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THE SYNTHESIS OF 11-SUBSTITUTED PROSTAGLANDIN INTERMEDIATES[1)]

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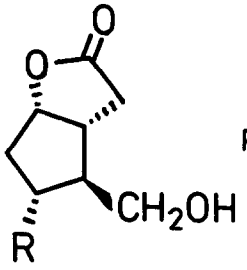
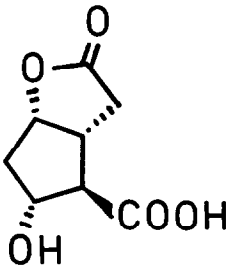
In a previous paper,[2)] we reported a convenient synthetic method for 11-deoxy prostaglandin intermediates. In connection with this method, we are further interested in the preparation of 11-substituted prostaglandins by Wittig reaction of α-dienols with stable ylides. Now we wish to report the synthesis of 11-hydroxymethyl PGs 1,[3)] 11-amino PGs 2[4)] and natural PGs 3[5)] synthetic intermediates which correspond to the Corey's intermediate.



R = CH_2OAc 1

NHAc 2



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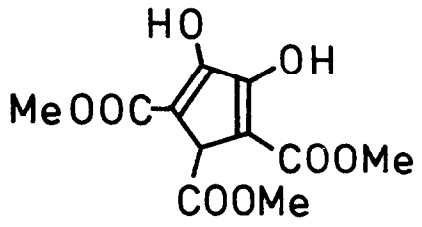
Wittig reaction of methyl-4,5-dioxo cyclopentane tricarboxylate 4 (pka_1 = 4.54 and pka_2 = 8.53) with carbomethoxymethylene triphenyl phosphorane in $CHCl_3$ under reflux for 24 hr gave a mixture of the exo form (mp. 91.5-93.5°C) 5[6)] and the endo form (oily) 6 [80.5%, (exo/endo=1/4); ir[7)]: 1750, 1680, 1620 cm^{-1}; m/e: 328 (M^+)]. Catalytic hydrogenation of the mixture of compounds 5 and 6 over 10% Pd-C in MeOH-AcOH, and decarboxylation with hot conc. HCl followed by treatment with CH_2N_2 yielded the keto triester 7[8)] [90%, bp. 149-156°C/0.02mmHg, ir: 1740 cm^{-1}; nmr: 3.73 and 3.67 (3X 3H, s, $COOCH_3$)] accompanying a small amount of the stereo isomer. Reduction of 7 with Raney Ni in MeOH afforded mainly the lactone diester 8 [82.5%, ir: 1780, 1730 cm^{-1}, nmr: 5.00 (1H, m, lactone), 3.70 (2X 3H, s, $COOCH_3$)]. Regioselective hydrolysis of 8 was accomplished by treatment with $Ba(OH)2 \cdot 8H_2O$ in MeOH at room temperature for 7 hr yielding 9[9)] [71.7%, ir: 3200,



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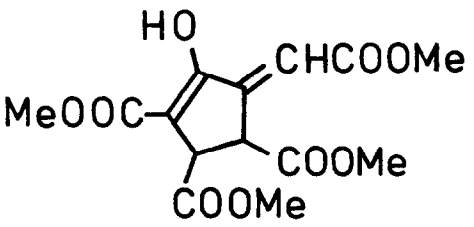

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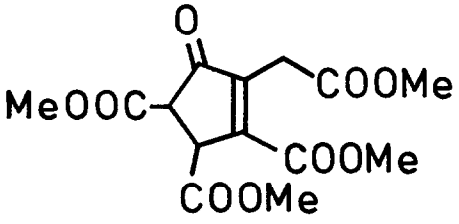

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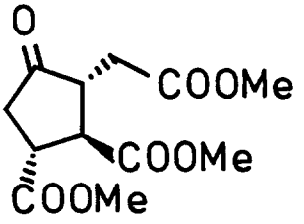

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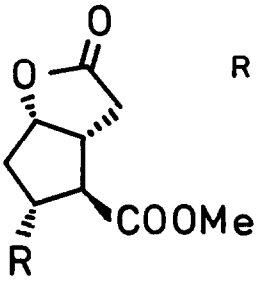
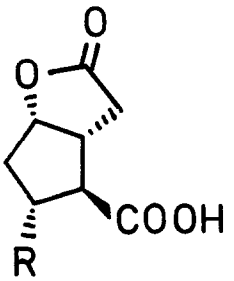


R = COOMe 8
COOH 9
CH_2OH 10
NHCOO tBu 12
COCl 15
COMe 16
OAc 17
OH 18



R = CH_2OAc 11
$NH_2 \cdot HCl$ 13
NHAc 14

1770, 1730 cm^{-1}; nmr: 10.5 (1H, s, COOH), 5.00 (1H, m, lactone), 3.70 (3H, s, $COOCH_3$)]. The monocarboxylic acid 9 is a versatile intermediate for the following 11-substituted PGs synthesis.

