# A Useful Oxidation Procedure for the Preparation of 3-Alkanoyltetronic Acids

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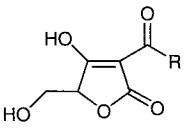
**Abstract**: An easy and convenient synthesis of 3-alkanoyl-5-hydroxymethyltetronic acids, the salts of which have inhibitory activity against HIV-1 protease, is described and a new direct route to 1,3-dicarbonylester from cyclic β-ketoester is developed.

In 1994, Roggo and his coworkers isolated six new homologues of sodium salt of 3-alkanoyl-5-hydroxymethyltetronic acids (**1a** - **f**) from cultures of the *Actinomycete* strain DSM 7357 and have been found to be inhibitors of HIV-1 protease (Figure 1).[1,2] We would like to synthesize these acids (**1**) and their analogs starting from easily available dibenzyl malonate (**2**). Although there is now a number of procedures for the preparation of simple acyltetronic acids,[3,4] there is a need to develop more improved methodology which may eventually be applicable to more complex systems. This paper describes an efficient and convenient synthesis of the tetronic acid (**1a**).



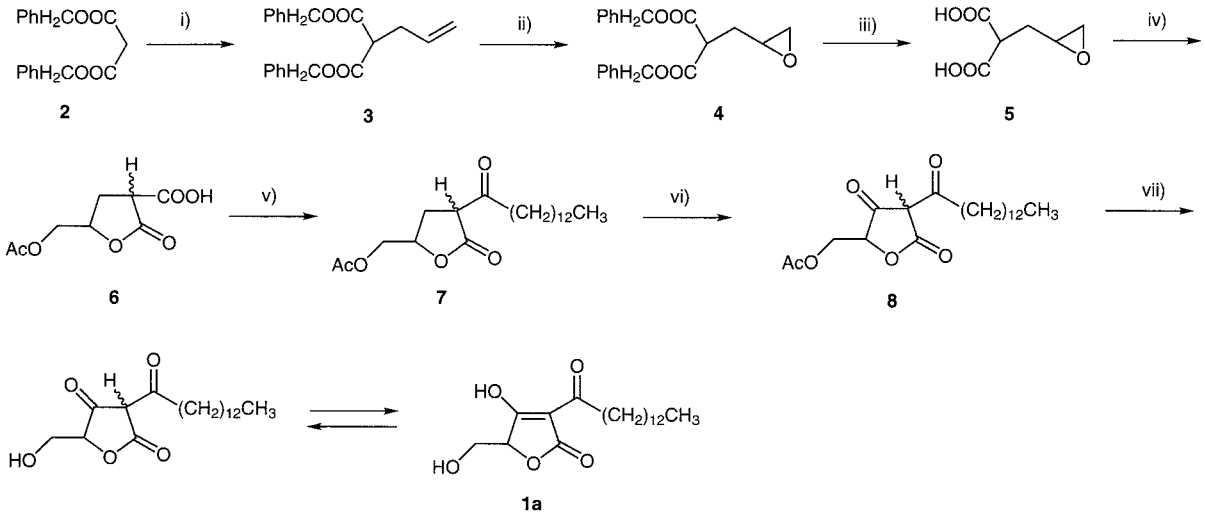
**1a**) R = $(CH_2)_{12}CH_3$
**1b**) R = $(CH_2)_{13}CH_3$
**1c**) R = $(CH_2)_{11}CH(CH_3)_2$
**1d**) R = $(CH_2)_{14}CH_3$
**1e**) R = $(CH_2)_{12}CH(CH_3)_2$
**1 f**) R = $(CH_2)_{12}CH(CH_3)(CH_2CH_3)$

**Figure 1**

Epoxidation with *m*-CPBA in dibenzyl allylmalonate (**3**) followed by hydrogenolysis afforded the corresponding epoxydicarboxylic acid (**5**), which was treated with $CF_3COOH$ followed by $Ac_2O$ to give 3-carboxy-5-acetoxymethyl-γ-butyrolactone (**6**, 86% from **5**). Acylation at $C_3$ was carried out by the condensation of the magnesium salt of this acid (**6**) with $CH_3(CH_2)_{12}COIm$ under a mild condition[5] and 3-tetradecanoyl-5-acetoxymethyl-γ-butyrolactone (**7**, 48% yield) was obtained as a diastereomeric mixture. Then we attempted to introduce a double bond at $C_3$-$C_4$ position in this novel lactone. For this purpose, phenylselenylation followed by oxidative elimination[6] of **7** in the presence of an excess of $H_2O_2$ was carried out. Surprisingly, the tetronic acid (**8**) was directly obtained as a sole product, and the structure of **8** was confirmed[7] by NMR, IR, and MS. For the hydrolysis of the acetyl group, the compound (**8**) was heated at 60°C in MeOH with dil. HCl for 10 hrs. and **1a** was obtained as the only isolated product (Scheme 1).

