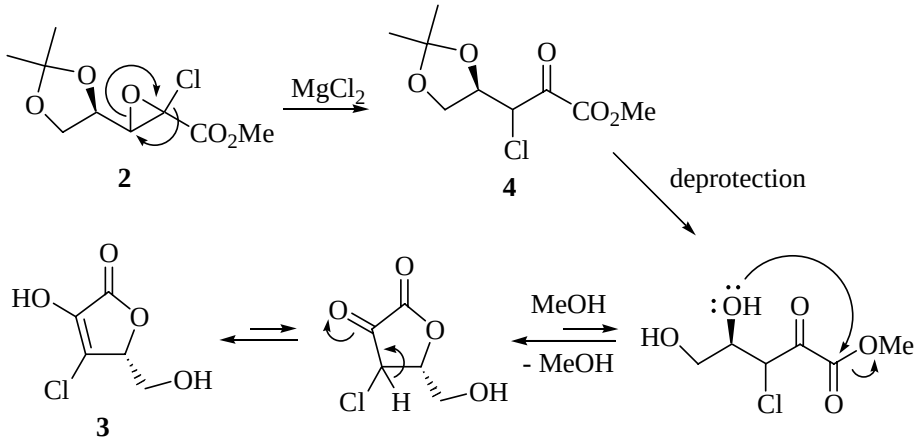


Scheme 1.

Then, we investigated the solvent effect on the synthesis of isotetronic acid (**3**) from 2-chloroglycidic ester (**2**) (Figure 1, Table 1). When water was used as a solvent, **3** was obtained in 41% yield (entry 1). Then we examined alcohol as a solvent and we found that **3** could be obtained in good yield when **2** was treated with $MgCl_2$ in MeOH at 50 °C (entry 4).

Table 1. Tandem cyclization reaction of 2-chloroglycidic ester **2**.

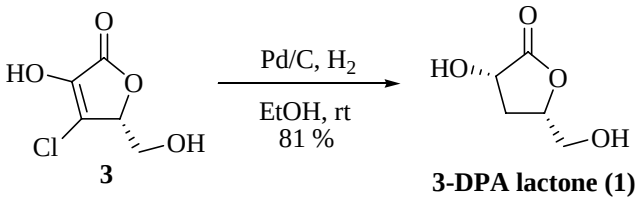
Entry	Solvent	Temp.	Time (h)	Yield of **3** (%)
1	H_2O	reflux	2	41
2	MeOH	reflux	7	50
3	EtOH	reflux	3	37
4	MeOH	50	30	81



Scheme 2.

Plausible mechanism for furnishing **3** from **2** is shown in Scheme 2. At first, as reported, 2-chloroglycidic ester (**2**) was transformed to 3-chloro-2-keto ester (**4**) in the presence of magnesium chloride.[8] Then, the deprotection of acetonide group and the following nucleophilic attack of the hydroxyl group to the carbonyl carbon was occurred. Finally, the tautomerization of the resulted compound furnished **3**.

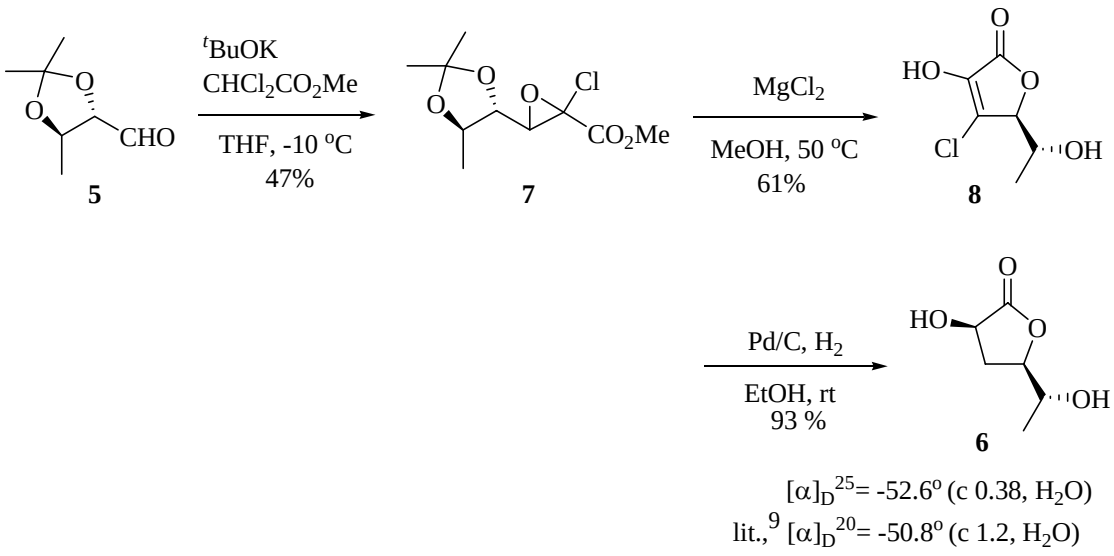
Then, we investigated the synthesis of 3-DPA lactone (**1**) from isotetronic acid (**3**) (Scheme 3). When **3** was treated with hydrogen in the presence of Pd/C in EtOH at room temperature, it was found that carbon double bond as well as chlorine atom was reduced, and desired 3-DPA lactone (**1**) was furnished in 81% yield at one step. Furthermore, by the same method reported in this paper, 3-DPA lactone derivative (**6**)[9] also could be synthesized from prepared acetonide protected glyceraldehyde derivative (**5**)[10] (Scheme 4).



