Synthesis of 3-(1,1-ethylenedioxyoctyl)-cyclopentanone

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1,4-Cyclohexanedione has been converted into compounds **8** and **9**. Treatment of **8** and **9** with base produces compound **10**, which has been converted into 3-(1,1-ethylenedioxyoctyl)-cyclopentanone.

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A number of publications have recently appeared (1–6) describing the syntheses of various naturally occurring prostaglandins and related compounds. With the exception of the elegant method of Corey *et al.* (1) all the syntheses described so far rely on the modification of a five-membered ring compound to produce the prostaglandin skeleton.

We have approached the problem by using a readily available six-membered carbocyclic ring compound as the starting material. A seven carbon atom side chain is added in the first step. At a later stage in the reaction sequence, the length of the seven carbon atom chain is increased by one carbon atom by the contraction of the six-membered ring to produce a suitably substituted five-membered ring. The ring contraction not only gives a side chain of the correct length but also generates a ketone function in the eight carbon side chain, in a position suitable for later introduction of the allyl alcohol function.

When a half-molar equivalent of *n*-heptyl magnesium bromide was added to 1,4-cyclohexanedione it was possible to separate 4-heptyl-4-hydroxycyclohexanone **1** as the mono-adduct from the reaction mixture.

The keto-alcohol **1** was quantitatively reduced to 1-heptyl-1,4-cyclohexanediol **2**. The nuclear magnetic resonance (n.m.r.) spectrum has broad multiplets at τ 6.15 and 6.5 of roughly equal area corresponding to epimeric alcohols. Thin-layer chromatography (t.l.c.) confirmed that two closely related compounds were present.

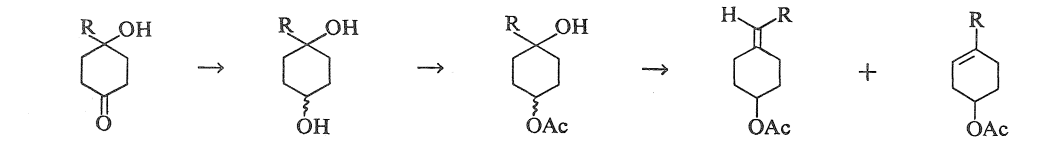
Acetylation of the epimeric mixture of diols with acetic anhydride – pyridine gave the monoacetate **3**. The acetate **3** was dehydrated by heating under reflux in acetic anhydride to give a product composed of two compounds (by t.l.c.). The n.m.r. spectrum has peaks due to a hydrogen atom on a double bond and a hydrogen atom attached to the same carbon atom as the acetoxy group. Also included in the spectrum are two sharp peaks at τ 8.06 and 8.02, due to two very similar acetate methyl groups. The chromatographic and n.m.r. evidence is compatible with the product being composed of exocyclic and endocyclic double bond isomers **4** and **5**, respectively.

Acid-catalyzed equilibration of this olefinic mixture converted it into the more stable endocyclic olefin **5** (7). The reaction could be followed conveniently by the disappearance of one of the spots on the t.l.c. plate. Further reactions in the synthetic sequence, and the broad peak in the n.m.r. spectrum at τ 4.7 indicate that the product is correctly represented by structure **5**.

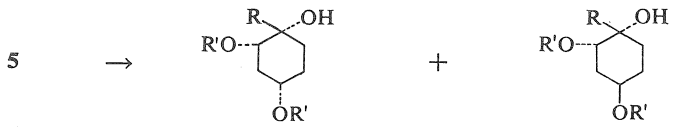
cis-Hydroxylation of 1-heptyl-4-acetoxy-1-cyclohexene **5** was effected by treating it with OsO_4–pyridine in ether (8). The intermediate complex was decomposed on treatment with mannitol. The decomposition of the complex also resulted in partial hydrolysis of the acetoxy group. Complete hydrolysis occurred on treatment of the product with KOH in aqueous alcohol, to give the two possible epimeric triols **6** and **7**.

