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SYNTHESIS AND PROPERTIES OF 16-HYDROXY ANALOGS OF PGE_2

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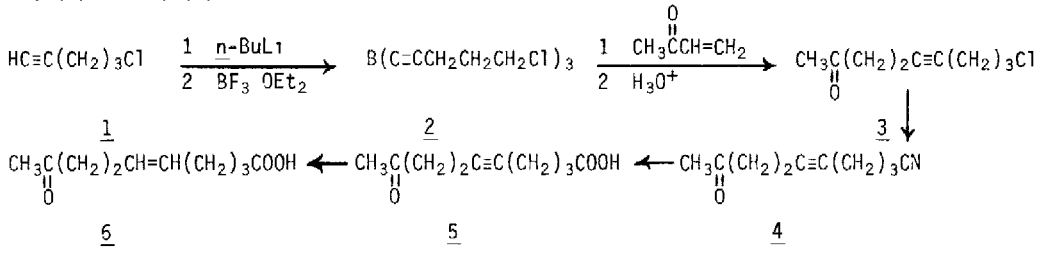
As an extension of our work[1,2] on the total synthesis of PGE_1 and its analogs we have investigated the synthesis of the corresponding compounds in the PGE_2 series for evaluation as inhibitors of gastric secretion

Taking advantage of our experience on the conjugate addition of 1-alkynes to α,β-unsaturated ketones,[1] we prepared the required keto acid 6 by a novel approach Starting from commercially available 5-chloro-1-pentyne 1, the corresponding lithium salt was obtained using butyl lithium at -40° in toluene This acetylide was then converted in situ to its trialkynyl boron derivative 2 by treatment with boron trichloride or boron trifluoride etherate at -40° first and then overnight at -10° The resulting mixture was cooled to -20° and after addition of methyl vinyl ketone, the 1,4-addition reaction was allowed to proceed at -40° for 4 hours The adduct 3 was thus obtained in 48% yield after acid hydrolysis, b p 76° (0 09 mm), PMR [11] (s) δ2 12, (t) δ3 61

It is noteworthy that the substitution of 2 by the corresponding dimethyl alkynylalane[3,4] in this reaction gave the 1,4 adduct 3, accompanied by an equal amount of the 1,2 adduct

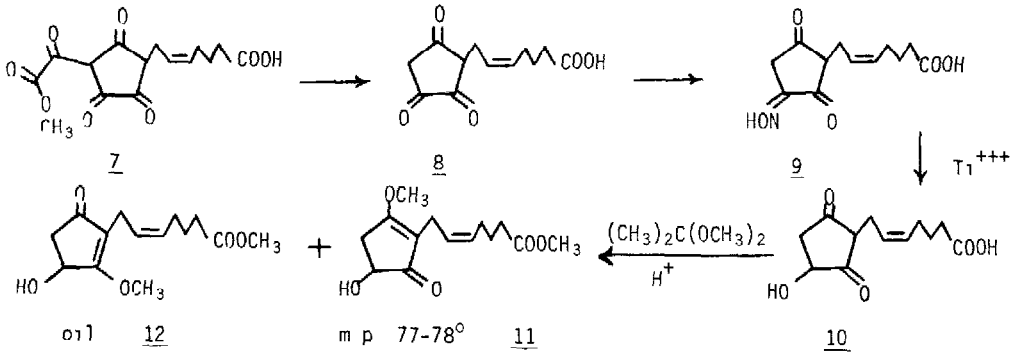
Refluxing 3 with sodium cyanide in aqueous ethanol gave the nitrile 4, IR ($CHCl_3$) 2250 cm^{-1} and 1715 cm^{-1}, PMR (s) δ2 15, which was hydrolyzed readily to the acid 5 Hydrogenation of 5 with palladium on barium sulfate yielded the desired cis-olefinic acid 6, PMR (s) δ2 12, (t) δ5 38, (s) δ10 2



The conversion of the keto-acid 6 to the key cyclopentenone derivative 13 was accomplished using the procedures developed previously in our laboratories for the synthesis of PGE_1 derivatives [5] Thus 6 was condensed with dimethyloxalate in the presence of potassium t-butoxide to yield the glyoxalate 7 The crude reaction product was then treated with aqueous hydrochloric acid at reflux and the resulting crude triketo acid 8 was purified either by chromatography or via the corresponding monooxime 9, m p 163-164°, PMR (D_2O) (t) δ5 47, (p) δ1 70, (s) δ3 13, (d) δ2 98, (t) δ2 43, (q) δ2 22, to give crystalline 8, m p 84-85°, PMR (s) δ2 95, (t) δ5 50, (d) δ3 17, (dd) δ1 55-δ2 02

