CHEMISTRY LETTERS, pp. 143-144, 1988.

A Short Synthesis of 15-Dehydroprostaglandin B_1 Methyl Ester

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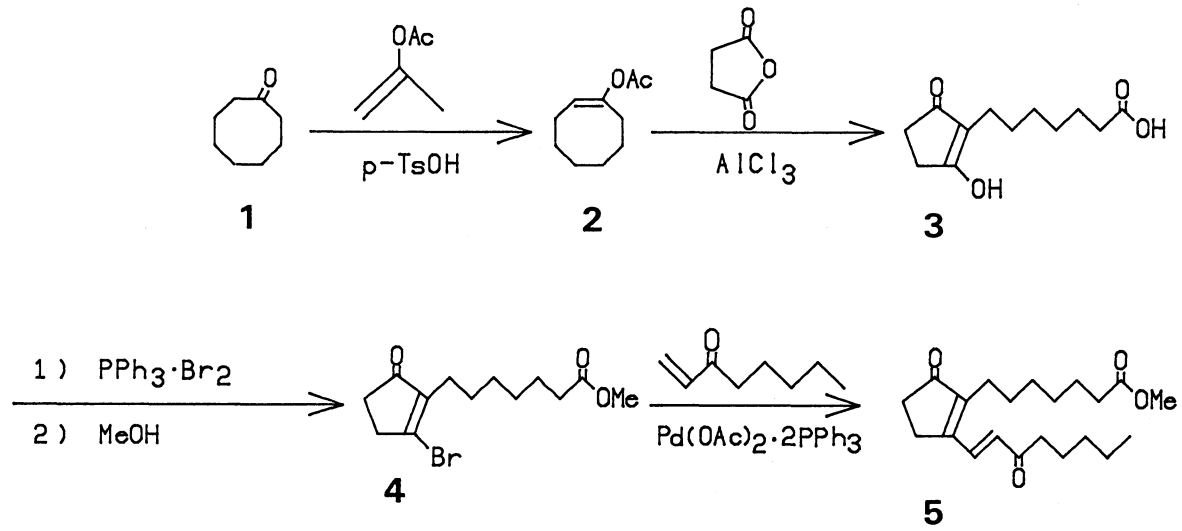
A new synthetic method for 15-dehydroprostaglandin B_1 methyl ester (15-dehydroPGB_1 methyl ester) in four steps from commercially available starting materials is described.

Prostaglandin B_x (PGB_x) is an oligomeric derivative of 15-dehydroPGB_1 methyl ester or its closely related compounds. PGB_x has been reported to restore oxidative phosphorylation of isolated degraded rat liver mitochondria in vitro and increase in survival after otherwise lethal episodes of myocardial ischemia in monkeys and hypoxia in dogs in vivo.[1)]

In this communication, we describe a novel short synthetic route to 15-dehydroPGB_1 methyl ester, which provides large quantities of this material for the preparation of PGB_x.



Cyclooctanone (1: Aldrich No.C10980-0) was easily converted to 1-cyclooctenyl acetate (2)[2)] with isopropenyl acetate in the presence of p-toluenesulfonic acid [bp 85-86 °C/7 mmHg (1 mmHg=133.322 Pa)].

Friedel-Crafts type reaction of 1-cyclooctenyl acetate (2) with succinic anhydride gave 7-(2-hydroxy-5-oxo-1-cyclopentenyl)heptanoic acid (3)[3] in 22% yield. The reaction was carried out in the presence of aluminium trichloride at 80 °C in 1,2-dichloroethane for 92 hours [mp 156-157 °C; ^{1}H NMR (methanol d_4, TMS) δ 2.43 (s, 4H), 2.4-1.9 (m, 4H), and 1.8-1.2 (m, 8H); IR (KBr) 3400, 2900, 2830, 1690, 1550, and 1360 cm^{-1}].

7-(2-Hydroxy-5-oxo-1-cyclopentenyl)heptanoic acid (3) was treated with 2.2 equimolar triphenylphosphine dibromide in benzene[4] followed by absolute methanol to yield methyl 7-(2-bromo-5-oxo-1-cyclopentenyl)heptanoate (4) in 68% yield. [bp 122 °C/0.15 mmHg; ^{1}H NMR (chloroform d_1, TMS) δ 3.56 (s, 3H), 2.95-2.7 (m, 2H), 2.65-2.4 (m, 2H), 2.4-2.15 (m, 4H), and 1.8-1.2 (m, 8H); IR (film) 2930, 2850, 1735, 1705, and 1630 cm^{-1}.]

1-Octen-3-one,[5] prepared by Jones' oxidation of 1-octen-3-ol, and 4 were heated to 100 °C over a catalytic amount of $Pd(OAc)_2 \cdot 2PPh_3$ to yield 15-dehydroPGB$_1$ methyl ester (5)[1] in 80% yield. The reaction was occurred in a sealed tube under Ar with an excess amount of triethylamine. The compound 5 was identified with an authentic sample prepared in similar to the literature.[1,3] [^{1}H NMR (chloroform d_1, TMS) δ 7.51 (d, J=16.5 Hz, 1H), 6.45 (d, J=16.5 Hz, 1H), 3.6 (s, 3H), 2.75-2.15 (m, 10H), 1.9-1.2 (m, 14H), and 0.9 (t, J=6 Hz, 3H); IR (film) 2930, 2850, 1735, 1705, and 1630 cm^{-1}.]

Application of the synthetic route described above to other prostaglandin B$_1$ derivatives will be reported in the near future.

References

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(Received October 29, 1987)