The triol epimers were converted into the corresponding secondary ditosylates by treating with tosyl chloride and pyridine. Two crystalline ditosylates **8** and **9** (R = Ts) could be isolated from the reaction product. Elemental analyses and almost identical infrared (i.r.) spectra were consistent with the fact that these two compounds were indeed epimeric at the secondary tosyl group in the 4-position.

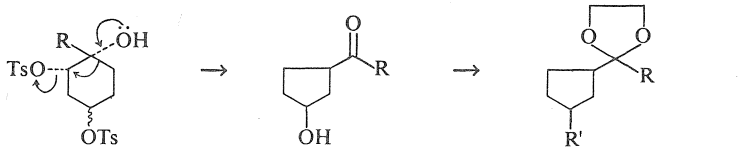
Treatment of the mixture of crystalline tosylates with $CaCO_3$ in dimethyl formamide under reflux brought about the desired ring contraction, as was shown by the appearance of a peak at 1700 cm^{-1} in the i.r. spectrum of the product **10** (9). The secondary tosyl group was also lost in the work-up as was shown by the absence of characteristic peaks in the i.r. and n.m.r. spectra, and by



1 R = *n*-heptyl **2** R = *n*-heptyl **3** R = *n*-heptyl **4** R = *n*-hexyl **5** R = *n*-heptyl



6 R = *n*-heptyl R′ = H **7** R = *n*-heptyl R′ = H
8 R = *n*-heptyl R′ = Ts **9** R = *n*-heptyl R′ = Ts



8 or **9** R = *n*-heptyl **10** R = *n*-heptyl **11** R = *n*-heptyl R′ = OH
12 R = *n*-heptyl R′ = =O

the presence of a peak at 3400 cm^{-1} in the i.r. spectrum of the product, due to the hydroxyl group.

The rearrangement product **10**, which was homogeneous on t.l.c., was converted into the ethylene ketal **11** by heating under reflux in benzene with ethylene glycol and a catalytic amount of *p*-toluenesulfonic acid.

The ketal was oxidized with chromium trioxide in pyridine to give the keto-ketal **12**. The product was homogeneous by t.l.c. analysis and had a peak in the i.r. spectrum at 1740 cm^{-1}, showing the presence of a five-membered ring ketone.

Elemental analyses and the n.m.r. spectrum were also in agreement with structure **12**. A sharp peak at τ 6.1 is indicative of the ethylene ketal protons and a broad multiplet centered at τ 7.8 is due to the hydrogen atoms α to the ketone. The remainder of the n.m.r. spectrum is in agreement with the presence of a large hydrocarbon side chain.

These results show that this approach to the prostaglandin skeleton is feasible and we are now in the process of incorporating the seven carbon atom side chain by direct alkylation or by rearranging the appropriately substituted cyclohexane ring.

Experimental

Infrared (i.r.) spectra were of chloroform or carbon tetrachloride solutions. Nuclear magnetic resonance (n.m.r.) spectra were of deuteriochloroform or carbon tetrachloride solutions with tetramethylsilane as internal standard.

4-Heptyl-4-hydroxycyclohexanone 1

A solution of *n*-heptyl bromide (17.5 g; 0.1 mole) in anhydrous ether (150 ml) was added dropwise over a period of 2 h to a stirred mixture of magnesium (2.43 g; 0.1 mole) and ether (50 ml). During the addition, reflux was maintained by occasional warming of the reaction flask. After addition was complete, reflux was continued for 1 h. The Grignard reagent solution was cooled and transferred to a dry 250 ml dropping funnel while maintaining a nitrogen atmosphere. The Grignard reagent was then added dropwise to a stirred solution of 1,4-cyclohexanedione (10 g; 0.1 mole), in anhydrous ether (200 ml). Addition was completed in 2 h after which the reaction was heated under reflux for 1 h.

