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SYNTHESIS OF dl-15-OXO-13,14-METHYLENEPROSTANOIC ACID[1)]

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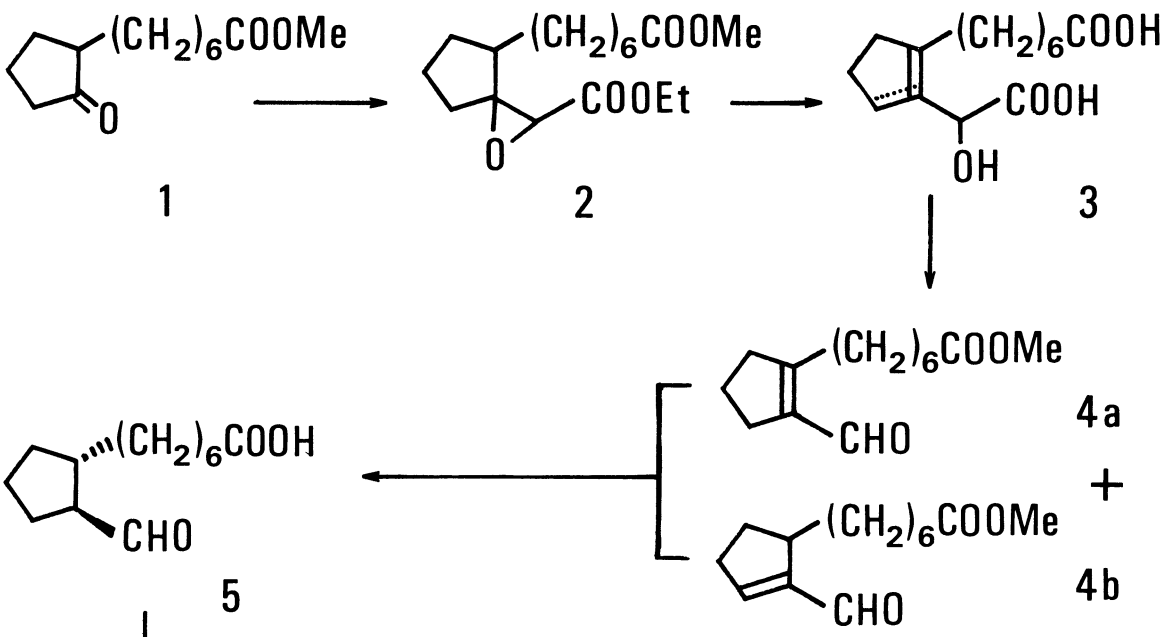
The Darzens reaction of 2-(6-methoxycarbonylhexyl)cyclopentanone with ethyl chloroacetate gave the stereoisomeric mixture of the epoxy esters which was connected with the synthesis of 15-oxo-13α,14α-methyleneprostanoic acid and 15-oxo-13β,14β-methyleneprostanoic acid. Both methylene compounds showed very potent inhibitory activity against 15-hydroxyprostaglandin dehydrogenase.

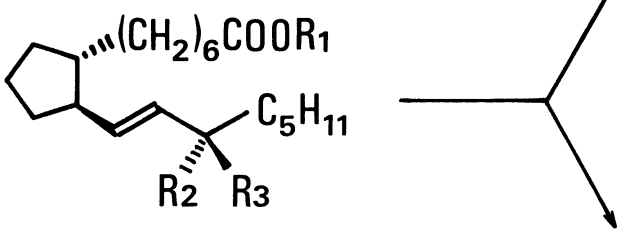
A considerable effort has been devoted to the elucidation of the relationship between the prostanoic acid derivatives and their biological activities.[2)] In a previous paper, we reported the synthesis of (+)-prostanoic acid[3)] which contains the basic structure of all prostaglandins. In connection with this work, we wish to describe the preparation of 15-oxo-13,14-methyleneprostanoic acid[4)] which was the most potent inhibitor for 15-hydroxyprostaglandin dehydrogenase.

