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Hydrogenation of 2,5-Diacetoxy-2,5-dimethyl-3-hexyne over Palladium[1a]

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Received July 19, 1977

The hydrogenation of **1** over 10% palladium on charcoal proceeds to give seven products (**2–8**). Alkene **2** is the precursor of the other products. A concerted process including hydrogenation, hydrogenolysis, and isomerization is postulated to account for the direct formation of **5** from **2**. The effect of added nitrogen bases on the product distribution is presented, and several mechanistic alternatives are discussed.

One of the most useful reactions for the preparation of pure cis olefins has been the catalytic hydrogenation of acetylenes over deactivated catalysts at room temperature and atmospheric pressure.[2] The classic catalyst for this reaction is Lindlar's catalyst, lead-poisoned palladium on calcium carbonate.[3] The partial hydrogenation of acetylenic carbinols has been studied by many workers. These are useful synthetic intermediates due both to their ease of synthesis and to the possibility of transforming them into molecules containing different functionality.[4] Thus, much of the work on acetylenic carbinols has been directed toward their selective hydrogenation to the olefinic stage without any further reduction to the alkane system.

Moderation of palladium catalysts with added pyridine has been employed to hydrogenate acetylenic carbinols to allylic alcohols.[5] The pyridine apparently functions to poison the catalyst by being absorbed more strongly on the catalyst surface than the alkene but less strongly adsorbed than the acetylene. This could result in selective hydrogenation,[6] although recently it has been suggested that selectivity in alkyne hydrogenation is not due to different strenghts of adsorption of alkenes and alkynes but rather to different kinds of surface adsorption sites.[7] The self-poisoning effect of pyridine on its own hydrogenation has been reviewed.[8] The reduction of pyridine to piperidine results in even stronger catalyst poisoning by the piperidine. The unshared electron pair on the nitrogen atom apparently causes the effect since pyridinium salts are readily hydrogenated without any self-poisoning of the catalyst.

Many other catalyst inhibitors have been employed for partial hydrogenation of acetylenes over palladium. These include, for example, morpholine,[9] barium carbonate,[10] calcium carbonate,[11] combinations of lead acetate and quinoline with calcium carbonate,[12] barium sulfate,[11] potassium hydroxide,[13] etc.

Although palladium is one of the most commonly used hydrogenation catalysts, isomerization[14] or hydrogenolysis[15] can be serious problems with this catalyst. In some cases catalyst modifiers can be employed to prevent these reactions. For example, potassium hydroxide prevents the hydrogenolysis of the hydroxyl groups of propargyl alcohols.[16]

We have undertaken a study of the hydrogenation of 2,5-diacetoxy-2,5-dimethyl-3-hexyne (**1**) over 10% palladium on charcoal in the presence of pyridine and piperidine as catalyst modifiers. We had inadvertently observed that upon hydrogenation of **1**, varying quantities of 2-acetoxy-2,5-dimethyl-4-hexene (**5**) were produced.[1a] The production of this novel reaction product involves hydrogenation, isomerization, and hydrogenolysis. The hydrogenation of **1** has been previously reported, but the only isolated product was the alkene **2**.[17]

Results and Discussion

Hydrogenation of **1** over 10% palladium on charcoal at atmospheric pressure in absolute ethanol results in the formation of seven different compounds (**2–8**, Scheme I) along with acetic acid from hydrogenolysis of some of the acetate groups. The composition of the reaction mixture was followed as a function of equivalents of hydrogen absorbed by the system. This plot is shown in Figure 1. Examination of the figure shows that the concentrations of **2** and **5** steadily increase to a maximum and then decrease as they are further transformed. Figure 2 shows the data for hydrogenation of **2** under similar conditions. It is clear that **2** is the precursor to the other reaction products, while **4**, **7**, and **8** are end products which are not further transformed. Scheme I shows a plausible sequence to account for each of the products observed.

