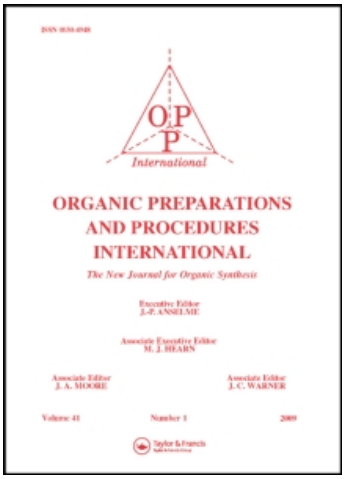

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THE SYNTHESIS OF TWO BICYCLO[4.3.0]NONANE DERIVATIVES

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THE SYNTHESIS OF TWO BICYCLO[4.3.0]NONANE DERIVATIVES

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(08/05/92)

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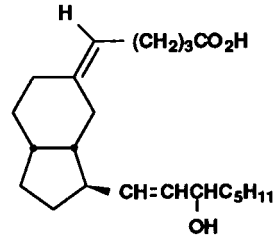
The synthesis of homocarbaprostacyclins such as **1**[1] necessitated access to appropriate bicyclo[4.3.0]nonane derivatives. An earlier successful application[1] of oxidative ring contraction to the generation of analogous bicyclo[3.3.0]octane derivatives led us to adopt a similar approach to the present case.

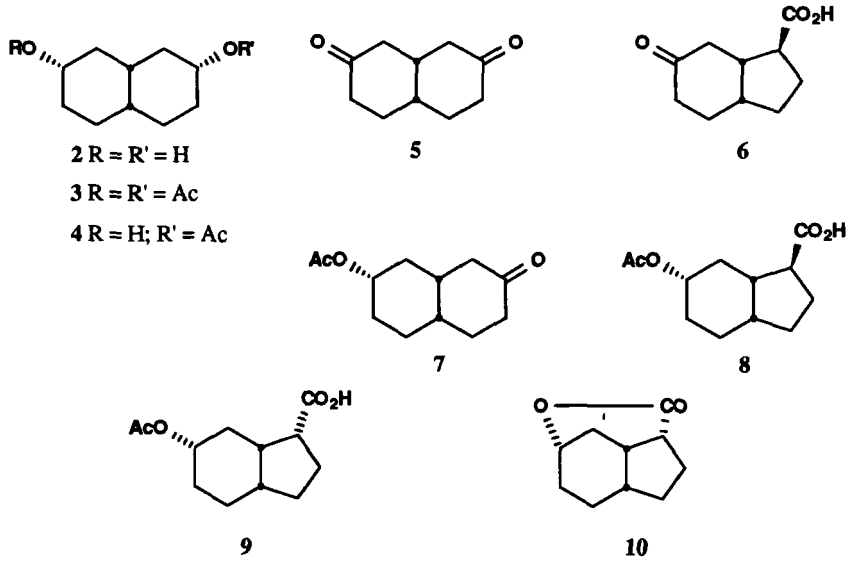


1

Following a literature procedure,[3] 2,7-dihydroxynaphthalene was catalytically hydrogenated to the bicyclo[4.4.0]decane-3,9-diol (**2**). The stereochemistry of this compound has not been assigned though the derived diketone **5** has been shown[4] to undergo reactions dependent upon the indicated *cis*-ring junction. Analogy with the stereochemical course of reduction of 2-naphthol[5] predicts the hydroxyl orientation depicted for **2**. In our hands diol **2** was best converted to dione **5** by oxidation with pyridinium dichromate in dimethylformamide. Oxidative ring contraction of decalindione **5** with thallic nitrate in acetic acid gave a 27% yield of keto-acid **6**. The course of such ring contractions is determined by the preferred direction of enolisation of the carbonyl group. In the present case, the *cis*-ring junction directs thallation to C-2 and hence the preferential

formation of **6** for which there is ample precedent.[2,6] The modest yields of **6** and the availability of enantiomerically pure 9-hydroxybicyclo[4.4.0]decan-3-one[7] by enzymatic reduction of **5** directed attention to the latter system.