3 **3-DPA lactone (1)**

$[\alpha]_D^{29}$= 22.5° (c 0.33, MeOH)
lit.,[1a] $[\alpha]_D^{20}$= 23.2° (c 3.61, MeOH)

Scheme 3.



5 **7** **8** **6**

$[\alpha]_D^{25}$= -52.6° (c 0.38, H_2O)
lit.,[9] $[\alpha]_D^{20}$= -50.8° (c 1.2, H_2O)

Scheme 4.

In conclusion, we have developed an efficient and novel method for the synthesis of 3-DPA lactone and its derivative *via* tandem cyclization reaction of acetonide protected methyl 4,5-dihydroxy-2-chloroglycidate.

EXPERIMENTAL

NMR spectra were recorded on JEOL JNM-AL300 instrument and calibrated using residual undeuterated solvent as an internal reference. IR spectra were recorded on a Thermo Nicolet Avatar 360T2 infrared spectrophotometer. Elemental analyses were performed on Perkin-Elmer 2400 series Ⅱ CHNS/O analyzer. For thin layer chromatography aluminum sheets Merk silica gel coated 60 F254 plates were used and the plates were visualized with UV light and phosphomolybdic acid (5% in EtOH). Merck silica gel 60 N (spherical, neutral) (40-50 μm) was used for the flash chromatography. Melting points were obtained in open capillary tubes on a Mel-Temp-II hot stage microscope. THF was distilled from sodium wire/ benzophenone before use. All other chemicals were used as received.

General procedure for the synthesis of 2 and 7 (synthesis of 2): To a stirred solution of 2,3-O-(isopropylidene)-$_D$-glyceraldehyde (2.13 g, 16.4 mmol) and methyl dichloroacetate (2.25 g, 15.8 mmol) in 45 mL of freshly distilled THF was added *t*-BuOK (2.13 g, 19.0 mmol) at -40 ^oC under atmosphere of nitrogen, and the reaction mixture was kept same temperature for 10 min. Then the reaction mixture was allowed to warm to 0^oC and saturated NH_4Cl solution (45 mL) was added. After the organic layer was extracted three times with EtOAc, the combined organic layer was washed with brine and dried over $MgSO_4$. After evaporation, the crude product was purified by column-chromatography (hexane/EtOAc 30:1) to give **2** (2.76 g, 74%) as two diastereomeric mixture (1.1:1).

Methyl 3-chloro-2,3-epoxy-4,5-O-isopropylidenepentanoate (2). Major isomer: colorless oil; $[\alpha]_D^{21}$ 21.3^o (c 1.73, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (s, 3H), 1.49 (s, 3H), 3.51 (d, *J*=7.2 Hz, 1H), 3.87 (s, 3H), 3.92 (dd, *J*=5.4, 8.1 Hz, 1H), 4.10-4.30 (m, 2H); IR (neat): 1756, 1252, 1069, 842 cm^{-1}. Anal. Calcd for $C_9H_{13}O_5Cl$: C, 45.68; H, 5.54. Found: C, 45.64; H, 5.59.

