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Synthesis of Clavulone Derivatives. Selective Cleavage of Ester Bonds in Clavulone

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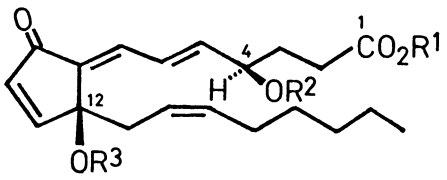
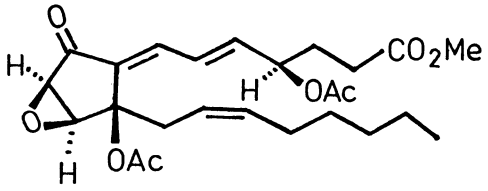
The clavulone derivatives (1-O-demethylclavulone II and 4-O-deacetylclavulone II) were synthesized from clavulone II (1) by selective enzymatic hydrolysis of 1 using porcin liver esterase (PLE) and orange peel acetylesterase, respectively. The derivative (12-O-deacetylclavulone II) was synthesized by organocuprate reduction of 10,11-epoxyclavulone II which was prepared from 1.

Recently coral-derived marine prostanoids, clavulones[1] and their congeners,[2] have received much attention owing to the unique structural features and strong antileukemic activities.[3] In order to get detailed informations of structure-activity relationship, we have been studying to synthesize a variety of derivatives[4] from clavulones[5] and to examine the biological activity of the derivatives.[7] In the course of this study, the selective cleavage of the ester bonds at C-1, -4, and -12 in clavulones has become a crucial problem[8] for the modification of clavulones. This paper describes an effective synthesis of the derivatives 2, 3, and 4 from clavulone II (1) by either enzymatic or chemical cleavage of the ester bonds.

Among the three ester bonds in 1, the methyl ester at C-1 and acetic acid ester of the secondary alcohol at C-4 were selectively hydrolyzed by the enzymatic reactions using porcin liver esterase (PLE)[9] and orange peel acetylesterase, respectively. Treatment of 1 in acetone and phosphate buffer solution (pH = 8.0) with PLE in aqueous ammonium sulfate solution[10] at 40 °C gave exclusively the carboxylic acid 2[11] in 96% yield. On the other hand, treatment of 1 in acetone and phosphate buffer solution (pH = 6.5) with orange peel acetylesterase[10] at 40 °C gave exclusively the alcohol 3[11] in 91% yield. The use of Baker's yeast or porcin





1 R^1=Me, R^2=R^3=Ac
2 R^1=H, R^2=R^3=Ac
3 R^1=Me, R^2=H, R^3=Ac
4 R^1=Me, R^2=Ac, R^3=H

5

pancreatic lipase (PPL), both of which were employed for the hydrolysis of the methyl ester in prostaglandin syntheses,[12,13] did not give good results. In the former case a mixture of many products including reduced products was formed, while in the latter case the reaction did not proceed.

The selective cleavage of the acetic acid ester of the tertiary alcohol at C-12 was chemically done *via* the epoxide 5 which was prepared from 1. The acetic acid ester at C-12 in the epoxide 5 was cleaved by the organocuprate-induced reaction which involved a neighboring group participation of the acetoxyl group at C-12. The epoxide 5[11,14] was synthesized in 53% yield by treatment of 1 in benzene with t-butyl hydroperoxide in the presence of Triton B at 0 °C. Reaction of 5 with lithium dimethylcuprate in ether at -78 °C gave the alcohol 4[11] in 52% yield. The compound 4 is presumably formed by the reaction pathway shown in Scheme 1. Initially the carbonyl group at C-9 is reduced by lithium dimethylcuprate, and then cleavage of the epoxide followed by further electron transfer to the oxygen at C-11 takes place. Acetyl migration from the 12-oxygen to the 11-oxygen followed by elimination of the acetoxyl group and protonation at the 12-oxygen during the work-up procedure gives rise to 4. The present reaction, which resulted in both reduction of the epoxide and cleavage of the acetic acid ester, is of interest in view of the organocuprate-induced reaction of α,β-epoxy ketones.[15]

The antileukemic activity of 2-5 against HL-60 cells were measured, and the remarkable enhancement of the activity of 4 with the hydroxy group at C-12 was observed. The details are described in the separate paper.[16]

