Tetrahedron Letters No. 17, pp 1367 - 1370, 1976. Pergamon Press. Printed in Great Britain.

TOTAL SYNTHESIS OF 11-DEOXY-11β-HYDROXYMETHYL PROSTAGLANDIN E_1[1)]

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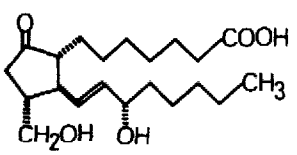
(Received in Japan 4 March 1976; received in UK for publication 17 March 1976)

Current interests in the prostaglandin field are focused on the synthesis of novel prostaglandin congeners possessing potential specific pharmacological properties free of undesirable side-effects.

In a previous communication[2)], we have reported a synthesis of 11-deoxy-11α-hydroxymethyl prostaglandins, among which 11-deoxy-11α-hydroxymethyl PGE_1[2)] 1 and PGE_2[2,3)] showed a strong uterus contraction activity in guinia pigs[4)]. In connection with these findings we are further interested in the biological activities arising from the stereochemical differences of prostaglandin homologs.

This publication describes a stereo-controlled synthesis of 11-deoxy-11β-hydroxymethyl PGE_1 2 and its 8-epimer 3, i.e., 8,12-cis-11,12-cis-isomer, which is an interesting homolog from chemical and biological view points.



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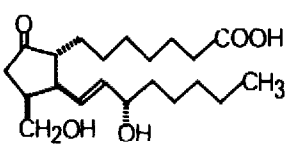

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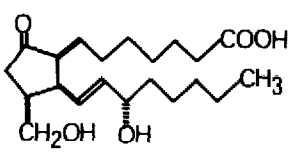
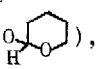


3

Oxidative cleavage of 4-cyclohexen-1,2-cis-diol dibenzylether 4[5)] with OsO_4-$NaIO_4$ in aq-dioxane followed by oxidation with Jone's reagent, after esterification with CH_2N_2, provided the meso-diester 5 [55%, ir[6)]: 1740, 1100; nmr: 4.45 (4H, s, OCH_2Ph), 3.60 (3H, s, $COOCH_3$), 3.48 (4H, m, $-CH_2O-$); m/e: 414 (M^+)]. Dieckmann condensation of 5 with t-BuOK in benzene under reflux gave 2-carbomethoxy-3,4-cis-dibenzyloxymethyl cyclopentanone 6 [88%, ir: 1760, 1735; nmr:

4.56 and 4.50 (4H, two s, OCH_2Ph), 3.84 (3H, s, $COOCH_3$); m/e: 382 (M^+)]. Alkylation[7] of 6 with methyl 7-iodo-5-heptynoate[8] and t-BuOK in toluene yielded diester 7 [95%, ir: 1760, 1735, 1220, 1095; nmr: 4.49 and 4.43 (4H, two s, OCH_2Ph), 3.65 and 3.50 (6H, two s, $COOCH_3$); m/e: 520 (M^+)]. Catalytic hydrogenation of 7 over 5% Pd-C in benzene gave the saturated diester 8 (95%, ir: 1755, 1740, 1730; m/e: 524 (M^+)], which was treated with NaOMe in MeOH under reflux to give the ring-opened triester 9 [96%, ir: 1738; nmr: 4.40 and 4.35 (4H, two s, OCH_2Ph), 3.64 (6H, s, $COOCH_3$), 3.56 (3H, s, $COOCH_3$); m/e: 556 (M^+)].

