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PROSTAGLANDIN CHEMISTRY VII[15]

A SYNTHESIS OF NEW 8-PHENYLTHIO-11-DEOXYPROSTAGLANDINS

Seizi Kurozumi*, Takeshi Toru, Toshio Tanaka,
Makiko Kobayashi, Shuji Miura, and Sachio Ishimoto
Teijin Institute for Biomedical Research
4-3-2 Asahigaoka, Hino, Tokyo 191, Japan

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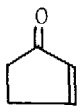
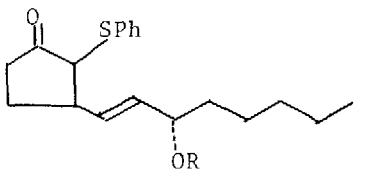
So great efforts in prostaglandin syntheses have been currently made on the synthesis of novel prostaglandin analogues and on much more convenient synthetic approach to these compounds. Recently, the conjugate addition-enolate trapping method has been used for the short and highly convergent approach to the prostanoids.[1-4] In a previous communication,[5] we have reported synthesis of new 7-oxoprostaglandins using the methodology of the conjugate addition-enolate trapping with acyl halides. In this communication, we wish to describe trapping of organocopper enolate with diphenyl disulfide or benzenesulfenyl chloride, giving new prostaglandin analogues.

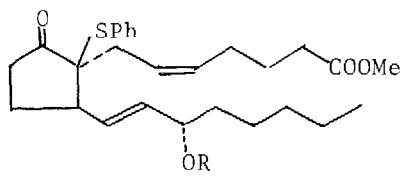
Conjugate addition[6] of lithium mixed organocuprate 4a[6,7] to cyclopent-2-en-1-one in ether (-78°, 1 hr) gave the β-alkenylated organocopper enolate which was added to 1.5 eq. of diphenyl disulfide in THF and HMPA (-40-0°, 1 hr) to give phenylthio ketone 1a [38 %; ir (film), 3030, 1740, 1580, 840, 780, 750, 690 cm^{-1}; nmr (CCl_4), 0.08(6H, s), 0.9(12H), 1.3(8H), 1.8-2.7 (5H), 3.0 (1H, d), 4.05 (1H, bs), 5.5 (2H, m), 7.1-7.5 (5H); mass (m/e), 432 (M^+)]. Trapping of the organocopper enolate resulted from lithium mixed organocuprate 4b[6,8] and cyclopent-2-en-1-one with benzenesulfenyl chloride (1.2 eq.) in THF and HMPA (-40-0°, 30 min) was also effective to give the phenylthio ketone 1b [24 %; ir (film), 3030, 1740, 1580, 750, 690 cm^{-1}; nmr(CCl_4), 0.9 (3H, t), 1.2-1.8 (14H), 1.8-2.7 (5H), 3.05 (1H, d), 4.0 (1H, bs), 4.6 (2H), 5.5 (3H, m), 7.3 (5H); mass (m/e),





1a R= -$SiMe_2{}^tBu$

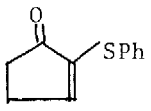
1b R= -THP



2a R= -$SiMe_2{}^tBu$

2b R= -THP

2c R= -H



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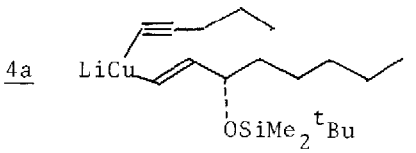
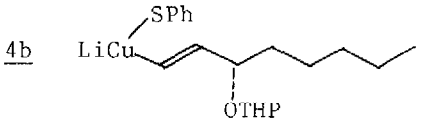
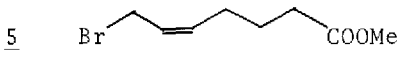


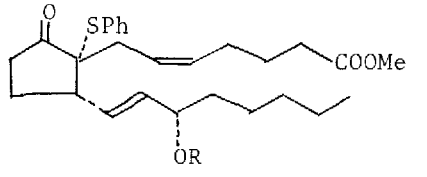
4a



4b



5



3a R= -$SiMe_2{}^tBu$

3b R= -THP

3c R= -H

402 (M^+)]. As a ligand of the lithium organocuprate, hexamethylphosphorous triamide[7] or tri-*n*-butylphosphine[6] was used. As shown in the nmr spectral data of the products 1a or 1b, the α-hydrogen attached to the phenylthio group of 1a or 1b appeared at 3.0 ppm as a doublet (J=6 Hz). Thus, it was considered that directed enolate sulfenylation[9] occurred. This observation is consistent with the fact that benzeneselenenyl halide regiospecifically trapped organocopper enolate to afford α-phenylseleno-β-substituted ketone in conversion of enones to β-substituted ketones.[10]

Regiospecificity of the present reaction was also confirmed by the

following experiments. Conjugate addition of lithium organocuprate 4a or 4b to 2-phenylthiocyclopent-2-en-1-one 6[11,12] were carried out in ether (-40°, 1 hr). There was obtained the phenylthio ketone 1a or 1b (25 %, 22 %, respectively) which were identical (tlc, ir, nmr) with the products obtained by the direct copper-enolate trapping method mentioned above.

Alkylation[13] of phenylthio ketone 1a with methyl 7-bromo-*cis*-5-heptenoate 5[2,14] using sodium hydride in THF (r,t., 12 hr) gave a mixture of the protected products 2a and 3a (36 %; nmr (CCl_4), 0.08 (6H, s), 0.9 (12H), 1.4 (10H), 1.7-2.4 (11H), 3.6 (3H, s), 4.0 (1H, m), 5.2 (2H, m), 7.3 (5H); mass (m/e), 572 (M^+)] which was hydrolyzed with AcOH-H_2O-THF (3 : 1 : 1) (r.t., 12 hr) to afford 8-phenylthio-11-deoxy-PGE_2 methyl ester 2c [29%; tlc (benzene/AcOEt: 4/1), Rf 0.30; ir (film), 3300, 3030, 1740, 1580, 750, 690 cm^{-1}; nmr (CCl_4), 0.9 (3H, t), 1.35 (10H), 1.8-2.8 (12H), 3.6 (3H, s), 4.0 (1H), 5.1-5.8 (4H, m), 7.3 (5H); mass (m/e), 458 (M^+)] and 8-phenylthio-11-deoxy-8,12-diepi-PGE_2 methyl ester 3c[26 %; tlc (benzene/AcOEt : 4/1), Rf 0.33; ir (film), 3300, 3030, 1740, 1580, 750, 690 cm^{-1}; nmr (CCl_4), 0.9 (3H, t),1.35 (10H), 1.7-2.8 (12H), 3.6 (3H, s), 4.0 (1H), 5.0-5.7 (4H,m), 7.25 (5H); mass (m/e), 458 (M^+)]. The same treatment of phenylthio ketone 1b with 5 gave a mixture of the protected products 2b and 3b (33 %) which was deprotected to afford 2c and 3c in a ratio of *ca.* 1 : 1 (68 %). Configurational assignments of the products 2c and 3c were tentatively determined from consideration of their Rf values of tlc in comparison with the observation that 11-deoxy PGE_2 methyl ester is more polar than its 8,12-diepi-isomer in tlc behaviour.[2,6]

Investigation on biological activities of 8-phenylthioprostaglandins and their derivation to other prostaglandin congeners are currently in progress.

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