Tetrahedron Letters,Vol.23,No.20,pp 2099-2102,1982 0040-4039/82/202099-04$03.00/0
Printed in Great Britain

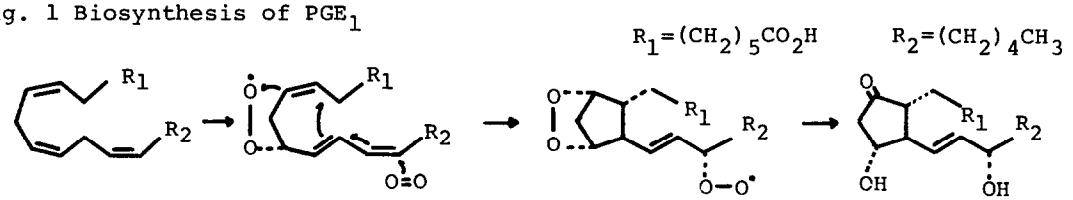
A BIOGENETICALLY PATTERNED TOTAL SYNTHESIS OF PROSTAGLANDIN E_1

Chisato Sato, Shun'ichi Ikeda, Haruhisa Shirahama and Takeshi Matsumoto
Department of Chemistry, Faculty of Science, Hokkaido University
Sapporo 060, JAPAN

Summary Methyl 11-tert-butyldimethylsilyloxyeicosa-8(Z),12(E),14(E)-trienoate was stereoselectively cyclized by treatment with $Hg(OCOCF_3)_2$ to give a properly functionalized PG skeleton, which was converted to PGE_1 in good over all yield.

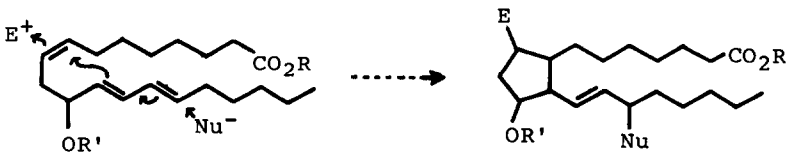
Synthesis of prostaglandins(PG) has attracted[1] the attention of a large number of chemists since their structures were elucidated. However, a biogenetically patterned pentannulation which properly provides four or five asymmetric centers of PGs at the same time, starting from an eicosapolyenoic acid derivative, has not yet been achieved.[2] We wish to report here the first stereocontrolled total synthesis of PGE_1 via a route which mimics the biosynthetic pathway (Fig 1).

Fig. 1 Biosynthesis of PGE_1



The effectiveness of the strategy (Fig 2) featured by a cationic rather than homolytic pentannulation was first examined employing a model compound 1. After several attempts the desired cyclization of triene 1[3] was realized by means of $Hg(OCOCF_3)_2$[4] [(1) 1.2 eq-Hg salt/CH_3NO_2/-20 °C/1 hr, (2) 2 eq-KBr/0 °C/1 hr, (3) catalytic amount of LiOH/MeOH/rt/5 min] to give highly stereoselectively except for C-15[5] a cyclopentane derivative 2, in 60% yield. The

Fig. 2



product was a mixture of two stereoisomers (2a/2b=1:1) with regard to the configuration at C-15. They were separated by tlc(silica gel, hexane/AcOEt= 7/3).

