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THE INTRAMOLECULAR THERMAL ENE REACTION ROUTE TO (+)-9(O)-METHANO-$\Delta^{6(9\alpha)}$-PGI_1

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Summary: (+)-9(O)-Methano-$\Delta^{6(9\alpha)}$*-*PGI_1*, a more potent carbon analog than carbacyclin, has been synthesized from the Corey lactone by utilizing the intramolecular thermal ene reaction as a key step.*

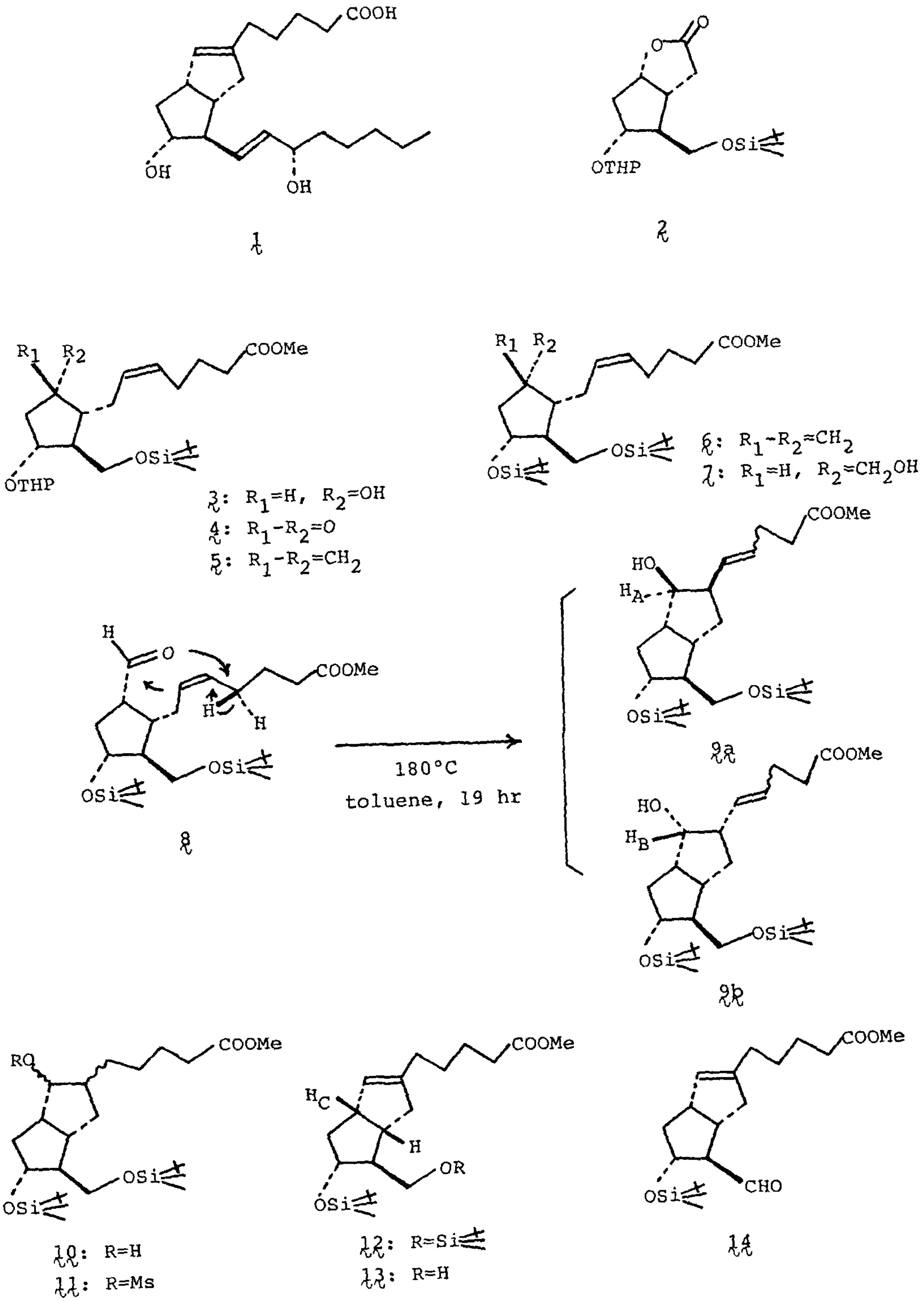
Since 9(O)-methano-$\Delta^{6(9\alpha)}$-PGI_1, a chemically stable carbon analog of prostacyclin, was found to be more potent than well-known carbacyclin in inhibiting platelet aggregation,[1] we have been concentrating on the development of a practical synthesis of this important compound. In this communication we wish to report an efficient synthesis of (+)-1, which utilizes the intramolecular thermal ene reaction for the construction of the suitable bicyclo[3.3.0]octane derivative readily convertible into 1.

