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TOTAL SYNTHESIS OF THE CARBON ANALOG OF Δ^6-PGI_1

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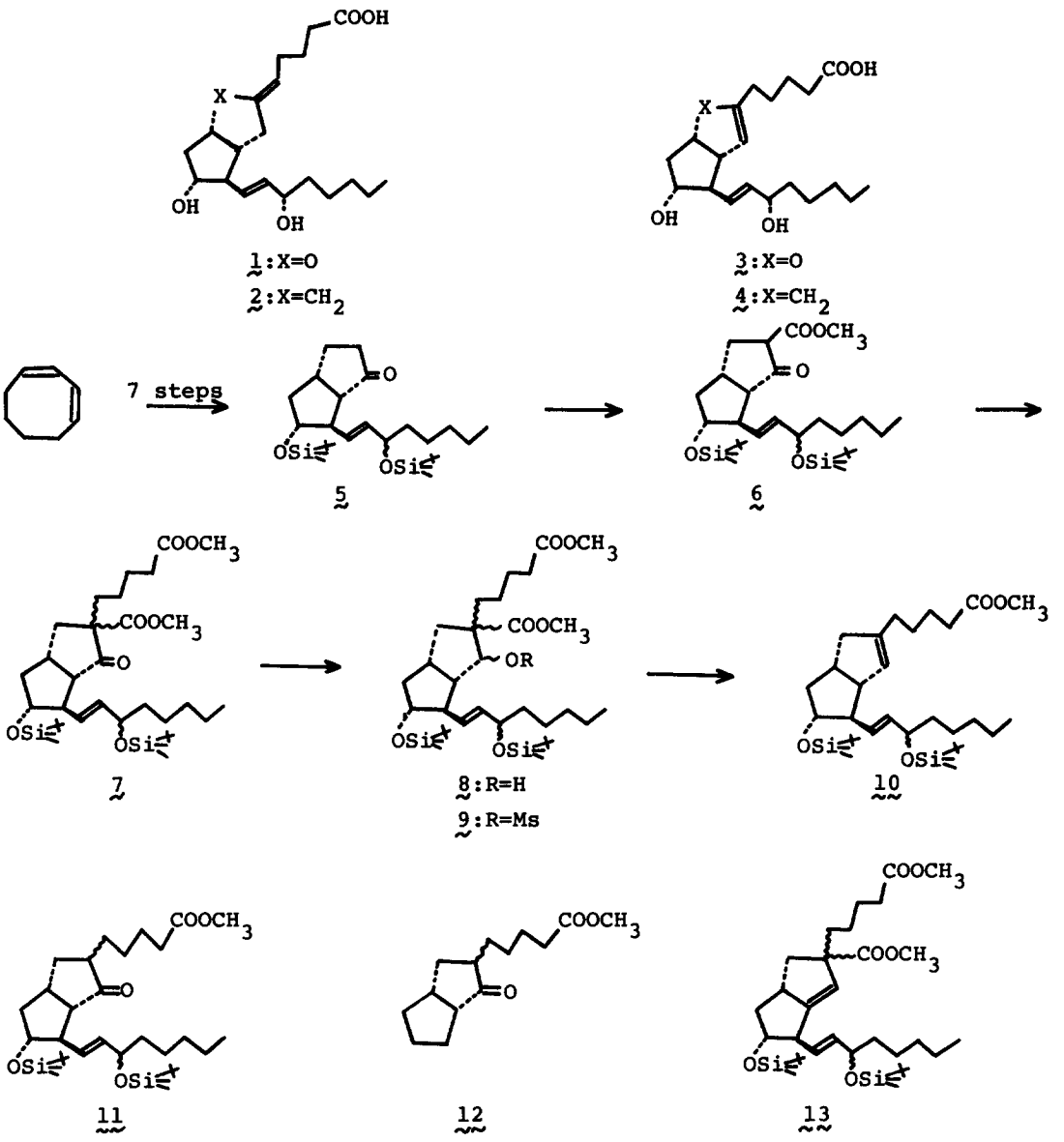
Summary: *The first total synthesis of the carbon analog of 6,9α-oxido-11α,15α-dihydroprosta-6(7),13E-dienoic acid (Δ^6-PGI_1) is described starting from 1,3-cyclooctadiene.*

Much effort has been directed toward development of therapeutically useful prostacyclin analogs since the discovery of prostacyclin (PGI_2) (1)[2]. 9(O)-Methanoprostacyclin (2) synthesized by 5 groups independently[3] is one of highly stable and biologically potent analogs and seems to be the most promising one. Considering the observation by Ono group[4] that Δ^6-PGI_1 (3) has similar activity to prostacyclin (1) in inhibiting platelet aggregation, it is expected that 9(O)-methano-Δ^6-PGI_1 (4) shows high chemical stability and potent activity. In addition to its biological activity, the synthetic study of 4 offers several synthetically interesting problems such as the regiocontrolled introduction of a double bond at the C-6 (PG numbering). In this communication we wish to report the first successful total synthesis of 4.

