Organic Synthesis Using Haloboration Reaction. XXI. A Synthesis of Prostaglandin B_1 Methyl Ester by the Stepwise Cross-Coupling Reaction Using (*E*)-(2-Bromoethenyl)diisopropoxyborane

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Synopsis. A prostaglandin B_1(PGB_1) analog and PGB_1 methyl ester were synthesized by the palladium-catalyzed stepwise cross-coupling reaction of (*E*)-(2-bromoethenyl)diisopropoxyborane with (1-methoxy-1-hexenyl)zinc chloride and 3-bromo-2-cyclopenten-1-one derivatives. According to this method, the skeleton of PGB_1 is prepared by the one-pot operation without isolation of any intermediates.

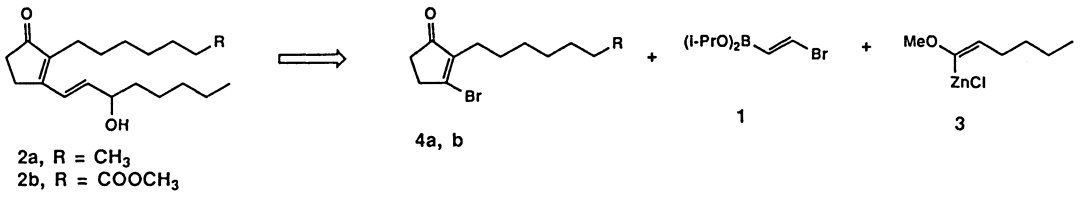
Recently we have shown[1] that (*E*)-(2-bromoethenyl)-diisopropoxyborane (**1**) can be used as a building block for the (*E*)-alkene synthesis by the palladium-catalyzed stepwise cross-coupling reaction with organozinc compounds and organic halides. We also showed[2] that α,β-unsaturated ketones can be prepared from **1** using (1-methoxy-1-alkenyl)zinc chlorides as organozinc reagents.

The application of this reaction for the syntheses of conjugated polyene ketones or functionalized ones was previously demonstrated partially.[2] In this paper, we wish to describe the facile synthesis of prostaglandin B_1(PGB_1) derivatives (**2a** and **2b**),[3] by the stepwise cross-coupling of (1-methoxy-1-hexenyl)zinc chloride (**3**) (C15-20 part), (*E*)-(2-bromoethenyl)diisopropoxyborane (**1**) (C13-14 part), and bromocyclopentenone derivative (**4a**,**b**) (C1-12 part) as depicted in Scheme 1.

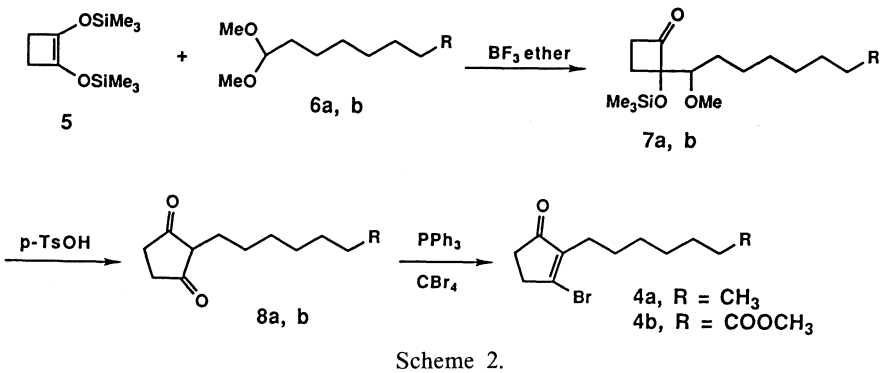
At first, we prepared a PGB_1 analog (**2a**) which has the same structure with PGB_1 except the absence of carboxylic acid function at C1 position. The key intermediate, 2-heptyl-3-bromo-2-cyclopenten-1-one (**4a**) (C1-12 part), was yielded from 1,2-bis(trimethylsiloxy)-cyclobutene (**5**) and octanal dimethyl acetal (**6a**) in 3 steps by Kuwajima and Nakamura's method[4] as shown in Scheme 2. The aldol condensation reaction between **5** and **6a** catalyzed by BF_3 etherate afforded **7a**, which was converted to the diketone **8a** by heating with *p*-TsOH. Finally, the desired **4a** was obtained by the bromination[5] of **8a**.

