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AN IMPROVED ROUTE TO (+)-9(O)-METHANO-$\Delta^{6(9\alpha)}$-PROSTAGLANDIN-I_1 (ISOCARBACYCLIN)

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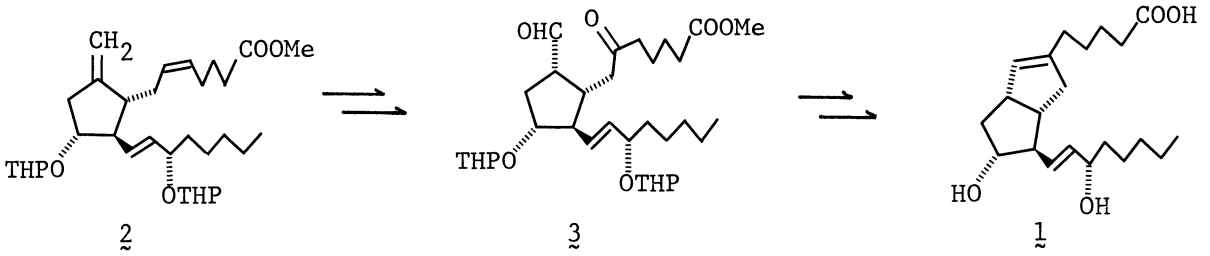
An improved synthesis of the title compound and a synthesis of its derivatives are described, in which the regiospecific transformation of the diene into the diol was effectively achieved by using thexylborane.

In a recent paper[1] we have reported the synthesis of the new carbon analog of PGI_2, (+)-9(O)-methano-$\Delta^{6(9\alpha)}$-PGI_1 (Isocarbacyclin) (1) and have shown that 1 was far more potent than the well-known carbacyclin (9(O)-methano-PGI_2). Owing to its intriguing biological activity with considerable chemical stability, we have continued our efforts to improve the original synthetic route shown in Scheme 1 with the aim of obtaining a versatile intermediate for the further modification of the ω-chain.



Scheme 1.

For the efficient conversion of the 1,5-diene (2) to the keto-aldehyde (3), we examined initially the reaction of the simple diene (4) with thexylborane ($H-BH_2$).[2] After several attempts, cyclic hydroboration of the diene (4) was best carried out when 4 was slowly added to a solution of thexylborane (1.26 equiv.) in THF at -78 °C and then the mixture was warmed to room temperature over 1 h. The boracycle (5) thus obtained was oxidized in a usual manner (5 M NaOH, 30% H_2O_2, 50 °C) to afford a mixture of the two diastereomeric diols (6a,6b) in nearly quantitative yield. These isomers were easily separated (6a:6b=8.5:1) by silica gel column chromatography and their structures were