The initial hydrogenation of **1** proceeds to give predominantly the cis alkene (**2**) along with a small quantity of the trans alkene (**3**). The trans alkene could have been formed directly from the acetylene[18] or as a result of isomerization of the cis alkene over the palladium catalyst.[19] The former is preferred since **3** is not formed during hydrogenation of **2** nor is **2** formed during hydrogenation of **3**. Presumably, in either case, formation of **3** would be due to a stepwise addition of hydrogen atoms, with the first addition step being reversible.[20]

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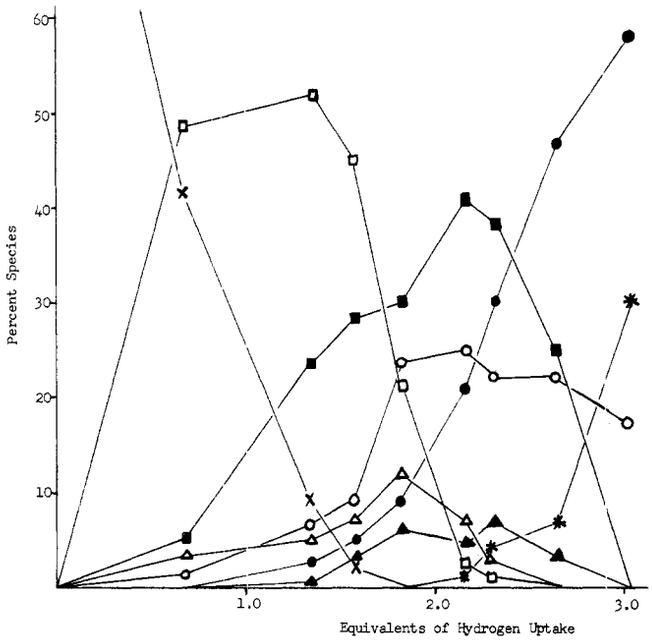


Figure 1. Plot of product composition vs. equivalents of hydrogen uptake during hydrogenation of 1: 1 (x), 2 (□), 3 (△), 4 (○), 5 (■), 6 (▲), 7 (●), 8 (*).

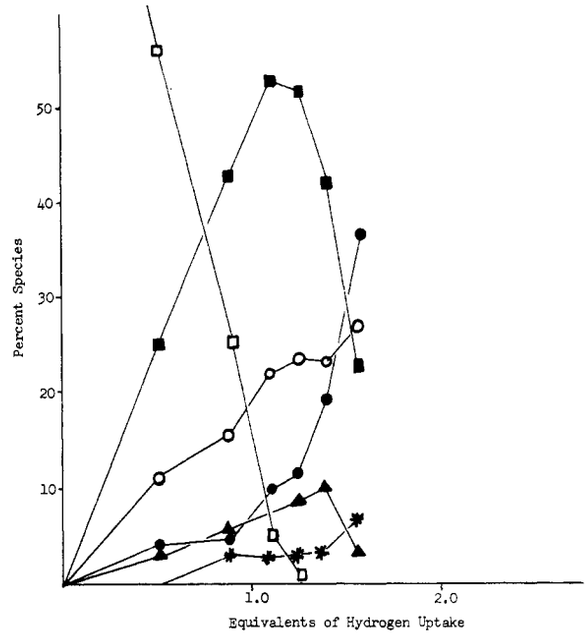
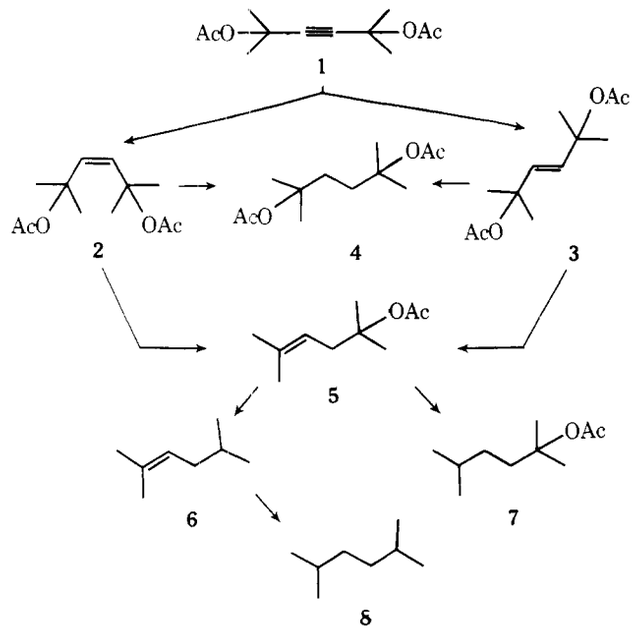