The stepwise cross-coupling reaction was carried out by the addition of **3** and Pd catalyst to a THF solution of **1**, followed by stirring at room temperature for 3 h (Scheme 3). Then **4a** was added with sodium acetate, and the reaction mixture was stirred under reflux overnight. The resulting trienyl ether was converted to diketone **9a** in 80% yield from **4a** by addition of methanolic sulfuric acid. Finally, the selective reduction of keto-function at C15 with $NaBH_4$ at 0 °C gave **2a** in 81% yield.

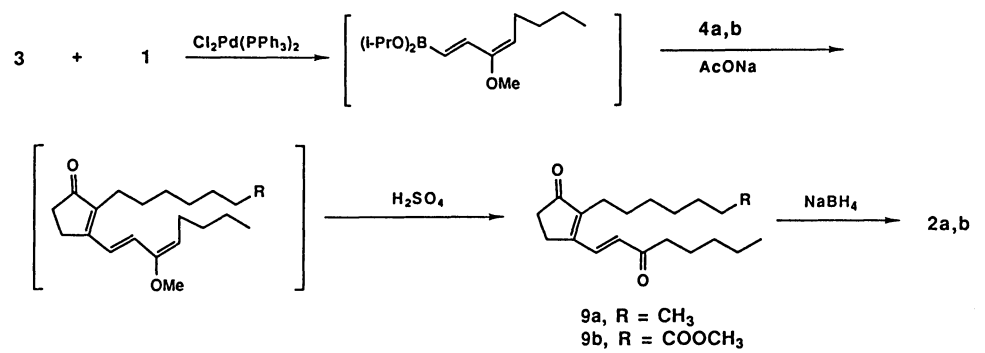
The synthesis of prostaglandin B_1 methyl ester (**2b**) was carried out almost in the similar way (Scheme 3). Bromocyclopentenone derivative **4b** was prepared from dimethyl acetal (**6b**) obtained from δ-valerolactone in 5 steps. 15-Dehydroprostaglandin B_1 methyl ester (**9b**) was obtained in 73% yield by the stepwise cross-coupling reaction using **4b**, **1**, and **3**, followed by the hydrolysis of methoxyvinyl group. Prostaglandin B_1 methyl ester (**2b**)[6] was obtained by the reduction of **9b** in 67% yield.



Scheme 1.



Scheme 2.



Scheme 3.

In both cases, the skeleton of PGB_1 was constructed in one-pot operation without isolation of any intermediates.

Experimental

^{1}H NMR spectra were taken on a Hitachi R-90H FT spectrometer (90 MHz) or measured at the NMR laboratory, Faculty of Engineering, Hokkaido University by using Bruker NSL-400 spectrometer (400 MHz) in $CDCl_3$ employing TMS as an internal standard. IR spectra were taken on a Hitachi 260-10 IR spectrophotometer in the form of film. High-resolution mass spectra were taken at the Center for the Instrumental Analysis, Hokkaido University. Merck silica gel 60 Art 7747 was used for the preparative tlc and Art 7734 for the column chromatography.

3-Bromo-2-heptyl-2-cyclopenten-1-one (4a). To a dry CH_2Cl_2 solution (10 mL) of octanal dimethyl acetal (**6a**) (1.74 g, 10.0 mmol) and BF_3 etherate (1.42 g, 10.0 mmol) was added at −78 °C 1,2-bis(trimethylsiloxy)cyclobutene (**5**) (2.65 g, 11.5 mmol). The mixture was stirred at −78 °C for 2 h and then aqueous solution of sodium hydrogencarbonate (5 mL) was added. The separated aqueous layer was extracted with dichloromethane twice and the combined organic layers were dried over magnesium sulfate. After concentration under reduced pressure, the product was purified by column chromatography (silica gel, 5% ethyl acetate in hexane as eluent) to give 2-(1-methoxyoctyl)-2-(trimethylsiloxy)cyclobutanone (**7a**) (2.70 g, 90% yield) as a mixture of two isomers (ca. 1 : 3 mixture): IR (film) 1795 (C=O) cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ=0.14 (s, 9H), 0.88 (t, J=5 Hz, 3H), 1.1—2.9 (m, 16H), 3.1—3.3 (m, 1H), 3.32 (s, 2.25H), 3.45 (s, 0.75H).

