CHEMISTRY LETTERS, pp. 1795-1798, 1982.

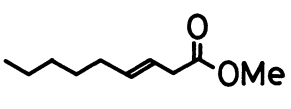
A SHORT-STEP SYNTHESIS OF (±)-PYRENOPHORIN UTILIZING 3-ALKENOATE AS A MASKED SYNTHON OF 4-OXO-2-ALKENOATE

Tamotsu FUJISAWA,* Masashi TAKEUCHI, and Toshio SATO
Chemistry Department of Resources, Mie University, Tsu, Mie 514

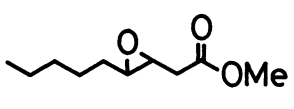
The use of 3-alkenoate as a masked synthon of 4-oxo-2-alkenoate was established by a three step conversion of 3-nonenoate into 4-oxo-2-nonenoate through epoxidation, isomerization to an allyl silyl ether, and oxidation in a high overall yield. This method was applied to the short step synthesis of pyrenophorin from 7-oxo-3-octenoic acid.

The structural unit of 4-oxo-2-alkenoate often exists in several macrolide antibiotics.[1] This structural function is also suitable for an acceptor toward nucleophiles or as a potent dienophile in Diels-Alder reactions.[2] Although a variety of methods have been devised for the synthesis of 4-oxo-2-alkenoates,[3] a few methods are applicable to the macrolide synthesis. In the previous paper, we described the efficient method for the preparation of 7-oxo-(*E*)-3-alkenoic acids by the regioselective ring-opening reaction of β-vinyl-β-propiolactone with bromomagnesium derivatives of *N*,*N*-dimethylhydrazones in the presence of a copper(I) catalyst.[4] This product has three functional groups, *i.e.*, a carbonyl function at the 7 position, a carbon-carbon double bond at the 3 position, and a terminal carboxylic function. Accordingly, it can be expected that the oxoalkenoic acid is a favourable starting material of macrolide antibiotics with the structural unit of 4-oxo-2-alkenoate, if the 3-alkenoate structure is easily transformed into 4-oxo-2-alkenoate structure. We wish to describe here an effective method for the conversion of 3-alkenoate into 4-oxo-2-alkenoate leading to the efficient short step synthesis of pyrenophorin.

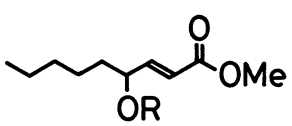
Although the conversion of olefinic compounds into allylic alcohols or vinyl ketones is well documented, the analogous method is difficult to apply to the transformation of 3-alkenoate into 4-oxo-2-alkenoate. Only one example of palladium catalyzed acetoxylation of 3-alkenoate into 4-acetoxy-2-alkenoate reported so far is an excellent procedure although their yields were not satisfactory.[5] An attempt for the direct allylic oxidation of methyl 3-nonenoate (1) by chromic acid[6] was resulted in a formation of methyl 4-oxo-2-nonenoate (5)



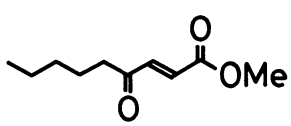
1



2



3 R=H 4 R=Me_3Si



5

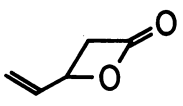
Table. The Conversion of Methyl 3,4-Epoxynonenoate into Methyl 4-Hydroxy-2-Nonenoate (3) or Its Silyl Ether Derivative (4)[a]

Entry	Reagents	Conditions	Solvent	Product (Yield%)[b]
1	LDA	-78 °C, 1 h	THF	3 (85%)
2	*t*-BuOK (20 mol%)	0 °C, 40 min	THF	3 (84%)
3	iPr$_2$N-AlEt$_2$	-50 °C, 20 min	toluene	3 (76%)
4	$Me_3SiOSO_2CF_3$ DBU 2,6-Lutidine	-78 °C, 4 h rt, 5 h	toluene	4 (trace)
5	Me_3SiI DBU	0 °C, 15 min reflux, 50 h	CH_3CN	4 (24%) 4-Oxononanoic Acid (47%)
6	$Me_3SiCH_2CO_2Et$ cat. Bu_4NF (5 mol%)	-20 °C → rt, 4 h	THF	4 (94%)