The reaction mixture was allowed to cool and then diluted to 600 ml with ether. The resulting organic layer was washed with a saturated solution of ammonium chloride until the aqueous washings were acidic. The organic layer was then washed with water, and after drying, the ether was removed by flash evaporation. The crude product was obtained as a clear, viscous, yellow oil (5.96 g). Thin-layer chromatography (silica–ether eluent) revealed the presence of four products, in an overall yield of 37%.

Vacuum distillation of the crude product gave 4-heptyl-4-hydroxycyclohexanone **1**; b.p. 0.9 mm 128°, in a 24% yield (3.84 g) as a clear, viscous, yellow oil; n_D^{25} 1.4741.

Thin-layer chromatography (silica–ether eluent) of the product showed the presence of one compound.

Infrared spectrum: 3600 cm^{-1}, 3400 cm^{-1}. Nuclear magnetic resonance spectrum: τ 6.4 (hydroxyl hydrogen, disappears when treated with D_2O), τ 8.1 (4 hydrogens α to the ketone) τ 8.6–9.1 (remaining methyl and methylene hydrogens).

1-Heptyl-1,4-cyclohexanediol **2**

1-Heptyl-4-hydroxycyclohexanone (1.80 g) was dissolved in methanol (50 ml). Sodium borohydride (1.50 g) was added in one portion to the solution. After 1 h, water (10 ml) was added to destroy the excess of sodium borohydride. The reaction mixture was diluted to 100 ml with ether and the organic layer was washed with 2% HCl solution followed by washing with water. The organic layer was dried over anhydrous magnesium sulfate, filtered, and the ether removed by flash evaporation to give 1.67 g of product (92% yield). Thin-layer chromatography (silica–ether eluent) indicated two products with no indication of starting material.

Infrared spectrum: 3600 cm^{-1}, 3400 cm^{-1}. Nuclear magnetic resonance spectrum: τ 6.15 and 6.5 (hydrogens on the same carbon atoms as the hydroxyls), τ 7.6 (hydroxyl hydrogen), τ 8.4–9.1 (methyl and methylene hydrogens).

A sample of the cyclohexanediol was recrystallized, to analytical purity (m.p. 74–77°) from petroleum ether (b.p. 30–60°) – ether. Thin-layer chromatography showed one spot.

Anal. Calcd. for $C_{13}H_{26}O_2$: C, 72.84; H, 12.23; O, 14.93. Found: C, 72.99; H, 12.24; O, 14.91.

1-Heptyl-4-acetoxy-1-cyclohexene **5**

1-Heptyl-1,4-cyclohexanediol (2.21 g) was dissolved in anhydrous pyridine (50 ml) to which acetic anhydride (30 ml) was added. The reaction was allowed to stand at room temperature for 24 h. The excess acetic anhydride and pyridine were removed by flash evaporator and the reaction residue was diluted to 150 ml with ether. The organic layer was washed with 2% HCl solution, sodium bicarbonate solution, followed by water. Removal of the dried ether gave 2.08 g of a clear, viscous, yellow oil in 80% yield. Thin-layer chromatography (silica–ether eluent) indicated that there were two new products.

The product mixture (2.08 g) was not further purified (i.r. and n.m.r. indicated mono-acetate), but was heated under reflux for 24 h in acetic anhydride (100 ml). The reaction was cooled and approximately one-half of the acetic anhydride was removed by flash evaporator. The residue was diluted to 250 ml with ether, then washed with a 1% sodium hydroxide solution until the aqueous extracts were basic then with water until neutral. Removal of the dried ether gave 1.85 g of a yellow, viscous oil, corresponding to a yield of 89%. Thin-layer chromatography (silica–benzene eluent) indicated the presence of two products.

The n.m.r. spectrum showed narrowly spaced singlets (τ 8.04, 8.06) probably due to the exocyclic and endocyclic forms of the alkene acetate **4** and **5** respectively.