A benzene solution (90 mL) of **7a** (2.70 g, 9 mmol) and *p*-TsOH monohydrate (4.3 g, 23 mmol) was stirred under reflux for 4 h. The reaction mixture was cooled to room temperature and 100 mL of ether was added to dissolve the precipitate of 1,3-dione **8a**. The mixture was washed with aqueous 0.1 M (1 M=1 mol dm^{-3}) HCl solution (30 mL) twice. The aqueous layer was extracted with 50 mL of ether twice and the combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure to give **8a** as a pale yellow solid. The crude product was used for the next step without further purification.

To a chloroform solution (18 mL) of **8a** prepared above and triphenylphosphine (3.54 g, 13.5 mmol) was added a chloroform solution (3 mL) of carbon tetrabromide (1.49 g, 4.5 mmol) at room temperature. The mixture was stirred under reflux for 3 h and then the volatile part was removed under reduced pressure. The resulting viscous material was purified by column chromatography (silica gel, 10% ethyl acetate in hexane as eluent) to give bromoenone **4a** (1.81 g, 70% yield from octanal dimethyl acetal): n_D^{20}=1.4992; IR (film) 1710 (C=O) cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ=0.87 (t, J=6 Hz, 3H), 1.1—1.5 (m, 10 H), 2.26 (t, J=7 Hz, 2H), 2.4—2.6 (m, 2H), 2.8—3.0 (m, 2H). Found: m/z 258.0594 and 260.0610. Calcd for $C_{12}H_{19}OBr$: M, 258.0620 and 260.0560.

Preparation of (1-Methoxy-1-hexenyl)zinc Chloride (3) in THF. To a hexane (32 mL) solution of (*E*)-1-methoxy-1-hexene[7] (1.82 g, 16 mmol) and TMEDA (2.1 g, 18 mmol) was added at −20 °C a pentane solution of *t*-BuLi (7.3 mL of 2.2 M solution, 16 mmol). After stirring for 3 h at the temperature, tributyltin chloride (5.2 g, 16 mmol) was added and the mixture was stirred at room temperature overnight. The reaction mixture was poured into water and the separated organic layer was dried over magnesium sulfate and then concentrated. The crude product was contaminated with a small amount of amine derivative, which was inseparatable by the distillation. To remove the impurity, the crude product was dissolved in toluene (8 mL) and heated with benzyl chloride (1.8 mL) at 100 °C for 24 h. After cooling to room temperature, the mixture was triturated with hexane and the precipitate was removed by filtration. The filtrate was concentrated under reduced pressure and the residue was distilled to give tributyl(1-methoxy-1-hexenyl)tin (2.83 g, 45% yield): Bp 150 °C/0.02 mmHg (1 mmHg=133.322 Pa); ^{1}H NMR (90 MHz, $CDCl_3$) δ=0.75—1.10 (m, 18H), 1.10—1.75 (m, 16H), 1.75—2.10 (m, 2H), 3.45 (s, 3H), 5.23 (t, J=7 Hz, 1H). Tributyl(1-methoxy-1-hexenyl)tin which can be stored in a refrigerator under nitrogen was converted to (1-methoxy-1-hexenyl)zinc chloride (**3**) as follows. To a THF (10 mL) solution of tributyl(1-methoxy-1-hexenyl)tin (604 mg, 1.5 mmol) was added at −78 °C butyllithium (0.93 mL of 1.62 M hexane solution, 1.5 mmol) and after stirring at the temperature for 1 h, a THF solution of zinc chloride (1.5 mL of 1 M solution, 1.5 mmol) was added. The generated (1-methoxy-1-hexenyl)zinc chloride (**3**) was used for the stepwise cross-coupling reaction with **1** immediately.

