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SYNTHESIS OF 11-DESOXY-12-METHYLPROSTAGLANDINS[1]

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The conjugate addition of lithium dimethyl copper to the tetrasubstituted enone (3b) gave a mixture of the keto esters (4a) and (4b), which was converted into the 11-desoxy-12-methylprostaglandins (14b), (15b), (16a) and (17a).

The synthesis of several ring methylated prostaglandin derivatives has recently[2-5] been described. The most interesting members of this group of compounds are, without doubt, the "metabolically blocked" 8-methylprostaglandin C_2 analogues reported by Corey and Sachdev.[4] The present publication describes the synthesis of some 12-methylprostaglandins, which, with the exception of the 11,12-difluoromethylene prostaglandins disclosed by Crabbé and Cervantes,[6] are the only known prostaglandins with a quaternary centre at C-12.

The known[7] hydroxy acid (1) was oxidized with Jones reagent[8] at -5°, and the keto acid (2) {oil; λ_{max} 211 nm (log ε 4.13)}[9] thus produced was isomerized to the tetrasubstituted enone (3a) {oil; λ_{max} 209, 217, 234 nm (log ε 4.02, 3.98, 4.19)} with 1,5-diazabicyclo{4.3.0}non-5-ene (D.B.N.) in refluxing methanol solution. The ester (3b), obtained from (3a) and diazomethane, upon alkylation with an excess (3 eq.) of lithium dimethyl copper in ether solution at -10°, gave an oily, inseparable, 60:40, mixture {46% from (1)} of the saturated ketones (4a) and (4b) {oil; n.m.r. 0.85 p.p.m. (s, 12α-methyl),[10] 1.08 (s, 12β-methyl), 3.22 (s, 8α-CH_2), 3.32 (s, 8β-CH_2)}, which was converted into a 1:1 mixture after treatment with D.B.N. in hot methanol solution. Sodium borohydride reduction of the ketones gave a mixture, which could be separated by thin layer chromatography (t.l.c.) on silica gel (hexane:ether, 1:1) into an epimeric pair (at C-12) of alcohols (5a,5b) (oil; ν_{max} 3490, 1725 cm^{-1}), and lactones (6a,6b) (oil; ν_{max} 1770 cm^{-1}). The above alcohols, which constituted 67% of the mixture, were quantitatively transformed into the lactones (6a,6b) on treatment with p-toluenesulfonic acid in boiling benzene {59%

from (4a,4b)}. Debenzylation (H_2/Pd-C) of (6a,6b) gave the corresponding primary alcohols, which were separated into the more polar (6c) {oil; ν_{max} 3650, 3510, 1770 cm^{-1}; n.m.r. 0.99 (s, 12-CH_3), 3.35 (s, 8-CH_2), 4.99 (q, J = 4.7, H-9)}, and the less polar (6d) {oil; ν_{max} 3650, 3500, 1770 cm^{-1}; n.m.r. 1.03 (s, 12-CH_3), 3.53 (s, 8-CH_2), 5.03 (m, H-9)} isomers.

The relative stereochemistry of compounds (6c) and (6d) was established by the following sequence of reactions. The epimeric mixture of ketones (4a,4b) was catalytically debenzylated and the alcohols obtained thereby, upon saponification and subsequent acidification, gave a mixture of the keto acid (7) {oil; ν_{max} 3515, 1743, 1718 cm^{-1}} and the 6-membered lactone (8) {oil; ν_{max} 1746 cm^{-1}; m/e 168 (M^+)}.[11] Sodium borohydride reduction of (8) produced a mixture of lactonic alcohols (9a,9b) which, when subjected to alkaline hydrolysis followed by acidification, gave back (9b) {oil; ν_{max} 3625, 3475, 1747 cm^{-1}} and a 5-membered lactone which was identical to the less polar lactonic alcohol (6d). The epimeric, more polar, lactone (6c) must, therefore, have the same relative configuration as that found in the natural prostaglandins. The above series of transformations also, incidentally establishes the relative stereochemistry of compounds (7) and (9b).

To prepare the 12-methylprostaglandins, the lactone (6c) was oxidized with Collins reagent[12] to the aldehyde (6e), which was immediately condensed with the sodium salt of dimethyl-2-oxoheptylphosphonate. The 12α-methyl enone (10) thus obtained {λ_{max} 225 nm (log ε 4.16); m/e 264 (M^+), 165 (M-$C_5H_{11}CO$)} was more polar than the 12β-methyl enone (11) derived from (6d) by an identical reaction sequence. The 12α-methyl enone (10) was reduced with zinc borohydride to a mixture of alcohols (12a) {oil; ν_{max} 3615, 3470, 1768, 970 cm^{-1}} which, without purification, was reacted sequentially with diisobutylaluminium hydride and disodium 5-triphenylphosphonio pentanoate.[13] The mixture of acids thus obtained was esterified with diazomethane, and then separated by t.l.c. on silica gel (hexane:ethyl acetate, 80:20). The more polar isomer {oil; n.m.r. 0.86 (t, J = 6, 20-CH_3), 1.06 (s, 12-CH_3), 3.63 (s, OCH_3), 4.01 (m, H-15), 4.28 (m, H-9), 5.36 (m, H-14), 5.41 (m, H-5,6), 5.59 (d, J = 15.7, H-13)} was tentatively assigned the 15α-configuration (14a) by analogy with the chromatographic behaviour of the methyl esters of the natural prostaglandins. Hydrolysis of the ester with aqueous methanolic sodium hydroxide gave the desired acid (14b) {oil; ν_{max} 3625, 3430, 1715 cm^{-1}}. The 12β-methyl enone (11), when subjected to a reaction sequence identical to that described above, gave a mixture of methyl esters, from which the required 15α-isomer (15a) {oil;

n.m.r. 0.86 (t, J = 6, 20-CH_3), 1.08 (s, 12-CH_3), 3.62 (s, OCH_3), 4.01 (m, H-15), 4.20 (m, H-9), 5.34 (q, $J_{13,14}$ = 16.0, $J_{14,15}$ = 7.0, H-14), 5.38 (m, H-5,6), 5.86 (d, $J_{13,14}$ = 16.0, H-13)} was separated by t.l.c. The ester was converted into the acid (15b) {oil; ν_{max} 3610, 3470, 1714 cm^{-1}} in the usual manner.