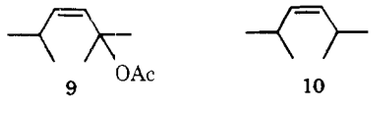
Figure 2. Plot of product composition vs. equivalents of hydrogen uptake during hydrogenation of 2: 2 (□), 3 (△), 4 (○), 5 (■), 6 (▲), 7 (●), 8 (*).

Scheme I



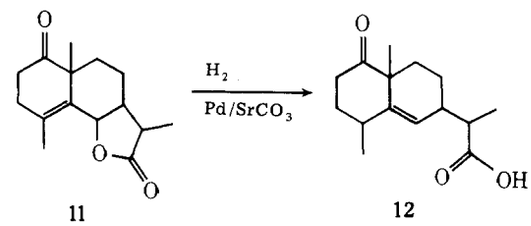
The fully saturated diester **4** is formed in a straightforward hydrogenation from either **2** or **3**.

The origin of acetate **5** is very intriguing since its direct formation from either **2** or **3** would require concomitant hydrogenolysis and double-bond isomerization. If hydrogenolysis occurs in allylic systems via initial C–O cleavage followed by hydrogen addition, as has been suggested,[21] it is not surprising that we observe addition of the hydrogen at a position allylic to the original acetate group. This results in the formation of the most substituted alkene isomer. Alternatively, hydrogenolysis without rearrangement would give **9**, which could then isomerize to **5**. The isomerization of **10** to **6** has been observed during hydrogenation of **10** (and its trans isomer) over palladium.[22]



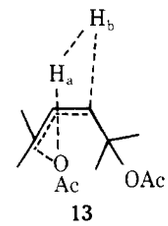
9 10

A reaction very similar to that reported here occurs during the hydrogenation of deoxypseudosantonin (**11**) over 5%



11 12

$Pd/SrCO_3$.[23] In this case the double bond has migrated to the less substituted position, while in our case the more substituted alkene is formed. In both cases, none of the other isomer was formed. These observations lead us to favor a third mechanism for the formation of **5**. A concerted (or nearly concerted) addition of hydrogen via the six-centered transition state **13** would give exclusive formation of **5**. Furthermore, a



13

similar mechanism for the hydrogenation of **11** would also lead to the formation of **12**. Models indicate that the two atoms to which hydrogen is being added can approach to within 2.6 Å of one another. The planarity of the C=C—C—O system would be insured by binding of both the π system and the oxygen atom to the catalyst surface.

A related system is the hydrogenolysis of benzylic esters which has been studied in great detail. They are thought to hydrogenolyze by hydride attack of the protonated ester in an S_N2-like reaction.[24] If transition state **13** were polarized with $H_a^{\delta+}$–$H_b^{\delta-}$, this would be similar to an S_N2' reaction and consistent with our results.

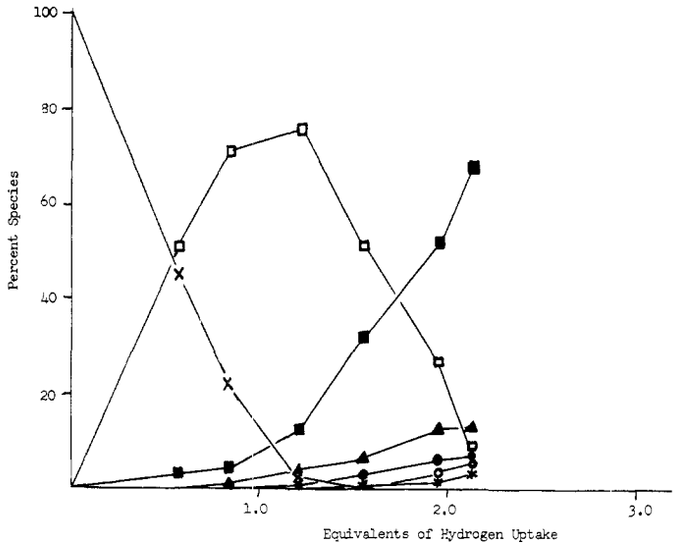


Figure 3. Plot of product composition vs. equivalents of hydrogen uptake during hydrogenation of 1 in the presence of pyridine: 1 (x), 2 (□), 4 (○), 5 (■), 6 (▲), 7 (●), 8 (*).

