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A SIMPLE, STEREOSELECTIVE SYNTHESIS OF A PROSTAGLANDIN ENDOPEROXIDE ANALOG

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The formation of an endoperoxide derivative during prostaglandin biosynthesis was first proposed[1] in 1965 and has recently been confirmed[2,3,4] by the isolation and characterization of several such intermediates designated as PGG and PGH. The fact that these intermediates possess biological activities, which in many instances are evidently greater than those of the classical prostaglandins, has stimulated considerable interest in preparing endoperoxide analogs which might act as mimics[5,6] or inhibitors[7] of the natural substances.

In connection with our interest in developing selective inhibitors of the prostaglandin synthetase we report herein a simple and potentially general route to prostaglandin endoperoxide analogs.

Alkylation of cyclopentadienyllithium with ethyl-7-bromoheptanoate (THF, 25°, 6 hr) afforded alkylated cyclopentadiene isomers 1[8] (55%, silica gel, petroleum ether/3% EtOAC). Diels-Alder reaction of 1 with diethyl acetylenedicarboxylate (benzene, 25°, 3 hr) gave a 55:45 mixture of 2 and 3. The bicyclo[2.2.1]heptadiene 2 was separated from 3 by argentation[9], dry column chromatography [silica gel/10% $AgNo_3$, activity III, $CHCl_3$/5% EtAOC; $\nu_{max}^{CCl_4}$ 1730, 1710, 1630, 1607 cm^{-1}; nmr ($CDCl_3$) δ 6.28 (broad s, 1H, =C-H)] and was treated sucessively with equimolar amounts of 1,1,2-trimethylpropylborane[10] (THF, -25°, 7 hr), 3-(α-ethoxylethoxy)-1-octyne (THF, 0-5°, 48 hr), and sodium hydroxide (3 N) followed by iodine[11] (THF, -5°, 2 hr). Presumably, 4 and 5 are the expected intermediates leading to the desired product 6, which was isolated[12] by dry column chromatography (silica gel, petroleum ether/10% EtOAC). Removal of the ethoxylethyl group (THF/H_2O/conc-HCl, 100:6:0.5, 25°, 4 hr) gave a mixture of two expected diastereoisomeric racemates 7, which were separated conveniently by HPLC (Micro Pak CN-10, 25 x 0.8 cm column, CH_2Cl_2/hexane/i-ProH, 70:30:1, 2 ml/min) and showed the following spectral characteristics. Low retention volume racemate [$\nu_{max}^{CCl_4}$ 3500, 1730, 1716, 1617 cm^{-1}; m/e 520.3405, calculated for $C_{30}H_{28}O_7$, 520.3398; nmr ($CDCl_3$) δ 0.89 (t, 3H, $\sim CH_3$), 2.79 (s, half width 4 Hz, 1H, $\geq C_4-H$), 3.22 (s, half width 8 Hz, 1H, $\geq C_1-H$), 5.37 and 5.50 (AB system, J_{AB}=10 Hz, 2H, $^{H}>C=C<^{H}$)]. High retention volume racemate [$\nu_{max}^{CCl_4}$ 3500, 1730, 1716, 1615 cm^{-1}; m/e 520 (M+); nmr ($CDCl_3$) δ 0.89 (t, 3H, $\sim CH_3$), 2.92 (s, half width 4 Hz, 1H $\geq C_4-H$), 3.29 (s, half width 8 Hz, 1H, $\geq C_1-H$) 5.43 and 5.54 (AB system, J_{AB}=10 Hz, 2H, $^{H}>C=C<^{H}$)].

The trans relationship of the two aliphatic chains in 7 has been tentatively assigned as follows. Hydroboration of 2 proceeds by an anti-Markovnikov cis addition

from the exo[13] face of the bicyclic system as judged from the alkaline hydrogen peroxide oxidation product of intermediate 4. Thus the alcohol 8 (80%) was found by GC-MS of the TMS derivative, to be more than 98% isomerically pure. The chemical shift and splitting pattern of the carbinol proton of 8 (3.6 δ, broad doublet, J=2.4 Hz, half width 4 Hz) is in good agreement with the corresponding values for the respective proton in exo-bicyclo[2.2.1]hept-5-ene-2-ol.[14] Since migration of the bicyclic moiety in the intermediate 5 has been reported[15] to occur with retention of configuration, this establishes the relative stereochemistry of the two new chiral centers as trans. The stereochemical assignment is corroborated by the pmr spectra of the two diastereoisomeric racemates. The width at half height (4 Hz) of the bridgehead proton on the side of the C_8-chain (most sensitive signal to change in chemical shift between the two racemates) is in agreement with the predicted one for an exo C_8-chain.

