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PROSTAGLANDIN CHEMISTRY VI.[1] SYNTHESIS OF 8-METHOXYCARBONYLPROSTAGLANDINS

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

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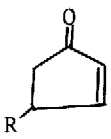
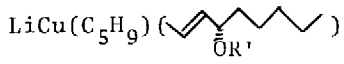
One of the attractive route to prostaglandins is the one-pot reaction of organocopper conjugate addition-α-alkylation[2] to 4-protected hydroxycyclopent-2-en-1-one. This methodology has been partly realized, although rather unreactive resultant enolates toward alkyl halides have made the reaction difficult.[3] In order to accomplish the reaction several devices have been made; i) Conversion of the resultant copper lithium enolate to the lithium enolate[4] ii) direct α-alkylation of the lithium enolate resulted from the Michael addition of cyclopent-2-en-1-one with lithium salt of the protected cyanohydrin[5] iii) use of formaldehyde as an enolate ion trapping agent[3] iv) the direct enolate ion trapping method with acyl halides instead of alkyl halides.[6] We now report the successful trap of the enolate ion by chlorocarbonate ester and subsequent alkylation to make prostaglandin analogues.

Treatment of cyclopent-2-en-1-one 1a with mixed cuprate 2a and subsequently with methyl chlorocarbonate 3 afforded C-methoxycarbonylated and C,O-dimethoxycarbonylated compounds 4a and 5a in 29 and 21% yields, respectively. The latter compound 5a was apparently formed by further methoxycarbonylation of the first formed one 4a. When 2b was used, C-methoxycarbonylated compound 4b and C,O-dimethoxycarbonylated one 5b was obtained in 55 and 15% yields. Formation of O-methoxycarbonylated derivative was not detected in both cases.[7] On the other hand, similar treatment of 4-tetrahydropyranyloxycyclopent-2-en-1-one[8] 1b gave O-methoxycarbonyl compound 6 in 21% yield in addition to C-methoxycarbonylated one 4c (10% yield). Formation of O-methoxycarbonyl compound 6 would be attributed that the 4-protected group of cyclopentenone 1b interferes the access of methyl chlorocarbonate 3 to C-2 position.

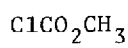
A typical procedure of the conjugate addition-α-alkylation sequence is as follows; Cyclopent-2-en-1-one 1b (150 μl, 1.8 mmol) was treated, at -75° for 15 min and at -40° for 30 min, with 1-(3(S)-tetrahydropyranyloxyoctenyl)-1-pentynyl copper lithium, prepared from 1-lithium-3-tetrahydropyranyloxyoct-1-ene[9] (676 mg, 2 mmol) and pentynyl copper[9] (260 mg, 2 mmol) in n-tributyl-



1a R=H
1b R=OTHP



2a R'=THP
2b R'=SiBu^{t}Me$_2$



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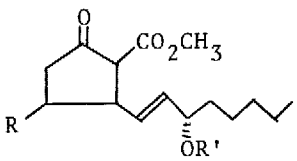
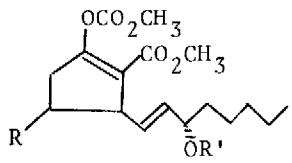
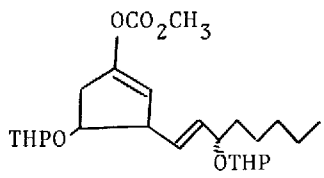


4a R=H, R'=THP
4b R=H, R'=SiBu^{t}Me$_2$
4c R=OTHP, R'=THP



5a R=H, R'=THP
5b R=H, R'=SiBu^{t}Me$_2$



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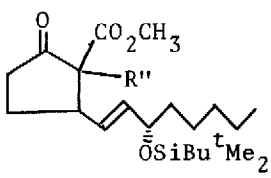
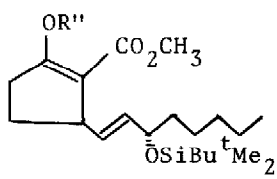
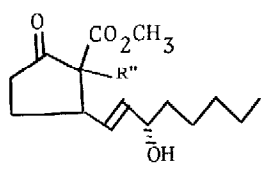


