A Modified Synthesis of 2,15-Hexadecanedione, a Precursor of Muscone, from a Butadiene Telomer

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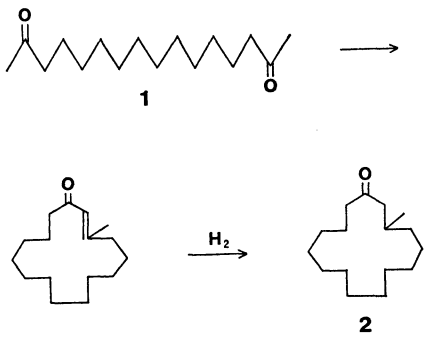
8-Acetoxy-1,6-octadiene was oxidized with $PdCl_2/CuCl/O_2$ to give 8-acetoxy-6-octen-2-one. Hydrolysis and hydrogenation of the ketone produced 8-hydroxy-2-octanone, which was converted to the tosylate after protection of the ketone. The tosylate was converted into the iodide and bromide. The bromide was converted into the Grignard reagent, and coupled with the iodide by the catalysis of CuI coordinated by 2,2'-bipyridyl to give 2,15-hexadecanedione.

Muscone (3-methylcyclopentadecanone **2**) is a naturally occurring fragrant compound with musk odor. Many synthetic attempts for this unique natural product have been carried out. One method carried out by Stoll is based on the intramolecular aldol condensation of 2,15-hexadecanedione (**1**) to form the 15-membered cyclic ketone.[1]

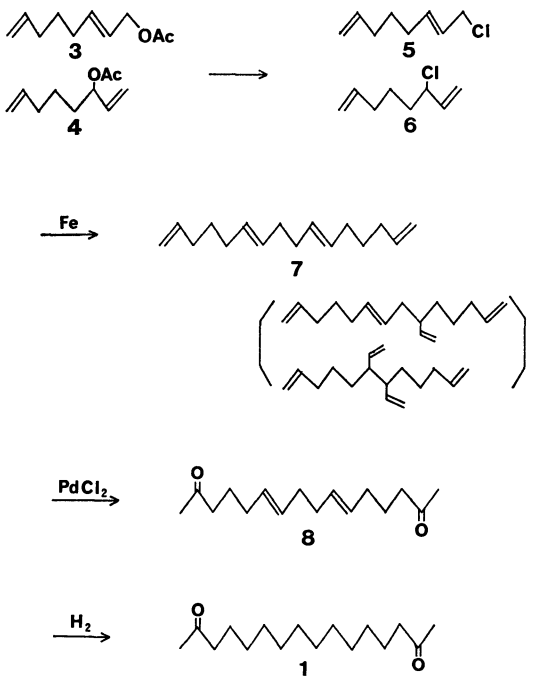


One drawback of the Stoll method is a low yield of the intramolecular aldol condensation, which competes with the intermolecular reaction. In order to make this method more useful and make up for the low yield of the aldol condensation, it is essential to synthesize the diketone **1** as the precursor easily in high yield. Only a few synthetic methods are known for this diketone. For example Stoll synthesized this diketone by the reaction of 1,10-dibromodecane with ethyl acetoacetate, followed by decarboxylation.[2] Another method is the cross Kolbe reaction of 10-oxoundecanoic acid and 6-oxoheptanoic acid.[1] The cross coupling inevitably produced a mixture of coupled products. We have reported the simple synthetic method for this diketone starting from a butadiene telomer easily obtained by the palladium catalyzed telomerization of butadiene with acetic acid.[3] We have carried out further elaboration of the synthesis from the telomer and results of the modification are presented in this paper.