Methyl 3-chloro-2,3-epoxy-4,5-O-isopropylidenehexanoate (7). Major isomer: pale yellow oil; $[\alpha]_D^{22}$ -23.3^o (c 1.36, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (d, *J*=6.3 Hz, 3H), 1.45 (s, 3H), 1.46 (s, 3H), 3.45 (d, *J*=8.1 Hz, 1H), 3.77 (t, *J*=8.1 Hz, 1H), 3.87 (s, 3H), 4.11-4.19 (m, 1H); IR (neat): 1756, 1262, 1053, 855 cm^{-1}. Anal. Calcd for $C_{10}H_{15}O_5Cl$: C, 47.91; H, 6.03. Found: C, 47.63; H, 6.07.

General procedure for the synthesis of 3 and 8 (synthesis of 3): To a stirred solution of the 2-chloroglycidic ester (**2**) (50 mg, 0.21 mmol) in MeOH (2 mL) was added magnesium chloride (80 mg, 0.84 mmol), and the reaction mixture was heated to 50^oC for 30h. Then the reaction mixture was allowed to cool to room temperature. After evaporation of MeOH, distilled water (2 mL) was added and the organic layer was extracted three times with EtOAc. The combined organic layer was dried over $MgSO_4$ and concentrated. The crude product was purified by column-chromatography (hexane/EtOAc 2:1) to give **3** (28 mg, 81%).

4-Chloro-3-hydroxy-5-hydroxymethyl-5*H*-furan-2-one (3). White crystal; mp 152-154°C; $[\alpha]_D^{24}$ 25.8° (c 0.74, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$+ CD_3OD) δ 3.77 (dd, *J*=3.9, 12.6 Hz, 1H), 4.03 (dd, *J*=2.4, 12.6 Hz, 1H), 4.24 (br, 2H), 4.87 (dd, *J*=2.4, 3.9 Hz, 1H); IR (neat): 3326, 1757, 1705, 1298, 1172, 1125 cm^{-1}. Anal. Calcd for $C_5H_5O_4Cl$: C, 36.50; H, 3.06. Found: C, 36.14; H, 3.09.

4-Chloro-3-hydroxy-5-(1-hydroxyethyl)-5*H*-furan-2-one (8). White crystal; mp 132-134°C; $[\alpha]_D^{24}$ -64.7° (c 0.62, MeOH);^{1}H NMR (300 MHz, $CDCl_3$+ CD_3OD) δ 1.41 (d, *J*=6.6 Hz, 3H), 2.5 (br, 2H), 4.12 (dq, *J*=2.1, 6.6 Hz, 1H), 4.66 (d, *J*=2.1 Hz, 1H); IR (neat): 3408, 1773, 1748, 1675, 1129 cm^{-1}. Anal. Calcd for $C_6H_7O_4Cl$: C, 40.36; H, 3.95. Found: C, 40.37; H, 3.95.

General procedure for the synthesis of 1 and 6 (synthesis of 1): A solution of the isotetronic acid (**3**) (20 mg, 0.12 mmol) in EtOH (2.5 mL) was vigorously stirred under hydrogen atmosphere in the presence of 10% Pd-C (4 mg) for 8 h at rt. The heterogeneous mixture was then filtered through celite and the filter cake was washed with EtOH. The combined organic solution was concentrated and then the crude product was purified by column-chromatography (hexane/EtOAc 1:1) to give **1** (13 mg, 81%).

3-DPA lactone (1).[1a] Colorless oil; $[\alpha]_D^{29}$ 22.5° (c 0.33, MeOH) {lit.,[1a] $[\alpha]^{20}_D$ -23.2° (c 3.61, MeOH)}; ^{1}H NMR (300 MHz, CD_3OD) δ 1.98 (ddd, *J*=10.8, 10.8, 12.3 Hz, 1H), 2.54 (ddd, *J*=5.7, 8.7, 12.3 Hz, 1H), 3.59 (dd, *J*=5.1, 12.3 Hz, 1H), 3.80 (dd, *J*=3.0, 12.3 Hz, 1H), 4.42-4.51 (m, 1H), 4.56 (dd, *J*=8.7, 10.8 Hz, 1H); IR (neat): 3394, 2923, 1769, 1329, 1201, 1127, 993, 958, 900 cm^{-1}.