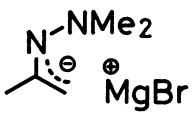
[a] All reactions were carried out on 1 mmol scale. [b] All products were identified by IR and NMR spectra, and values reported are for isolated products.

in a yield of 15%. On the other hand, much attention has recently been paid to the conversion of epoxides into allylic alcohols.[7] Thus this type of conversion was applied to methyl 3,4-epoxynonanoate (2), prepared from the corresponding olefinic ester 1 by the epoxidation with *m*-chloroperbenzoic acid. As shown in Table, considerable methods using a base such as lithium diisopropylamide, potassium *t*-butoxide or an aluminum amide[7a] are found to be applicable to give methyl 4-hydroxy-2-nonenoate (3) in high yields. The existence of free hydroxy group, however, should be avoided as an intermediate of macrolide synthesis because of disproportionation of the lactone ring *(vide infra)*. Thus the transformation of the epoxy ester into the hydroxy ester protected by a silyl group was further performed. By the known method using Lewis acidic silylating agent such as trimethylsilyl triflate[7b] or trimethylsilyl iodide[7c,d] and DBU, methyl 4-trimethylsiloxy-2-nonenoate (4) was obtained in unsatisfied yields. Good result was obtained, when ethyl trimethylsilylacetate and tetrabutylammonium fluoride[8] was used as a base. Further, the silyl ether linkage was found to be oxidized easily by pyridinium chlorochromate to the corresponding ketone 5 in a yield of 87% without deprotection of the silyl group.

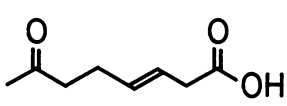
This three step conversion of 3-alkenoate into 4-oxo-2-alkenoate can be widely applicable, since each step can be performed in a high yield, and 3-alkenoic acids are easily prepared by the regiospecific ring-opening reaction of β-vinyl-β-propiolactone.[9] Thus, the application of this strategy was demonstrated in the synthesis of pyrenophorin. The starting material, 7-oxo-3-octenoic acid (8) was easily obtained by the reaction of β-vinyl-β-propiolactone (6) with the bromomagnesium derivative of aceton *N*,*N*-dimethylhydrazone (7).[4] The selective



