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Stereoselective conversion of (+)-cis-2-oxabicyclo[3.3.0]oct-6-en-3-one into methyl R-(+)-7-(3-hydroxy-5-oxo-cyclopentenyl)-5-cis-heptenoate

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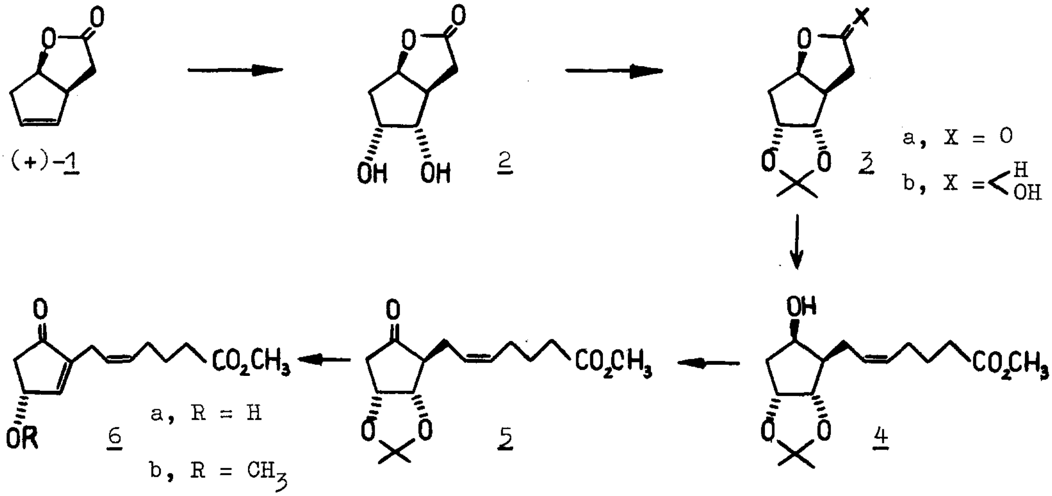
The antipode of the unsaturated lactone 1 has been recently reported in several papers[1-3] as a starting material for prostanoid syntheses. Since optical resolution of racemic 1 with α-methylbenzylamine affords both antipodes in a single process each with more than 60% yield, the use of (+)-1, the enantiomer so far discarded, increases the attrictiveness of 1 in the field of prostanoid syntheses. A highly stereoselective route from 1 to 6a a well established precursor of PGE_2[4] and modified analogs[1] is illustrated below.



$Ph_3P{=}CH{-}(CH_2)_3{-}CO_2Na$

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Hydroxylation was carried out with catalytic amount of OsO_4 in the presence of 1.1 mole $NaClO_3$ in water at ambient temperature. Usual work-up and recrystallization from ethyl acetate afforded 2 [80-92%, m.p.124-5°(racemic), 88-90°(+), $[\alpha]_D$ +31°(c 0.8,MeOH), ir:3450,1770 cm^{-1}, H^1-nmr[6]:4.9(m,1-H),3.9(m,2-H),1.7-3.0 ppm(m,5-H)] . Since only the stereochemistry at C-3 was preserved during further steps, the opposite configuration at C-1 and C-5 is immaterial. The stereochemistry of hydroxylation is ascertained by known configuration[4] of (-)-6a obtained from (+)-1 of similarly known configuration[3]. Conversion of 2 into dioxolane 3a was made with 2,2-dimethoxypropane and catalytic amount TsOH in benzene [92%, m.p.67.5-68° (racemic), 76-78°(+), $[\alpha]_D$+83.2° (c 0.55, MeOH), ir:1763, 1392,1378,1075 cm^{-1}, C^{13}-nmr[6]: 176.7(C=O),111.4(acetonide-C),86.8,82.1,80.9 (C-O),43.6,36.8,30.8(CH_2,CH),25.6,23.8 ppm(CH_3)]. 3a was reduced with 1.4 equivalents i-Bu_2AlH in toluene at -60°(2 hrs) to give 3b [85%, ir:3400,1390 1380,1070 cm^{-1}, R_f 0.35(major) and 0.12(minor), silica gel, benzene-methanol,9:1]. Treatment of lactol acetonide with 1.1 equivalent 7 in DMSO[5] at room temperature followed by esterification with methyl iodide in DMF or, alternatively, acidification to pH 4.5 with oxalic acid, extraction, and titration with ethereal diazomethane afforded 4 [100%, oil, R_f 0.75 silica gel, benzene-MeOH, 9:1, ir: 3600,1745,725 cm^{-1}, H^1-nmr: 5.5(m,2-H),4.7(m,2-H),4.0(m,1-H), 3.65(s,3-H), 2.3(m,8-H),1.7(m,3-H),1.5(s,3-H),1.3 ppm(s,3-H)] which was further oxidized with 5 equivalent CrO_3-pyridine complex at 15° in methylene chloride to give 5 [96%, oil, ir: 2960,2910,2850,1730 cm^{-1}]. Splitting of the dioxolane ring and dehydration was first attempted in a single process by refluxing 5 with small amount of TsOH in methanol. Chromatography on silica gel 1% MeOH-benzene afforded two products (R_f 0.3 and 0.61, benzene-methanol,9:1) in about the same amount. The more polar substance proved to be 6a [$[\alpha]_D$+11.2°(c 1.92,MeOH), ir: 3450,1750,1720,1645 cm^{-1}, uv max(MeOH) 220 nm (ϵ 7.200), H^1-nmr: 7.15 (m,1-H), 5.5(m,2-H),4.95(m,1-H),3,68(s,3-H),2.2(m,8-H), 1.75 ppm (m,2-H)]. Structure 6b was assigned to the less polar material on nmr and ir evidences [ir: 1750,1720,1648 cm^{-1}, H^1-nmr: 7.2(m,1-H),5.5(m,2-H),4.5(m,1-H),3.65(s,3-H), 3.45(s,3-H), 2.3(m,8-H), 1.7 ppm (m,2-H)].

Careful hydrolysis of the acetonide 5 in 20% sulfuric acid at 0° followed by a dehydration procedure adopted from Sih and coworkers[4] gave 6a free from appreciable contaminations in 83% yield.

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