Results and Discussion

Our original synthesis of the diketone **1** was carried out by the following sequence.[4]

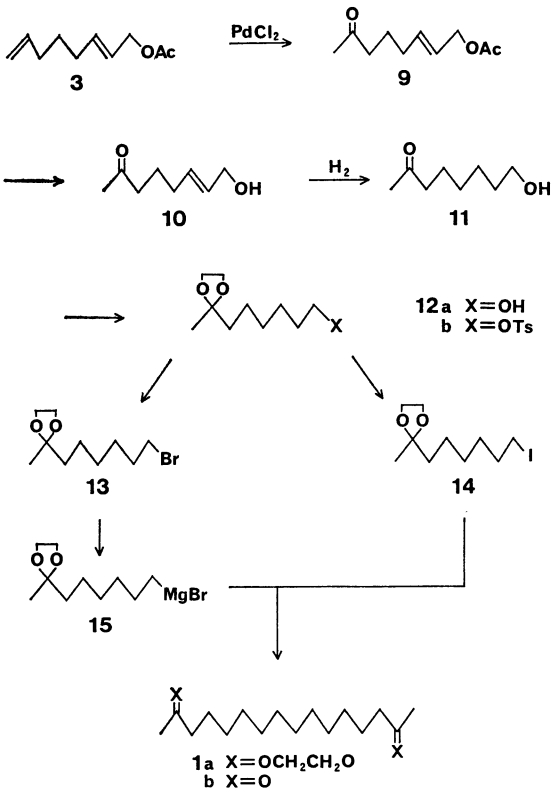
In this synthetic method, there are two problems to be improved. The first one is the iron catalyzed coupling of the allylic chlorides **5** and **6**. Although the desired tetraene **7** was obtained as a main product in 55%, the



formation of the branched isomers as by-products cannot be avoided. The coupling of even pure 8-chloro-1,6-octadiene (**5**) produced the same mixture as expected for a usual allylic coupling. Another problem is the selective oxidation. The oxidation of the terminal double bonds of the tetraene **7** catalyzed by $PdCl_2/CuCl/O_2$ produced the unsaturated diketone **8**. Usually the oxidation of the internal double bond is very sluggish and the selective formation of **8** is expected. However, the prolonged oxidation of **7** caused the slow oxidation of the internal olefin to form a trione. This is due to the fact that these internal olefins are 1,5-diolefins and can coordinate easily to palladium as bidentate ligand. Therefore, in order to avoid over-oxidation, the oxidation must be stopped before the complete consumption of the tetraene, and hence chromatographic separation of the products is necessary. In order to solve these problems, the present study has been carried out.

The new method starts from 8-acetoxy-1,6-octadiene (**3**)[3] and the synthesis of the diketone **1b** was carried out by the following sequence of reactions.

In this method, the selective oxidation of **3** was carried out at first. Also the formation of by-product in the coupling reaction was avoided by applying a reaction



of the saturated Grignard reagent **15** with the saturated iodide **14**. Thus the above mentioned problems of the first method were solved.

The selective oxidation[5] of the terminal olefin of **3** with $PdCl_2/CuCl/O_2$ in aqueous DMF at room temperature proceeded smoothly with high selectivity to form the keto acetate **9** in 82% yield. The hydrolysis of **9** with K_2CO_3 in aqueous ethanol, followed by hydrogenation using Raney nickel catalyst produced the keto alcohol **11** in 87% yield. When the hydrogenation of the allylic acetate **9** was carried out, extensive hydrogenolysis was observed to give 2-octanone. The ketone moiety of **11** was protected as an ethylene acetal and the resulting alcohol **12a** was converted into the tosylate **12b**. The tosylate **12b** was transformed into the bromide **13** and the iodide **14** by treatment with LiBr and NaI in acetone in 72 and 74% overall yields from the alcohol **12a**, respectively. A direct bromination of the alcohol gave **13** in rather poor yield.

The formation of the C_{16} diketone **1b** was carried out by the coupling of the C_8 halide with the corresponding Grignard reagent. In general, a satisfactory coupling of a Grignard reagent with an aryl or vinyl halide proceeds by using transition metal complexes, especially nickel compounds, as catalyst.[6-8] On the other hand, the coupling of alkyl halides is more difficult, although several catalysts are known.[9,10] At first nickel complexes of phosphine or 2,2'-bipyridyl were used, but these complexes did not give satisfactory results. The coupling by the catalysis of $CuCl_2/LiCl$ and CuCl/LiCl[11] was tried without much success. The most satisfactory results were obtained by the use of CuI coordinated by 2,2'-bipyridyl. The reaction of the bromide **13** with the Grignard reagent **15** with this catalyst gave the coupled product in 60% yield. Then the iodide **14** was used for the reaction together with a slight excess of the Gringnard reagent **15** in THF, the yield increased to 83%. The hydrolysis of the acetal under mild conditions produced 2,15-hexadecanedione as colorless crystals, which was identified on the basis of its melting point,[2] spectral data and elemental analysis.