Reduction of the monocarboxylic acid 9 with $NaBH_4$ in THF-H_2O at -50°C for 15 min via the mixed anhydride (ClCOOEt-Et_3N) gave the hydroxymethyl lactone 10 [60.7%, ir: 3480, 1770, 1730 cm^{-1}; nmr: 4.90 (1H, m, lactone), 3.70 (3H, s, $COOCH_3$)]. The hydrolysis of 10 with 8% HCl followed by acylation with Ac_2O-BF_3·-Et_2O gave the acetoxymethyl carboxylic acid 11 [75.1%, ir: 3170, 1775, 1740 cm^{-1}; nmr: 9.75 (1H, s, COOH), 2.00 (3H, s, CH_3CO)]. Further reduction of 11 via the mixed anhydride yielded the acetoxymethyl alcohol 1 [75.5%, ir: 3460, 1770, 1740 cm^{-1}; nmr: 4.85 (1H, m, lactone), 4.03 (2H, d, $-CH_2OAc$), 3.64 (2H, d, $-CH_2OH$), 2.00 (3H, s, CH_3CO)].

Modified Curtius reaction of 9 with diphenyl phospholyl azaide[10] in t-BuOH under reflux for 20 hr gave the carbamate 12 [46.8%, mp. 153.5-155.0°C; ir: 3380, 1770, 1730, 1680, 1515 cm^{-1}; nmr: 5.00 (2H, m, lactone and ≥NH), 4.20 (1H, m, ≥CH-N), 1.40 (9H, s, t-Bu)]. Hydrolysis of 12 with 8% HCl at 70°C for 2 hr followed by recrystallization from hot water provided the amino acid hydrochloride 13 [83.0%, mp. 244-246°C; ir: 3200, 1760, 1610, 1585, 1500 cm^{-1}; nmr: 5.20 (1H, m, lactone), 4.00 (1H, m, ≥CH-N)]. Acylation of 13 with Ac_2O-AcOK in dioxane at room temperature for 24 hr gave the acetamide 14 [53%, mp. 234-238°C; ir: 3375, 1765, 1740, 1625 cm^{-1}; nmr (DMSO-d_6): 8.10 (1H, d, ≥NH), 4.95 (1H, m, lactone), 4.30 (1H, m, ≥CH-N), 1.80 (3H, s, CH_3CO)]. Reduction of the carboxyl group of 14 via the mixed anhydride yielded the acetamide alcohol 2[4] [38.5%, mp. 118-120°C; ir: 3380, 3280, 1775, 1655, 1165 cm^{-1}; nmr (CD_3OD): 5.00 (1H, m, lactone), 4.80 (2H, s, OH), 4.10 (1H, m, ≥CH-N), 3.65 (2H, d, $-CH_2O$), 1.95 (3H, s, CH_3CO)].

Treatment of 9 with thionyl chloride gave the acyl chloride 15 [mp. 80.5-82.0°C]. By methylation with dimethyl copper lithium in ether at -50°C for 30 min the chloride 15 yielded the acetyl lactone 16 [29.4%, mp. 57.0-59.0°C; ir: 1780, 1740, 1720 cm^{-1}; nmr: 5.00 (1H, m, lactone), 3.70 (3H, s, $COOCH_3$), 2.20 (3H, s, CH_3CO)]. Baeyer Villiger oxidation of 16 with trifluoroperacetic acid-Na_2HPO_4 in CH_2Cl_2 at room temperature for 10 hr gave the acetoxy lactone 17 [65.4%, ir: 1790, 1725 cm^{-1}; nmr: 5.40 (1H, q, like, ≥CH-OAc), 5.10 (1H, m, lactone), 3.70 (3H, s,

$COOCH_3$), 2.00 (3H, s, CH_3CO); m/e: 242 (M^+)]. Hydrolysis of 17 with 8% HCl at 40°C for 5 hr yielded the hydroxy acid 3[5] which was esterified with diazomethane to give the hydroxy lactone 18 [quantitative yield, mp. 66-68°C; ir: (5% $CHCl_3$) 3450, 1765, 1730 cm^{-1}; nmr: 5.00 (1H, m, lactone), 4.50 (1H, q, >CH-O), 3.70 (3H, s, $COOCH_3$), 3.60 (1H, s, OH)].

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1) Synthetic studies on Prostanoid XIV.

2) K. Inoue and K. Sakai, Tetrahedron Letters, 4107 (1976).

3) 11-Hydroxymethyl PG E_1 and PG E_2 showed strong uterus contraction activity in guinia pigs:
K. Sakai, J. Ide and O. Oda, Tetrahedron Letters, 3021 (1975).
A. Guzman and J. M. Muchowski, Tetrahedron Letters, 2053 (1975).
G. L. Bundy, Tetrahedron Letters, 1957 (1975).

4) Although 11-amino PGs derivatives are not prepared yet, 2 will by the promising intermediate for the synthesis of 11-amino PGs derivatives.

5) The synthesis of PGs from the hydroxy acid 3 was already accomplished by:
R. Peel and J. K. Sutherland, J. C. S., Chem. Commun., 1974 151.
K. G. Paul, F. Johnson and D. Favara, J. Amer. Chem. Soc., 98 1285 (1976).

6) The stereochemistry of 5 and 6 were not assigned. The ratio of the exo and endo forms was assigned by NMR.

7) IR (cm^{-1}) spectra were taken in neat or nujol mull and NMR (δ) spectra were taken in $CDCl_3$ containing TMS as internal standard unless otherwise stated.

8) It is noteworthy that the trans-trans compound 7 is mainly obtained in these reactions.

9) The structure of the acid 9 was confirmed by an unambiguous alternative synthesis (unpublished data).

10) K. Ninomiya, T. Shioiri and S. Yamada, Tetrahedron, 30 2151 (1974).