2-Heptyl-3-[(*E*)-3-oxo-1-octenyl]-2-cyclopenten-1-one (9a). To a THF (10 mL) solution of (1-methoxy-1-hexenyl)zinc chloride (10 mmol) prepared before was added at room temperature $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol) and [(*E*)-2-bromoethenyl]diisopropoxyborane (**1**) (235 mg, 1.0 mmol) successively. After stirring at room temperature for 3 h, sodium acetate (1.64 g, 20 mmol) in 15 mL of methanol and bromoenone **4a** were added. The mixture was stirred under reflux for 12 h and then methanolic sulfuric acid (10 mL of 1.5 M solution) was added at 0 °C. After stirring for 1 h, the product was extracted with 20 mL of ether three times. The combined organic layers were washed with water and then aqueous sodium hydrogencarbonate, dried over magnesium sulfate, and concentrated under reduced pressure. Purification with preparative TLC (silica gel, 20% ethyl acetate in hexane as eluent) afforded 244 mg (80%) of **9a** as a pale yellow oil: n_D^{20}=1.5217; IR (film) 1679 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ=0.87 (t, J=7 Hz, 3H), 0.91 (t, J=7 Hz, 3H), 1.2—1.5 (m, 14H), 1.68 (quintet, J=7 Hz, 2H), 2.36 (t, J=7 Hz,

2H), 2.46—2.52 (m, 2H), 2.66 (t, J=7 Hz, 2H), 2.64—2.74 (m, 2H), 6.55 (d, J=16 Hz, 1H), 7.63 (d, J=16 Hz, 1H). Found: m/z 304.2385. Calcd for $C_{20}H_{32}O_2$: M, 304.2402.

2-Heptyl-3-[(*E*)-3-hydroxy-1-octenyl]-2-cyclopenten-1-one (2a). A methanol (10 mL) solution of **9a** (304 mg, 1 mmol) was treated with sodium borohydride (10 mg, 0.25 mmol) at 0 °C. The reaction was monitored by TLC. When the reaction was completed (ca. 1 h), the product was extracted with 20 mL of ether three times. The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. After the purification by preparative TLC (silica gel, 30% ethyl acetate in hexane), 248 mg (81% yield) of **2a** was isolated as colorless oil: n_D^{20}=1.5168; IR (film) 3420 (-OH), 1682 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ=0.87 (t, J=7 Hz, 3H), 0.90 (t, J=7 Hz, 3H), 1.2—1.5 (m, 16H), 1.58—1.66 (m, 2H), 1.82 (d, J=3 Hz, 1H), 2.26 (t, J=7 Hz, 2H), 2.40—2.45 (m, 2H), 2.62—2.67 (m, 2H), 4.3—4.4 (m, 1H), 6.25 (dd, J=16 and 6 Hz, 1H), 6.79 (d, J=16 Hz, 1H). Found: m/z 306.2563. Calcd for $C_{20}H_{34}O_2$: M, 306.2559.

