Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 24 Oct 2006.

To cite this article: I. Martin , J. Anvelt , T. Vlime , T. Pehk & O. Lille (1990) Copper (II) Bromide Utilization in the Synthesis of 15-Keto-PGB_1 and its 16, 16-Dimethyl Analog, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 20:17, 2597-2605, DOI: 10.1080/00397919008051467

To link to this article: http://dx.doi.org/10.1080/00397919008051467

SYNTHETIC COMMUNICATIONS, 20(17), 2597-2605 (1990)

COPPER (II) BROMIDE UTILIZATION IN THE SYNTHESIS OF 15-KETO-PGB$_1$ AND ITS 16,16-DIMETHYL ANALOG

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Title compounds, monomeric intermediates of biologically active prostaglandin oligomers were synthesized using cupric bromide for introduction of a double bond into the prostanoid cyclopentane ring.

The synthesis of PGB-s was actual during the sixties [1-5]. Later, the attempts were shifted to the synthesis of biologically active prostaglandins of the E, F and A series, and prostacyclin analogs. Contrary to the monomeric PGB-s, the prostaglandin B$_1$ oligomers (n=3-5) synthesized from 15-keto-PGB$_1$ or its 16,16-dimethyl analog have been shown to maintain oxidative phosphorylation during the hypotonic degradation in aged mitochondria [6-7] and stimulate the release of Ca^{2+} from mitochondrial pool in isolated hepatocytes (Ca^{2+} ionophoric activity) [8-9].

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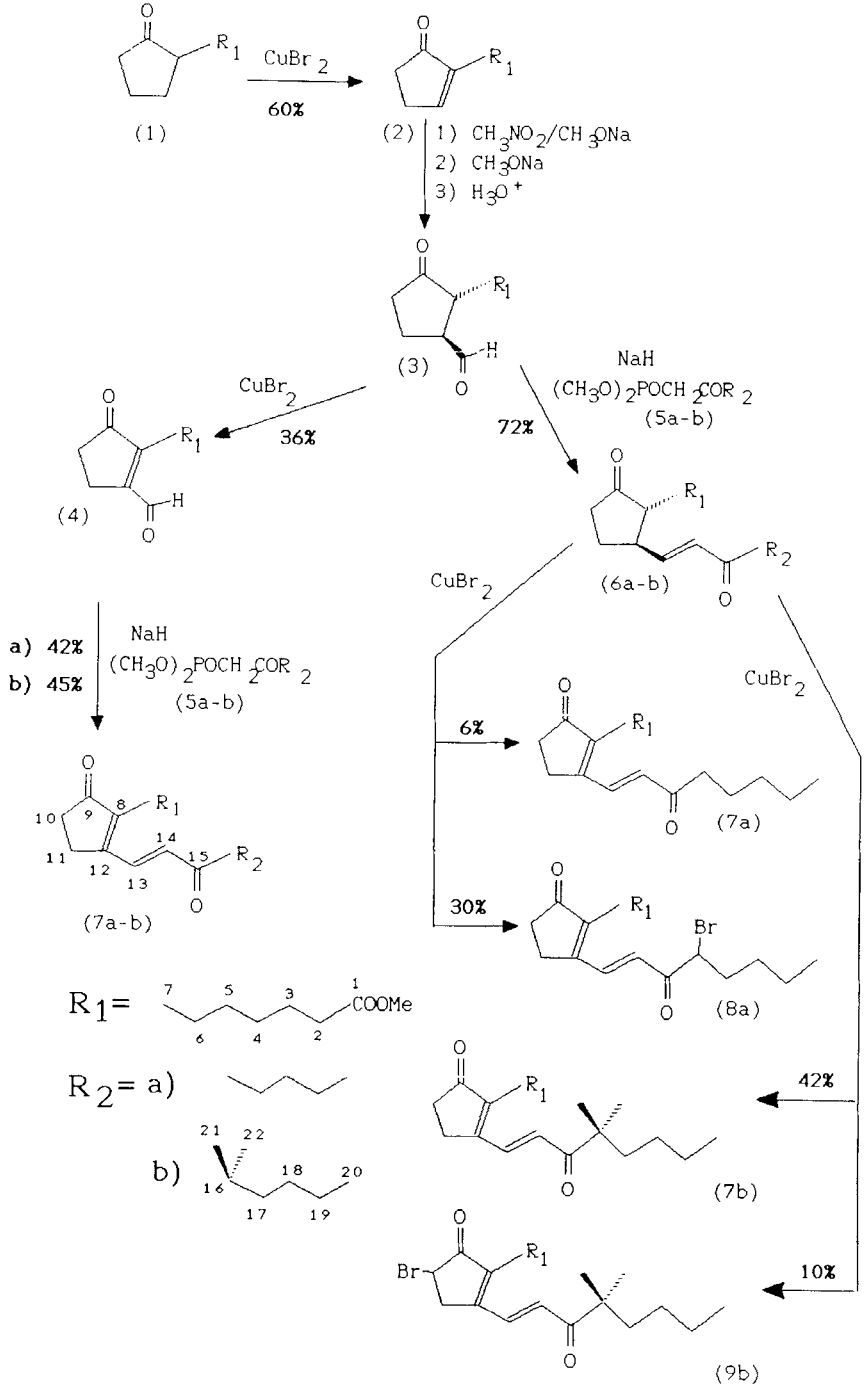
It has been reported that *in vivo* PGB oligomers exhibit the protection of animals following cardiac [10] and cerebral ischemia [11], hypoxia [12]. These unique properties gave occasions to the synthesis of PGB analogs.