Experimental

Melting points were taken on SHIBATA (No. 297) melting point apparatus. Infrared spectra were determined on a JASCO (IRA-2) spectrophotometer. NMR spectra were determined in CCl_4 solution on a HITACHI (R-24A) spectrometer using tetramethylsilane as an internal standard.

Oxidation of 8-Acetoxy-1,6-octadiene (3). A mixture of $PdCl_2$ (1.60 g, 9.03 mmol), CuCl (8.86 g, 89.5 mmol), *N,N*-dimethylformamide (45 ml) and water (5.4 ml) was placed in a 200 ml glass vessel fitted with a gas inlet tube and shaken under oxygen atmosphere for 1 h, during which time 430 ml of oxygen was absorbed. 8-Acetoxy-1,6-octadiene (14.9 g, 88.4 mmol) was added and the reaction mixture was shaken for 6 h (total absorption was 1080 ml). The reaction was quenched with 3N-hydrochloric acid (50 ml). The mixture was extracted with dichloromethane. The extract was washed with brine and dried over Na_2SO_4. Filtration and concentration of the extract *in vacuo* gave a crude product (15.7 g) as yellow oil, which was distilled (bp 67—85 °C/2.5 Torr) to give 8-acetoxy-6-octen-2-one (**9**) (13.2 g, 72.0 mmol, 81.5%). NMR (CCl_4): δ 5.75 (double d, J=4 and 14 Hz, 1H), 5.40 (double d, J=6 and 14 Hz, 1H) 4.45 (d, J=4 Hz, 2H), 2.40 (t, J=7 Hz, 2H), 2.2—1.8 (m, 2H), 2.05 (s, 3H), 1.95 (s, 3H), and 1.62 (m, 2H). IR (neat): 2950, 1740, 1710, 1670, 1370, 1240, 1165, 1030, 980, and 610 cm^{-1}.

Preparations of 8-Hydroxy-6-octen-2-one (10). A mixture of the keto acetate **9** (10.3 g, 55.9 mmol), 13% aqueous K_2CO_3 (50 ml) and ethanol (100 ml) was stirred for 72 h at room temperature. The reaction mixture was extracted with dichloromethane. The aqueous layer was extracted with dichloromethane several times. The combined extract was washed with brine and dried over Na_2SO_4. Filtration and concentration of the extract *in vacuo* gave a crude product (7.68 g), which was further purified by distillation (bp 78—81 °C/3 Torr) to give 8-hydroxy-6-octen-2-one (6.92 g, 48.7 mmol) 87.2%). NMR (CCl_4): δ 5.2—5.8 (m, 2H), 3.95 (broad, 2H), 3.20 (broad, 1H, -OH), 2.40 (t, J=7.0 Hz, 2H), 2.10 (s, 3H), 1.80—2.10 (broad, 2H), and 1.40—1.70 (broad, 2H). IR (neat): 3600—2950, 2925, 1710, 1360, 1160, 1090, 1000, and 970 cm^{-1}.

Preparation of 8-Hydroxy-2-octanone (11). 8-Hydroxy-6-octen-2-one (3.86 g, 27.2 mmol) in ethanol (20 ml) was hydrogenated with a Raney nickel catalyst (80 mg) under 11.5 atm of hydrogen at 25 °C with stirring for 1.5 h, during which time 650 ml of hydrogen was absorbed. The reaction mixture was filtered through celite and the celite was washed with ethanol. The combined filtrate was evaporated *in vacuo* to give 8-hydroxy-2-octanone (**11**) (3.89 g) which was used without purification. NMR (CCl_4): δ 3.80 (broad, 1H, -OH), 3.60 (t, J=7.0 Hz, 2H), 2.45 (t, J=7.0 Hz, 2H), 2.10 (s, 3H), and 1.10—1.80 (broad, 8H). IR (neat): 3600—2950, 2920, 1710, 1360, 1165, 1055, 720, and 600 cm^{-1}.