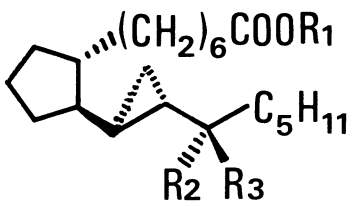
The Darzens condensation reaction of 2-(6-methoxycarbonylhexyl)cyclopentanone (1) with ethyl chloroacetate and t-BuOK in THF afforded a stereoisomeric mixture of epoxy esters (2) [yield: 88.5%, IR(neat): 1755 and 1745 cm^{-1}]. The cleavage reaction of the epoxide 2 in the presence of p-TsOH in benzene under reflux for 30 min, followed by hydrolysis (5% aq. NaOH) gave a mixture of isomeric hydroxy acids (3) [yield: 67.5%, IR(neat): 3200 and 1710 cm^{-1}]. Without the separation of isomers, 3 was submitted to oxidation by $Pb(OAc)_4$ in AcOH or $NaIO_4$ in aq. acetone followed by treatment with CH_2N_2 to yield a 6:1 mixture of a $\Delta^{8(12)}$ olefinic aldehyde (4a) [yield: 65.8%, IR(neat): 1745, 1665, and 1630 cm^{-1}, NMR($CDCl_3$): δ 10.3 (1H, s, CHO) and 3.66 (3H, s, $COOCH_3$)] and a Δ^{11} olefinic aldehyde (4b) [yield: 11.2%, IR(neat): 1740, 1680, and 1615 cm^{-1}, NMR($CDCl_3$): δ 9.80 (1H, s, CHO), 6.83 (1H, m, olefin), and 3.68 (3H, s, $COOCH_3$)]. Catalytic hydrogenation of the

mixture of 4a,b over 5% Pd-C in THF followed by isomerization and hydrolysis by 3% aq. NaOH-MeOH gave a trans acid aldehyde (5) [yield: 73.2%, IR(neat): 1720 and 1705 cm^{-1}, NMR($CDCl_3$): δ 9.6 (1H, d, J=3 Hz, CHO) and 10.4 (1H, bs, COOH)], which was identified by the comparison with a standard sample.[3] 15-Epimeric alcohols (6) were obtained from the acid aldehyde 5 in 74% yield by the usual method: i) (2-oxoheptylidene)tributylphosphorane, ii) $NaBH_4$ in MeOH. An attempt to separate the 15-epimeric alcohols 6 by silica gel chromatography was unsuccessful. However, p-bromophenacyl ester (7) obtained by reaction of the potassium salt of 6 with p-bromophenacyl bromide was found to be very effective in the separation of the 15-epimeric alcohols. Recrystallization of a semisolid p-bromophenacyl ester 7 from hexane gave a crystalline (7a) [yield: 36.5%, mp: 55.0-56.5°C, IR($CHCl_3$): 3660, 1745, 1710, and 1580 cm^{-1}, NMR(CCl_4): δ 7.67 (4H, m, aromatic), 5.40 (2H, m, olefin), 5.15 (2H, s, $-CH_2-$), and 3.90 (1H, m, >CH-O-)] and an oily ester (7b) from the mother liquor. The reductive hydrolysis of 7a with Zn-AcOH gave 15α-hydroxyprost-13-enoic acid (6a)[5] [yield: 88.0%, mp: 37.0-38.5°C, IR(neat): 3380 and 1715 cm^{-1}, NMR(CCl_4): δ 7.1 (2H, bs, OH and COOH), 5.4 (2H, m, olefin), and 4.0 (1H, m, >CH-O-)]. Similarly, 15β-hydroxyprost-13-enoic acid (6b) was obtained from 7b [yield: 76.5%, mp: 38.0-39.0°C]. The configuration of C_{15}-alcohol of 6a was tentatively assigned as an α-form by the fact that the ester 6a is a little more polar than 6b in the mixed solvent system of AcOEt (1): hexane (2.6) on TLC.[6]