Treatment of 8 with aqueous sodium borohydride at 0-5° gave the hydroxydione 10, m p 83-84°, PMR (D_2O) (t) δ5 45, (s) δ4.75, (dd) δ4 63, (d) δ2 85, (dd) δ2 94, (dd) δ2 32 Alternatively the monooxime 9 was reduced with titanium trichloride in aqueous acetic acid buffered with excess sodium acetate to yield 10 in 77% yield, the intermediate trione 8 produced being reduced further by the reagent

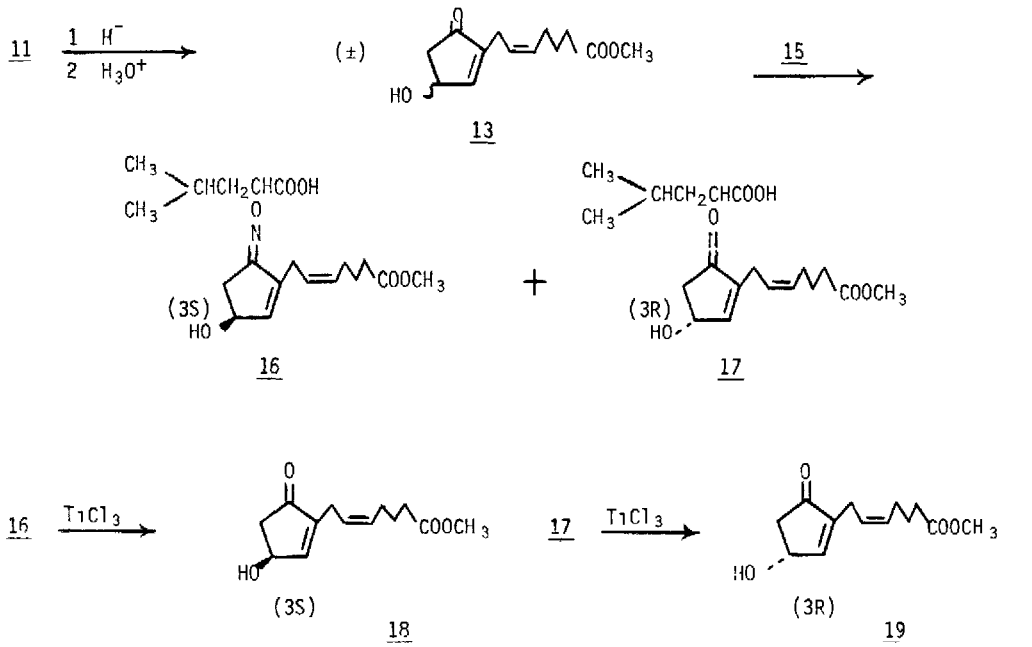
The ketol 10 was converted to the enol ether 11, m p 77-78°, PMR (dd) δ3 12, (s) δ3 68, (s) δ3 98, (m) δ4 28, (m) δ5 39, advantage being taken of its low solubility in ether relative to its oily isomer 12, as described previously for the PGE_1 series [5] The ketone group of the enol ether 11 was reduced with sodium dihydro-bis(2-methoxyethoxy)aluminate at -65° in toluene and the resulting alcohol 14 rearranged and hydrolyzed in situ with dilute acid to 13, which was purified by chromatography over Mallinckrodt Silicar CC7 silica gel to yield an oil, PMR (dd) δ2 27, (dd) δ2 87, (s) δ3 68, (m) δ4 96, (m) δ7 20, (t) δ5 55 This compound 13 prepared by a different route, has been previously described [6]