Acetalization of 8-Hydroxy-2-octanone. A mixture of the alcohol **11** (2.71 g, 18.8 mmol), ethylene glycol (30 g, 480 mmol), benzene (120 ml) and a catalytic amount of *p*-toluenesulfonic acid was placed in a 200 ml flask, equipped with a

water-separator and a condenser. The reaction mixture was refluxed for 8 h. After the usual work-up, a crude product (3.20 g) was chromatographed on silica gel. Elution with 1% isopropyl alcohol in hexane gave the acetal **12a** (2.96 g, 15.8 mmol, 83.6%). NMR (CCl_4): δ 4.30 (s, 4H), 3.90 (t, J=7.0 Hz, 2H), 3.0 (broad, 1H, -OH), 1.30—1.80 (broad, 10H), and 1.40 (s, 3H). IR (neat): 3600—3100, 2925, 1380, 1250, 1220, 1140, 1060, 950, and 850 cm^{-1}.

Preparation of 6-(2-Methyl-1,3-dioxolan-2-yl)hexyl p-*Toluenesulfonate (12b).* A solution of the acetal **12a** (1.08 g, 5.77 mmol) in dry pyridine (10 ml) was treated at 0 °C under nitrogen with freshly recrystallized *p*-toluenesulfonyl chloride (2.0 g, 10.6 mmol) overnight. The reaction mixture was poured into dichloromethane, and the dichloromethane solution was washed with ice-cold 1N-hydrochloric acid (until the aqueous layer reached pH 4). The aqueous layer was extracted with dichloromethane several times, the combined extract was washed with an ice-cold $NaHCO_3$ solution and brine and dried over $MgSO_4$. Filtration and concentration of the extract *in vacuo* gave the tosylate **12b** (1.92 g, 5.60 mmol, 97%), which was used without purification. NMR (CCl_4): δ 7.7 (d, J= 8.0 Hz, 2H), 7.25 (d, J=8.0 Hz, 2H), 3.90 (t, J=6.0 Hz, 2H), 3.80 (s, 4H), 2.4 (s, 3H), 1.1—1.8 (broad, 10H), and 1.20 (s, 3H). IR (neat): 2925, 1600, 1360, 1180, 1100, 955, 920, 810, 660, and 560 cm^{-1}.

Preparation of 1-Bromo-6-(2-methyl-1,3-dioxolan-2-yl)hexane (13). A mixture of the tosylate **12b** (4.5 g, 13.4 mmol), LiBr (6.71 g, 77.2 mmol) and dry acetone (80 ml) was refluxed for 3 h. Most of acetone was removed *in vacuo* at 25 °C. The residue was diluted with ether, insoluble material was removed by filtration and the ethereal filtrate was washed with water. The aqueous layer was extracted with ether several times and the combined ethereal extract was washed with brine and dried over $MgSO_4$. Filtration and concentration of the extract *in vacuo* gave a crude product (3.08 g), which was chromatographed on silica gel. Elution with 20% ether in hexane gave pure bromide **13** (2.50 g, 9.97 mmol, 72.2% (2 steps) based on **12a**). NMR (CCl_4): δ 3.80 (s, 4H), 3.3 (t, J=6.0 Hz, 2H), 1.2—2.0 (broad, 10H), and 1.20 (s, 3H). IR (neat): 2925, 1380, 1250, 1220, 1060, 950, 870, 730, 650, 560, and 530 cm^{-1}.

Preparation of 1-Iodo-6-(2-methyl-1,3-dioxolan-2-yl)hexane (14). The iodide **14** was prepared by the same procedure as described above, from the tosylate **12b** (1.48 g, 4.34 mmol) and NaI (3.10 g, 20.7 mmol) in dry acetone (40 ml). Chromatography on silica gel and elution with 20% ether in hexane gave the iodide **14** (0.99 g, 3.32 mmol, 74.2% (2 steps) based on **12a**). NMR (CCl_4): δ 3.75 (s, 4H), 3.10 (t, J=6.0 Hz, 2H), 1.1—2.0 (broad, 10H), and 1.2 (s, 3H). IR (neat): 2925. 1380, 1260, 1220, 1060, 950, 870, 710, 600, and 530 cm^{-1}.