3-Hydroxy-5-(1-hydroxyethyl)dihydrofuran-2-one (6).[9] White crystal; mp 84-85°C (lit.,[9] mp 85-86 °C) ; $[\alpha]_D^{25}$ -52.6° (c 0.38, H_2O) {lit.,[9] $[\alpha]^{20}_D$ -50.8° (c 1.2, H_2O)}; ^{1}H NMR (300 MHz, CD_3OD) δ 1.26 (d, *J*=6.3 Hz, 3H), 2.02 (ddd, *J*=9.6, 9.6, 12.6 Hz, 1H), 2.58 (ddd, *J*=6.0, 8.7, 12.6 Hz, 1H), 2.72 (br, 2H), 3.75-3.83 (m, 1H), 4.22-4.29 (m, 1H), 4.50 (dd, *J*=8.7, 9.6 Hz, 1H); IR (neat): 3387, 1766, 1331, 1202, 1132, 999, 970, 913 cm^{-1}.

REFERENCES AND NOTES

1. a) O. Uchikawa, N. Okukado, T. Sakata, K. Arase, and K. Terada, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 2025. b) T. Nakano, Y. Ino, and Y. Nagai, *Chem. Lett.*, 1989, 567. c) P. L. Wu, Y. L. Hsu, C. W. Zao, A. G. Damu, and T. S. Wu, *J. Nat. Prod.*, 2005, **68**, 1180. d) M. F. Brana, M. L. Garcia, B. Lopez, B. Pascual-Teresa, A. Ramos, J. M. Pozuelo, and M. T. Dominguez, *Org. Biomol. Chem.*, 2004, **2**, 1864.
2. Y. Oomura and H. Nishimura, *Kagaku*, 1987, **42**, 440.
3. a) T. Komiyama, Y. Takaguchi, and S. Tsuboi, *Tetrahedron Lett.*, 2004, **45**, 6299. b) T. Komiyama, Y. Takaguchi, A. T. Gubaidullin, V. A. Mamedov, I. A. Litvinov, and S. Tsuboi, *Tetrahedron*, 2005, **61**, 2541.

4. a) A. G. M. Barrett and H. G. Sheth, *J. Org. Chem*., 1983, **48**, 5017. b) G. Stork and S. D. Rychnovsky, *J. Am. Chem. Soc*., 1987, **109**, 1564. c) I. R. Vlahov, P. I. Vlahova, and R. R. Schmidt, *Tetrahedron Lett*., 1992, **33**, 7503. d) J. Bigorra, J. Font, C. O. Echaguen, and R. M. Ortuno, *Tetrahedron*, 1993, **49**, 6717. e) D. Enders, H. Dyker, and F. R. Leusink, *Chem. Eur. J*., 1998, **4**, 311. f) K. Juhl, N. Gathergood, and K. A. Jorgensen, *Chem. Commun*., 2000, 2211. g) R. Dede, L. Michaelis, and P. Langer, *Tetrahedron Lett*., 2005, **46**, 8129. h) P. Dambruoso, A. Massi, and A. Dondoni, *Org. Lett*., 2005, **7**, 4657.
5. a) C. C. Bonini, C. Iavarone, C. Trogolo, and G. A. Poulton, *Org. Mass Spectrom.,* 1980, **15**, 516. b) M. Ashwell, W. Clegg, and R. F. W. Jackson, *J. Chem. Soc., Perkin Trans. 1,* 1991, 897.
6. C. R. Schmid, J. D. Bryant, M. Dowlatzedah, J. L. Phillips, D. E. Prather, R. D. Schantz, N. L. Sear, and C. S. Vianco, *J. Org. Chem.*, 1991, **56**, 4056.
7. a) A. Takeda, S. Tsuboi, S. Wada, and H. Kato, *Bull. Chem. Soc. Jpn.*, 1972, **45**, 1217. b) A. Takeda, S. Tsuboi, and I. Nakashima, *Bull. Chem. Soc. Jpn.*, 1975, **48**, 1067. c) S. Tsuboi, H. Furutani, A. Takeda, K. Kawazoe, and S. Sato, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 2475.
8. P. Coutrot, C. Grison, M. Tabyaoui, S. Czernecki, and J. M. Valery, *J. Chem. Soc., Chem. Commun*., 1988, 1515.
9. K. Bock, I. Jundt, and C. Pedersen, *Acta Chem. Scand. B,* 1981, **35**, 155.
10. S. Servi, *J. Org. Chem.,* 1985, **50**, 5865.