AN EFFICIENT SYNTHESIS OF *cis*-OXABICYCLO[3.3.0]OCT-6-EN-3-ONE

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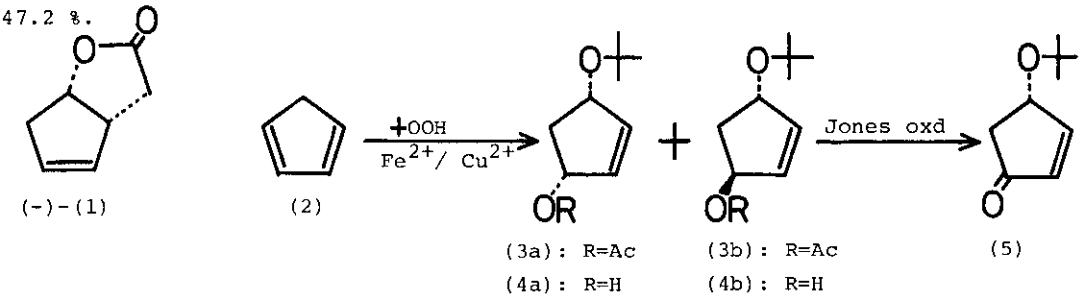
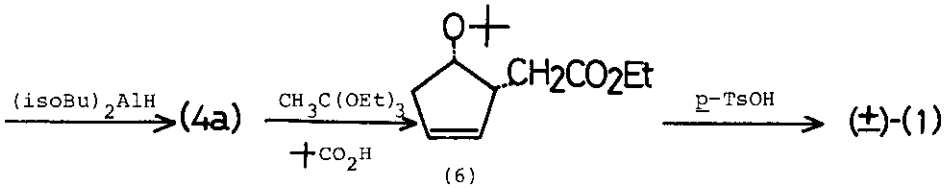
Abstract-----An efficient synthesis of a prostaglandin synthon (±)-*cis*-oxabicyclo[3.3.0]oct-6-en-3-one(1) has been developed using cyclopentadiene(2) as starting material. Employing the same methodology optically active(1) is also synthesized in low optical purity.

The importance of (-)-*cis*-oxabicyclo[3.3.0]oct-6-en-3-one(1) as one of the most useful prostaglandin synthons[1,2] has prompted many efforts towards the development of the efficient synthesis of this molecule. There have been developed various methods[3~10] including chiral routes[4,6,7,8,10], however very few methods which allow large scale production have been available. We describe here an efficient synthesis of the racemic bicyclolactone(1) from cyclopentadiene(2) through 5 steps in 48.0 % overall yield without employing any difficult conditions which prevent large scale production.

According to the known procedure[11] cyclopentadiene(2) was transformed into diastereomeric 3-acetoxy-5-t-butoxycyclopentenes, (3a) and (3b)(1:1), in 80.6 % yield by treating with t-butyl hydroperoxide(70 % aqueous) in the presence of cupric acetate and ferrous sulfate. Methanolysis of the mixture in the presence of potassium carbonate gave the diastereomeric allylic alcohols, (4a) and (4b), in 89.7 % yield, which on exposure to Jones reagent afforded the enone(5) in 89.3 % yield. Reduction of (5) with diisobutylaluminum hydride in toluene at -78 °C yielded *cis*-3-t-butoxy--5-hydroxycyclopentene(4a) accompanied by about 10 % of the trans isomer(4b), which on reflux with an excess of ethyl orthoacetate in the presence of pivalic acid[6] afforded *cis*-4-t-butoxy-3-ethoxycarbonylmethylcyclopentene(6) in 84.7 % yield from (5). Upon reflux in toluene in the presence of p-toluenesulfonic acid, (6) produced (±)-*cis*-oxabicyclo[3.3.0]oct-6-en-3-one(1) in 80.3 % yield. By the same sequence the racemic bicyclic lactone(1) could be obtained directly from diastereomeric allylic alcohols,

(4a) and (4b), through the inseparable diastereomeric 4-t-butoxy-3-ethoxycarbonylmethylcyclopentenes, (6) and its isomer, however overall yield from (4) decreased to 47.2 %.