Preparation of the Grignard Reagent (15). A 25 ml two neck round bottom flask, equipped with a magnetic bar, a condenser, a rubber septum and a gas inlet was flame-dried. Sliced metal magnesium (154 mg, 6.34 mmol) was added to the flask, and nitrogen was introduced into the apparatus, to which a solution of the bromide **13** (1.02 g, 4.05 mmol) in dry tetrahydrofuran (2 ml) was added dropwise with stirring at room temperature over 10 min. A catalytic amount of 1,2-dibromoethane was added as an initiator, and then the reaction mixture was stirred for 1 h at 40 °C. The Grignard reagent was titrated with 0.1N-hydrochloric acid. The normality of the Grignard reagent was 0.24N.

Coupling of the Grignard Reagent 15 and the Iodide 14. A 25 ml two neck round bottom flask equipped with a magnetic bar, a rubber septum and a gas inlet was flame dried. Purified CuI (40.4 mg, 0.2 mmol) and 2,2′-bipyridyl (31.7 mg, 0.2 mmol) were added to the flask, and nitrogen was introduced. Then dry tetrahydrofuran (2 ml) was added to the flask. The mixture was stirred for 30 min at room temperature and cooled to 2 °C to which a solution of the iodide **14** (299 mg, 1.0 mmol) in dry tetrahydrofuran (2 ml) was added at once at 2 °C and the mixture was stirred for 10 min. To this solution a solution of the Grignard reagent **15** in tetrahydrofuran (6.3 ml of 0.24N solution, 1.5 mmol) was added dropwise at 2 °C over 10 min. The reaction mixture was stirred for 2 h at 2 °C and quenched with a saturated NH_4Cl solution. The reaction mixture was extracted with dichloromethane and the organic layer was washed with a saturated NH_4Cl solution (until the aqueous layer remained colorless), brine and dried over $MgSO_4$. Filtration and concentration of the extract *in vacuo* gave colorless oil, which was purified by chromatography on silica gel. The column was eluted with 20% ether in hexane. Concentration of the eluent *in vacuo* gave the coupled product **1a** (269 mg, 0.79 mmol, 79%) as a crystalline material. Further purification by recrystallization from methanol gave pure 1,12-bis(2-methyl-1,3-dioxolan-2-yl)dodecane (**1a**) mp 69.0—70.5 °C). NMR (CCl_4): δ 3.80 (s, 8H), 1.1—1.7 (broad, 24H), and 1.2 (s, 6H). IR (KBr disk): 2965, 2900, 2850, 1465, 1450, 1370, 1250, 1230, 1140, 1070, 1050, 1030, 950, 860, 810, 730 and, 580 cm^{-1}.

2,15-Hexadecanedione (1b) by Deacetalization of 1a. The diacetal **1a** (42 mg, 0.12 mmol) and $CuSO_4$ (50 mg) in MeOH (2 ml) and water (0.5 ml) were heated under reflux for 15 min. Undissolved $CuSO_4$ was filtered off, and most of methanol was removed *in vacuo* at room temperature. The residue was dissolved in ether, and the ethereal solution was washed with brine and dried over $MgSO_4$. Filtration and concentration of the solution *in vacuo* gave the diketone **1b** (25.6 mg) as a crystalline material. Further purification by recrystallization from MeOH gave pure 2,15-hexadecanedione **1b** (mp 83.5—84.5 °C. reported mp 83—84 °C[2]). NMR (CCl_4): δ 2.2 (t, J=7.0 Hz, 4H), 1.95 (s, 6H), and 1.0—1.7 (broad, 20H). IR (KBr): 2900, 2830, 1710, 1460, 1160, 800, 720, and 600 cm^{-1}. Found: C, 75.77; H, 11.81, Calcd for $C_{16}H_{30}O_2$: C, 75.54; H, 11.89%.

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