6

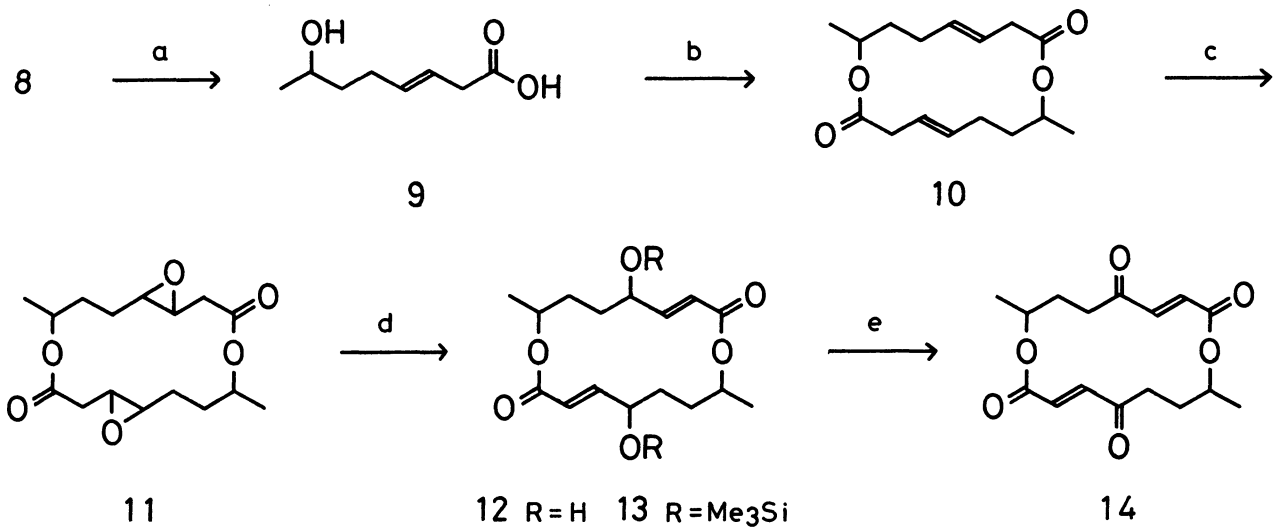


7



8

reduction of the carbonyl group of 8 was achieved by the treatment with sodium borohydride in slightly alkaline aqueous solution at room temperature for 3 h to furnish 7-hydroxy-3-octenoic acid 9 in a quantitative yield. The dimerized cyclization of 9 was performed by the treatment with diethyl azodicarboxylate and triphenylphosphine[10] in THF-toluene (1:9, 2×10^{-2}M) at -25 °C for 1.5 d then at 0 °C for 1 d to give dilactone 10[11] in 47% yield. The epoxidation of the dilactone 10 with *m*-chloroperbenzoic acid in CH_2Cl_2 at room temperature for 3 h gave quantitatively diepoxide 11.[12] Although this diepoxide 11 was converted into pyrenophorol 12 by the treatment of a base such as lithium diisopropylamide, potassium *t*-butoxide, or an aluminum amide, the yields of pyrenophorol were lower than 47% in every cases. This is due to the ester exchange reaction by alkoxide ion produced. On the other hand, the treatment of the diepoxide 11 with ethyl trimethylsilylacetate in the presence of a catalytic amount (10 mol%) of tetrabutylammonium fluoride in THF at 0 °C to room temperature for 36 h gave disiloxy dilactone 13,[13] and the subsequent oxidation of 13 with pyridinium chlorochromate in dichloromethane at room temperature for 4 h afforded a mixture of dl- and meso-pyrenophorin (14) (ca. 1:1) in 60% yield from the diepoxide 11.



a) $NaBH_4$, rt, 3 h; b) $EtO_2CN{=}NCO_2Et/Ph_3P/PhMe$-THF, -25 °C, 1.5 d to 0 °C, 1 d; c) mCPBA, CH_2Cl_2, rt, 3 h; d) $Me_3SiCH_2CO_2Et/Bu_4NF$ (10 mol%), THF, 0 °C ∿ rt, 36 h; e) PCC, CH_2Cl_2, rt, 4 h.

Although a number of the synthetic methods of pyrenophorin have recently been reported,[14] the protection of the 4-oxo group was required due to a labile structure of 4-oxo-2-alkenoate for the step of construction of the 16-membered ring in these methods except one case.[14f] Since 3-alkenoate was used as a masked synthon of 4-oxo-2-alkenoate in the present synthesis, troublesome processes of the protection and deprotection of the carbonyl group could be omitted.

As mentioned above, an efficient short-step synthesis of 4-oxo-2-alkenoate was achieved from easily available 3-alkenoate and the present method provides a promising route for the synthesis of various macrolide antibiotics with the structural unit of 4-oxo-2-alkenoate.