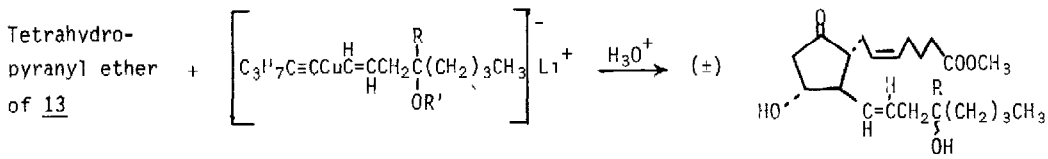
The key intermediate 13 was then separated into its enantiomers using the method described previously for the resolution of methyl 3-hydroxy-5-oxocyclopent-1-eneheptanoate [7] Treatment of 13 with (R)-2-aminooxy-4-methylvaleric acid 15 yielded a mixture of oximes which were separated by chromatography using a mixture of 0 5% acetic acid and 1 5% isopropanol in chloroform as eluent on E Merck Silica Gel to yield 16, $[\alpha]_D$=-53 4 ($CHCl_3$), and 17, $[\alpha]_D$=+46 3 ($CHCl_3$) [8] Regeneration of the ketones 18, $[\alpha]_D$=-9 9 (MeOH), and 19, $[\alpha]_D$=+8 4 (MeOH), was accomplished with titanium trichloride [7]

The configuration at C-3 of 18 and 19 was determined by comparing the ORD and CD curves with the published data[7] on the analogous (3R)- and (3S)-methyl-3-hydroxy-5-oxocyclopent-1-ene-1-heptanoate Proof of structure of 13 was obtained by converting it to (±)PGE_2 methyl ester via the cuprate reaction described previously [2]

The conversion of 13 and 19 to potent gastric anti-secretory compounds was then undertaken Thus 1,4 addition of the cuprate reagent derived from trans-1-iodo-4,4-dimethyl-1-octen-3-ol 3-t-butyldimethylsilyl ether[9] to the tetrahydropyranyl ether derivative of 19 (20) led to a mixture of products which was separated by chromatography on silica gel to yield 16,16-dimethyl PGE_2 methyl ester,[10] PMR (s) δ0 86, (s) δ0 90, (s) δ3 69, (d) δ3 86, (q) δ4 10,



(m) δ5 45-5 93, (m) δ5 30-5 45, $J_{14,15}$ 6.5, $J_{13,14}$ 15 0, and 15-epi-16,16-dimethyl PGE_2 methyl ester, PMR (s) δ0 88, (s) δ0 91, (s) δ3 68, (d) δ3 88, (q) δ4 12, (m) δ5 45-5 93, (m) δ5 30-5 45, $J_{14,15}$ 5 5, $J_{13,14}$ 15 0



21 R=H, R'=t-BuSi$(CH_3)_2$
22 R=CH_3, R'=$SiEt_3$

23 R=H
24 R=CH_3

Interestingly the use of the cuprate reagents 21 and 22[2] led to a new and very important series of prostaglandin analogs Thus reaction of the tetrahydropyranyl ether of 13 with 21 led to (±)15-deoxy-16-hydroxy PGE_2 methyl ester (23), PMR (p) δ1 67, (dd) δ2 75, (s) δ3 69, (q) δ4 08, a mixture of two racemates isomeric at C_{16}, which was active as a gastric anti-secretory agent Similarly 22 afforded (±)15-deoxy-16-hydroxy-16-methyl PGE_2 methyl ester (24), PMR (s) δ1 19, (p) δ1 68, (dd) δ2 75, (q) δ4 09, again as a mixture of two racemates, isomeric at C_{16} Moreover the reaction of the tetrahydropyranyl derivative of the (3R)-ketone 19 with the racemic cuprate reagent 22 yielded a mixture of (16R)-15-deoxy-16-hydroxy-16-methyl PGE_2 methyl ester and (16S)-15-deoxy-16-hydroxy-16-methyl PGE_2 methyl ester $[\alpha]_D^{25°}$= -47 7 (MeOH) The separation of these isomers is under study

In line with the results disclosed previously for the E_1 analogs,[2] the 16-hydroxy derivative 24 was found to be an extremely potent gastric anti-secretory agent when administered either intravenously or intragastrically to Heidenhain pouch dogs

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8 Using (S)2-aminooxy-4-methylvaleric acid gave similar results except that the order of elution of the oximes on chromatography was reversed.
9 This reagent was prepared by the general procedure described in reference 2 from 4,4-dimethyl-1-octyn-3-ol by addition of catechol borane to the corresponding 3-t-butyldimethylsilyl ether, followed by iodination to yield the trans-1-iodo-4,4-dimethyl-1-octen-3-ol silyl ether Halogen metal interconversion proceeded rapidly with butyl lithium leading to the cuprate derivative after treatment with $CuC{\equiv}C(CH_2)_2CH_3$
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11 All PMR spectra were run in deuteriochloroform unless noted otherwise