The ketone (5), which is now readily available from 1,3-cyclooctadiene in the stereo and regiospecific manner by our recent effort[3c,5], appeared to be the most suitable intermediate to 4 as a result of antithetic analysis. In order to obtain 11 by the introduction of an upper side chain, the direct alkylation was first attempted under a variety of conditions, however, the desired product (11) could not be obtained in any case. Then, we turned our attention to the regiocontrolled methoxycarbonylation of the ketone (5). 5 was reacted with dimethyl carbonate[6] in the presence of sodium hydride (6 equiv.) and a catalytic amount



of dry ethanol[7] at room temperature for 6 hr to give the keto-ester (6) [Rf 0.44[8] (silica gel, methylene chloride-petr. ether 1:1), IR(ν,film): 1759, 1730, 1662, 1621 cm-1, PMR($CDCl_3$,δ): 3.68 (s, 3H, $-COOCH_3$)] in 85% yield[9]. The regiochemistry of this methoxycarbonylation, one of the crucial problems in the present total synthesis, was clarified by the fact that the keto-ester (6) could be successfully alkylated in an excellent yield. Namely, 6 was treated

with methyl 5-iodopentanoate[10] (1.2 equiv.) and potassium *t*-butoxide (1.1 equiv.) in DMSO at 50-60° for *ca.* 6 hr to afford the alkylated product (7) [IR(ν,film): 1739 cm-1, PMR($CDCl_3$,δ): 3.77, 3.63 (two singlets, 6H, two methyl esters)] in *ca.* 80% yield probably as a mixture of stereoisomers at the C-6 (PG numbering).

To introduce a double bond at the C-6(7) position, the decarboxylation of the β-keto-ester (7) was examined under various conditions (e.g. lithium iodide-collidine etc.). However, none of the desired product (11) was obtained after treatment with ethereal diazomethane, although in model study, the desired compound (12) was formed in 50-60% yield. Therefore, another strategy was undertaken to accomplish the synthesis. The ketone (7) was reduced with sodium borohydride in methanol at 0° to afford a mixture of the diastereomeric alcohols (8) in *ca.* 90% yield [IR(ν,film): 3450 cm-1], followed by mesylation (10 equiv. of methanesulfonyl chloride-triethylamine) in methylene chloride at 0°. The mesylate (9) was directly used for the next decarboxylative elimination without purification.

The stereochemistry of the mesylate (9), a mixture of stereoisomers, deems not to be a serious problem, since it is already recognized that decarboxylative elimination of salts of β-halo-acids proceeds *via* a non-stereospecific mechanism involving the initial ionization of the β-carbon (E_1 elimination) in highly polar solvents[11]. The mesylate (9) was heated with sodium hydroxide in methanol-water (2:1) at 95° for 1 hr, then treated with ethereal diazomethane. Under these conditions, it is plausible that the ester moieties of 9 are initially hydrolyzed, followed by the decarboxylative elimination of the resulting sodium salt to afford the desired product. In fact, the compound (10) [Rf 0.66 (silica gel, ether-petr. ether 1:3)] was obtained as one of major products in 20-30% yield from the alcohol (8). Unlike our anticipation, the undesired product (13), probably formed *via* E_2 elimination, was also obtained in similar yield.

Although the yield of 10 was relatively modest, it is noteworthy that in the present synthesis the methoxycarbonyl functional group at the C-6 plays a key role for not only the successful alkylation at the C-6 but also the introduction of a double bond at the C-6(7) position. The product (10) was treated with CH_3COOH-H_2O-THF(3:1:1) at 45° for 3 hr to hydrolyze the silyl protecting

groups, followed by treatment with sodium hydroxide in methanol-water (2:1) to give 9(O)-methano-Δ^6-PGI_1 (4) as a mixture of the diastereoisomers at the C-15 (PG numbering). The more polar isomer was tentatively assigned the structure of the 15α-isomer [Rf 0.23 (silica gel, ethyl acetate), PMR($CDCl_3$,δ): 5.62 (m, two olefinic protons), 5.35 (broad s, one olefinic proton), Mass(m/e): 332 [M^+-H_2O], 314 [M^+-$2H_2O$], 288 [M^+-H_2O-CO_2]], while the less polar isomer [Rf 0.36] as the 15β.

Preliminary biological results obtained with 9(O)-methano-Δ^6-PGI_1 (4) and its 15-epimer indicate very weak inhibitory activity in human platelet aggregation induced by collagen[12].

References and Notes

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6) Dimethyl carbonate was purified as follows. It was stirred with potassium carbonate, filtered and distilled in the presence of phosphorus pentoxide.
7) E.J.Corey and D.E.Cane, J. Org. Chem., *36*, 3070 (1971).
8) Rf Value of the starting material (5) is 0.49.
9) The IR spectrum indicates that 6 is in equilibrium with the keto and enol-forms.
10) Prepared from δ-valerolactone in two steps; i) hydriodic acid, ii) sulfuric acid-methanol. B.p. 116-118°/17 mmHg.
11) H.E.Zaugg, Organic Reactions, *8*, 305 (1954).
12) Test of biological activity was carried out by Dr. M.Mori and his coworkers Mitsubishi Pharmaceutical Co., Ltd.

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