References

1) Reviews: K. C. Nicolaou, *Tetrahedron*, 33, 683 (1977); T. G. Back, *ibid.*, 33, 3041 (1977); S. Masamune, G. S. Bates, and J. W. Corcoran, *Angew. Chem. Int. Ed. Engl.*, 16, 585 (1977); S. Masamune, *Aldrichimica Acta*, 11, 23 (1978).
2) S. Danishefsky and M. Kahn, *Tetrahedron Lett.*, 22, 485 and 489 (1981).
3) I. Böhm, R. Schulz, and H.-U. Reissig, *Tetrahedron Lett.*, 23, 2013 (1982), and references cited therein.
4) T. Fujisawa, M. Takeuchi, and T. Sato, *Chem. Lett.*, 1982, 1521.
5) J. Tsuji, K. Sakai, H. Nagashima, and I. Shimizu, *Tetrahedron Lett.*, 22, 131 (1981).
6) M. Nakayama, S. Shinke, Y. Matsushita, S. Ohira, and S. Hayashi, *Bull. Chem. Soc. Jpn.*, 52, 184 (1979).
7) For instance, a) A. Yasuda, H. Yamamoto, and H. Nozaki, *Bull. Chem. Soc. Jpn.*, 52, 1705 (1979). b) S. Murata, M. Suzuki, and R. Noyori, *J. Am. Chem. Soc.*, 101, 2738 (1979). c) H. Sakurai, K. Sasaki, and A. Hosomi, *Tetrahedron Lett.*, 21, 2329 (1980). d) G. A. Kraus and K. Frazier, *J. Org. Chem.*, 45, 2579 (1980). e) T. Inoue, T. Uchimaru, and T. Mukaiyama, *Chem. Lett.*, 1977, 1215. f) M. R. Detty and M. D. Seidler, *J. Org. Chem.*, 46, 1283 (1981). g) S. Terao, M. Shiraishi, and K. Kato, *Synthesis*, 1979, 467, and references cited therein.
8) E. Nakamura, K. Hashimoto, and I. Kuwajima, *Tetrahedron Lett.*, 1978, 2079.
9) T. Sato, M. Takeuchi, T. Itoh, M. Kawashima, and T. Fujisawa, *Tetrahedron Lett.*, 22, 1817 (1981).
10) T. Kurihara, Y. Nakajima, and O. Mitsunobu, *Tetrahedron Lett.*, 1976, 2455.
11) NMR (CCl_4) δ 5.7 $\sim$ 5.4 (m, 4H), 5.2 $\sim$ 4.7 (m, 2H), 3.0 $\sim$ 2.8 (m, 4H), 2.4 $\sim$ 2.0 (m, 4H), 1.9 $\sim$ 1.5 (m, 4H), and 1.2 (d, J = 6 Hz, 6H). IR (KBr liq. film) 1710 and 960 cm^{-1}.
12) NMR ($CDCl_3$) δ 5.3 $\sim$ 4.7 (m, 2H), 3.3 $\sim$ 2.4 (m, 8H), 2.1 $\sim$ 1.5 (m, 8H), and 1.3 (d, J = 6 Hz, 6H). IR (KBr liq. film) 1720 and 1250 cm^{-1}.
13) NMR ($CDCl_3$) δ 6.95 (dd, J = 15.5 and 1.5 Hz, 2H), 6.00 (dd, J = 15.5 and 5 Hz, 2H), 5.7 $\sim$ 4.7 (m, 2H), 4.6 $\sim$ 4.0 (m, 2H), 2.0 $\sim$ 1.4 (m, 8H), 1.25 (d, J = 6 Hz, 6H), and 0.12 (s, 18H). IR (KBr liq. film) 1710, 1640, and 1060 cm^{-1}.
14) a) E. W. Colvin, T. A. Purcell, and R. A. Raphael, *J. Chem. Soc., Perkin Trans. 1*, 1976, 1718. b) R. S. Mali, M. Pohmakotr, B. Weidmann, and D. Seebach, *Liebigs Ann. Chem.*, 1981, 2272. c) H. Gerlach, K. Oertle, and A. Thalmann, *Helv. Chim. Acta*, 60, 2860 (1977). d) P. Bakuzis, M. L. P. Bakuzis, and T. F. Weingartner, *Tetrahedron Lett.*, 27, 2371 (1978). e) M. Asaoka, N. Yanagida, N. Sugimura, and H. Takei, *Bull. Chem. Soc. Jpn.*, 53, 1061 (1980). f) M. Asaoka, T. Mukuta, and H. Takei, *Tetrahedron Lett.*, 22, 735 (1981). g) T. A. Hase, A. Ourila, and C. Holmberg, *J. Org. Chem.*, 46, 3137 (1981).

(Received August 21, 1982)