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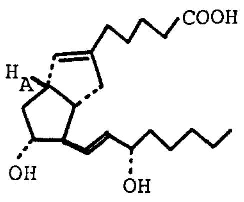
REGIOCONTROLLED CONVERSION OF α,β-UNSATURATED KETONES TO OLEFINS VIA ALLYLSILANES: SYNTHESIS OF dl-9(O)-METHANO-$\Delta^{6(9\alpha)}$-PGI$_1$

Masakatsu Shibasaki[†], Hidemi Fukasawa, and Shiro Ikegami[*]
Faculty of Pharmaceutical Sciences, Teikyo University, Sagamiko, Kanagawa 199-01, Japan

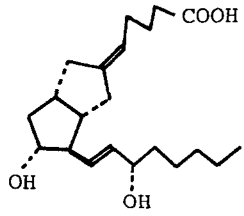
Summary: A synthesis of dl-9(O)-methano-$\Delta^{6(9\alpha)}$-PGI$_1$ (1), a more potent prostacyclin analog than carbacyclin, has been accomplished utilizing regiocontrolled transformation of the enone to the olefin via the allylsilane as a key step.

Our discovery that 9(O)-methano-$\Delta^{6(9\alpha)}$-PGI$_1$ (1) is more potent than carbacyclin (2) in inhibiting platelet aggregation[1] has prompted us to develop an improved synthesis of 1. In this communication we wish to report a direct synthesis of dl-1 starting from 1,3-cyclooctadiene, which involves regiocontrolled transformation of the enone to the olefin via the allylsilane as a key step.

Since we had already established the efficient synthesis of the ketone (3) starting with 1,3-cyclooctadiene,[2] the present synthesis was focused on regiocontrolled transformation of the ketone (3) to the carbon analog (1).[3] Toward this end, model studies were carefully carried out by the use of the simple ketone (5).[4] Reaction of the lithium enolate of 5 with ethyl 5-oxopentanoate[5] afforded the aldols, which were followed by successive treatment with MsCl-NEt$_3$ in benzene and DBU to give the enone (6) (82%); δ(ppm) 6.53 (bt, J=7Hz, 1H, olefinic proton). The endo-enone (7), δ(ppm) 7.20 (m, 1H, olefinic proton), was readily obtained by treatment of 6 with RhCl$_3$·3H$_2$O (0.13 molar equiv) and potassium carbonate (0.72 molar equiv) in ethanol (70°C, 24 hr, 76%).[6] Deoxygenation reaction of 7 without scrambling of the double bond is an extremely difficult synthetic problem hitherto unsolved. It occurred to us that the organosilicon chemistry involving 1) Michael addition of trimethylsilyl anion to the enone, 2) formation of the allylsilane and 3) protodesilylation would solve this synthetic problem.[7] Indeed our idea worked quite well. Thus, reaction of 7 with Me$_3$SiSiMe$_3$ (1.5 equiv) and Bu$_4$N$^+$F$^-$ (0.3 molar equiv) in HMPA at room temperature for 0.5 hr cleanly provided 8 (85%).[8,9] The alcohol (9)[9] was subsequently obtained by reduction of 8 with L-Selectride in THF at -78°C (90%). Treatment of 9 with trifluoromethanesulfonic anhydride (10 equiv), pyridine (20 equiv) and a catalytic amount of 4-dimethylaminopyridine in CH$_2$Cl$_2$ at 0°C for 2 hr yielded the olefin (12) directly together with a small amount of the allylsilane (11).[10] The crude reaction



1



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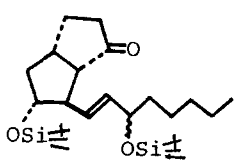

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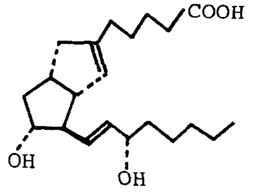

