A Synthesis of 2-Formyl-5,5,9-trimethyl-*trans*-Δ^2-1-octalone

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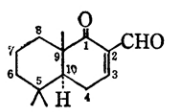
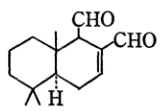
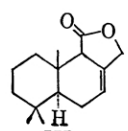
It is expected that 2-formyl-5,5,9-trimethyl-*trans*-Δ^2-1-octalone (I) would be a key intermediate in the total syntheses of sesquiterpenes, such as polygodial[1] (II) and drimenin[2] (III).



I



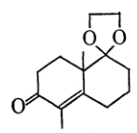
II



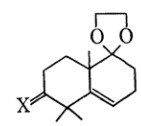
III

From this point of view, the stereoselective synthesis of I is desirable; it will be described in this Note. The methylation of 5-ethylenedioxy-1,10-dimethyl-$\Delta^{1(9)}$-2-octalone (IV)[3] with methyl iodide in the presence of dried potassium pentoxide[4] in benzene produced a high yield of (V). The NMR spectrum*2 showed the sharp signals of three quarternary methyl groups at δ 1.03 (3H) and 1.13 (6H) and of one olefinic proton at 5.43 (broad triplet, J= 4.5 cps).

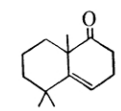
V underwent a modified Barton's Wolff-Kishner reduction[5] to give the desoxy compound (VI), which was then hydrolyzed to the corresponding ketone (VII).



IV



V, X=O
VI, X=H_2



VII

Since the catalytic reduction of the double bond of VII proceeded non-stereospecifically,*3 the carbonyl group of VII was reduced with lithium tri-*t*-butoxy alumino hydride[6] to give the corresponding alcohol (VIII), mp 117—118°C, exclusively.

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2) H. H. Appel, R. P. M. Bond and K. H. Overton, *Tetrahedron*, **19**, 635 (1963); E. Wenkert and D. P. Strike, *J. Am. Chem. Soc.*, **86**, 2044 (1964).

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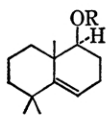
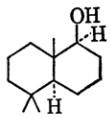
*2 All the NMR spectra were measured on a Varian A-60 spectrometer; they are expressed in terms of ppm, using tetramethylsilane as an internal standard.

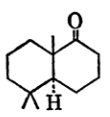
*3 An inspection of the Dreiding model showed that the β-side of VIII was more hindered than that of VII.



VIII, R=H
IX, R=Ac



X



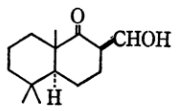
XI

The β-configuration of the hydroxyl group on the C_1 of VIII was established by an examination of the NMR spectrum of (IX), in which the proton at C_1 appears as a clear double doublet at 4.65 (J=9.0 and 6.5 cps).[7] VIII was hydrogenated stereoselectively to 5,5,9-trimethyl-*trans*-1-decalol (X) in a good yield over platinum oxide; it was subsequently oxidized to the corresponding ketone (XI).[8]

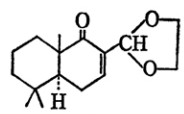
The condensation of the *trans*-decalone XI with ethyl formate in the presence of sodium methoxide afforded the hydroxymethylene derivative (XII) mp 35—37°C, which was then dehydrogenated by 2,3-dichloro-5,6-dicyanoquinone[9] to give the unsaturated ketoaldehyde I, mp 74—76°C.

The formyl group of I was converted to ethylenedioxy ketone (XIII) exclusively by treatment with ethyleneglycol.

The introduction of the C_1-unit into the C_1 of XIII is now being investigated.



XII



XIII

Experimental*4

Methylation of 5-Ethylenedioxy-1,10-dimethyl-$\Delta^{1(9)}$-2-octalone. To an ice-cold solution of dried potassium *t*-pentoxide (from 3.25 g of potassium) in benzene (200 m*l*), 5-ethylenedioxy-1,10-dimethyl-$\Delta^{1(9)}$-2-octalone (9.4 g) was added, drop by drop with occasional shaking. The mixture was refluxed for an hour under a nitrogen atmosphere, then cooled to room temperature, treated slowly with methyl iodide (20 m*l*), and refluxed for another hour. The product was worked up; on distillation, it furnished the trimethylketone, V, $C_{15}H_{22}O_3$ (8.0 g, 80%), bp 150°C/2 mmHg.

Reduction of 5-Ethylenedioxy-1,1,10-trimethyl-Δ^{8}-2-octalone (V). Sodium (370 mg) in diethyleneglycol (18 m*l*) was heated to 180°C, and then anhydrous hydrazine (prepared by refluxing hydrazine hydrate (12 m*l*) over sodium hydroxide pellets (6 g) for 3 hr) was distilled in. The solution was cooled, ketoketal V (690 mg) was added, and the solution was refluxed overnight. The temperature was then raised to 210°C by distilling out some of the hydrazine, and the solution was refluxed at this temperature for 24 hr. Dilution with water and extraction with ether gave the desoxy compound VI, $C_{15}H_{24}O_2$ (450 mg, 70%).