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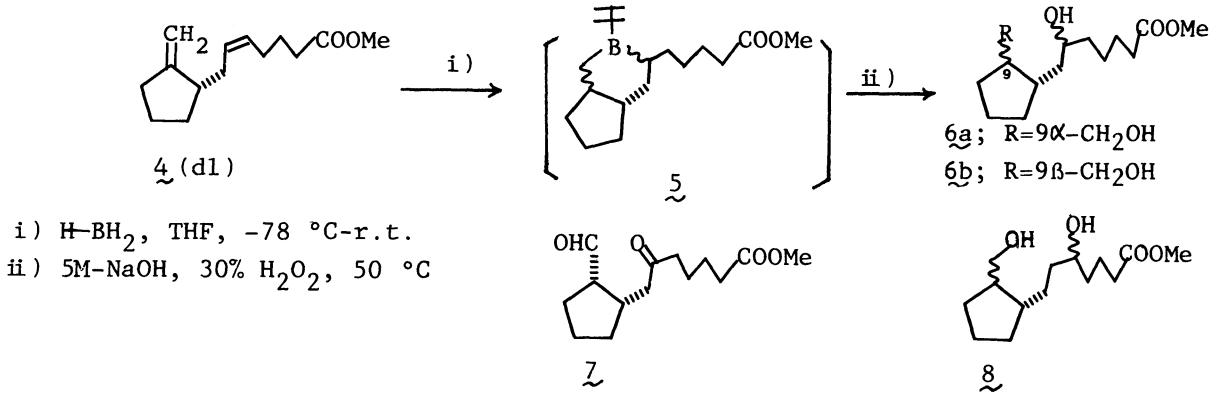
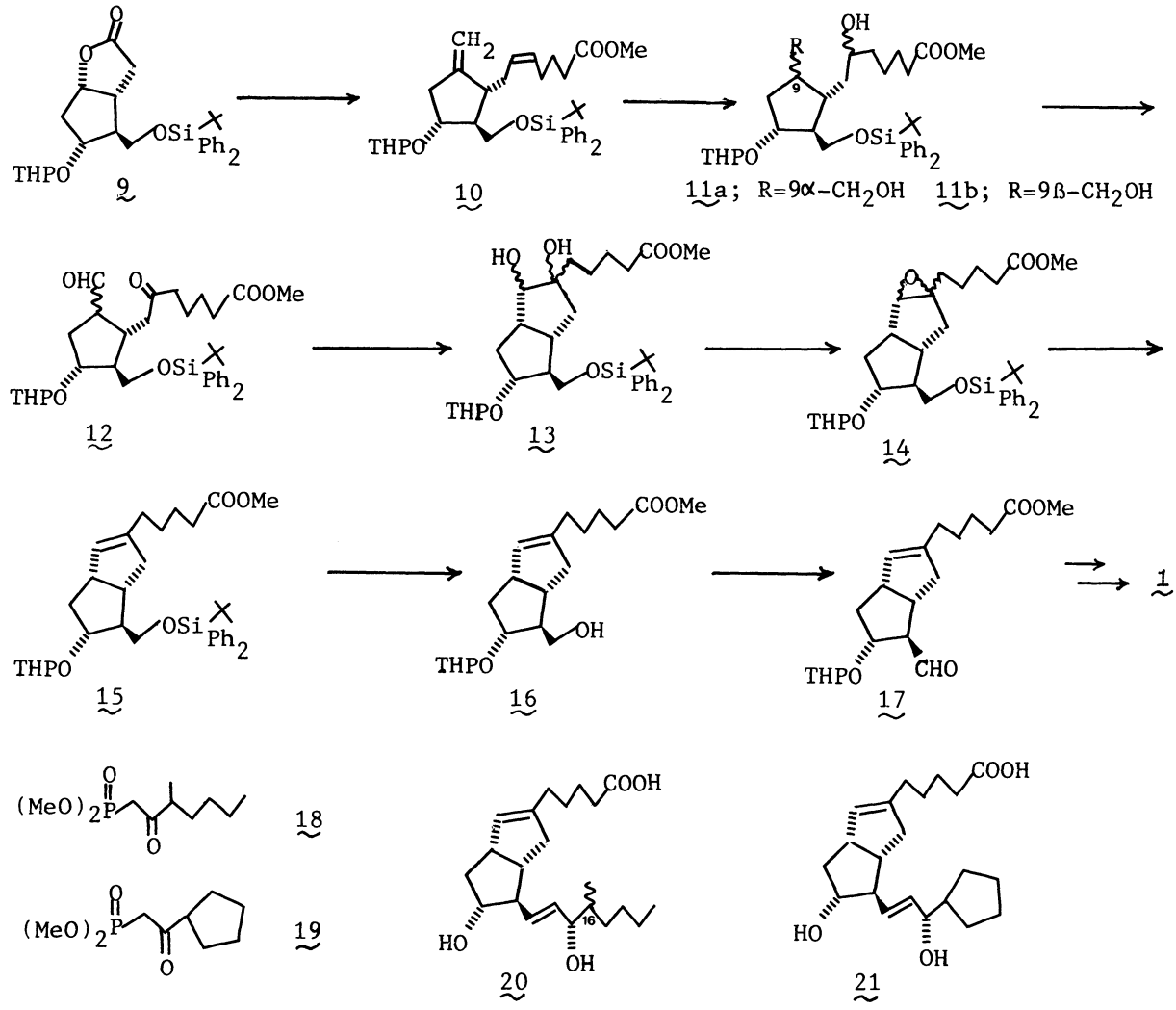


Scheme 2.



Scheme 3.

unambiguously determined. The major diol (6a) showed satisfactory IR, ^{1}H-NMR and mass spectra[3] and could be successfully converted to the known keto-aldehyde (7).[1] The minor diol (6b) revealed quite similar spectral deta[4] to 6a, while its mass spectrum did not give fragment peaks to be arisen from its positional isomer (8). Collins oxidation of 6a afforded the keto-aldehyde (7) in quantitative yield. Although direct oxidation of the borane derivative (5) to 7 with PCC or other oxidizing agents[5] was unsuccessful, the above method offered a short synthetic way from the diene (4) to the keto-aldehyde (7).

This methodology, in the next place, was applied to the fully functionalized 1,5-diene (10) which can be easily obtained from the suitably protected Corey lactone (9)[6] in the usual way. The diene (10) was slowly added to a stirred solution of thexylborane (1.5-2 equiv.) at -78 °C and then the mixture was warmed to 0 °C over 1 h. Subsequent oxidation was carefully carried out (5 M NaOH, 30% H_2O_2, -10-50 °C) to give the isomeric diols (11) in 75% isolated yield. On the basis of the model study (Scheme 2), the major product (66.2%) was tentatively assigned as the desired cis-diol (11a), while the minor product (8.8%) as the trans-diol (11b).[7]

For convenience these two diols, without separation, were directly oxidized to the keto-aldehyde (12) with excess Collins reagent.[8] Conversion of 12 to the desired endo-olefin (15) was conducted by the same sequence as before[1] with slight modification. Crucial pinacol coupling of 12 was again best carried out with $TiCl_4/Zn$[1,9] to furnish the bicyclic diols (13), which after usual extractive isolation, was subjected to mono-mesylation followed by treatment with excess DBU. The epoxide (14, 40% yield from 11) was then reacted with $(CF_3CO)_2O/NaI$ followed by treatment with large excess zinc powder at 60 °C to afford the endo-olefin (15) in 60% yield. Desilylation (n-$Bu_4N^+F^-$) afforded the alcohol (16), from which the ω-chain was easily constructed in a conventional manner. Thus, the oxidation of 16 with Collins reagent provided the aldehyde (17). The Horner-Emmons reaction to 17 using dimethyl (1-sodio-2-oxoheptyl)phosphonate and subsequent transformation (i) $Zn(BH_4)_2$-reduction, ii) deprotection, iii) separation of 15-isomers) successfully furnished the title compound (1) in good yield.