The modified Simmons-Smith reaction[7] of the methyl ester of 6a with CH_2I_2 in the presence of Et_2Zn in diisopropyl ether at room temperature for 48h proceeded smoothly to afford in 65% yield a sole methylene addition product (8a), which was hydrolyzed by 1N NaOH-MeOH to yield 15α-hydroxy-13α,14α-methyleneprostanoic acid (9a) [yield: 66.0%, mp: 65.0-66.0°C, IR(nujol): 3540, 3310, 1710, and 1022 cm^{-1}, NMR($CDCl_3$): δ 6.4 (2H, bs, OH and COOH), 2.9 (1H, m, >CH-O-), 2.5-2.2 (2H, t, CH_2COO), and 0.6-0.1 (4H, m, cyclopropane)]. Collins oxidation of 8a followed by hydrolysis with dil NaOH gave 15-oxo-13α,14α-methyleneprostanoic acid (10a) [yield: 67.6%, mp: 29-36°C, IR(neat): 1707 and 1037 cm^{-1}, NMR($CDCl_3$): δ 10.5 (1H, bs, COOH) and 0.9-0.6 (4H, m, cyclopropane)]. By the same procedure, 15β-hydroxy-13β,14β-methyleneprostanoic acid (9b) [yield: 66.0%, mp: 51-52°C, IR(nujol): 3270, 1687, and 1028 cm^{-1}, NMR($CDCl_3$): δ 10.5 (1H, bs, COOH), 2.7-2.1 (5H, m), and 0.7-0.3 (4H, m, cyclopropane)] and 15-oxo-13β,14β-methyleneprostanoic acid (10b) [yield: 66.5%, mp: 49.5-51.0°C, IR(nujol): 1700 and 1032 cm^{-1}, NMR($CDCl_3$): δ 11.0 (1H, bs, COOH),

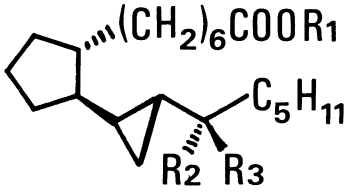






	R1	R2	R3
8a	Me	OH	H
9a	H	OH	H
10a	H	=O	

	R1	R2	R3
6a	H	OH	H
6b	H	H	OH
7a	CH_2CO-C6H4-Br	OH	H
7b	CH_2CO-C6H4-Br	H	OH



	R1	R2	R3
8b	Me	H	OH
9b	H	H	OH
10b	H	=O	

2.7-2.2 (5H, m), and 0.9-0.7 (4H, m, cyclopropane)] were obtained from 6b. The configuration of cyclopropane ring was tentatively assigned by the rule that the cyclopropanation in this reaction is governed by the configuration of the neighboring hydroxy group.[8,9]

The most potent inhibitor for the 15-hydroxyprostaglandin dehydrogenase (15-OH PGDH) obtained from swine lung was dl-15-oxo-13β,14β-methyleneprostanoic acid 10b, and its Ki value was 0.14 μM. Therefore, 10b appears to be the most potent among the known inhibitors for 15-OH PGDH. The Ki value of the α-methylene acid 10a was 0.8 μM. The biological data will be published elsewhere.

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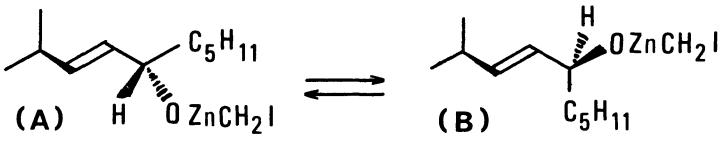
9) On the assumption that the reaction proceeds on the transition state (B) as shown in Eq. 1, the above tentative assignment for the configuration of cyclopropane ring might be reverse.



Eq. 1

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