Methyl 8,8-Dimethoxyoctanoate (6b). A THF solution of potassium t-butoxide (38.7 mL of 0.31 M solution, 12 mmol) was added to a suspension of (3,3-trimethylenedioxypropyl)-triphenylphosphonium bromide[8] (5.5 g, 12 mmol) in THF (12 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 30 min and then methyl 5-oxopentanoate[9] (1.63 g, 12.5 mmol) was added. After stirring for 10 min, the cooling bath was removed and the mixture was stirred at room temperature for 2 h. The reaction mixture was quenched by addition of aqueous solution of ammonium chloride and extracted with 20 mL of ether three times. The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The cyclic acetal of the crude product was converted to the corresponding dimethyl acetal by treatment with p-TsOH mono hydrate (10 mg) in refluxing methanol (10 mL) for 1 h. The consumption of the cyclic acetal was determined by TLC and then the product was extracted with 20 mL of ether three times. The combined organic layers were dried over magnesium sulfate, concentrated under reduced pressure, and the resulting crude product was used for the hydrogenolysis without further purification. The hydrogenolysis of crude methyl 8,8-dimethoxy-5-octenoate (950 mg, 4.43 mmol) was carried out in methanol (10 mL) under the atmosphere of hydrogen (1 atom) in the presence of palladium carbon (47.5 mg) as catalyst. When the hydrogen absorption has ceased, the catalyst was removed by the filtration through celite. The filter cake was washed repeatedly with ether and the filtrate was concentrated under reduced pressure. Purification by column chromatography on silica gel with 15% ethyl acetate in hexane afforded **6b** as a colorless liquid: n_D^{20}=1.4305 (lit,[10] n_D^{20}=1.4300); IR (film) 1740 (C=O) cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ=1.2—1.8 (m, 10H), 2.31 (t, J=7 Hz, 2H), 3.31 (s, 6H), 3.66 (s, 3H), 4.34 (t, J=5 Hz, 1H).

3-Bromo-2-[6-(methoxycarbonyl)hexyl]-2-cyclopenten-1-one (4b). This material was prepared by the procedure described for the preparation of **4a**. 2-[1-Methoxy-7-(methoxycarbonyl)hexyl]-2-(trimethylsiloxy)cyclobutanone (**7b**) was prepared from **5** and **6b** in 90 % yield. The desired cyclopentanone derivative **4b** was obtained in 68% yield from **7b** in two steps after purification by column chromatography (silica gel, 25% ethyl acetate in hexane): n_D^{20}=1.5006; IR (film) 1738 (C=O), 1707 (C=O) cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ=1.2—1.8 (m, 8H), 2.1—2.4 (m, 4H), 2.4—2.6 (m, 2H), 2.8—3.0 (m, 2H), 3.66 (s, 3H). Found: m/z 302.0534 and 304.0499. Calcd for $C_{13}H_{19}O_3Br$: M, 302.0519 and 304.0499.

15-Dehydroprostaglandin B_1 Methyl Ester (9b). Following the procedure described for the preparation of **9a**, the title compound was obtained in a 73% yield after preparative TLC (silica gel, 30% ethyl acetate in hexane): n_D^{20}=1.5245; IR (film) 1735 (C=O), 1694 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$ δ=0.91 (t, J=7 Hz, 3H), 1.2—1.5 (m, 10H), 1.60 (quintet, J=7 Hz, 2H), 1.68 (quintet, J=7 Hz, 2H), 2.30 (t, J=7 Hz, 2H), 2.36 (t, J=7 Hz, 2H), 2.46—2.52 (m, 2H), 2.66 (t, J=7 Hz, 2H), 2.64—2.74 (m, 2H), 3.66 (s, 3H), 6.57 (d, J=16 Hz, 1H), and 7.63 (d, J=16 Hz, 1H). Found: m/z 348.2283. Calcd for $C_{21}H_{32}O_4$: M, 348.2299.

Prostaglandin B_1 Methyl Ester (2b). Following the procedure described for the reduction of **2a**, **2b** was obtained in a 67% yield as a colorless oil after the purification by preparative TLC (silica gel, 50% ethyl acetate in hexane): n_D^{20}=1.5189; IR (film) 3410 (-OH), 1735 (C=O), 1686 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ=0.90 (t, J=7 Hz, 3H), 1.2—1.5 (m, 12H), 1.56—1.66 (m, 4H), 2.16 (d, J=3 Hz, 1H), 2.27 (t, J=7 Hz, 2H), 2.30 (t, J=7 Hz, 2H), 2.40—2.46 (m, 2H), 2.62—2.70 (m, 2H), 3.67 (s, 3H), 4.3—4.4 (m, 1H), 6.27 (d, d, J=16 and 6 Hz, 1H), and 6.80 (d, J=16 Hz, 1H). Found: m/z 350.2447. Calcd for $C_{21}H_{34}O_4$: M, 350.2457.

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