In a number of approaches, 2-oxocyclopentane heptanoate 1 has been reported as an important intermediate, especially for the 11-deoxy PG-s [13-14].

D.Miller and coworkers have found an unusual reaction of copper(II) bromide that allows a one-step introduction of a double bond into the prostanoid cyclopentane ring system [15]. This reaction is superior to the awkward consecutive bromination-dehydrobromination procedure and makes possible the utilization of commercially available 1 for the synthesis of PGB.

The target compounds, 15-keto-PGB_1 7a and 16,16-dimethyl-15-keto-PGB_1 7b were synthesized from the keto aldehyde 3 by the two ways: via aldehyde 4 (3 → 4 → 7a-b) and via 11-deoxy-15-keto-PGE_1 6a or its 16,16-dimethyl analog 6b (3 → 6a-b → 7a-b). The main differences are in the orders of the cupric bromide and the Wittig-Horner reactions. We found the second way to be better for the preparation of 7b. The Wittig-Horner reaction applied to aldehyde 3 afforded 72% of 6a-b whereas the same reaction to aldehyde 4 afforded only 45% of 7a-b. This phenomenon can be explained by the delocalization of the positive charge at the electrophilic carbon in the aldehyde group by the conjugated π-electron system in 4. The $CuBr_2$



reactions with 6b and 3 gave the corresponding 7b and 4 in rather same yields (42% and 36% respectively), whereas the transformation of 1 to 2 proceeds in higher yield (60%[15]). Unfortunately, the main product of the reaction of 6a with $CuBr_2$ was 16-bromo-15-keto-PGB_1 8a, while 7a as desired product was separated as minor component. For that reason the synthesis of 7a is favoured via the aldehyde 4. The unfavourable C-16 bromination in 6b is impossible due to the presence of two methyl groups in that position. However, the other possible bromination product, 10-bromo compound 9b was found as minor by-product in the crude product of the reaction of 6b with $CuBr_2$.

Table

^{13}C n.m.r. chemical shifts of 3 - 9b.