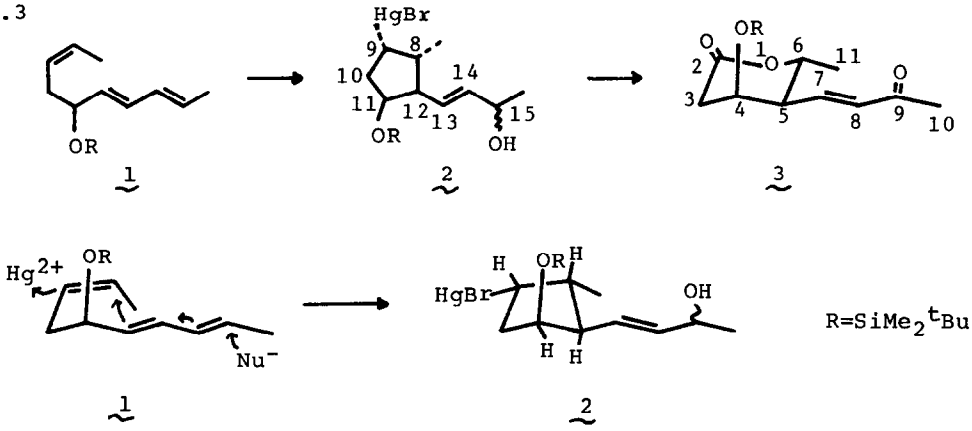
2a(less polar isomer): mp 68-70°, ^{1}H NMR(400 MHz, $CDCl_3$) δ 1.06(3H, d, J=7, 7-H_3[5]), 1.27 (3H, dd, J=1.5, 6, 16-H_3), 1.93(1H, dt, J=5, 9, 12α), 2.04(1H, ddd, J=2, 8, 13, 10-H), 2.40(1H, dt, J=13, 7, 10-H), 2.53(1H, dquint, J=9, 7, 8β), 3.45(1H, q, J=7, 9β), 4.27(1H, dt, J=2, 6, 11α), 4.30(1H, quint, J=7, 15-H), 5.57(1H, ddd, J=1.5, 8, 16, 14-H), 5.65(1H, dd, 9, 16, 13-H).

2b(more polar isomer): mp 68-70°, ^{1}H NMR(400 MHz, $CDCl_3$) δ 1.08(3H, d, J=7, 7-H_3), 1.27(3H, d, J=6, 16-H_3), 1.93(1H, dt, J=5, 9, 12α), 2.05(1H, ddd, J=3, 8, 14, 10-H), 2.38(1H, ddd, J=6, 7, 14, 10-H), 2.55(1H, dquint, J=9, 7, 8β), 3.45(1H, q, J=7, 9β), 4.24(1H, dt, J=3, 6, 11α), 4.29(1H, quint, J=6, 15-H), 5.55(1H, dd, J=6, 16, 14-H), 5.64(1H, dd, J=9, 16, 13H).

Configuration of the functional groups on the cyclopentane ring was determined as follows. The bromomercury group of 2 was replaced by a hydroxy group (O_2/$NaBH_4$/DMF)[6] and the resultant alcohol was directly subjected to Jones oxidation followed by peracid oxidation (mCPBA/$NaHCO_3$/CH_2Cl_2/rt/9 hr), to give a δ-lactone 3 in 40% yield from 2. The ^{1}H NMR spectrum of 3 revealed the stereochemistry as shown in formula 3 and therefore the configuration of 2 was in turn established as depicted by 2. A probable steric course of the mercury induced cyclization reaction is shown in Fig 3.

3: IR 1750, 1680, 1635 cm^{-1}; ^{1}H NMR(60 MHz, $CDCl_3$) δ 1.45(3H, d, J=7, 11-H_3), 2.25(3H, s, 10-H_3), 2.40(1H, ddd, J=2, 8, 11, 5α), 2.65(2H, d, J=3, 3-H_2), 4.17(1H, dt, J=2, 3, 4α), 4.73(1H, dq, J=11, 6, 6β), 6.23(1H, d, J=16, 8-H), 6.65(1H, dd, J=8, 16, 7-H).

Fig.3

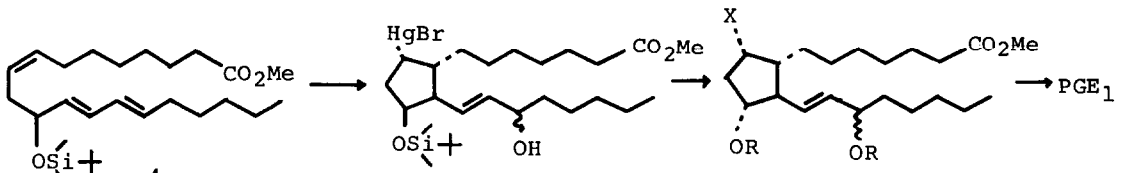


The successful cyclization of the model compound prompted us to attempt the cyclization of a C_{20}-trienoic acid to a PG. The trienoic acid 4[7] was treated with the mercuric salt under the similar conditions as employed in the above model synthesis to give a properly functionalized PG skeleton 5, in a similar stereoselectivity in 48% yield. Two stereoisomers concerning the configuration

at C-15(5a/5b=1/1) were separated by tlc(silica gel, benzene/CH_2Cl_2/AcOEt=15/8/1). The NMR signals attributable to protons on C-8 through C-15 of the less polar isomer 5a and the more polar isomer 5b exhibited essentially the same patterns as those of model compounds 2a and 2b respectively, the cyclization was proved to be successful.