To synthesise the 9-keto derivatives, the mixture of 15α- and 15β-tetrahydropyranyl ethers (14c,14d) or (15c,15d), obtained from (12b) or (13b) via the usual Corey sequence,[13] was oxidized with Jones reagent at -10°. Removal of the tetrahydropyranyl group, in dimethoxyethane containing aqueous perchloric acid, also resulted, in both cases, in epimerization at C-8, and an equimolar mixture (45% yield) of the four possible esters (16a,16b,17a, and 17b) was produced. The mixture was completely resolved by t.l.c. and there was thus obtained the 12α-methyl-15α-hydroxy-9-ketone (16a) {oil; ν_{max} 3620, 3490, 1738 cm^{-1}; m/e (15-trimethylsilyl-ether) 436 (M^+), 365 (M^+-C_5H_{11})}, and the 12β-methyl-15α-hydroxy-9-ketone (17a) {oil; ν_{max} 3620, 3500, 1737 cm^{-1}; m/e (15-trimethylsilyl ether) 436 (M^+), 365 (M^+-C_5H_{11})}. The α-stereochemistry of the 12-methyl group in (16a) was assigned on the basis of the ^{13}C n.m.r. spectrum, which showed, as expected,[14] that the resonance for this carbon was at a much higher field (18.530 p.p.m.) than for the epimeric 12β-methyl compound (26.138 p.p.m.). A similar chemical shift difference was observed for compounds (14a) and (15a).

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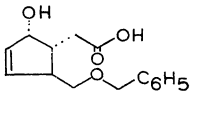

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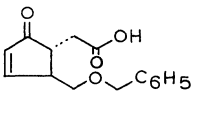

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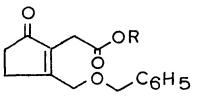

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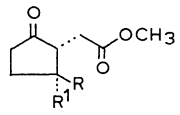
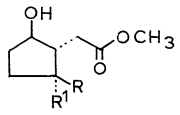
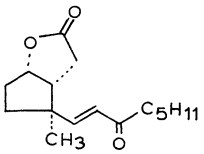


(4) a) R= $CH_2OCH_2C_6H_5$
R^1= CH_3
b) R= CH_3
R^1= $CH_2OCH_2C_6H_5$



(5) a) R= $CH_2OCH_2C_6H_5$
R^1= CH_3
b) R= CH_3
R^1= $CH_2OCH_2C_6H_5$



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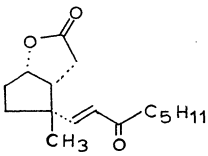

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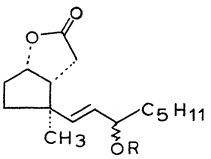
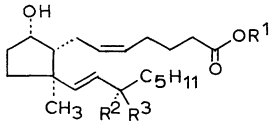
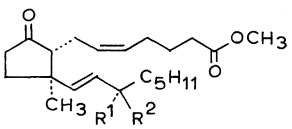


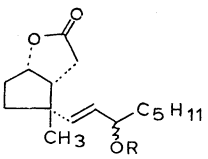
(12) a) R= H
b) R= THP



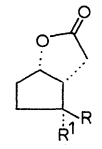
(14) a) R^1= CH_3, R^2= OH, R^3= H
b) R^1= R^3= H, R^2= OH
c) R^1= CH_3, R^2= OTHP, R^3= H
d) R^1= CH_3, R^2= H, R^3= OTHP



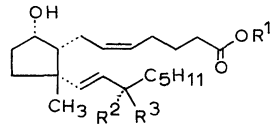
(16) a) R^1= OH, R^2= H
b) R^1= H, R^2= OH



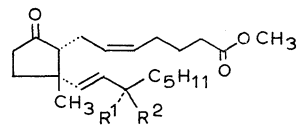
(13) a) R= H
b) R= THP



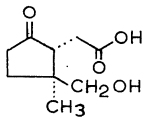
(6) a) R= $CH_2OCH_2C_6H_5$
R^1= CH_3
b) R= CH_3
R^1= $CH_2OCH_2C_6H_5$
c) R= CH_2OH, R^1= CH_3
d) R= CH_3, R^1= CH_2OH
e) R= CHO, R^1= CH_3
f) R= CH_3, R^1= CHO



(15) a) R^1= CH_3, R^2= OH, R^3= H
b) R^1= R^3= H, R^2= OH
c) R^1= CH_3, R^2= OTHP, R^3= H
d) R^1= CH_3, R^2= H, R^3= OTHP



(17) a) R^1= OH, R^2= H
b) R^1= H, R^2= OH



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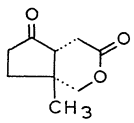

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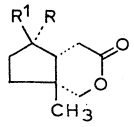

(9) a) R= OH, R^1= H
b) R= H, R^1= OH

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