	3	4	6a	6b	7a	7b	8a	9b
1	174.5	173.9	173.9	174.1	174.1	173.8	173.7	174.1
2	34.0	33.8	34.2	34.1	34.0	33.9	33.9	33.8
3	24.8	24.5	24.9	24.8	24.8	24.9	24.8	24.4
4	28.8	28.6	28.9	28.9	28.9	28.9	28.9	28.6
5	29.2	29.0	29.4	29.3	29.2	29.3	29.3	28.4
6	26.4	29.1	26.7	28.9	28.9	28.9	28.7	28.9
7	28.8	22.6	27.3	23.5	23.4	23.3	23.5	23.6
8	52.0	153.6	54.4	54.2	147.8	147.7	148.7	145.1
9	217.9	210.5	217.5	217.3	208.8	209.1	208.9	201.9
10	37.4	33.9	37.4	37.4	33.9	34.3	34.3	40.9
11	24.8	23.1	28.0	27.9	25.5	25.6	25.4	37.4
12	46.5	158.6	45.6	45.5	160.1	160.3	159.4	157.5
13	179.8	190.1	147.9	147.5	134.0	134.8	136.4	133.7
14	-	-	130.4	126.9	130.6	125.7	126.6	126.9
15	-	-	199.8	203.7	200.2	203.9	192.3	203.7
16	-	-	40.3	46.9	41.6	46.9	53.2	46.9
17	-	-	23.9	39.5	23.8	39.5	33.0	39.4
18	-	-	31.5	26.8	31.4	26.9	29.5	26.8
19	-	-	22.5	23.2	22.5	23.4	22.1	23.2
20	-	-	14.0	13.9	13.9	13.9	13.8	13.9
21	-	-	-	24.0	-	24.1	-	24.0
22	-	-	-	24.0	-	24.1	-	23.9

The ^{13}C n.m.r. chemical shifts of 3-9b are presented in Table. The carbons are numerated according to [16].

Both, 7a and 7b were utilized as starting material for the preparation of biologically active oligomeric prostaglandins [17-19].

Experimental

^{13}C n.m.r. spectra were recorded on a Bruker AM-500 spectrometer in $CDCl_3$ solution. The chemical shifts are reported relative to internal tetramethylsilane. I.r. spectra were recorded on a Specord 71 IR spectrophotometer and u.v. spectra on a Specord M40. Tetrahydrofurane (THF) and dimethoxyethane (DME) were dried on KOH granules and distilled from $LiAlH_4$ shortly before use. Ethyl acetate was dried on anhydrous $CaCl_2$. Dry methanol was distilled from Na, chloroform and methylene chloride from P_2O_5. Other solvents were distilled before use. Column chromatography was performed on silica gel L 40-100 (Chemapol), TLC with DC-Alufolien Kieselgel 60-F_{254} (Merck). Methyl 2-oxocyclopent-1-en heptanoate 2 was generous gift from prof. J.Freimanis, Institute of Organic Synthesis of the Latvian Academy of Sciences, Riga. The other chemicals and reagents were purchased and were not worked up before use.

2-(7-methoxycarbonylheptyl)-3-formylcyclopentan-1-on (3). A 9.01 g (38.15 mmole) of 2 was added dropwise to the mixture of 100 ml methanol, 15 ml nitromethane and 0.772 g (14.3 mmole) sodium methoxide at r.t. The reaction mixture was allowed to reflux for 5 h, then cooled to r.t. and 100 ml brine and 12 ml 1 M HCl was added. Methanol was removed under reduced pressure. The water solution was extracted three times with 100 ml ethyl acetate and washed with brine. The organic layer was dried with Na_2SO_4 and

solvent was evaporated to afford 10.24 g of nitrocompound; R_f=0.31 (hexane - ethyl acetate 2:1), i.r. ν_{max} (film) 3021, 1729, 1563, 1005, 964, 742 cm^{-1}. The corresponding acetal was synthesized by Nef reaction according to [20]; 8.30 g, R_f=0.37 (hexane - ethyl acetate 2:1), i.r. ν_{max} (film) 3020, 1740, 1126, 1060, 1000, 960, 740 cm^{-1}. 4.74 ml 10 M HCl was added to the suspension of 23.7 g silica gel L 40-100 and 8.30 g of acetal in 240 ml CH_2Cl_2 at r.t. by vigorous stirring. The suspension was stirred for 95 min. and filtered through the glass filter. After evaporation of the solvent, 3 was obtained as pale yellow oil (6.3 g 62% overall yield from 2); R_f=0.36 (hexane - ethyl acetate 2:1), i.r. ν_{max}(film) 3020, 2730, 1745, 1735 cm^{-1}.