5,5,9-Trimethyl-$\Delta^{4(10)}$-1-octalone (VII). Ketal VI (9.0 g) and *p*-toluenesulfonic acid (900 mg) in dioxane (40 m*l*) and water (18 m*l*) were warmed at 90°C for 4 hr. After cooling, the reaction mixture was diluted with ether, and the ethereal solution was washed with 0.1 N sodium hydroxide and then water. Drying the ethereal solution over magnesium sulfate and evaporation of the ether gave the residual oil; on distillation, VII, $C_{13}H_{20}O$, was obtained as a pale yellow oil (6.7 g, 90%), bp 140—150°C/2 mmHg.

5,5,9-Trimethyl-$\Delta^{4(10)}$-1-octalol (VIII). Into an ice-cold tetrahydrofuran solution (45 m*l*) of lithium aluminium hydride (1.7 g), *t*-butanol (9.8 g) was stirred, drop by drop, under a nitrogen atmosphere. A tetrahydrofuran (45 m*l*) solution of 5,5,9-trimethyl-$\Delta^{4(10)}$-1-octalone VII (5.6 g) was stirred into the solution of tri-*t*-butoxy alumino hydride, and the mixture was kept overnight. The reaction mixture was then diluted with water, neutralized with 2 N hydrochloric acid, and extracted with ether. From the ether solution, VIII, $C_{13}H_{22}O$ (4 g, 71%), was obtained as white crystals, mp 117—118°C (recrystallized from pet. ether-benzene).

Acetate of VIII. The alcohol VIII (124 mg) was stirred with acetic anhydride (1 m*l*) and pyridine (1 m*l*) overnight, and then the reaction mixture was diluted with ether. From the ethereal solution, after it had been washed with aqueous sodium bicarbonate and then water, and dried over magnesium sulfate, the acetate (IX) (80 mg, 53%) was obtained as a pale yellow oil, bp *ca.* 110—120°C/2 mmHg.

5,5,9-Trimethyl-*trans*-1 β-decalol (X). The unsaturated alcohol VIII (8.21 g), dissolved in acetic acid (110 m*l*), was shaken in hydrogen over platinum oxide (630 mg) at room temperature and at atmospheric pressure. After the absorption of gas had stopped, the catalyst was removed, the filtrate was diluted with water, and the product was extracted with ether. The amorphous residue obtained by the evaporation of the ether was sublimed at 85—95°C/1 mmHg. The resulting crystalline saturated alcohol X (7.1 g, 86%) showed a mp of 67—69°C. The analytical sample was obtained by recrystallization from *n*-pentane, $C_{13}H_{24}O$, mp 74—75°C.

5,5,9-Trimethyl-*trans*-1-decalone (XI). A solution of chromium trioxide (7.7 g) in water (18 m*l*) and acetic acid (67 m*l*) was added to a stirred solution of X (7.35 g) in acetic acid (95 m*l*) over a 20 min period with ice cooling. The mixture was allowed to stand overnight at room temperature and then diluted with water. Extraction with ether, followed by distillation, produced the saturated ketone XI, $C_{13}H_{22}O$ (6.0 g, 83%), mp 40—42°C.

2-Formyl-*trans*-decalone (XII). Absolute benzene (100 m*l*) was added to dried sodium methoxide (from 1.78 g of sodium). To this suspension, saturated ketone XI (3.0 g) and ethyl formate (18 m*l*) were added, and the mixture was stirred overnight at room temperature.

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9) J. A. Edwards, M. C. Calzada, L. C. Ibanez, M. E. Cabezas Rivera, R. Urquiza, L. Cardona, J. C. Orr and A. Bowers, *J. Org. Chem.*, **29**, 3481 (1964); W. L. Meyer, G. B. Clemans and R. W. Huffman, *Tetrahedron Letters*, **1966**, 4255.
*4 Satisfactory analyses have been obtained for all the new compounds in this paper.

The reaction mixture was then diluted with water and neutralized with dilute sulfuric acid; after the aqueous layer had separated, the benzene solution was washed with water, dried ($MgSO_4$), and evaporated to yield 2-formylketone XII (2.8 g). The recrystallization of a small sample from methanol afforded an analytical specimen, $C_{14}H_{22}O_2$, mp 35—38°C.

Dehydrogenation of 2-Formyl-decalone (XII). A solution of the formyl decalone XII (222 mg) in dioxane (10 m*l*) was treated with dichlorodicyanobenzoquinone (291 mg) in dioxane (10 m*l*). After it had stood for 5 min, the reaction mixture was diluted with methylene chloride (20 m*l*). This methylene chloride solution was filtered through a column of neutral alumina, and the column was washed with the same solvent. The combined methylene chloride solution was then evaporated to yield the dehydrogenation product I (86 mg, 39%). Recrystallization from pet. ether gave the analytical sample, $C_{14}H_{20}O_2$, mp 74—76°C.

Ethyleneketalization of 2-Formyl-5,5,9-trimethyl-Δ^2-*trans*-1-octalone (I). A solution of I (232 mg) and *p*-toluenesulfonic acid monohydrate (10 mg) in benzene (10 m*l*) and ethyleneglycol (2 m*l*) was heated under reflux, with a continuous separation of water, until water no longer distilled from the reaction mixture (4 hr). The cooled reaction mixture was washed with aqueous sodium bicarbonate and then water, dried ($MgSO_4$), and concentrated to yield ethylene ketal of I (206 mg) as a pale yellow oil.

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