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A SYNTHESIS OF 12-SUBSTITUTED PROSTAGLANDINS[1)]

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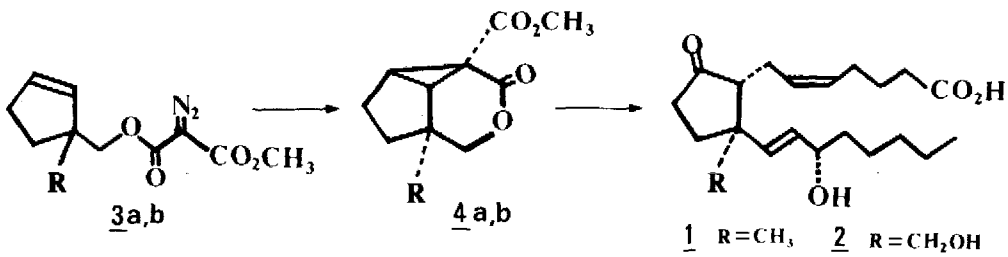
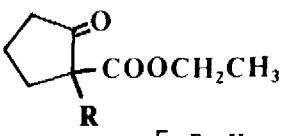
Several 12-methyl prostaglandins (PGs) have recently been synthesized[2)] in attempts to obtain more potent PGs than natural products. We now wish to report the synthesis of 11-deoxy-12α-methylPGE$_2$ (1) and 11-deoxy-12α-hydroxymethylPGE$_2$ (2)(as a mixture with the 15β-isomer), *via* the tricyclic lactones 4a,b obtained by the intramolecular cyclopropanation of the *cyclopentenyl diazoesters* 3a,b.



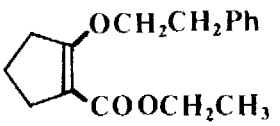
Reaction of the potassium salt of ethyl 2-oxocyclopentanecarboxylate (5) with benzyloxymethyl chloride[3)] in Et_2O or THF at 25° yielded an 1:1 mixture of the C-alkylated keto ester 7b and the O-alkylated product 6. After conversion of undesirable 6 with 10% HCl to 5, 7b was isolated by distillation (bp 120-122°/0.01 mmHg, 67% based on recovered 5). The keto esters 7a,b[3)] were reduced with $NaBH_4$ to the hydroxy esters 8a,b,[4)] whose methanesulfonates 9a,b were heated in HMPA at 145° for 3 hr to afford the unsaturated esters 10a,b. Reduction of 10a,b with $LiAlH_4$ gave the alcohols 11a,b. Acylation of 11a,b with methyl chloroformylacetate afforded the esters 12a,b (62-66% from 7a,b; 12a, bp 107-110°/4 mmHg; 12b, bp 150-152°/0.02 mmHg). *These malonates 12a,b were treated with* TsN_3 *and* Et_3N in CH_3CN[5)] to give the diazoesters 3a,b, quantitatively.

In the intramolecular cyclopropanation of 3a,b, best results were obtained

a : R = CH_3 b : R = $CH_2OCH_2C_6H_5$



5 R = H
7 a,b



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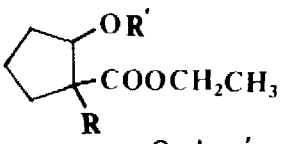
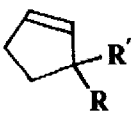
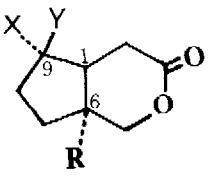


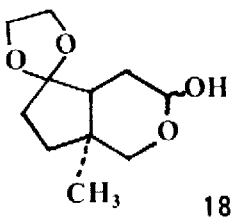
8 a,b R′ = H
9 a,b R′ = SO_2CH_3



10 a,b R′ = $CO_2CH_2CH_3$
11 a,b R′ = CH_2OH
12 a,b R′ = CH_2OCO $CH_2CO_2CH_3$



13 a,b x = $OCOCH_3$ y = H
14 a,b x = OH y = H
15 a,b x,y := O
16 a,b x,y : $-OCH_2CH_2O-$
17 R = CH_2OCOCH_3
x = $OCOCH_3$ y = H



