Communications to the Editor

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TOTAL SYNTHESES OF STABLE PGI_2 DERIVATIVES[1)] — SYNTHESES OF 7-HYDROXY- AND 7-FLUORO-PGI_2 —

Satoshi Sugiura, Takeshi Toru, Toshio Tanaka, Noriaki Okamura
Atsuo Hazato, Kiyoshi Bannai, Kenji Manabe, and Seizi Kurozumi*
Institute for Bio-Medical Research, Teijin Ltd.,
4-3-2 Asahigaoka, Hino, Tokyo 191, Japan

Stable PGI_2 analogs (7-hydroxy- and 7-fluoro-PGI_2) were synthesized from the chiral synthon, (4R)-4-hydroxy-2-cyclopentenone, using a three component coupling reaction followed by selective reduction, intramolecular cyclization reaction, and fluorination.

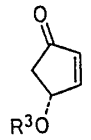
KEYWORDS—7-hydroxy-PGI_2; 7-fluoro-PGI_2; stereoselective reduction; intramolecular cyclization with mercuric trifluoroacetate; fluorination of hydroxy group

Several kinds of PGI_2 analogs have been proposed using a variety of synthetic methods.[2)] Most synthetic designs of these analogs have focused on the construction of chemically stable PGI_2 analogs which exhibit pharmacological activities similar to natural PGI_2. One example is to synthesize bio-isosters which have moieties similar to the enol ether unit of the PGI_2 molecule.[2a)] Another is to synthesize analogs which have stabilized enol ether units in them.[2b,2c)] In the latter category we have proposed several PGI_2 analogs[2c)] which have electron-withdrawing groups near or on the enol ether unit. These compounds were synthesized starting from PGI_2, and 7-fluoro-PGI_2 had attractive pharmacological activities in preliminary evaluation.[2c)] In this communication we wish to report the total syntheses of 7-hydroxy- and 7-fluoro-PGI_2 starting from the protected (4R)-4-hydroxy-2-cyclopentenone (1) which is a useful synthon for the versatile syntheses of prostaglandins.[3)]

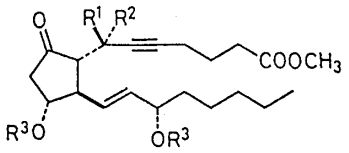
The key intermediates in these syntheses are the 7-hydroxy-5,6-dehydro-PGE_2 derivatives (2) which were obtained in 50% yield[4,5)] according to the method of "three component coupling process".[3)]

Stereoselective reduction of the 9-oxo group of 2 was investigated with sodium borohydride and L-Selectride under several conditions. When $NaBH_4$[6)] was used under the condition cited in entries 2 and 5 (Table I), mainly PGF_α-type compounds 3[7)] were obtained with a little formation of PGF_β-type compounds 4, regardless of the stereochemistry of the 7-hydroxy group. Exclusive formation of the compounds 3 was achieved by L-Selectride as a selective reducing agent.

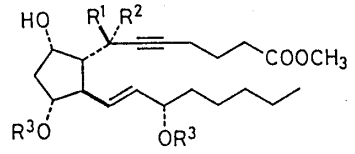
Intramolecular cyclization[8)] of 3 into the 7-hydroxy-PGI_2 derivatives 5[9)] was accomplished by the reaction of 3 with mercuric trifluoroacetate in THF at -78°C



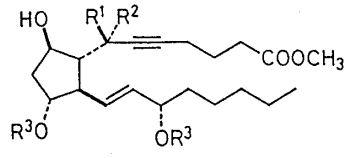
1: R^3=Si(CH$_3$)$_2$-t-C$_4$H$_9$



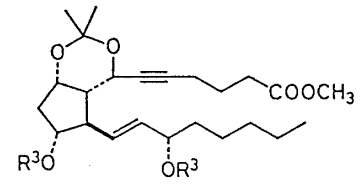
2a: R^1=H R^2=OH, R^3=Si(CH$_3$)$_2$-t-C$_4$H$_9$
2b: R^1=OH, R^2=H, R^3=Si(CH$_3$)$_2$-t-C$_4$H$_9$



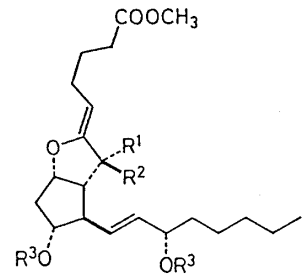
3a: R^1=H R^2=OH, R^3=Si(CH$_3$)$_2$-t-C$_4$H$_9$
3b: R^1=OH, R^2=H, R^3=Si(CH$_3$)$_2$-t-C$_4$H$_9$
8a: R^1=H, R^2=OH, R^3=COCH$_3$
8b: R^1=OH, R^2=H, R^3=COCH$_3$