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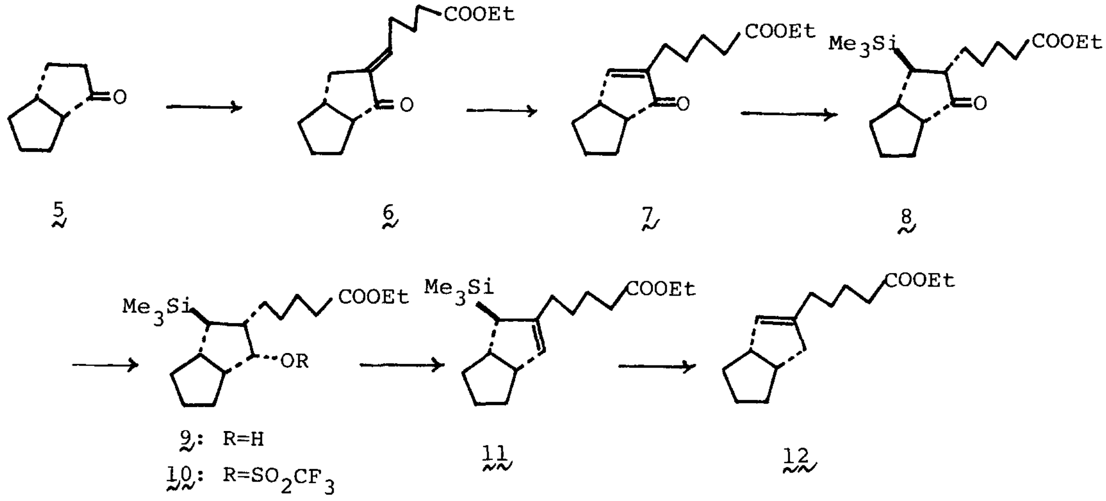
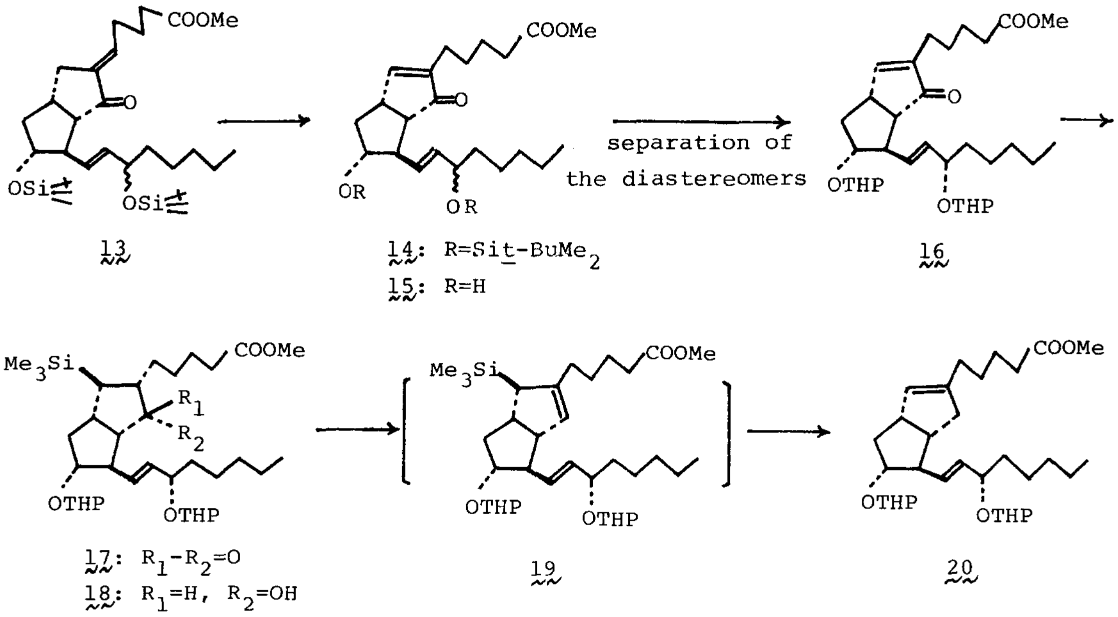

5
6
7
8
9: R=H
10: R=SO$_2$CF$_3$
11
12
COOEt
Me$_3$Si
OR
O


13
14: R=Sit-BuMe$_2$
15: R=H
separation of the diastereomers
16
17: R$_1$-R$_2$=O
18: R$_1$=H, R$_2$=OH
19
20
COOMe
OSi
OR
OTHP
Me$_3$Si
R$_1$
R$_2$

mixture was subjected to protodesilation by treatment with hydriodic acid in benzene at room temperature for 2 hr, affording 12 in 87% yield based on the recovery of 9 (40%). The recovered alcohol (9) could be again converted to the olefin (12) in the same yield, denying the possibility that the undesired stereoisomers of 9 remained intact under the reaction conditions described above. Although it was presumed with confidence that the deoxygenation reaction proceeded without scrambling of the double bond, we had to wait until completion of the synthesis of 9(0)-methano-$\Delta^{6(9\alpha)}$-PGI_1 (1) to obtain unequivocal proof of the regiochemistry.