5a(less polar isomer): ^{1}H NMR(400 MHz, $CDCl_3$) δ 0.86(3H, t, J=7, 20-H_3), 1.98(1H, dt, J=6, 10, 12α), 2.29(2H, t, J=8, 2=H_2), 2.39(1H, dq, J=9, 6, 8β), 3.36(1H, q, J=7, 9β), 3.65(3H, s, CO_2Me), 4.06(1H, q, J=7, 15β), 4.27(1H, dt, J=3, 6, 11α), 5.46(1H, dd, J=7, 16, 14-H), 5.63(1H, dd, J=9, 16, 13-H).

5b(more polar isomer): ^{1}H NMR(400 MHz, $CDCl_3$) δ 0.84(3H, t, J=7, 20-H_3), 1.98(1H, dt, J=6, 10, 12d), 2.28(2H, t, J=8, 2-H_2), 2.38(1H, dq, J=9, 6, 8β), 3.35(1H, q, J=7, 9β), 3.65(3H, s, CO_2Me), 4.06(1H, q, J=7, 15β), 4.25(1H, dt, J=3, 6, 11α), 5.48(1H, dd, J=7, 16, 14-H), 5.64(1H, dd, J=9, 16, 13-H).



5a: 15α OH 6a: 11β OH, 15α OAc 7: X=HgBr, R=Ac
5b: 15β OH 6b: 11β OH, 15β OH 8: X= ~OH, R=$SiMe_2{}^tBu$

The configuration at C-11(β-OR) of our cyclized products 5a and 5b was unfortunately wrong. Inversion of the 11β-silyloxy group of 5a was therefore attempted by Mitsunobu's method[8] through 11β-hydroxy-15α-acetoxy compound 6a[9] [(1)Ac_2O/py (y=95%), (2)40% HF/CH_3CN(→6a, y=74%), (3)EtO_2C-N=N-CO_2Et/ϕ_3P/AcOH/THF/-50°(→7, y=70%)]. Similarly, 5b was converted to 7 through inversion at C-11 and C-15 at once [(1)HF(→6b, y=58%), (2)EtO_2C-N=N-CO_2Et(→7, y=20%)]. The two acetoxy groups of 7[9] were then replaced by silyloxy groups(65%) [(1)K_2CO_3aq/MeOH, (2)^{t}BuMe_2SiCl/imidazole/DMF/rt/10 min] and the bromomercury group was substituted by a hydroxy group (O_2/$NaBH_4$/DMF)[6] to yield a protected PGF_1 8[9] containing an equal amount of the C-9 isomer in 95% yield. The isomeric mixture of PGF_1 derivative 8 was then treated with Jones reagent and subsequent desilylation with HF/CH_3CN afforded PGE_1 methyl ester, whose nmr spectrum (400 MHz) and Rf values on tlc were identical with those of an authentic sample. On the other hand, by successive hydrolysis, oxidation and desilylation [(1)NaOHaq/MeOH, (2)Jones reagent, (3)40% HF/CH_3CN], 8 was converted to PGE_1 in 65% yield (through 3 steps). The synthetic acid was completely identical with an authentic sample of PGE_1 in spectral data and behavior on tlc using various solvent systems.