Dieckmann condensation of 9 with NaOMe in DMSO-MeOH[9] afforded regiospecifically the tetrasubstituted cyclopentanone 10 [81%, ir: 1755, 1735; nmr: 4.41 and 4.38 (4H, two s, OCH_2Ph), 3.66 and 3.64 (6H, two s, $COOCH_3$); m/e: 524 (M^+)]. Cleavage of dibenzylether group of 10 was accomplished by catalytic hydrogenolysis over 10% Pd-C in THF in the presence of p-TsOH to afforded the diol 11. Without purification, treatment of the crude diol 11 with catalytic amount of p-TsOH in benzene-dioxane yielded the cis-fused bicyclolactone 12 [92%, 1784, 1740; m/e: 312 (M^+)]. After masking the hydroxyl group of 12 with dihydropyran, hydrolytic decarboxylation of the lactone 12 with Na_2HPO_4 in aq-dioxane under reflux, gave the 8,12-trans-alcohol 13[10] [83%, ir: 3460, 1740; nmr: 4.60 (1H, br s, ), 3.66 (3H, s, $COOCH_3$), 2.56 (1H, s, OH); m/e: 442 (M^+)]. Removal of the tetrahydropyranyl group of 14 with p-TsOH in aq-MeOH, after protecting the hydroxyl group of 13 with ethyl chloroformate and pyridine in THF, gave the alcohol 15 [73% from 13, ir: 3500, 1740; nmr: 4.25 (2H, m, $EtOCO_2CH_2$-), 4.19 (2H, q, J=7.0 Hz, $MeCH_2OCOO$), 3.00 (2H, m, $-CH_2OH$), 2.18 (1H, s, OH), 1.30 (3H, t, J=7.0 Hz, $OCO_2CH_2\underline{CH_3}$); m/e: 358 ($M^+$)].

Collins oxidation of 16, after usual thioketalization of 15 with ethanedithiol and BF_3-etherate in CH_2Cl_2, followed by Wittig reaction with tri-n-butyl-2-oxo-heptylidene phosphorane in ether at room temperature, yielded the enone 17 [64% from 15, ir: 1690, 1670, 1620; nmr: 3.27 (4H, s, ), 3.65 (3H, s, CO_2CH_3), 6.07 (C-14 H, d, J=16.0 Hz), 6.77 (C-13 H, d d, J=8.0, 16.0 Hz); m/e: 528 (M^+)]. Reduction of the enone 17 with $NaBH_4$ in abs. MeOH at 0° followed by hydrolysis with K_2CO_3-MeOH gave a mixture of 15-epimeric alcohols

18a and 18b, which were effectively separated by silica-gel chromatography. The more polar fraction on TLC was tentatively assigned to the desired 15α-epimer 18a and the less polar one to the 15β-epimer 18b.

Dethioketalization of 19a after successively protecting[11] the hydroxyl group with dihydropyran and hydrolysis of the ester group of 18a with 10% NaOH in aq-MeOH, was effected with $HgCl_2$-HgO in aq-MeOH at 45° followed by removal of the tetrahydropyranyl group with p-TsOH in aq-THF to afford 11-deoxy-11β-hydroxymethyl PGE_1 2 [20% from 18a: m.p. 55-56.5° ir: 3500, 1730; nmr (CD_3COCD_3): 3.56 (2H, m, $-CH_2O$), 4.04 (1H, m, $-\underset{OH}{CH}-$), 5.52 (C-12 H, q_{AB}, J=4.5 and 15.0 Hz), 5.82 (C-13 H, q_{AB}, J=9.0 and 15.0 Hz); m/e: 350 (M^+-H_2O)].

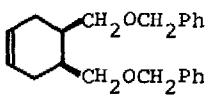
It is noteworthy that treatment of 11-deoxy-11β-hydroxymethyl PGE_1 2 with 20% NaOH at room temperature for 30 min gave the 8-epimerized isomer 3 in the equilibration of 2 in the ratio of 1 : 1 [3: m.p. 107.5-109°: ir: 3500, 1730; nmr (CD_3COCD_3): 3.57 (2H, br d, $-CH_2O$), 4.02 (1H, m, $-\underset{OH}{CH}-$), 5.16 (C-14 H, q_{AB}, J=9.0 and 15.0 Hz), 5.60 (C-13 H, q_{AB} J=6.1 and 15.0 Hz); m/e: 350 (M^+-H_2O)].