The requisite prostanoid aldehyde(8) for the intramolecular thermal ene reaction was readily prepared as described below. The lactone(2)[2] was converted to the hydroxy-ester(3)[3] in the usual manner (i. DIBAL-H in toluene, ii. 4-carboxybutyltriphenylphosphonium bromide-potassium *t*-butoxide in THF,[4] iii. CH_2N_2, 98% overall yield), which was followed by oxidation with PCC in the presence of sodium acetate to afford the keto-ester(4)[3] (92%). Methylenation of 4 was effectively carried out by the action of Zn-CH_2Br_2-$TiCl_4$,[5] giving the diene(5)[3] (81%). Owing to thermal instability of THP ethers,[6] 5 was converted to the disilyl ether(6), $[\alpha]_D^{20}$ -38°(*c* 1.36, MeOH), in two steps (i. Me_2AlCl in CH_2Cl_2,[7] ii. *t*-butyldimethylsilyl chloride-imidazole in DMF, 89%). Hydroboration of 6 with 9-BBN in THF (2.5 equiv, 0°C) followed by treatment with alkaline hydrogen peroxide provided the primary alcohol(7), $[\alpha]_D^{20}$ +4°(*c* 1.36, MeOH), in a stereocontrolled manner (72%), which was subsequently treated with Collins reagent to lead to the aldehyde(8) in 92% yield.[8]

In order to construct the bicyclo[3.3.0]octane derivatives(9a and 9b) from 8, the Lewis acid catalyzed ene reaction of 8 was first attempted under the various conditions, giving the unsatisfactory result even by the use of dialkylaluminium chloride as catalyst.[9] However, the thermal ene reaction of 8[10] in toluene at 180°C proceeded quite nicely to provide two ene-products (87% yield) in a ratio of *ca.* 5 : 3,[11] which were tentatively assigned as 9a (major more polar isomer), δ(ppm) 3.70 (m, 1H, H_A),[12, 13] and 9b (minor less polar isomer), δ(ppm) 4.15 (m, 1H, H_B),[12, 13] on the basis of mechanistic ground of the thermal ene reaction coupled with examination of models for the transition state.[14] Stereochemistry of both 9a and 9b was further supported by the fact that both the ene-products could be readily converted to the bicyclo[3.3.0]octene derivative(12) by a series of reactions involving E_2 elimination.

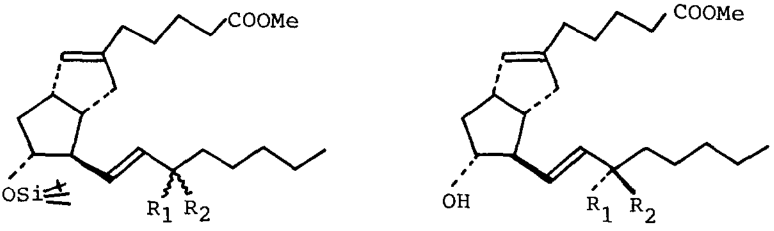
A mixture of 9a and 9b underwent hydrogenation (10% Pd on C in methanol) to give 10

Scheme I


COOH
OH
OH
1
O
O
OTHP
OSi
2
R1
R2
COOMe
OTHP
OSi
3: R1=H, R2=OH
4: R1-R2=O
5: R1-R2=CH2
R1
R2
COOMe
OSi
OSi
6: R1-R2=CH2
7: R1=H, R2=CH2OH
H
O
H
H
COOMe
OSi
OSi
8
180°C
toluene, 19 hr
COOMe
HO
HA
OSi
OSi
9a
COOMe
HO
HB
OSi
OSi
9b
RO
COOMe
OSi
OSi
10: R=H
11: R=Ms
COOMe
HC
H
OR
OSi
12: R=Si
13: R=H
COOMe
OSi
CHO
14

in quantitative yield. Reaction of 10 with methanesulfonyl chloride and triethylamine in toluene at room temperature afforded the mesylates(11), which, after addition of DBU, was heated at 120°C to provide 12, $[\alpha]_D^{20}$ -21.6°(c 1.76, MeOH); δ(ppm) 5.25 (bs, 1H, olefinic proton), 2.90 (m, 1H, H_C), in 70% overall yield from 10. The bicyclo[3.3.0]octene derivative (12) was converted to the key intermediate(13), $[\alpha]_D^{20}$ -34.9°(c 1.63, MeOH); δ(ppm) 5.27 (bs, 1H, olefinic proton), 2.90 (m, 1H, H_C), just by treatment of 12 with a catalytic amount of PPTS in aqueous ethanol[15] at room temperature for 15 hr (71% yield based on the recovery of 12 [16]).