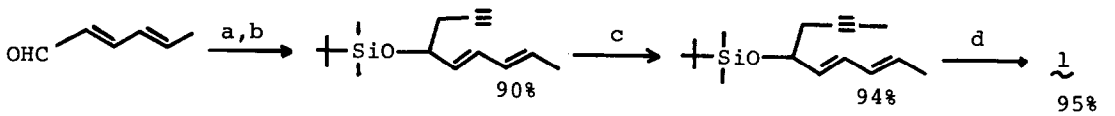
Acknowledgment: We are indebted to Dr. N. Hamanaka (Ono Pharmaceutical Co.) for a sample of PGE_1.

References and Notes

1) A huge number of synthetic works have been reported for these 15 years and a number of reviews concerning this subject have also been published: J. S. Bindra in "The Total Synthesis of Natural Products", vol 4, ApSimon Ed., Wiley, New York 1981, p.353 and references cited therein.

2) Approaches to biogenetic type ring closure using a short chain compound: E. J. Corey, G. W. Fleet, M. Kato, Tetrahedron Lett., 3963 (1973), J. Martel, E. Toromanoff, J. Mathieu, G. Nomie, ibid, 1491 (1971).

3) The triene 1 was prepared in the following manner[9]:



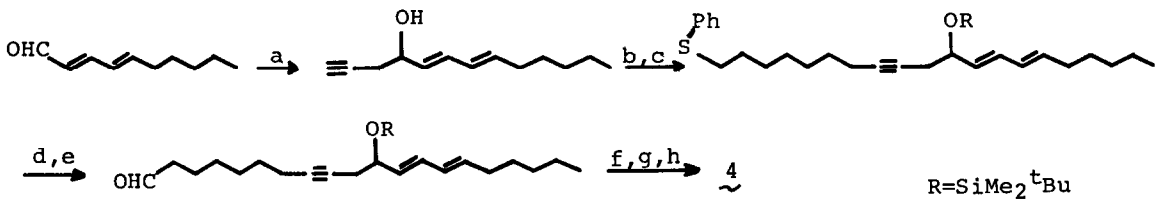
a: Al/$BrCH_2C{\equiv}CH$/THF/-78 °C/30 min, b: t-$BuMe_2SiCl$/imidazole/DMF/0 °C/30 min, c: n-BuLi/THF/MeI, d: H_2/Pd-$BaSO_4$/quinoline/AcOEt

4) A 1,5-diene humulene was converted to cyclopentane derivatives on treatment with mercuric salts. S. Misumi, T. Ohtsuka, H. Hashimoto, Y. Ohfune, H. Shirahama, T. Matsumoto, Tetrahedron Lett., 35 (1979), S. Misumi, T. Ohtsuka, Y. Ohfune, K. Sugita, H. Shirahama, T. Matsumoto, ibid, 31 (1979), S. Misumi, Y. Ohfune, A. Furusaki, H. Shirahama, T. Matsumoto, ibid, 2865 (1976).

5) The PG numbering is applied here for convenience.

6) C. L. Hill, G. M. Whitesides, J. Am. Chem. Soc., 96, 870 (1979).

7) The triene 4 was furnished by the following scheme[9]



a: Al/$BrCH_2C{\equiv}CH$/THF/-78 °C/-30 min (y=99%), b: t-$BuMe_2SiCl$/imidazole/DMF/0 °C/15 min(y=91%). c: n-BuLi/THF/-78 °C/HMPA/$I(CH_2)_7SPh$(y=78%), d: $NaIO_4$(THF-MeOH-H_2O/rt (2 hr), 40-50 °C(1 hr) y=80%), e: (1) $(CF_3CO)_2O$/Pyr/CH_2Cl_2/rt/20 min, (2) $NaHCO_3$/THF-H_2O/rt/8 hr(y=84%), f: Jones oxid.(y=60%), g: CH_2N_2/ether(y=99%), h: H_2/Pd-$BaSO_4$/quinoline/AcOEt(y=84%)

8) O. Mitsunobu, M. Eguchi, Bull. Chem. Soc., Jpn., 44, 3427 (1971), O. Mitsunobu, J. Kimura, K. Iiizumi, N. Yanagida, Bull. Chem. Soc., Jpn., 44, 510 (1976).

9) Satisfactory spectroscopic (IR, MS, NMR) data were obtained for all the new compounds in this paper.

(Received in Japan 27 January 1982)