Acknowledgement: The authors thank Director Dr. K. Arima, Assistant Director Dr. Y. Kishida and former Assistant Director Dr. K. Tanabe of this laboratories for their valuable help and advice.

References and Notes

1. Synthetic studies on Prostanoids X. Part IX. K. Kojima and K. Sakai: Tetrahedron Lett., 101 (1976).
2. K. Sakai, J. Ide, O. Oda: Tetrahedron Lett., 3021 (1975).
3. a) A. Guzman, J. M. Muchowski: Tetrahedron Lett., 2053 (1975), b) G. L. Bundy: Tetrahedron Lett., 1957 (1975).
4. In the uterus contraction of guinia pigs dl-11-deoxy-11α-hydroxymethyl PGE_1 showed an activity about half as potent as PGE_1 and dl-11-deoxy-11α-hydroxymethyl-PGE_2 about one sixth as potent as PGE_2.
5. E. L. Eliel, C. Pillar: J. Amer. Chem. Soc., 77, 3600 (1955).

6. IR(cm^{-1}) spectra were taken in neat and nmr (δ) spectra in $CDCl_3$ solution containing tetramethylsilane as internal standard unless otherwise stated.
7. Alkylation of 6 with 7-iodoheptanoate gave a mixture of O-alkylated and C-alkylated products.
8. E. S. Ferdinandi, G. Just: Can. J. Chem., 49, 1070 (1971).
9. M. Fieser, L. Fieser: Reagents for Organic Synthesis vol. 2, 158 (1969).
10. Treatment of 13 with K_2CO_3 in MeOH partially gave the 8-epimerized product.
11. Dethioketalization of 19a without protecting the 11-hydroxyl group resulted in a complex mixture.



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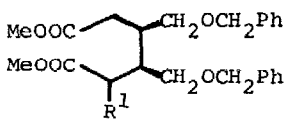
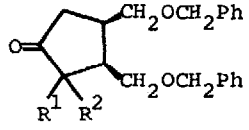


5 R^1= H

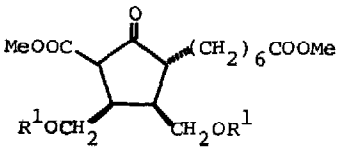
9 R^1= $(CH_2)_6COOMe$



6 R^1= COOMe R^2= H

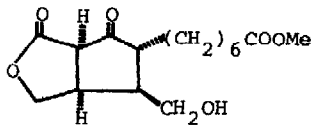
7 R^1= $CH_2C{\equiv}C(CH_2)_3COOMe$ R^2= COOMe

8 R^1= $(CH_2)_6COOMe$ R^2= COOMe



10 R^1= CH_2OPh

11 R^1= H



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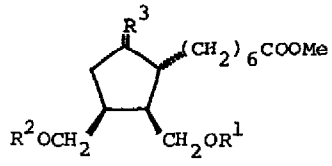
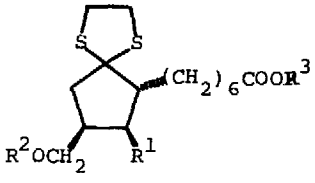


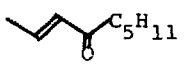
13 R^1= THP R^2= H R^3= O

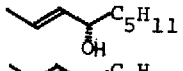
14 R^1= THP R^2= $COOC_2H_5$ R^3= O

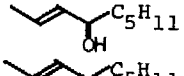
15 R^1= H R^2= $COOC_2H_5$ R^3= O

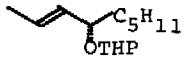
16 R^1= H R^2= $COOC_2H_5$ R^3= 



17 R^1=  R^2= $COOC_2H_5$ R^3= CH_3

18a R^1=  R^2= H R^3= CH_3

18b R^1=  R^2= H R^3=CH_3

19a R^1=  R^2= THP R^3= H