Tetrahedron Letters,Vol.26,No.45,pp 5575-5578,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

STEREOSPECIFIC SYNTHESIS OF (5E)-PGE_2 BY PALLADIUM-CATALYZED DECARBOXYLATIVE 2-ALKENYLATION OF 2-ALKENYLOXYCARBONYLATED CYCLOPENTANONE DERIVATIVE[1)]

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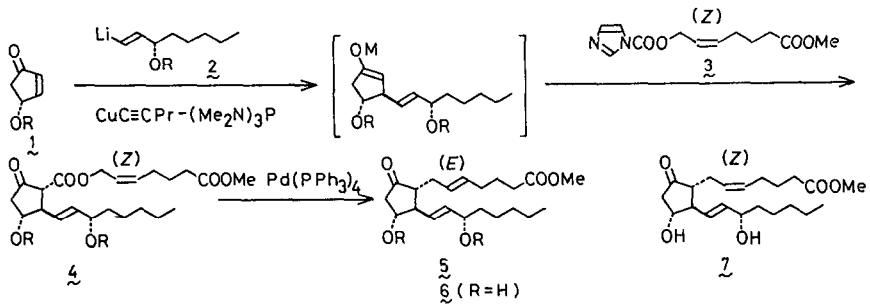
Summary: (5E)-Prostaglandin E_2 methyl ester was synthesized from (R)-4-t-butyldimethylsiloxy-2-cyclopentenone by in situ 2-alkenyloxycarbonylation of the organocopper conjugate-addition adduct followed by intramolecular palladium-catalyzed decarboxylative 2-alkenylation. A (E)-2-butenylated cyclopentanone derivative was obtained from either 2-[(E)- or (Z)-2-butenyloxycarbonyl]cyclopentanone derivative under the similar reaction condition.

In the three-component coupling process[2)] of prostaglandin (PG) synthesis starting from (R)-4-t-butyldimethylsiloxy-2-cyclopentenone (**1**),[3)] the carbon-carbon bond formation between the cyclopentanone ring and the α side-chain is the most important reaction as an enolate trapping step. The enolate trapping agents for this purpose are carboxylic acid chlorides,[4)] methyl chloroformate,[5)] aldehydes,[6)] ketene bis(methylthio)acetal monoxide,[7)] alkenyl or alkynyl halides,[8)] nitro-olefin,[9)] and allyl chloroformate.[10)] The enolate trapping with allyl chloroformate followed by intramolecular palladium-catalyzed

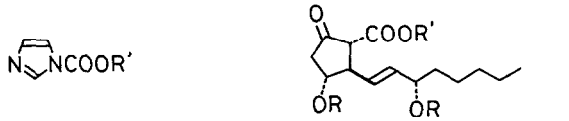
Scheme 1 (R=$SiMe_2^tBu$)



decarboxylative allylation presented an indirect 2-allylation method of a 3,4-disubstituted cyclopentanone ring. Extension of the indirect allylation[10] was applied to the synthesis of PGE_2 skeleton using 2-alkenyloxycarbonylimidazole **3** as the enolate trapping agent (Scheme 1).

The enolate generated by the conjugate addition of the organocopper reagent[11] of (E,3S)-3-t-butyldimethylsiloxy-1-lithio-1-octene (**2**) to the chiral enone **1**, $[\alpha]_D^{24}$ + 64.5° (c 1.02, CH_3OH), was trapped with N-[(Z)-6-methoxycarbonyl-2-hexenyloxycarbonyl]imidazole (**3**)[13a] (1.18 equiv, -40°C, 3 h) in THF containing hexamethylphosphoramide to give the corresponding 2-alkenyloxycarbonylated product **4**, $[\alpha]_D^{22}$ - 27.8° (c 0.58, CH_3OH), in 41% yield. Treatment of the product **4** with 5 mol% of $Pd(PPh_3)_4$ in DMF (50°C, 30 min) provided protected (5E)-PGE_2 **5** (64%), $[\alpha]_D^{22}$ + 42° (c 0.81, CH_3OH),[14] which afforded (5E)-PGE_2 methyl ester **6** (85%), $[\alpha]_D^{24}$ - 62° (c 0.90, CH_3OH) after deprotection (HF-pyridine in CH_3CN, r.t., 3 h). The 5E-geometry of the product was confirmed by the ^{13}C NMR measurement. The product **6** showed the chemical shifts at δ 31.7 and 30.1 ppm corresponding to C-7 and C-4 carbon atoms (PG numbering), respectively, whereas an authentic PGE_2 methyl ester **7**, $[\alpha]_D^{20}$ - 71.7° (c 1.04, CH_3OH),[6c] showed the corresponding higher shifts at δ 25.2 and 26.5 ppm. These higher field shifts were caused by γ-steric compression effect of the carbons with (Z)-geometrical surroundings. This olefin-geometry was also supported by the fact that **6** was less polar than natural PGE_2 methyl ester **7** on a $AgNO_3$-impregnated thin layer chromatoplate.[15]