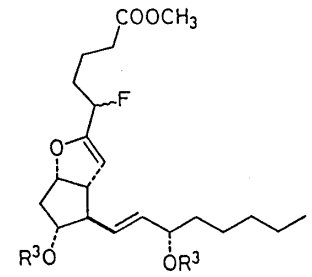
4a: R^1=H, R^2=OH, R^3=Si(CH$_3$)$_2$-t-C$_4$H$_9$
4b: R^1=OH, R^2=H, R^3=Si(CH$_3$)$_2$-t-C$_4$H$_9$



6: R^3=Si(CH$_3$)$_2$-t-C$_4$H$_9$
7: R^3=COCH$_3$



5a: R^1=H, R^2=OH, R^3=Si(CH$_3$)$_2$-t-C$_4$H$_9$
5b: R^1=OH, R^2=H, R^3=Si(CH$_3$)$_2$-t-C$_4$H$_9$
9a: R^1=H, R^2=OH, R^3=COCH$_3$
9b: R^1=OH, R^2=H, R^3=COCH$_3$
10: R^1=H, R^2=F, R^3=COCH$_3$



11: R^3=Si(CH$_3$)$_2$-t-C$_4$H$_9$

and subsequent treatment with $NaBH_4$. The cyclized product (63% yield) from 3a was assigned to 5a (7S-isomer), since the product was identical in all spectral data (NMR, IR, MS) with the compound reported previously[2c]. The less polar product[11] (7R)-7-hydroxy-PGI_2 derivative 5b[12] was newly obtained from 3b in 58% yield. From these results, we assigned the absolute configuration at C-7 of the "a" series compounds to S, and consequently the "b" series to R.

The silyl-protected 7-hydroxy-PGI_2 derivatives 5 were not good substrates for the fluorination of 7-hydroxy-PGI_2 with diethylaminosulfur trifluoride (DAST).[2c] Thus the silyl-protecting groups of 5 were transformed into acetyl-protecting groups by the following procedure: i) protection of hydroxyl groups at C-7 and C-9 of 3 with acetone dimethylacetal into 6[13] ($(CH_3)_2C(OCH_3)_2$, $C_5H_5\overset{+}{N}H\cdot\bar{O}Ts$, CH_2Cl_2, rt,

TABLE I. Stereoselective Reduction of 7-Hydroxy-5,6-dehydro-PGE_2 Derivatives

Entry	Substrate	Reducing agent	Isolated yield (%) 3[d]	4[d]
1	2a	$NaBH_4$[a]	58	34
2	2a	$NaBH_4$[b]	81	2
3	2a	L-Selectride[c]	68	0
4	2b	$NaBH_4$[a]	68	20
5	2b	$NaBH_4$[b]	87	6
6	2b	L-Selectride[c]	87	0

a) A methanol solution of $NaBH_4$ (1 eq) was added to an ice cooled methanol solution of 2. b) The methanol solution of 2 was added to the ice cooled methanol solution of $NaBH_4$ (6 eq). c) An L-Selectride-THF solution was added to THF solution of 2 at -78°C, then, after 10 min, 20% aq. NaOH and 30% aq. H_2O_2 were added. d) The structures of compounds 3 and 4 were confirmed by NMR, IR, and mass spectral analyses and by results from the subsequent reaction.[7]

9 h), ii) desilylation ($(n\text{-}C_4H_9)_4NF$, THF, rt, 3 days), iii) acetylation ($(CH_3CO)_2O$, C_5H_5N, rt, 2 days) of C-11 and C-15 hydroxyl groups giving 7,[14] and iv) removal of the acetonide group ($C_5H_5\overset{+}{N}H\cdot\bar{O}Ts$, CH_3OH, 40°C, 1 day). Thus acetyl-protected 7-hydroxy-5,6-dehydro-$PGF_{2\alpha}$ derivatives 8[15] were obtained from 3. Cyclization of 8 (8a or 8b) with mercuric trifluoroacetate by the method described above gave acetyl-protected 7-hydroxy-PGI_2 derivatives 9 (9a or 9b) in 56% or 55% yields, which correspond to overall 29% or 39% yields from 3a or 3b, respectively.