7a, 7b, 7c

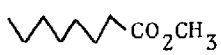


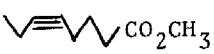
8a, 8b, 8c



9a, 9b, 9c

a: R''= 

b: R''= 

c: R''= 

phosphine (1 ml) and ether (12 ml). To this -40° solution was added a solution of methyl chlorocarbonate (232 µl, 3 mmol) in THF (8 ml) and HMPA (1 ml). The mixture was stirred for 15 min and then allowed to warm up to room temperature (45 min). Usual work-up and purification by thin layer chromatography gave 4a (29% yield)[ir (neat) 1760, 1725, 1655 cm^{-1}, nmr (CCl_4)δ 0.98 (3H, m), 1.1-2.7 (19H, m), 2.98 (1H, m), 3.68 (3H, s), 3.7 (2H, m), 4.00 (1H, m), 4.55 (1H, m), 5.50 (2H, m)] and C,O-dimethoxycarbonylated compound 5a (21% yield)[ir (neat) 1760, 1740, 1655, 1640 cm^{-1}, nmr (CCl_4)δ 0.98 (3H, m), 1.1-2.8 (19H, m), 3.7 (2H, m), 3.67, 3.80 (6H, 2s), 4.55 (1H, m), 5.50 (2H,m)].[10] Compound 4-tetrahydropyranyloxycyclopent-2-en-1-one 1b was similarly treated to afford 4c (10% yield)[ir (neat) 1760, 1740, 1660, 1630 cm^{-1},

nmr (CCl_4)δ 0.9 (3H, m), 1.1-2.1 (20H, m), 2.1-2.98 (4H, m), 3.16-3.98 (4H, m), 3.70 (3H, s), 4.00 (2H, m), 4.65 (2H, m), 5.55 (2H, m)] and O-methoxycarbonylated compound 6 (21% yield)[ir (neat) 1760, 1650 cm^{-1}, nmr (CCl_4)δ 0.9 (3H, m), 1.13-2.13 (20H, m), 2.13-2.95 (3H, m), 3.15-3.98 (4H, m), 3.78 (3H, s), 4.02 (2H, m), 4.65 (2H, m), 5.25 (1H, bs), 5.55 (2H, m)].

Methoxycarbonylcyclopentanone 4b was then alkylated with methyl 7-bromohept-5-enoate[11] (K_2CO_3, reflux, acetone)[12] to give C-alkylated compound 7a in 55% as well as O-alkylated one 8a (18% yield)[ir (neat) 1735, 1715, 1700, 1620 cm^{-1}, nmr (CCl_4)δ 0.1 (6H, s), 0.9 (12H, m), 1.1-2.9 (19H, m), 3.60 (6H, s), 4.00 (1H, m), 4.54 (2H, m), 5.50 (4H, m)]. Similar alkylation of 4b with methyl 7-bromoheptanoate[13] resulted in the formation of C-alkylated compound 7b (32% yield) and O-alkylated one 8b (39% yield)[ir (neat) 1740, 1700 1625 cm^{-1}, nmr ($CDCl_3$)δ 0.10 (6H, s), 0.81 (12H, s), 1.03-1.90 (18H, m), 1.90-2.70 (6H, m), 3.52, 3.58 (6H, 2s), 3.98 (3H, m), 5.40 (2H, m)]. Alkylation of 6 with more reactive methyl 7-iodohept-5-ynoate[16] resulted in exclusive formation[17] of C-alkylated compound 7c (80% yield) which was deprotected to lead methyl 11-deoxy-8-methoxycarbonylprost-5-ynoate 9c[14][ir (neat) 3450, 1735 cm^{-1}, nmr ($CDCl_3$)δ 0.90 (3H, m), 1.18-1.92 (12H, m), 2.08-2.90 (9H, m), 3.30 (1H, m), 3.66, 3.68 (6H, 2s), 4.10 (1H, m), 5.66 (2H, m)].

Exposure of compounds 7a and 7b to a solution of AcOH-THF-H_2O (3:1:1) gave 11-deoxy-8-methoxycarbonylprostaglandin E_2[14, 15] 9a [ir (neat) 1730 cm^{-1}, nmr ($CDCl_3$) δ 0.88 (3H, m), 1.0-1.9 (12H, m), 1.9-3.0 (9H, m), 2.78 (1H, bs), 3.62, 3.67 (6H, 2s), 4.08 (1H, m), 5.0-5.76 (4H, m)] and 11-deoxy-8-methoxycarbonylprostaglandin E_1[14, 15] 9b [ir(neat) 3450, 1740 cm^{-1}, nmr ($CDCl_3$) δ 0.90 (3H, m), 1.08-1.94 (18H, m), 1.94-2.72 (7H, m), 2.84 (1H, bs), 3.64, 3.68 (6H, 2s), 4.08 (1H, m), 5.60 (2H, m)], respectively.

Acknowledgements

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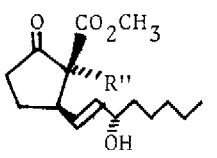
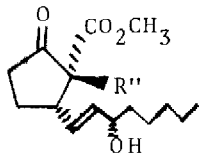


A



B

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