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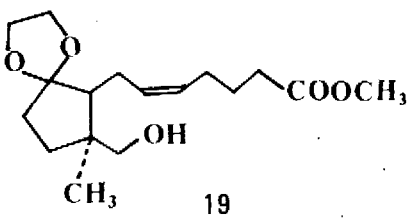

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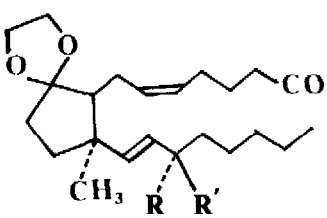
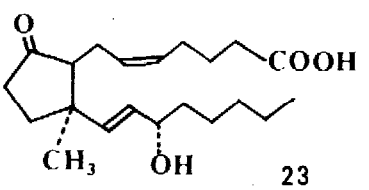


20 R,R′ := O
21 R = OH R′ = H
22 R = H R′ = OH



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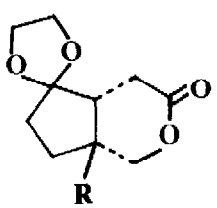
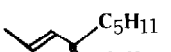
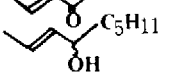
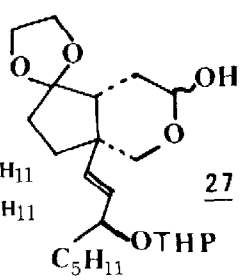


24 R = CH_2OH
25 R = 
26 R = 



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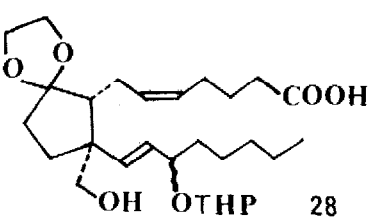

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by heating 3a,b in refluxing n-octane for 4 hr in the presence of copper. Crystalline tricyclic esters 4a,b were isolated [4a, mp 86-87°, 67%, NMR (δ in CCl_4), 4.13 and 3.73 (2H, AB q., J=10 Hz, $-CH_2-O-CO-$), 3.67 (3H, s., $-CO_2CH_3$), 1.25 (3H, s., $-CH_3$): 4b, mp 84.5-85.5°, 52%, NMR, 7.36 (5H, s., C_6H_5-), 4.76 (2H, s., $PhCH_2O-$), 4.43 and 3.98 (2H, AB q., J=11 Hz, $-CH_2-O-CO-$), 3.73 (3H, s., $-CO_2CH_3$), 3.48 (2H, s., $-CH_2OCH_2Ph$)]. Stereospecific cleavage of the cyclopropane ring was furnished by heating 4a in AcOH-H_2SO_4(40:1) at 90° for 3 hr to give the 9α-acetoxy bicyclic lactone 13a [bp 125-128°/0.04 mmHg, 90%; NMR, 4.70 (1H, d. t., J=4 and 5 Hz, C_9-H), 3.88 (2H, s., $-CH_2-O-CO-$), 1.97 (3H, s., $-O-CO-CH_3$), 1.19 (3H, s., C_6-CH_3)], as the single product. Similar reaction of 4b (75°, 5 hr) gave 13b [bp 172-180°/0.003 mmHg, 67%; NMR, 7.33 (5H, s., C_6H_5-), 4.80 (1H, d.t., J=4 and 5 Hz, C_9-H), 4.55 (2H, s., $-OCH_2Ph$), 4.36 and 3.93 (2H, AB q., J=12 Hz, $-CH_2-O-CO-$), 3.39 and 3.34 (2H, AB q., J=9 Hz, C_6-CH_2-O-), 1.97 (3H, s., $-OCOCH_3$)] in addition to the diacetate 17 (mp 75-77°, 22%). Treatment of 13a,b with K_2CO_3 in MeOH afforded the alcohols 14a,b, which were oxidized to the ketones 15a,b (15a, mp[2d] 66-68°) with modified Collins reagent[6] and then converted to the ketals 16a,b ($BF_3 \cdot Et_2O$-ethyleneglycol in CH_2Cl_2; 16a, 85%; 16b, 90% from 13a,b). Reduction of 16a with i-Bu_2AlH in toluene gave the lactol 18. Reaction of this six-membered lactol with the Wittig reagent derived from 5-triphenylphosphoniopentanoic acid in DMSO[7] was slow (3 days at 25°) but successfully afforded the hydroxy ester 19 (55%) after esterification with CH_2N_2. Collins oxidation of 19 followed by the reaction of the resulting aldehyde with sodium salt of dimethyl 2-oxo-heptylphosphonate (18 hr reflux in DME) gave the enone 20 (77%). Reduction of 20 with $NaBH_4$ in MeOH (-15°, 30 min) afforded the isomeric alcohols 21 and 22,[8] quantitatively, which were separated by column chromatography. The 15α-alcohol 21 was treated successively with 5% HCl-Me_2CO and 1N-NaOH-MeOH at 25° to yield a mixture of 1 and the 8,12-cis[9] isomer 23 (ca. 6:4). Separation by preparative layer chromatography afforded pure 1 [oil, NMR (δ in Me_2CO-d_6), 0.93 (3H, s., $C_{12}-CH_3$)] and 23 [oil, NMR, 1.26 (3H, s., $C_{12}-CH_3$)]. The higher field signal for the 12α-methyl group of 1 proved the stereochemistry of 1 and 23.[2d]