Although acetoxyketone **7** could be obtained by partial oxidation of diol **1** and subsequent acetylation, a more satisfactory method commenced with conversion of diol **2** to diacetate **3** in 68% yield. This was then partially hydrolyzed to the monoacetate **4** (68%) and oxidized to acetoxyketone **7** (58%) with pyridinium chlorochromate. The oxidation of **7** with thallic nitrate in acetic acid gave 37% of acid **8**. Comparable yields of **8** were obtained by using the little publicized[8] combination of hydrogen peroxide and a catalytic amount of selenium dioxide. The stereochemistry assigned to **8** is in accord with unsuccessful attempts to effect lactone formation as would be anticipated for the epimer **9**, leading to **10**.



EXPERIMENTAL SECTION

Infrared spectra were measured for liquid films or nujol mulls as appropriate on a Perkin-Elmer 398 IR spectrophotometer. Unless otherwise indicated, NMR spectra were recorded for $CDCl_3$ solutions with TMS as internal standard using either a Perkin-Elmer R90, a Nicolet 200 or a Bruker WM 250 instrument. Analytical TLC and flash chromatography were carried out on silica gel (Merck Darmstadt). TLC plates were visualized by spraying with either potassium permanganate or phosphomolybdic acid (PMA, 10% in ethanol) or by exposure to iodine vapor.

CAUTION: Thallium salts are poisonous. Exercise due caution!

Bicyclo[4.4.0]decan-3,9-dione (5).- Bicyclo[4.4.0]decane-3,9-diol (**2**) (4.3 g, 25 mmol) was dissolved in dimethylformamide (122 mL) and cooled to 0°. Pyridinium dichromate (61.0 g, 162 mmol) was then added to the stirred solution. After an additional 24 hrs stirring, the reaction mixture was poured into water and extracted with diethyl ether. The combined ethereal extracts were dried (Na_2SO_4) and

filtered through silica gel Subsequent evaporation gave **5** as a white solid (4.1 g, 93%), mp. 55-56° (petroleum ether-diethyl ether), lit.[4] mp 62-64°. IR: 1720 cm^{-1}; ^1H NMR (90MHz): δ 1.9-2.3 (m, 6H), 2.3-2.7 (m, 8H); ^{13}C NMR (decoupled): δ 27.74, 33.46, 38.64, 39.77, 44.59, 210.13; MS (EI) m/z 166 (M^+, 40), 138 (8), 110 (38), 95 (12), 68 (75), 55 (100).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.29; H, 8.43. Found: C, 72.03; H, 8.54

3-Ketobicyclo[4.3.0]nonane-9-carboxylic Acid (6).- Thallic nitrate (8.2 g, 18 mmol) was added to a stirred solution of bicyclo[4.4.0]decan-3,9-dione (1.2 g, 7 mmol) in glacial acetic acid (7 mL) and the mixture stirred for 40 minutes. The thallous nitrate which precipitated as a white solid was filtered off and the cake was washed with acetic acid (3x5 mL). The combined filtrate and washings were gently heated under reflux until all brown gas evolution had ceased (about 30 minutes). The acetic acid was removed by distillation under reduced pressure affording a dark brown viscous liquid. Water (10 mL) was added, the reaction mixture neutralized to pH 5 with sodium hydroxide and then to pH 7 with sodium bicarbonate. The resulting solution was extracted with chloroform, acidified with conc. hydrochloric acid to pH 1 and extracted again. The combined chloroform extracts were dried ($MgSO_4$) and evaporated to give a brown viscous oil which was chromatographed in hexane-ethyl acetate-acetic acid (11:9:1) to give the desired ketoacid (**6**) as a viscous oil (0.36 g, 27%) IR: 2600-3500, 1705 cm^{-1}; ^1H NMR (250MHz): δ 0.80-2.24 (m, 8H), 2.24-3.21 (m, 4H), 8.6-10.14 (br, COOH).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.93; H, 7.69. Found: C, 65.52; H, 7.89

3,9-Diacetoxybicyclo[4.4.0]decane (3).- A solution of bicyclo[4.4.0]decane-3,9-diol (**2**) (48 g, 0.28 mol) in acetic anhydride (170 mL) containing sodium acetate (2.4 g) was heated under gentle reflux overnight, cooled and then poured into water. The mixture was extracted with chloroform and the combined extracts were washed successively with water, sodium bicarbonate solution and water prior to drying over sodium sulfate. Evaporation of the chloroform gave a pale yellow oil which was distilled to yield **3** (48.6 g, 68%) bp. 190-194°/5mmHg. IR: 1740 cm^{-1}. ^1H NMR (90MHz): δ 1.0-1.8 (m, 14H), 1.93 (s, 6H), 4.4-5.1 (m, 2H).

Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.14; H, 8.66. Found: C, 66.46; H, 8.75

3-Acetoxybicyclo[4.4.0]decan-9-ol (4).- A stirred mixture of 3,9-diacetoxybicyclo[4.4.0]decane (**3**) (14.3 g, 56 mmol) and powdered potassium hydroxide (2.7 g, 48 mmol) in ethanol (70 mL) was refluxed for 2 hrs. The solution was cooled and the ethanol evaporated to give a viscous brown oil which was partitioned between chloroform and water. The combined chloroform extracts were dried (Na_2SO_4) and evaporated *in vacuo* to give a reddish brown oil which was distilled to give **4** (8.1 g, 68%) bp. 140-142°/1mmHg. A portion was further purified by chromatography in hexane-ethyl acetate (1:2). IR: 3400,1750 cm^{-1}; ^1H NMR (90MHz): δ 0.75-2.00 (m, 15H), 2.08 (s, 3H), 3.7-4.3 (m, 1H), 4.8-5.15 (m, 1H); ^{13}C NMR (decoupled): δ 24.74, 29.09, 30.09, 33.99, 35.25, 35.92, 36.25, 40.68, 66.34, 66.55, 71.27, 170.27; MS(EI): m/z 194 (M^+-H_2O), 152 (M^+-AcOH, 15), 134 (M^+-H_2O, AcOH).

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.92; H, 9.43. Found: C, 67.98; H, 9.81

3-Acetoxybicyclo[4.4.0]decan-9-one (7).- A solution of 3-acetoxybicyclo[4.4.0]decan-9-ol (**4**) (1.35 g, 7 mmol) in dichloromethane (2 mL) was added to a stirred suspension of pyridinium chlorochro-

mate (2.0 g, 9 mmol) in dichloromethane (13 mL), and the mixture heated under reflux for 4 hrs. The reaction mixture was cooled and anhydrous diethyl ether added. The supernatant liquid was decanted and the black residue washed with ether until it became granular. The combined ethereal solutions were filtered through a small pad of magnesium sulfate and the solvents evaporated *in vacuo* to give **7** as a viscous oil which was purified by chromatography in hexane-ethyl acetate (2:1) (0.78 g, 58%). IR: 1725, 1705 cm^{-1}; ^1H NMR (200MHz): δ 0.85-1.96 (m, 10H), 2.04 (s, 3H),2.15-3.04 (m, 4H), 4.68-5.13 (m, 1H); MS (EI): m/z 210 (M^+, 2), 168 (5), 151 (20), 150 (40), 134 (22), 108 (23), 43 (100).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.57; H, 8.57. Found C, 68.85; H, 8.57

4-Acetoxybicyclo[4.3.0]nonane-7-carboxylic Acid (8).- (A) The procedure used for the conversion of **5** to **6** was employed to convert 3-acetoxybicyclo[4.4.0]decan-9-one (**7**) to **8** which was obtained as an oil and purified by chromatography in hexane-ethyl acetate-acetic acid (10:5:1) (27%). IR: 2400-3650, 1705 cm^{-1}; ^1H NMR (200MHz): δ 1.0-3.3 (m, 13H), 2.10 (s, 3H), 4.7-5.12 (m, 1H), 8.6-9.2 (br, COOH); MS (EI): m/z 181 (M^+-CO_2H), 166 (5), 152 (30), 136 (23), 121 (25), 81 (100).

Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.72; H, 7.97. Found C, 64.06; H, 8.18

(B) 3-Acetoxybicyclo[4.4.0]decan-9-one (**7**) (0.6 g, 2.8 mmol) was added to a refluxing solution of hydrogen peroxide (1.2 g, 30% w/v) and selenium dioxide (18 mg) in *t*-butanol (12 mL). The resulting reaction mixture was refluxed for 0.5 hr, where upon red selenium deposited; it was then allowed to stand at room temperature for 24 hrs. The solvent was evaporated *in vacuo* and diethyl ether added to the residue prior to extraction with aqueous potassium carbonate solution (20%). The combined aqueous extracts were acidified to pH 1 with conc. hydrochloric acid and in turn extracted with diethyl ether. The dried ethereal extracts were evaporated and chromatographed as above to give **8** (0.24 g, 37%).

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