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SYNTHESIS OF E-TYPE 7-THIAPROSTAGLANDINS**

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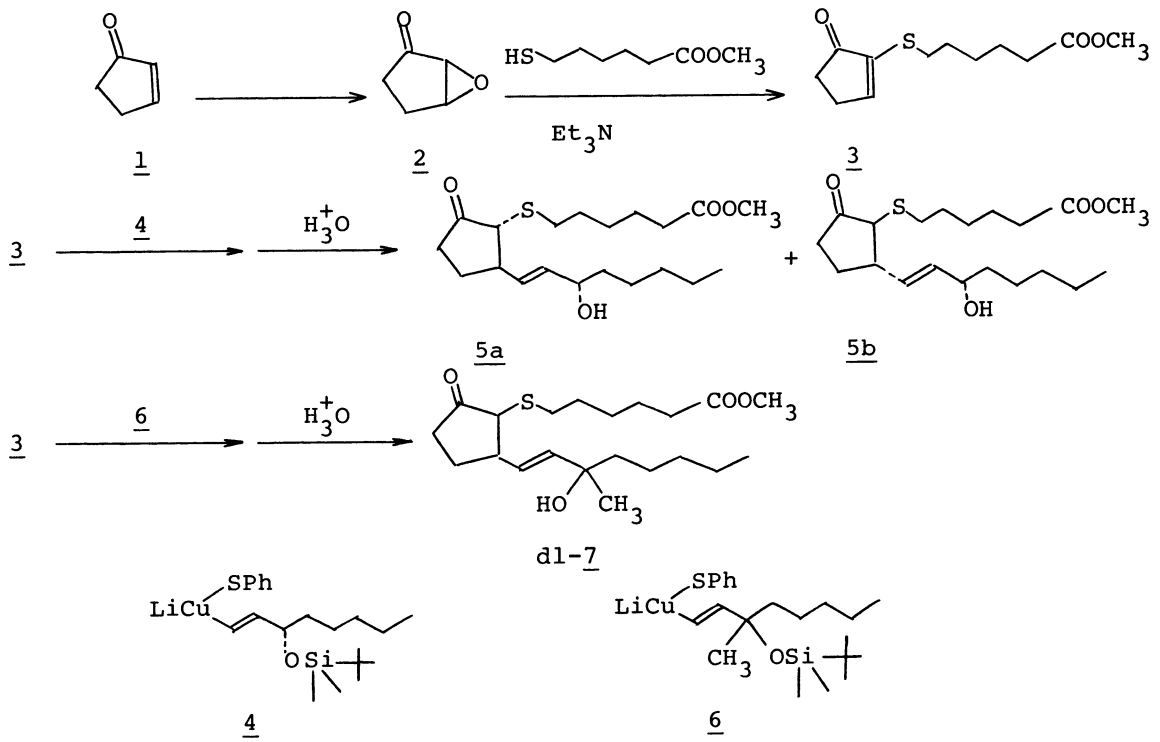
2-Alkylthiocyclopent-2-en-1-one derivative was prepared from cyclopent-2-en-1-one. From this intermediate, E-type 7-thiaprostaglandins were synthesized by conjugate addition of lithium organocuprates.

Research efforts of preparing various prostaglandin anlogues have been intensively made including a flood of their elegant total syntheses. Particularly, interest in the synthetic heteroprostaglandins, in which carbon atoms of the prostanoids skeleton are replaced by heteroatoms such as oxygen,[1] sulfur,[2] and nitrogen,[3] has rapidly developed. They provided advantages in development of medicines with specific pharmacological properties different from those of the naturally occurring prostaglandins. Among these novel prostaglandins,"F-type" 7-thiaprostaglandins[2b] and 7-thiaprostynoic acids[2b] are attractive compounds since they showed agonistic or antagonistic activities.

We wish to report here the synthesis of "E-type" 7-thiaprostaglandins from a new key-intermediate, 2-alkylthiocyclopent-2-en-1-one derivative 3, by conjugate addition of organocopper agents 4 and 6.

A compound, epoxycyclopentanone 2 (1.0 equiv.) obtained from cyclopent-2-en-1-one 1 by ordinary epoxidation, was treated[5] with methyl ω-mercaptocaproate[2b,4] (1.0 equiv.) in the presence of catalytic amount of triethylamine[6] in ether or methanol at room temperature. There was obtained a new sulfur containing cyclo-



pentenone derivative 3 [Y = 74%, mp = 45-46°c, ir (CCl_4, cm^{-1}) 1740, 1720, 955; nmr (CCl_4, δ) 1.6 (6H), 2.1-3.0 (8H), 3.60 (3H, s), 7.10 (1H, t, J = 3 Hz); mass (m/e) 242 (M^+)]. This compound was subjected to conjugate addition[7] of organocopper agent. The enone 3 (1.0 equiv.) was treated with optically active mixed organocuprate 4[8] (1.5 equiv.) in ether (-78 - -20°C, 1 hr) to give the diastereomeric mixture of the protected Michael addition product [Y = 22%, ir (film, cm^{-1}) 1740, 840, 775; nmr (CCl_4, δ) 0.08 (6H, s), 0.90 (3H, t, J = 6 Hz), 0.90 (9H, s), 1.1-1.9 (14H), 2.0-2.8 (9H), 3.1 (1H), 3.60 (3H, s), 4.05 (1H), 5.45 (2H, m); mass (m/e) 484 (M^+)]. Deprotection (AcOH : H_2O : THF = 3 : 1 : 1, r.t., 7 hrs) of the product gave ca. 1 : 1 mixture of 7-thia-11-deoxy-PGE_1 methyl ester 5a [Y = 30%, $[\alpha]^{20}D$ +7° (c = 1, MeOH), ir (film, cm^{-1}), 3450, 1740; nmr (CCl_4, δ) 0.9 (3H, t, J = 7 Hz), 1.1-1.9 (14H), 2.0 (10H), 3.1 (1H), 3.60 (3H, s), 4.0 (1H, m), 5.55 (2H, m); mass (m/e) 370 (M^+)] and 7-thia-11-deoxy-8,12-diepi-PGE_1 methyl ester 5b [Y = 34%, $[\alpha]^{20}D$ +14° (c = 3, MeOH), the spectral data of 5b were substancially the same as those of 5a]. Configurational assignments of 5a and 5b were tentatively carried out comparing the results of 11-deoxy-PGE series.[7] The isomer with lower

Rf value (Rf = 0.18; cyclohexane : AcOEt = 6 : 4) was assigned to 5a with natural configuration, and one with higher Rf value (Rf = 0.22) to 5b.

Similar treatment of 3 with a mixed organocuprate 6[8,9] and deprotection gave dl-7-thia-11-deoxy-15-methyl-PGE_1 methyl ester 7 [Y = 10% from 3, ir (film, cm^{-1}) 3500, 1740; nmr (CCl_4, δ) 0.9 (3H, t, J = 6 Hz), 1.2 (3H, s), 1.1-1.9 (14H), 1.9-3.2 (11H), 3.60 (3H, s), 5.57 (2H, m); mass (m/e) 366 (M^+- 18)].

Preliminary biological investigation of these obtained 7-thiaprostaglandins showed that these analogues inhibited ulceration induced by anti-inflammatory drugs such as indomethacin. These also contracted guinea-pig aorta strip ca. twice as strong as natural $PGF_{2\alpha}$. Further detailed studies on their biological activities are now in progress and their results will be reported elsewhere.

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