2-(7-methoxycarbonylheptyl)-3-formylcyclopent-2-en-1-on (4). Dropwise addition of 3.15 g (11.75 mmole) of 3 in 25 ml of $CHCl_3$ was carried out over a 10 min. period to a refluxing suspension of 5.5 g $CuBr_2$ (24.5 mmole) in 25 ml anhydrous ethyl acetate with vigorous stirring. The stirred suspension was allowed to reflux for additional 2 hours until the colour of the precipitate changed from black to white ($CuBr_2 \rightarrow CuBr$). After cooling to room temperature and filtration, the solvent was removed, the residue was dissolved in benzene and purified by chromatography on silica gel using hexane - isopropanol 30:1 as an eluent to afford 1.2 g 4 (36% yield); u.v. λ_{max} 260 nm (acetonitrile) ϵ=9200, i.r. ν_{max}(film) 3020, 1770, 1740, 1710, 1180 cm^{-1}

O,O'-dimethyl-3,3-dimethyl-2-oxoheptyl phosphonate (5b) 2,2-dimethyl-methylhexanoate was synthesized from 2-methyl methyl propionate and *n*-butyl iodide according to [21]; ^{13}C n.m.r. C_1-178.4(s), C_2-42.4(s), C_3-40.7(t), C_4-27.3 (t), C_5-23.3(t), C_6-14.0(q), C_1'-25.3(q), C_1''-25.3(q), C_1'''51.5(q). Methyl ester was hydrolysed and the carboxylc acid was converted to the chloroanhydride by the

treatment with thionyl chloride. Chloroanhydride of 2,2-dimethylhexanoic acid was distilled, b.p. 100°C 20 mmHg. Acylation of O,O'-dimethyl methyl phosphonate with chloroanhydride of 2,2-dimethyl hexanoic acid was performed according to [22]. Purification of crude product by column chromatography (benzene - acetone 2:1) afforded 5b in 65% yield; i.r. ν_{max}(film) 3020, 1740, 1295, 1050, 1020 cm^{-1}. The synthesis of 5a was performed analogously to that described above using methyl hexanoate as starting material.

Methyl ester of 11-deoxy-15-keto-PGE_1 (6a) and methyl ester of 11-deoxy-16,16-dimethyl-15-keto-PGE_1 (6b) To a suspension of sodium hydride (0.53 g of 55% dispersion, 12.2 mmole) in 45 ml of dry DME under argon was added dropwise 2.98 g, 13.35 mmole of 5a in 25 ml DME. The mixture was stirred for 15 min at r.t., then cooled to 0°C and a solution of 3.15 g, 11.75 mmole of 3 in 25 ml DME was added. After 25 min at 0°C and 2 h at r.t. the reaction mixture was neutralized with 1.5 ml of glacial acetic acid. Reaction mixture was filtered, solvent was removed under reduced pressure, and the residue chromatographed on silica gel (hexane - isopropanol 50:1) to give the 3.07 g (72% yield) pure 6a. See Table for spectral data. The synthesis of 6b was performed analogously to that described above using 3.36 g of 5b instead of 5a.

Methyl ester of 15-keto-PGB_1 (7a) and 16,16-dimethyl-15-keto-PGB_1 (7b) A. The 7a-b was synthesized analogously to that of 6a-b using aldehyde 4 instead of 3. For 7a-b, u.v. λ_{max}=296 nm (n-hexane), ε=24900. See Table for spectral data. B. The 7b was synthesized from 6b in the same conditions to that of 4 from 3. The purification of the reaction product was performed by the preparative HPLC using the Automated Preparative Liquid Chromatography System PVK-31 (Special Design Office, Estonian Academy of Sciences, Tallinn, Estonia [23]) with silica gel column and

7% isopropanol in *n*-hexane as eluent. The chromatography afforded 1.39 g (42% yield) 7b and 0.4 g (10% yield) 9b. For 9b u.v. λ_{max}=299 nm (*n*-hexane), ε=26200. See Table for spectral data.

Methyl ester of 16-bromo-15-keto-PGB$_1$ (8a) The synthesis of 8a from 6a and the purification of the reaction products were performed analogously to that of 7b, case B. The 1.12 g (30% yield) of 8a, u.v. λ_{max}=301 nm (*n*-hexane), ε=27300 and 0.18 g (6% yield) of 7a were obtained.

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(Received in UK 18 June, 1990)