Fluorination of 9a (7S-OH-isomer) with DAST successfully gave a ca. 1:2 mixture of 7-fluoro-PGI_2 derivative 10[2c,17] and 5-fluoro-6,7-dehydro-PGI_1 derivatives 11[2c,16] in 70% yield. Interestingly fluorination of 9b (7R-OH-isomer) with DAST also gave a similar mixture of 10 and 11 in 78% yield.

These results open the possibility of synthesizing a variety of chemically modified stable-PGI_2 derivatives.

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2) a) W. Skuballa and H. Vorbrüggen, Angew. Chem. Int. Ed. Engl., 20, 1046 (1981) and references cited therein; M. Shibasaki, Y. Torisawa, and S. Ikegami, Tetrahedron Lett., 24, 3493 (1983); M. Shibasaki, H. Fukasawa, and S. Ikegami, ibid., 24, 3497 (1983); K. C. Nicolaou, W. E. Barnette, and R. L. Magolda, J. Am. Chem. Soc., 103, 3472 (1981) and references cited therein; G. L. Bundy

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3) M. Suzuki, T. Kawagishi, and R. Noyori, Tetrahedron Lett., 23, 4057 (1982); idem, ibid., 23, 5563 (1982).

4) To the mixed cuprate formed from (3S)-3-t-butyldimethylsilyloxy-octenyllithium (1 eq), 1-pentynyl copper (1 eq) and hexamethylphosphorous triamide (2 eq) at -78°C, was added the chiral enone 1 (1 eq), then the resultant enolate was trapped with methyl 7-oxo-5-heptynoate.

5) 2a:2b ≒ 1:1, 2a was less polar than 2b.

6) The usual sodium borohydride reduction lacks stereochemistry as shown in entries 1 and 4 as well as in the following reference by S. Bergström, L. Krabisch, B. Samuelsson, and J. Sjövall; Acta Chem. Scand., 16, 969 (1962).

7) Stereochemistry of the 9α-hydroxy group was determined by the fact that only 3 gave 7-hydroxy-PGI_2s by the following intramolecular cyclization while 4 did not.

8) Similar cyclization reactions were recently reported; M. Riediker and J. Schwartz, J. Am. Chem. Soc., 104, 5842 (1982); M. Suzuki, A. Yanagisawa, and R. Noyori, Tetrahedron Lett., 24, 1187 (1983).

9) Alternatively, 5a was obtained from 3a by hydrogenation of the triple bond into the cis-double bond, subsequent bromoetherification and dehydrobromination.[10]

10) I. Tömösközi, G. Calambos, G. Kovács, and L. Radics, Tetrahedron Lett., 1978, 581; E. J. Corey, G. E. Keck, and I. Székely, J. Am. Chem. Soc., 99, 2006 (1977).

11) Rf value of 5b[12] was 0.56 (cyclohexane:ethyl acetate = 7:3) while 5a, 0.42.

12) 5b ^{1}H NMR ($CDCl_3$) δ 3.60(3H, s), 3.9–4.2(2H, m), 4.39(1H, t, J=7.0 Hz), 4.50(1H, d, J=9.0 Hz), 4.64–4.95(1H, m), 5.35–5.55(2H, m); MS m/e 610 [M^+].

13) 6a ^{1}H NMR ($CDCl_3$) δ 3.66(3H, s), 3.7–4.5(3H, m), 4.7–5.0(1H, m), 5.4–5.7(2H, m); 6b ^{1}H NMR ($CDCl_3$) δ 3.66(3H, s), 3.7–4.65(4H, m), 5.4–5.7(2H, m).

14) 7a ^{1}H NMR ($CDCl_3$) δ 1.43(6H, s), 2.00(6H, s), 3.66(3H, s), 4.1–4.5(1H, s), 4.7–5.4(3H, m), 5.4–5.7(2H, m); 7b ^{1}H NMR ($CDCl_3$) δ 1.36(3H, s), 1.44(3H, s), 2.00(6H, s), 3.66(3H, s), 4.1–4.6(2H, m), 4.81(1H, q, J=7.0 Hz), 5.0–5.4(1H, m), 5.4–5.7(2H, m).

15) 8a ^{1}H NMR ($CDCl_3$) δ 3.66(3H, s), 4.1–5.35(4H, m), 5.4–5.7(2H, m); 8b ^{1}H NMR ($CDCl_3$) δ 3.66(3H, s), 4.1–5.35(4H, m), 5.4–5.7(2H, m).

16) The compound was a mixture of 5R and 5S isomers judging by its ^{13}C-NMR spectrum.

17) The stereochemistry of the 5,6-double bond has already been discussed by K. Bannai in reference (2c).

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