

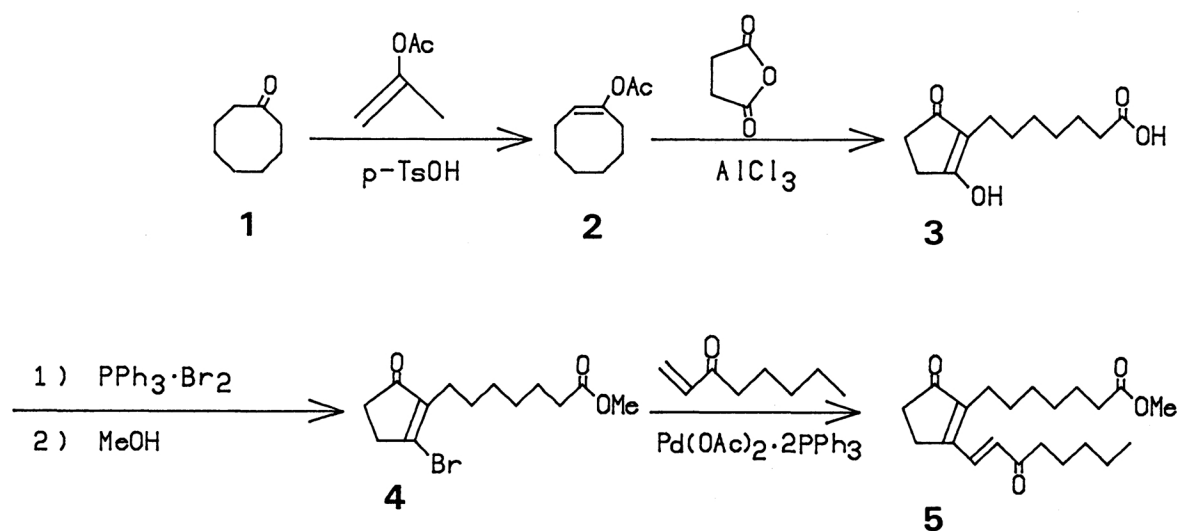
A Short Synthesis of 15-Dehydroprostaglandin B₁ Methyl Ester

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A new synthetic method for 15-dehydroprostaglandin B₁ methyl ester (15-dehydroPGB₁ methyl ester) in four steps from commercially available starting materials is described.

Prostaglandin B_x (PGB_x) is an oligomeric derivative of 15-dehydroPGB₁ 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-dehydroPGB₁ 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; ¹H NMR (methanol d₄, 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 benzene⁴⁾ 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; ¹H NMR (chloroform d₁, 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 · 2PPh₃ to yield 15-dehydroPGB₁ 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)} [¹H NMR (chloroform d₁, 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 B₁ derivatives will be reported in the near future.

References

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