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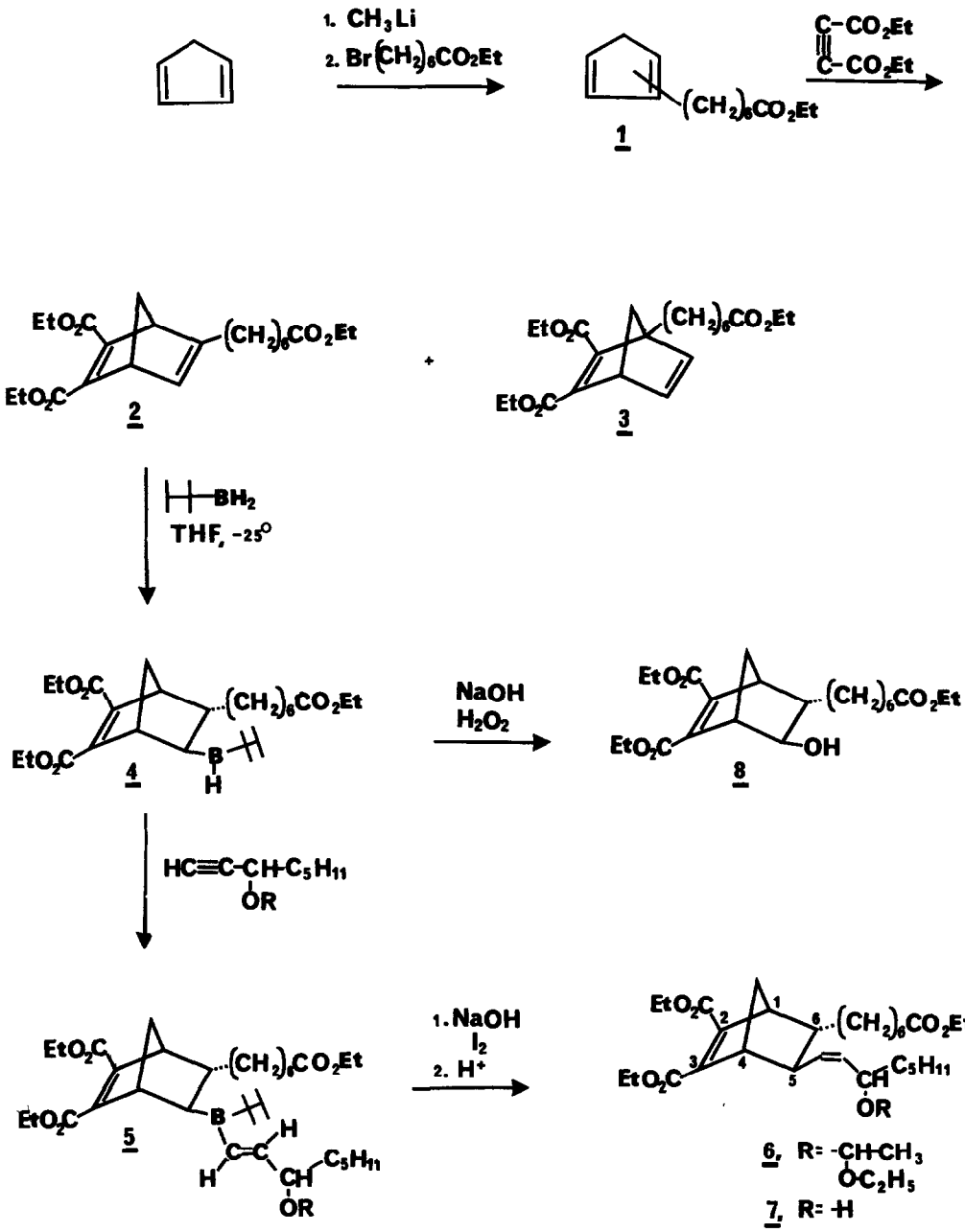
1. CH3Li
2. Br(CH2)6CO2Et
C-CO2Et
C-CO2Et
(CH2)6CO2Et
1
EtO2C
(CH2)6CO2Et
EtO2C
2
EtO2C
(CH2)6CO2Et
EtO2C
3
BH2
THF, -25°
EtO2C
(CH2)6CO2Et
EtO2C
B
H
4
NaOH
H2O2
EtO2C
(CH2)6CO2Et
EtO2C
OH
8
HC≡C-CH-C5H11
OR
EtO2C
(CH2)6CO2Et
EtO2C
B
C=C
H
H
CH
C5H11
OR
5
1. NaOH
I2
2. H+
EtO2C
(CH2)6CO2Et
EtO2C
CH
C5H11
OR
6, R= -CH-CH3
OC2H5
7, R= -H

References and Notes

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12. Among the contaminants are unreacted protected acetylenic alcohol, thexyl migrated product, non polar organoborane species (trialkylboranes?) and lower molecular weight alcohols (oxidation products of organoboranes by NaIO formed in situ). It appears that the low yield of 6 (~10%) is due to the low yield of the intermediate 4.
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