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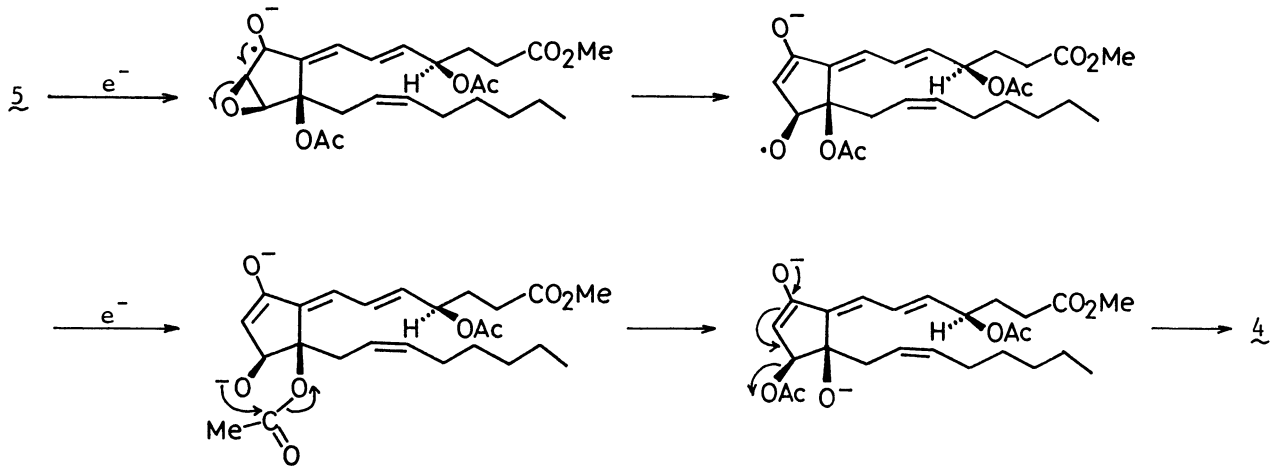

Scheme 1.

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2) K. Iguchi, S. Kaneta, K. Mori, Y. Yamada, A. Honda, and Y. Mori, Tetrahedron Lett., 26, 5787 (1985); K. Iguchi, S. Kaneta, K. Mori, and Y. Yamada, Chem. Pharm. Bull., 35, 4375 (1987) and other references cited therein.

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4) K. Iguchi, S. Kaneta, C. Tsune, and Y. Yamada, Abstracts of Papers, the 108th Annual Meeting of Pharmaceutical Society of Japan, 1988, p293.

5) We used clavulones as a starting material for the synthesis of clavulone derivatives, because clavulones are abundant in the soft coral Clavularia viridis (about 0.4% yield based on the freeze-dried organisms) and the total syntheses of clavulones were already accomplished.[6)]

6) For example: E. J. Corey and M. M. Mehrotra, J. Am. Chem. Soc., 106, 3384 (1984); H. Nagaoka, T. Miyakoshi, and Y. Yamada, Tetrahedron Lett., 25, 3621 (1984); M. Shibasaki and Y. Ogawa, ibid., 26, 3841 (1985).

7) A. Honda, Y. Mori, K. Iguchi, and Y. Yamada, Mol. Pharmacol., 32, 530 (1987).

8) Usual acid catalyzed hydrolysis (e.g. hydrochloric acid) and base catalyzed solvolysis (e.g. sodium hydroxide, potassium carbonate, sodium methoxide) of 1 were attempted under various conditions, but these reactions resulted in formation of a mixture of many products and selective cleavage of the ester bonds was not observed.

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10) The enzyme solutions were available from Sigma Chemical Company.

11) 2: colorless oil; $[\alpha]_D$ +12.2° (c 2.0, $CHCl_3$); IR (film) 3400-2800, 1742, 1708, 1644 cm^{-1}; UV (EtOH) 232 (ε 13400), 294 (ε 15100) nm. 3: colorless oil; IR (film) 3470, 1739, 1700, 1641 cm^{-1}; UV (EtOH) 234 (ε 12200), 295 (ε 14100) nm. 4: pale yellow oil; $[\alpha]_D$ -51.9° (c 0.31, $CHCl_3$); IR (film) 3456, 1739, 1642 cm^{-1}; UV (EtOH) 230 (ε 11600), 295 (ε 12000) nm. 5: pale yellow oil; $[\alpha]_D$ +13.4° (c 6.0, $CHCl_3$); IR (film) 1730, 1720, 1705 cm^{-1}; UV (EtOH) 285 (ε 15000) nm.

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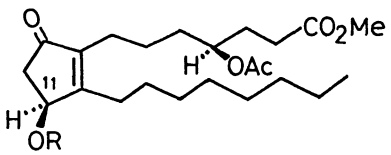
14) The stereochemistry of the epoxide moiety in 5 was determined by conversion of 5 to the allylic alcohol 6: hydrogenation of 5 over palladium on carbon gave 6. The CD spectrum of the p-bromobenzoate 7, which was prepared by treatment of 6 with p-bromobenzoyl chloride in pyridine, showed a negative Cotton effect at 240 nm (Δε -7.0), which indicated the 11S configuration in both 6 and 7.



6 R=H

7 R=C(=O)-C6H4-Br

15) J. R. Bull and H. H. Lachmann, Tetrahedron Lett., 1973, 3055.

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