Scheme II



15: R_1-R_2=O
16: R_1=OH, R_2=H

17a: R_1=OH, R_2=H
17b: R_1=H, R_2=OH

The alcohol(13) was then transformed to 9(O)-methano-$\Delta^{6(9\alpha)}$-PGI_1(1) in the usual manner. Oxidation of 13 with sulfur trioxide pyridine complex-triethylamine in DMSO gave the aldehyde (14), which was directly treated with dimethyl (2-oxoheptyl)phosphonate-sodium hydride in THF to provide the enone(15) in 71% overall yield, $[\alpha]_D^{20}$ -9°(c 1.82, MeOH). Reduction of 15 with sodium borohydride in methanol at -20°C afforded the C_{15}-epimeric alcohols(16) (PG numbering), which, after deprotection of a *t*-butyldimethylsilyl ether, gave the more polar diol(17a), $[\alpha]_D^{20}$ +10°(c 0.55, MeOH), in 55% overall yield together with less polar 17b (22%). Finally, hydrolysis of 17a with sodium hydroxide in aqueous methanol followed by acidic extraction provided 9(O)methano-$\Delta^{6(9\alpha)}$-PGI_1(1) as a colorless powder (quantitative yield). The spectral data of (+)-1 thus obtained were identical with those of an authentic material.[1]

In this way a new synthetic route to 9(O)-methano-$\Delta^{6(9\alpha)}$-PGI_1(1) utilizing the intramolecular thermal ene reaction as a key step has been realized. This efficient synthesis has proven feasible on a large scale and should make this important compound more readily available for additional biological studies.

Acknowledgment. The authors take this opportunity to express their thanks to Prof. S. Ikegami, Teikyo University, for his interest and encouragement throughout this work.

References and Notes

1) (a) M. Shibasaki, Y. Torisawa, and S. Ikegami, Tetrahedron Lett., **24**, 3493 (1983); (b) M. Shibasaki, H. Fukasawa, and S. Ikegami, ibid., **24**, 3497 (1983).
2) The optically pure lactone having the proper absolute configuration was used in the present synthesis.
3) The optical rotation was not measured due to the presence of a THP ether.
4) C. Howard, R.F. Newton, D.P. Reynolds, and S.M. Roberts, J. Chem. Soc., Perkin Trans., 1,

2049 (1981).

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

6) THP ethers were readily removed under the conditions of the thermal ene reaction. See T.W. Greene, "Protective Groups in Organic Synthesis," p. 298, John Wiley & Sons, New York, N.Y. , 1981.

7) Selective removal of tetrahydropyranyl ethers in the presence of *t*-butyldimethylsilyl ethers is a new and synthetically useful reaction. Y. Ogawa and M. Shibasaki, Tetrahedron Lett., in press.

8) Stereochemistry of **8**, δ (ppm) 9.87 (d, J=4 Hz, 1H, aldehyde proton), was determined by comparing with the *trans* isomer(**i**) obtainable in a low yield by the thermal reaction of **8**, δ(ppm) 9.62 (d, J=2 Hz, 1H, aldehyde proton).

9) For the Lewis acid catalyzed ene reactions, see B.B. Snider, Acc. Chem. Res., **13**, 426 (1980). It seems likely that the Lewis acid catalyzed ene reaction of **8** provided the *trans* 5-6 membered skeleton as a major product *via* acid-induced epimerization of the aldehyde functionality.

10) The thermal ene reaction of **8** was carried out as follows. The aldehyde (**8**, 1.65 g) was dissolved in toluene (33 ml). The solution was heated at 180°C in a sealed tube under argon atmosphere (18 hr).

11) The *trans* isomer(**i**), which was probably formed *via* thermal epimerization of the aldehyde functionality, was obtained in 13% yield.

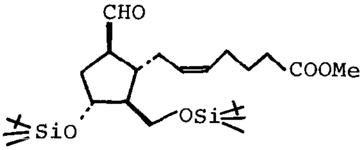
12) Structural assignment was also supported by the literature concerning with the NMR spectrum of bicyclo[3.3.0]octane derivatives, I. Tabushi, K. Fujita, and R. Oda, J. Org. Chem., **35**, 2383 (1970).

13) Stereochemistry of the newly formed double bond has not been determined.

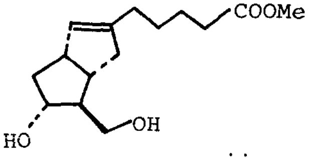
14) For the thermal ene reactions, see (a) H.M.R. Hoffmann, Angew. Chem. Int. Ed. Eng., **8**, 556 (1969); (b) W. Oppolzer and V. Snieckus, ibid., **17**, 476 (1978).

15) M. Miyashita, A. Yoshikoshi, and P.A. Grieco, J. Org. Chem. **42**, 3772 (1977).

16) In addition to the recovery of **12** (35%) the diol(**ii**), which could be again converted to **12**, was formed in 18% yield.



i



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