CHEMISTRY LETTERS, pp. 579 - 582, 1984.

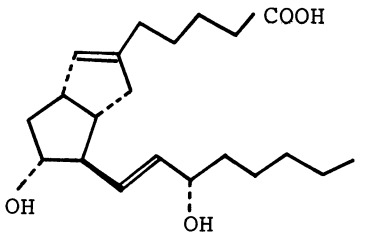
PRACTICAL SYNTHESIS OF (+)-9(O)-METHANO-$\Delta^{6(9\alpha)}$-PGI$_1$. THE HIGHLY POTENT CARBON ANALOG OF PROSTACYCLIN

Mikiko SODEOKA and Masakatsu SHIBASAKI*
Sagami Chemical Research Center, Nishi-Ohnuma, Sagamihara, Kanagawa 229

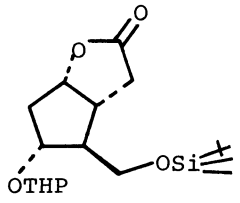
A practical synthesis of (+)-9(O)-methano-$\Delta^{6(9\alpha)}$-PGI$_1$, potentially a useful therapeutic agent, has been accomplished by utilizing the intramolecular aldol condensation as a key step followed by the Wittig reaction and the regioselective hydrogenation.

Since 9(O)-methano-$\Delta^{6(9\alpha)}$-PGI$_1$ (1) was found to be more potent than well-known carbacyclin in inhibiting platelet aggregation,[1] 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.[2]

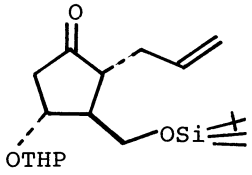
It was expected that the intramolecular aldol condensation would be a reasonable methodology for the construction of the bicyclo[3.3.0]octane derivative readily convertible into 1. Thus, the lactone(2)[3] was first transformed to the allyl-ketone(3)[4] in 3 steps (94% overall yield) (i. DIBAL-H in toluene, ii. methyltriphenylphosphonium bromide-potassium t-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(5)[4] in a stereocontrolled manner[6] (quantitative yield). Oxidation of 5 with reagents such as PCC, PDC and CrO_3·2py 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(6) together with the aldol(7)[8] in a ratio of ca. 1:1, to which was added dibenzylammonium trifluoroacetate[9] (ca. 1 equiv.). After change of the solvent for benzene, the reaction mixture was heated at 70 °C for 6 h , providing the α,β-unsaturated aldehyde(8)[4,10] in "one-pot" from the diol(5) (76% overall yield from 5), δ(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-carboxypropyltriphenylphosphonium bromide[11] and potassium t-butoxide in THF gave the diene(9), which was subsequently converted to 10[4] by treatment with ethereal diazomethane in 85% yield from 8, δ(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