The mixture of **4** and **5** (1.85 g) and *p*-toluenesulfonic acid (1.9 g) were dissolved in benzene (50 ml) heated under reflux for 2 h. The reaction was cooled and diluted to 150 ml with benzene. The benzene layer was washed with a 2% sodium bicarbonate solution followed by water. Removal of the dried benzene gave 1.85 g of 1-heptyl-4-acetoxy-1-cyclohexene as a viscous, yellow oil; n_D^{25} 1.4547. The yield was quantitative. Thin-layer chromatography (silica–benzene eluent) indicated one product.

Infrared spectrum: 1740 cm^{-1}, 1600 cm^{-1}. Nuclear magnetic resonance spectrum: τ 4.7 (hydrogen on double bond), τ 5.15 (hydrogen attached to the same carbon atom as the acetoxy group), τ 8.05 (singlet, acetoxy methyl hydrogens), τ 8.7–9.1 (remaining methyl and methylene hydrogens).

Anal. Calcd. for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99; O, 13.42. Found: C, 75.88; H, 11.05; O, 13.15.

1-Heptyl-1,2,4-cyclohexanetriol **6** *and* **7**

Osmium tetroxide (7.0 g) was added to a cold solution of 1-heptyl-4-acetoxy-1-cyclohexene (6.97 g) in dry ether (150 ml) and dry pyridine (4.5 ml). The reaction was left for 6 days at room temperature. The dark colored reaction mixture was filtered to give 6.96 g of a brown complex.

The complex was decomposed by stirring overnight with a solution composed of mannitol (2 g) and KOH (10 g) in water (100 ml). Ether extraction gave 2.44 g of product which was a mixture of the desired triol and monoacetylated triol. Hydrolysis of this mixture with 5% KOH EtOH–H_2O solution (60 ml) converted it into 2.38 g of crude triol.

The above filtrate was similarly treated with mannitol–KOH solution to give a further 2.33 g of product identical with that obtained from the complex. Total product: 4.77 g–72% yield. Infrared spectrum had absorption peaks at 3600 cm^{-1} and 3400 cm^{-1} due to non-bonded and bonded —OH. The n.m.r. spectrum had peaks at τ 5.9 (1 H broad multiplet), τ 6.2 (1 H poorly resolved triplet), τ 7.4 broad peak due to hydroxyl hydrogens, τ 8.0–9.1 envelope due to remaining methylene and methyl hydrogens.

Anal. Calcd. for $C_{13}H_{26}O_3$: C, 67.79; H, 11.38; O, 20.84. Found: C, 67.67; H, 11.63; O, 20.92.

Tosylation of 1-Heptyl-1,2,4-cyclohexanetriol **6** *and* **7**

p-Toluenesulfonic acid chloride (4.6 g) and 2.0 g of a mixture of **6** and **7** were dissolved in dry pyridine (90 ml). The resulting solution was left at room temperature for 20 h.

The majority of the pyridine was removed under reduced pressure, and the residue was dissolved in benzene. The benzene solution was washed with 5% aqueous $NaHCO_3$, and after drying the benzene was removed under reduced pressure to give 4.3 g of crude product.

Crystallization of the residue from a mixture of ether – petroleum ether (b.p. 30–60°) yielded 500 mg of a compound, which after repeated crystallizations melted at 107°.

Infrared spectrum: 3500 cm^{-1}, 1600 cm^{-1}, 1180 cm^{-1}. Nuclear magnetic resonance spectrum: τ 2.15–2.7 (AB quartet, aromatic hydrogens), τ 5.6 (broad multiplet due to hydrogens on same carbon atoms as O-tosyl), τ 7.5 (singlet, aromatic methyl hydrogens), τ 8.0–9.1 (remaining methyl and methylene hydrogens).

Anal. Calcd. for $C_{27}H_{38}S_2O_7$: C, 60.19; H, 7.10; O, 20.79; S, 11.90. Found: C, 60.37; H, 7.32; O, 20.06; S, 11.98.