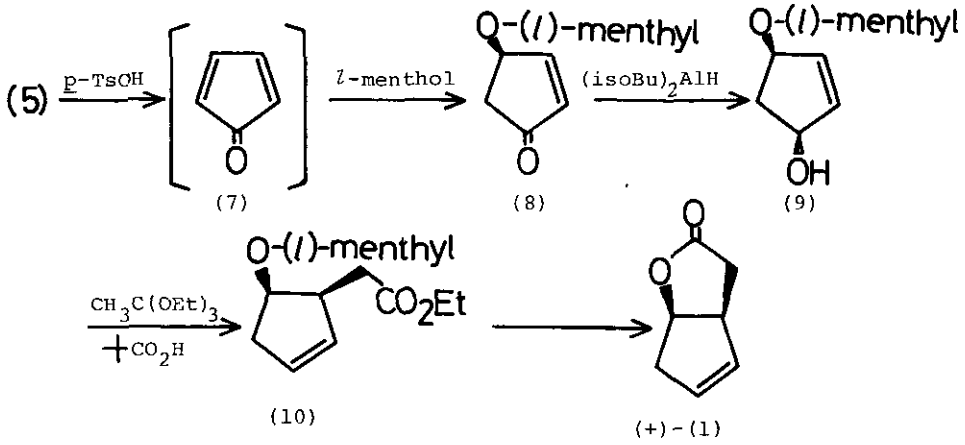




Scheme 1

On the other hand an asymmetric synthesis of the bicyclic lactone(1) was also investigated. Hoping to initiate acid catalyzed elimination of t-butoxy moiety and concurrent asymmetric addition of a chiral alcohol to transient cyclopentadienone(7), (5) was treated with p-toluenesulfonic acid in boiling benzene in the presence of *l*-menthol. The following convertion leading to the bicyclic lactone(1) proved that the asymmetric induction did really occured, however the optical yield obtained as well as the overall yield was too low to be practical. Namely the menthyloxyenone (8) obtained in 60 % yield from (5) by 3.5 hr refluxing was reduced with diisobutylaluminum hydride in toluene at -78 °C to give the *cis*-allylic alcohol(9) quantitatively, which gave *cis*-3-ethoxycarbonylmethyl-4-(*l*)-menthyloxycyclopentene(10) in 73.0 % yield on heating with ethyl orthoacetate as above. Treatment of (10) with boron tribromide in methylene chloride at 0 °C furnished 36.2 % of the partially optically active bicyclic lactone(1), $[\alpha]_D$ +9.17°(C=0.6, MeOH)[lit.[4] $[\alpha]_D$ -104°(C=1.0, MeOH)], which, as its optical rotation indicated, possessed the antipodal chirality that required for the synthesis of prostaglandins.

Despite its limitation to the asymmetric synthesis of the bicyclic lactone(1), the present methodology would have considerable practical value, since a recent report[12] described an efficient conversion of the undesirable (+)-enantiomer(1) into (-)-enantiomer(1) after resolution.



Scheme 2

TABLE

Compound	bp(°C/mmHg)	IR(neat)cm^{-1}	NMR($CDCl_3$) δ ppm	MS(m/e)
3(a+b)	62-64(0.2)	1700	1.2(9H, s), 2.0(3H, s), 4.5(0.5H, br.t, J=6Hz), 4.9(0.5H, br.t, J=4Hz), 5.4(0.5H, br.t, J=6Hz), 5.7(0.5H, br.t, J=4Hz), 5.9(2H, br.d, J=4Hz)	170(M^+-28), 57(100%)
4(a+b)	55-60(0.15)	3050-3600	1.2(9H, s), 4.5(1H, m), 4.9(1H, m), 5.8(2H, m)	156(M^+), 57(100%)
5	40-42(0.12)	1705	1.3(9H, s), 2.2(1H, dd, J=3, 18Hz), 2.7(1H, dd, J=6, 18Hz), 4.7(1H, m), 6.1(1H, dd, J=2, 6Hz), 7.4(1H, dd, J=3, 6Hz)	154(M^+), 81(100%)
4a	*	3050-3600	1.2(9H, s), 4.5(0.9H, m), 4.9(0.1H, m), 5.8(2H, m)	156(M^+), 57(100%)
6	70-72(0.07)	1725	1.3(9H, s), 1.3(3H, t, J=7Hz), 2.8(1H, m), 4.2 (2H, q, 7Hz), 4.3(1H, m), 5.6(2H, br.s)	141(M^+-85), 82(100%)
8	95-100(0.4) (Kugelrohr)	1700	0.86(6H, d, J=8Hz), 1.0 (3H, s), 3.3(1H, m), 4.8 (1H, m), 6.2(1H, dd, J=1, 6Hz), 7.5(1H, m)	236(M^+), 81(100%)
9	*	3050-3600	0.86(6H, d, J=8Hz), 1.0 (3H, s), 3.2(1H, m), 4.6 (2H, m), 5.9(2H, br.s)	238(M^+), 83(100%)
10	118-122(0.2) (Kugelrohr)	1720	0.86(6H, d, J=8Hz), 1.0 (3H, s), 1.3(3H, t, J=7 Hz), 4.2(2H, q, J=7Hz), 4.7(1H, m), 5.8(2H, m)	308(M^+), 170(100%)

* Practically pure, not distilled.

ACKNOWLEDGMENT

We thank Mr. K. Kawamura and Miss Y. Enomoto for spectral measurements.

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Received, 27th January, 1981