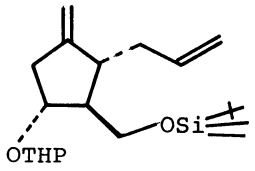
1



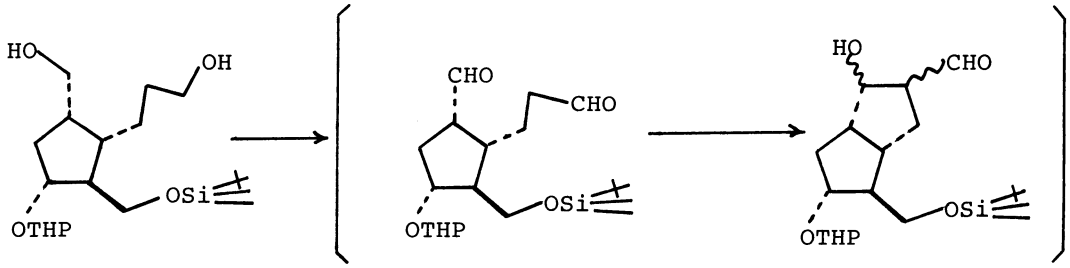
2



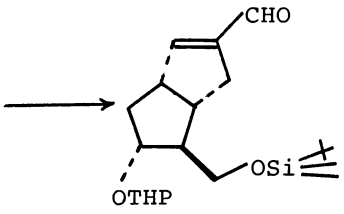
3



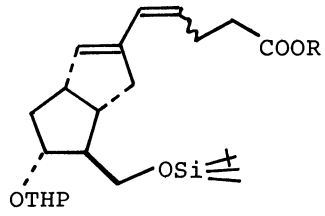
4



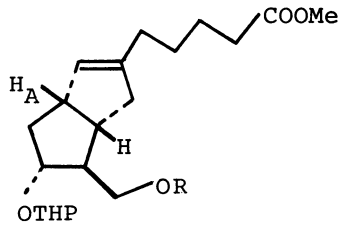
5 6 7



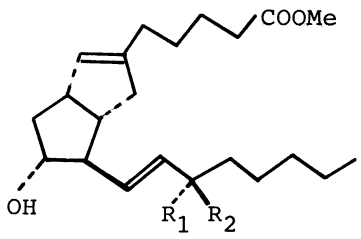
8



9: R=H
10: R=Me



11: R=Si
12: R=H



13a: R_1=OH, R_2=H
13b: R_1=H, R_2=OH

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

The alcohol(12) was then transformed to 9(O)-methano-$\Delta^{6(9\alpha)}$-PGI_1(1) in the usual manner; that is, (i) SO_3·pyridine complex-triethylamine in DMSO, (ii) $(CH_3O)_2P(O)CH_2COC_5H_{11}$-NaH in THF, (iii) CH_3COOH-H_2O-THF,[13] (iv) diisobutyl-aluminium-2,6-di-t-butyl-4-methylphenoxide[14] (13a[15] : 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.[1]

The synthesis of (+)-9(O)-methano-$\Delta^{6(9\alpha)}$-PGI_1(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.

The authors take this opportunity to express their thanks to Prof. S. Ikegami Teikyo University, for his interest and encouragement throughout this work. We also thank Profs. T. Hino and M. Nakagawa, Chiba University, for taking the 270-MHz ^1H NMR spectra.

References

1) M. Shibasaki, Y. Torisawa, and S. Ikegami, Tetrahedron Lett., 24, 3493 (1983); M. Shibasaki, H. Fukasawa, and S. Ikegami, ibid., 24, 3497 (1983).

2) Another synthesis by utilizing the intramolecular thermal ene reaction as a key step has been accomplished. Y. Ogawa and M. Shibasaki, Tetrahedron Lett., in press.

3) The optically pure lactone having the proper absolute configuration was used in the present synthesis.

4) The optical rotation was not measured due to the presence of a THP ether.

5) L. Lombardo, Tetrahedron Lett., 23, 4293 (1982).

6) Stereochemistry of 5 had been anticipated from the literature precedent [G.L. Bundy, Tetrahedron Lett., 1975, 1957], and was confirmed by the experimental fact that 5 could be readily converted to the α,β-unsaturated aldehyde(8). 9-BBN was also an excellent reagent for this reaction.

7) A.J. Mancuso, S.-L. Huang, and D. Swern, J. Org. Chem., 43, 2480 (1978). Treatment of 5 with SO_3·pyridine-DMSO-triethylamine gave the less satisfactory result.

8) The aldol product was in a state of equilibrium between 7 and the lactol form.

9) E.J. Corey, R.L. Danheiser, S. Chandrasekaran, P. Siret, G.E. Keck, and J.L. Gras, J. Am. Chem. Soc., 100, 8031 (1978).

10) It should be mentioned that the α,β-unsaturated aldehyde(8) is also an extremely versatile synthetic intermediate for the preparation of various analogs of 9(O)-methano-$\Delta^{6(9\alpha)}$-PGI_1(1).

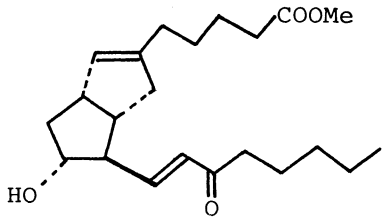
11) W. Seidel, J. Knolle, and H.J. Schäfer, Chem. Ber., 110, 3544 (1977).

12) These by-products could be removed at this stage by silica gel column chromatography.

13) The optical rotation of i was as follows. $[\alpha]_D^{20}$ +21° (c 1.49, MeOH).

14) S. Iguchi, H. Nakai, M. Hayashi, and H. Yamamoto, J. Org. Chem., 44, 1363 (1979).

15) The optical rotation of 13a was as follows. $[\alpha]_D^{20}$ +10° (c 0.55, MeOH).



i

(Received January 13, 1984)