Catalytic hydrogenation of 16b (10% Pd-C in MeOH, 8.5 hr) gave the alcohol

24[10] (mp 100-101°, 86%). Collins oxidation of 24 and the condensation of the resulting aldehyde with 2-oxoheptylidenetributylphosphorane afforded the enone 25 (69%). Reduction of 25 with $NaBH_4$ to the alcohol 26, tetrahydropyranylation, and reduction with i-Bu_2AlH_4 gave the lactol 27. Wittig reaction of 27 similar to that of 18 to 19 produced the acid 28 (81% from 25). Treatment of 28 with 50% AcOH gave 2 as an oily substance[11] which was separated by preparative layer chromatography from accompanying 8,12-cis isomer (ca. 5%). Basic treatment of 2 (1N-NaOH-MeOH) yielded a mixture of 2 and the cis-isomer (6:4).

References and Footnotes

1) Synthetic Studies on Prostanoids XI. Part X, J. Ide and K. Sakai, Tetrahedron Lett.,

2) a) E.J. Corey, C.S. Shiner, R.P. Volante and C.R. Cyr, Tetrahedron Lett., 1161 (1975); b) P.A. Grieco, C.S. Pogonowski and M. Miyashita, J. Chem. Soc. Chem. Comm., 592 (1975); c) P.A. Grieco, C.S. Pogonowski, M. Nishizawa and C.-L.J. Wang, Tetrahedron Lett., 2541 (1975); d) L. Godoy, A Guzman and J. M. Muchowski, Chemistry Lett., 327 (1975). Compound 15a was described as oil

3) Benzyloxymethylation in Me_2CO gave 6 as the major product, contrary to the published data: A. Barco, S. Bennetti and G.P. Pollini, Synthesis, 316 (1973).

4) Satisfactory IR, NMR and mass spectral data were obtained for all new compounds.

5) M. Regitz, Chem. Ber., 99 3128 (1966).

6) R. Ratcliffe and R. Rodehorst, J. Org. Chem., 35 4000 (1966).

7) E.J. Corey, N.M. Weinshenker, T.K. Schaaf and W. Huber, J. Am. Chem. Soc., 91 5675 (1969).

8) The more polar alcohol 21 was assumed to be the 15α-isomer.[2a] The deketalized compounds 1 and 23 derived from 21 were also more polar than the corresponding 15β-isomers derived from 22.

9) The terms cis and trans refer to the two long chains at 8- and 12-positions.

10) The structures of 24 - 28 are shown in the enantiomeric forms opposite to those in 13b - 17 series.

11) This compound could not be separated into the isomers at 15-position.