On the other hand, the Horner-Emmons reaction to 17 with the sodium salts derived from the other phosphonate reagents (18[10] and 19[11]) and subsequent transformation afforded the new modified analogs (20[12] and 21[13]) of the ω-chain.

To our delight, these analogs (20,21) were found to be slightly more potent than the original analog (1) in inhibition of platelet aggregation.[14] It is of special interest, in the case of 20, to know whether or not one diastereoisomer is more potent than the other. Further study along this line is under current way.

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References

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

2) G.Zweifel and H.C.Brown, J. Am. Chem. Soc., 85, 2066 (1963); H.C.Brown and E.Negishi, Tetrahedron, 33, 2331 (1977); W.C.Still and K.P.Darst, J. Am. Chem. Soc., 102, 7385 (1980).

3) 6a: IR ν_{max}(neat) cm^{-1}; 3320, 2925, 2860, 1740. ^{1}H-NMR($CDCl_3$) δ(ppm); 3.70 (3H, s, OCH_3), 3.90-3.15 (3H, m). MS m/z; 222 ($M^+-OCH_3-H_2O$), 143 ($M^+-(CH_2)_4COOCH_3$), 125 ($M^+-(CH_2)_4COOCH_3-H_2O$), 113 ($M^+-CH(OH)(CH_2)_4COOCH_3$), 107 ($M^+-(CH_2)_4COOCH_3-2H_2O$).

4) 6b: IR ν_{max}(neat) cm^{-1}; 3320, 2920, 2850, 1740. ^{1}H-NMR($CDCl_3$) δ(ppm); 3.70 (3H, s, OCH_3), 3.90-3.15 (3H, m). MS m/z; 222, 209, 143, 125, 113, 107.

5) H.C.Brown and C.P.Garg, J. Am. Chem. Soc., 83, 2951 (1961).

6) The compound (9) was prepared from commercially available (-)-(1S,5R,6S,7R)-7-benzoyloxy-6-hydroxymethyl-2-oxabicyclo[3.3.0]octan-3-one in the usual manner.

7) 11a: IR ν_{max}(neat) cm^{-1}; 3325, 2915, 2845, 1725. ^{1}H-NMR($CDCl_3$) δ(ppm); 7.44 (10H, s), 4.73-4.43 (1H, m), 3.69 (3H, s, OCH_3), 3.84-3.03 (3H, m). MS m/z; 525 (M^+-OTHP). 11b: IR ν_{max}(neat) cm^{-1}; 3350, 2910, 2845, 1720. ^{1}H-NMR ($CDCl_3$) δ(ppm); 7.35 (10H, s), 4.75-4.45 (1H, m), 3.68 (3H, s, OCH_3), 3.83-3.03 (m, 3H). MS m/z; 525 (M^+-OTHP).

8) Other oxidizing agents such as PDC, SO_3·Py gave less satisfactory results.

9) Direct olefin formation according to McMurry's method (J.E.McMurry and K.L.Kees, J. Org. Chem., 42, 2655 (1977)) was unsuccessful and coupling reaction using Zn/Me_3SiCl (E.J.Corey and S.G.Pyne, Tetrahedron Lett., 24, 2821 (1983)) was also found to be ineffective.

10) The compound (18) was prepared from the reaction of methyl 2-methylhexanoate with carbanion derived from dimethyl methylphosphonate and n-BuLi.

11) The compound (19) was prepared from the reaction of methyl cyclopentanecarboxylate with carbanion derived from dimethyl methylphosphonate and n-BuLi.

12) 20: IR ν_{max}($CHCl_3$) cm^{-1}; 3350, 2925, 2850, 1705. ^{1}H-NMR($CDCl_3$) δ(ppm); 5.57-5.45 (2H, m, olefinic protons), 5.35 (1H, br s, olefinic proton), 5.00-4.50 (3H, m, OH), 1.10-0.80 (6H, m, CH_3).

13) 21: mp 115-116 °C, IR ν_{max}($CHCl_3$) cm^{-1}; 3400, 2950, 2865, 1705. ^{1}H-NMR ($CDCl_3$) δ(ppm); 5.60-5.40 (2H, m, olefinic protons), 5.20 (1H, br s, olefinic proton), 4.30-3.30 (9H, m).

14) Details of the biological evaluation will be published in due course.

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