PRACTICAL SYNTHESIS OF (+)-9(0)-METHANO- $\Delta^{6}(9\alpha)$ -PGI<sub>1</sub>. THE HIGHLY POTENT CARBON ANALOG OF PROSTACYCLIN

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A practical synthesis of (+)-9(0)-methano $-\Delta^{6(9_{\alpha})}-PGI_{1}$ , potentially a useful therapeutic agent, has been accomplished by utilizing the intramolecular aldol condensation as a key step followed by the Wittig reaction and the regioselective hydrogenation.

Since 9(0)-methano- $\Delta^{6(9\alpha)}$ -PGI<sub>1</sub>(1) was found to be more potent than wellknown carbacyclin in inhibiting platelet aggregation,<sup>1)</sup> we have been concentrating on the development of a practical synthesis of this important compound. In this communication we wish to report a remarkably efficient synthesis of (+)-1 suitable for the preparation of multi-gram quantities.<sup>2)</sup>

It was expected that the intramolecular aldol condensation would be a reasonable methodology for the construction of the bicyclo[3.3.0]octane derivative readily convertible into 1. Thus, the lactone  $(2)^{3}$  was first transformed to the allyl-ketone(3)<sup>4)</sup> in 3 steps (94% overall yield) (i. DIBAL-H in toluene, ii. methyltriphenylphosphonium bromide-potassium <u>t</u>-butoxide in THF, iii. PCC-sodium acetate in  $CH_2Cl_2$ ). Methylenation of 3 was effectively carried out by the action of  $Zn-CH_2Br_2-TiCl_4^{(5)}$  to afford the diene  $(4, )^{(4)}$  in 90% yield. Hydroboration of 4 with disiamylborane in THF at 0 °C followed by treatment with alkaline hydrogen peroxide led to the diol( $\xi$ )<sup>4</sup>) in a stereocontrolled manner<sup>6</sup>) (quantitative yield). Oxidation of 5 with reagents such as PCC, PDC and CrO3.2py afforded the 7-membered lactone exclusively. However, the application of the Swern oxidation 7) led to the formation of the desired products. Thus, treatment of 5 with oxalyl chloride (3.0 equiv.) and DMSO (6.5 equiv.) in  $CH_2Cl_2$  (-60 °C) followed by addition of triethylamine (15 equiv.) (-60 °C-r.t.) led to the dialdehyde  $(\underline{6})$ together with the aldol((7))<sup>8)</sup> in a ratio of <u>ca</u>. 1:1, to which was added dibenzylammonium trifluoroacetate<sup>9)</sup> (ca. 1 equiv.). After change of the solvent for benzene, the reaction mixture was heated at 70 °C for 6 h , providing the  $\alpha,\beta\text{-}$ unsaturated aldehyde  $(8)^{4,10}$  in "one-pot" from the diol (5) (76% overall yield from 5),  $\delta$  (ppm) 9.78 (1H, s, aldehyde proton), 6.71 (1H, d, J=2 Hz, olefinic proton). Wittig reaction of 8 with the ylide derived from 3-carboxypropyl-triphenylphosphonium bromide<sup>11)</sup> and potassium <u>t</u>-butoxide in THF gave the diene(2), which was subsequently converted to  $10^{4}$  by treatment with ethereal diazomethane in 85% yield from 8,  $\delta$  (ppm) 6.24 ( $\frac{1}{3}$ H, d, J=16 Hz, trans olefinic proton), 5.98  $(\frac{2}{3}H, d, J=11 Hz, cis$  olefinic proton). The feature of the present synthesis is the regioselective hydrogenation of 10. Thus, treatment of 10 (2 g) with a catalytic amount of 10% Pd on C (480 mg) in methanol (40 ml) under hydrogen



atmosphere (1 atm) at room temperature for <u>ca</u>. 1 h provided the desired bicyclo-[3.3.0]octene derivative  $(11)^{4}$  in <u>ca</u>. 85% yield,  $\delta$  (ppm) 5.25 (1H, d, J=1 Hz, olefinic proton), 2.90 (1H, m, H<sub>A</sub>), together with the over-reduction product (<u>ca</u>. 13%) and the 1,4-reduction product (<u>ca</u>. 2%).<sup>12</sup>) Removal of a <u>t</u>-butyldimethylsilylether by reaction with tetrabutylammonium fluoride in THF led to the versatile intermediate  $(12)^{4}$  in 100% yield,  $\delta$  (ppm) 5.25 (1H, d, J=1 Hz, olefinic proton), 3.00 (1H, m, H<sub>A</sub>). The overall yield of 12 from 2 in this 9-step sequence is about 50%.

The alcohol(12) was then transformed to 9(0)-methano- $\Delta^{6}(9\alpha)$ -PGI<sub>1</sub>(1) in the usual manner; that is, (i) SO<sub>3</sub>·pyridine complex-triethylamine in DMSO, (ii) (CH<sub>3</sub>O)<sub>2</sub>P(O)CH<sub>2</sub>COC<sub>5</sub>H<sub>11</sub>-NaH in THF, (iii) CH<sub>3</sub>COOH-H<sub>2</sub>O-THF,<sup>13)</sup> (iv) diisobutyl-aluminium-2,6-di-t-butyl-4-methylphenoxide<sup>14</sup>) (13a<sup>15</sup>) : 13b =2.5 : 1), (v) NaOH in aqueous methanol. The overall yield of (+)-1 from 12 in 5-step sequence is about 41%. The spectral data of (+)-1 thus obtained were identical with those of an authentic sample.<sup>1</sup>

The synthesis of (+)-9(0)-methano- $\Delta^{6}(9_{\alpha})$ -PGI<sub>1</sub>(1) described above not only allows the preparation of larger amount of this substance, but it also enables us to prepare various analogs of 1 which are presently under biological evaluation for potentially a useful therapeutic agent. Furthermore it seems likely that this synthesis is suitable for the industrial-scale preparation of (+)-1 and its analogs.

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- The optically pure lactone having the proper absolute configuration was used in the present synthesis.
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- 10) It should be mentioned that the  $\alpha, \beta$ -unsaturated aldehyde(§) is also an extremely versatile synthetic intermediate for the preparation of various analogs of 9(0)-methano- $\Delta^{6}(9\alpha)$ -PGI<sub>1</sub>(1).
- 11) W. Seidel, J. Knolle, and H.J. Schafer, Chem. Ber., <u>110</u>, 3544 (1977).
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- 15) The optical rotation of  $l_{\lambda a}$  was as follows. [ $\alpha$ ]<sub>D</sub><sup>20</sup> +10° (<u>c</u> 0.55, MeOH).



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