Crystallization of the material from the above mother liquors from ether – petroleum ether (b.p. 30–60°) yielded 400 mg of a second compound which after repeated crystallizations melted at 62°.

Infrared spectrum: 3500 cm^{-1}, 1600 cm^{-1}, 1180 cm^{-1}. Nuclear magnetic resonance spectrum: τ 2.15–2.7 (AB quartet, aromatic hydrogens), τ 5.4 (broad multiplet due to hydrogens on same carbon atoms as O-tosyl), τ 7.55 (singlet, aromatic methyl hydrogen), τ 8.1–9.1 (remaining methyl and methylene hydrogens).

Anal. Calcd. for $C_{27}H_{38}S_2O_7$: C, 60.19; H, 7.10; O, 20.79; S, 11.90. Found: C, 60.19; H, 7.14; O, 20.97; S, 11.99.

The two crystalline compounds had distinctly different R_f values -0.31 for the isomer melting at 107° and 0.59 for the isomer melting at 62°—on t.l.c. (silica – petroleum ether (b.p. 30–60°) eluent). The i.r. spectra were almost identical (small differences in 900–950 cm^{-1} range).

Rearrangement of 1-Heptyl-1,2,4-cyclohexanetriol-2,4-ditosylate ***8*** *and* ***9***

Crystalline ditosylate (500 mg) was dissolved in freshly distilled dimethyl formamide (30 ml) and dry $CaCO_3$ (500 mg) was added. The resulting suspension was heated under reflux with stirring for $2\frac{1}{2}$ h.

The reaction mixture was added to benzene (100 ml) and washed several times with water. Removal of the benzene gave 175 mg of an oily product **10**—88% yield. Thin-layer chromatography showed one spot. The i.r. spectrum showed absorption bands at 3600 cm^{-1}, 3400 cm^{-1}, and 1700 cm^{-1}. The n.m.r. spectrum showed peaks at τ 5.7 (broad multiplet, hydrogen on some carbon atom as the hydroxyl), τ 7.6 (broad multiplet, methine hydrogen α to ketone), τ 8.1 (poorly resolved triplet, methylene hydrogens α to ketone), τ 8.7–9.1 (broad envelope, due to remaining methylene and methyl hydrogens).

Preparation of Ethylene Ketal ***11***

The hydroxy ketone **10** (163 mg) and a catalytic amount of *p*-toluenesulfonic acid were dissolved in benzene (50 ml) in the presence of ethyleneglycol (1 ml). The resulting mixture was heated under reflux for 3 h. All traces of water were removed by means of a water separator.

After cooling, the benzene solution was washed with 5% $NaHCO_3$ and water. Removal of the benzene yielded 148 mg of ketal. The product gave one spot on t.l.c. examination, showed no ketone in the i.r. spectrum, and had a sharp peak at τ 6.15 in the n.m.r. spectrum due to the ethylene ketal hydrogens.

Preparation of Ketal–Ketone ***12***

The hydroxy ketal **11** (133 mg) dissolved in dry pyridine (2 ml) was added to a slurry of CrO_3 (500 mg) in dry pyridine (15 ml). The resulting mixture was stirred at room temperature for 24 h.

Ether extraction of the product yielded 98 mg of ketone found to be homogeneous by t.l.c. The i.r. spectrum had a band at 1740 cm^{-1}. The n.m.r. spectrum had a sharp peak at τ 6.1 (hydrogens of ethylene ketal), τ 7.8 (broad multiplet, hydrogens α to ketone), τ 8.7–9.1 (broad envelope, due to methylene, methine, and methyl hydrogens).

Anal. Calcd. for $C_{15}H_{26}O_3$: C, 70.82; H, 10.30; O, 18.87. Found: C, 71.28; H, 10.07; O, 17.97.

Acknowledgments

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