In order to study the stereochemistry of the double bond in the indirect alkenylation product, we prepared (E)- and (Z)-2-butenyl β-keto esters **10** and **12** from the chiral enone **1** as follows. A similar alkenyloxycarbonylation of the corresponding enolate with N-[(E)-2-butenyloxycarbonyl]imidazole (**8**),[13b] gave the E-isomer **10** (40%) [^{13}C NMR for C-1, C-4 of (E)-2-butenyl: δ 66.1, 17.7 ppm]. Another alkenyloxycarbonylation of the enolate by N-(2-butynyloxycarbonyl)imidazole (**9**)[13b] afforded the acetylenic product **11** (46%), which was hydrogenated by using of 5% Pd-$BaSO_4$ in CH_3OH containing guinoline to give the Z-isomer **12** (76%) [^{13}C NMR for C-1, C-4 of (Z)-2-butenyl: δ 60.7, 13.1 ppm]. Both E and Z compounds **10** and **12** were treated with a catalytic amount (5 mol%) of $Pd(PPh_3)_4$ in DMF (50°C, 1 h and 25°C, 2 h, respectively) to afford the same (E)-2-butenylated product **13** in 58% and 63% yield, respectively. In the ^{13}C NMR spectrum of **13**, signals corresponding to C-1 and C-4 carbons of (E)-2-butenyl group were observed at δ 30.5 and 17.9 ppm, respectively. A simultaneous formation of a rearranged product **14** (8-9%) together with a by-product **15** in these reactions suggested π-allylpalladium intermediate[16] in the decarboxylative 2-alkenylations (Scheme 2). On the other hand, in the reported intermolecular alkenylation of enolate species, both examples of the inversion[17] and the retention[18] of olefin geometry are known.



8, R' = -CH$_2$CH=CHCH$_3$ (E)

9, R' = -CH$_2$C≡CCH$_3$

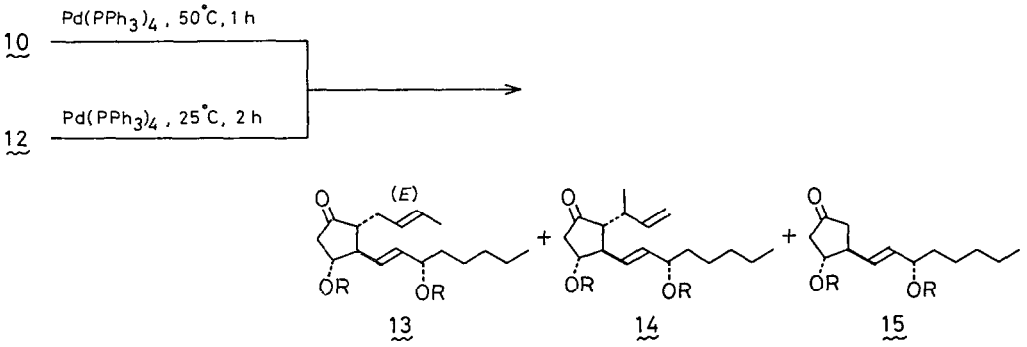
10, R' = -CH$_2$CH=CHCH$_3$ (E)

11, R' = -CH$_2$C≡CCH$_3$

12, R' = -CH$_2$CH=CHCH$_3$ (Z)

(R = SiMe$_2$^{t}Bu)

Scheme 2 (R = SiMe$_2$^{t}Bu)



This indirect E-2-alkenylation provides an alternative vicinal dialkylation method for enone systems. An application of this methodology was the convenient synthesis of (5E)-PGE$_2$ which is less available from natural resources[19] or by practical preparation.[15]

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11. This vinylcopper reagent was prepared by treatment of (E,3S)-3-t-butyldimethysiloxy-1-iodo-1-octene,[12] $[\alpha]_D^{21}$ - 30.6° (c 1.57, CCl_4), with 2 equiv of t-butyllithium in ether at -78°C for 1 h followed by addition of an ethereal solution of 1-pentynylcopper (1 equiv) and hexamethylphosphoroustriamide (2 equiv).
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13. (a) This starting material was obtained (73%) by reaction (r.t., 1 h, in THF) of N,N'-carbonyldiimidazole with methyl (Z)-7-hydroxy-5-heptenoate which was prepared by hydrogenation (5% Pd-$BaSO_4$ in CH_3OH containing guinoline) of methyl 7-hydroxy-5-heptynoate in 96% yield. (b) Each compound **8** or **9** was similarly prepared by treatment of (E)-2-buten-1-ol or 2-butyn-1-ol with N,N'-carbonyldiimidazole in 95% or 92%, respectively.
14. The corresponding PGE_2 derivative with 5Z geometry exhibited $[\alpha]_D^{21}$ - 52.7° (c 1.28, CH_3OH).[6c]
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(Received in Japan 3 September 1985)