This interesting reaction was applied to several compounds (**9** - **13**) and the results are summarized in Table 1. Among these 6 samples, cyclic β-ketoesters (**7**, **9** - **11**) gave the desired products (Scheme 1 and Entries 1 - 3), on the other hand, acyclic β-ketoester (**12**) or β-diester (**13**) afforded the olefinic product (**18**, **19**, respectively) (Entries 4 and 5).

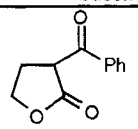
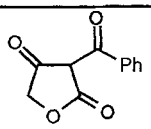
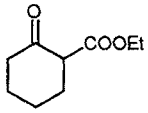
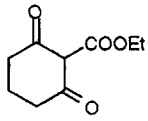
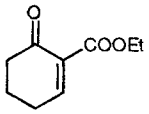
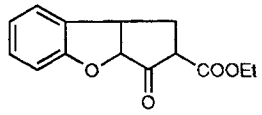
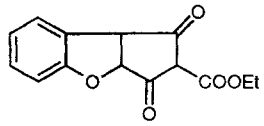
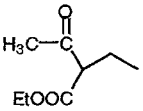
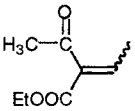
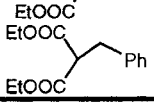
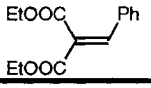
Thus using an appropriate 1-acylimidazole for acylation of the lactonic acid (**6**) these 3-alkanoyl-5-hydroxymethyltetronic acids (**1b** - **f**) will be able to be prepared readily. Preparation of several analogs of **1**, which have an appropriate function on the long side-chain or on the hydroxymethyl group, by application of the present methodology is in progress for evaluation of their HIV-1 protease inhibitory activity.[9]



Reagents and conditions : i) NaH, allyl bromide, rt, 12 hrs., 90%. ii) *m*-CPBA, dry $CHCl_3$, rt, 24 hrs., 98%. iii) $H_2$, Pd-C, 97%. iv) a) $CF_3COOH$, $H_2O$-acetone, b) $Ac_2O$, 86%. v) $Mg(OEt)_2$, $CH_3(CH_2)_{12}COIm$, 48%. vi) a) PhSeCl, AcOEt, 24 hrs., b) 30% $H_2O_2$ (*ca.* 15eq.), THF, 2 hrs., 45%. vii) MeOH, dil. HCl, 60°C, 10 hrs., 50%.

**Scheme 1**

**Table 1**. $H_2O_2$ Oxidation of β-Dicarbonyl Compounds *via* the Corresponding Selenides

| Entry | Substrate | Condition[a] | Product (Yield)[b] | |
|---|---|---|---|---|
| 1 | **9** :  | **A** | **14** :  | (51 %) |
| 2 | **10** :  | **B** | **15** :  ( 35 %); **16** :  | (10 %) |
| 3 | **11** :  | **B** | **17** :  | (65 %) |
| 4 | **12** :  | **B** | **18** :  | (49 %) |
| 5 | **13** :  | **B** | **19** :  | (70 %) |

Condition: A i) PhSeCl/AcOEt, rt, ii) 30% $H_2O_2$ (*ca.* 15 eq.), THF, rt.
B i) PhSeCl/NaH, THF, rt, ii) 30% $H_2O_2$ (*ca.* 15 eq.), THF, rt.
a: Reaction was monitored by TLC.
b: Products were characterized by NMR, IR, MS and/or EA.

**References and Notes :**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(5) Brookes, D. W.; Lu, L. D. L.; Masamune, S. *Angew. Chem. Int. Ed. Engl.* **1979**, *18* , 72.

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(7) As upon treatment with $Ac_2O$/pyridine there was no change, while trying to oxidized with PCC, also there was no change.

(8) Grieco, P. A.; Yokoyama, Y.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1977**, *42*, 2034. Kametani, T.; Nemoto, H.; Fukumoto, K. *Heterocycles* , **1977**, *6* , 1365.

(9) Recently, a total synthesis of **1d** has been reported [Sodeoka, M.; Sampe, R.; Kagamizono, T.; Osada, H. *Tetrahedron Lett.*, **1996**, *37*, 8775].