The ketone (3)[2] was transformed to the endo-enone (14) in the same way as described above (62% overall yield) via the exo-enone (13). The endo-enone (14) was then treated with $Bu_4N^+F^-$ in THF to give 15 (~100%) as a mixture of the diastereoisomers at C-15 (PG numbering). Protection of the easily separable 15α-isomer (the more polar isomer, silica gel, CH_2Cl_2-acetone, 2:1) as THP ether afforded 16 in quantitative yield, which underwent Michael addition of trimethylsilyl anion providing 17[9] (82%). Sodium borohydride reduction of 17 in methanol containing cerium(III) chloride heptahydrate[11] (1 molar equiv) at -25°C for 5 min afforded the alcohol (18)[9] (87%). Treatment of 18 with trifluoromethanesulfonic anhydride (10 equiv), pyridine (20 equiv) and a catalytic amount of 4-dimethylaminopyridine in CH_2Cl_2 at 0°C for 2 hr provided the olefin (20) [49% yield based on the recovery of 18 (24%)[10]], giving none of the allylsilane (19). Also in this case the recovered alcohol (18) could be again converted to the olefin (20) in the same yield as above. The olefin (20) was successively treated with acetic acid and alcoholic sodium hydroxide to result in the formation of dl-9(0)-methano-$\Delta^{6(9\alpha)}$-PGI_1 (1) in nearly quantitative yield; δ(ppm) 3.00 (m, 1H, H_A), whose spectral data were identical with those of an authentic sample.[1] Careful TLC analysis indicated the absence of the regioisomer (4),[12] thus giving the unequivocal proof of the regiochemistry of the present deoxygenation reaction.

Further studies along this line are under investigation.

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References and Notes

† Present address: Sagami Chemical Research Center, Nishi-Ohnuma, Sagamihara, Kanagawa 229, Japan.

1) M.Shibasaki, Y.Torisawa, and S.Ikegami, preceding paper in this issue.

2) (a) M.Shibasaki, K.Iseki, and S.Ikegami, Chemistry Lett., 433 (1979); (b) K.Iseki, M. Yamazaki, M.Shibasaki, and S.Ikegami, Tetrahedron, 37, 4411 (1981).

3) We had already known that the separation of 1 and its regioisomer (4) is extremely difficult, see references 1 and 12.

4) J.K.Crandall and L.-H. Chang, J. Org. Chem., 32, 532 (1967).

5) A.W.Bungstahler, L.O.Weigel, and C.G.Shaefer, *Synthesis*, 767 (1976).

6) J.Andrieux, D.H.R.Barton, and H.Patin, *J. Chem. Soc., Perkin Trans.*, **1**, 359 (1977).

7) Tertiary alcohols with a γ-silyl group generally undergo a simple carbonium ion rearrangement in acid giving a single alkene product with loss of the silyl group, see (a) I. Freming and S.K.Patil, *Tetrahedron Lett.*, **22**, 2321 (1981); (b) S.R.Wilson and A.Shedrinsky, *J. Org. Chem.*, **47**, 1983 (1982).

8) T.Hiyama, M.Obayashi, I.Mori, and H.Nozaki, *J. Org. Chem.*, **48**, 912 (1983). Attempts of Michael addition using other reagents such as Me_3SiLi and Me_3SiLi-CuI afforded none of **8** with the recovery of the starting enone (**7**).

9) Stereochemistry was tentatively assigned on the basis of steric environment of the *cis*-bicyclo[3.3.0]octane ring system.

10) It seems likely that the olefin was formed directly by protodesilylation of the allylsilane probably with $CF_3SO_3^-Py^+H$. It was also found that major part of the recovered alcohol existed as its trimethylsilyl ether at this stage, which was possibly formed by the competitive reaction of the alcohol with $CF_3SO_3SiMe_3$.

11) A.L.Gemal and J.-L.Luche, *J. Am. Chem. Soc.*, **103**, 5454 (1981). Reduction of **17** with sodium borohydride in the absence of cerium(III) chloride gave the saturated alcohol as the major product.

12) (a) M.Shibasaki, K.Iseki, and S.Ikegami, *Tetrahedron Lett.*, **21**, 169 (1980); (b) K.Iseki, T.Mase, T.Okazaki, M.Shibasaki, and S.Ikegami, submitted to *Chem. Pharm. Bull.*

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