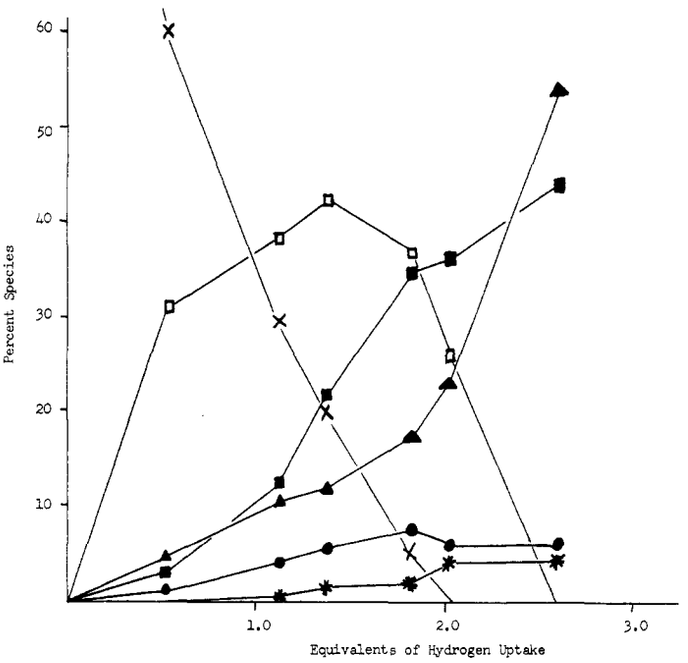


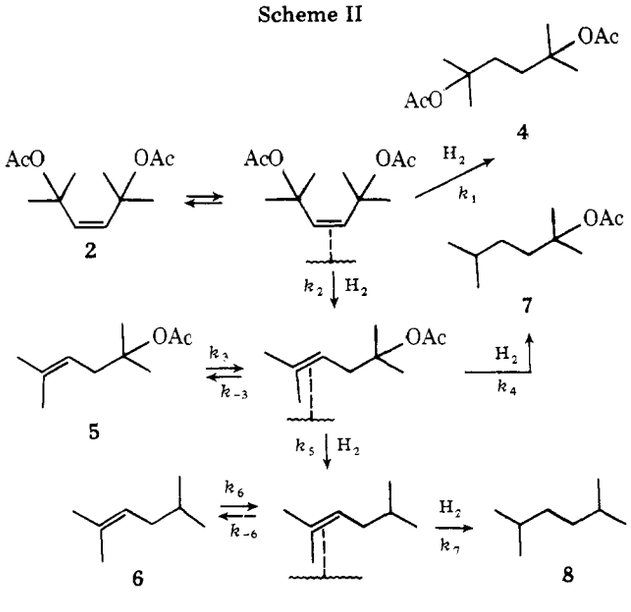
Figure 4. Plot of product composition vs. equivalents of hydrogen uptake during the hydrogen of 1 in the presence of piperidine: 1 (x), 2 (□), 5 (■), 6 (▲),7 (●), 8 (*).

Several other pathways in Scheme I have been verified by separate hydrogenation. Hydrogenation of **3** gives very similar results to those obtained with **2**. Acetate **7** is cleanly produced by hydrogenation of pure **5**, while **8** is produced quantitatively by hydrogenation of **6**. The formation of **6** by hydrogenolysis of **5** will be discussed later. Hydrogenation of **4** and **7** both failed to give any reaction under a variety of conditions, thus ruling out **4** → **7** and **7** → **8**.

The hydrogenation products from **1** and **2** as well as the rate of hydrogen uptake are significantly altered by the addition of small quantities of nitrogen bases. The product ratio plotted vs. equivalents of hydrogen absorbed for both pyridine and piperidine is shown in Figures 3 and 4, respectively. Hydrogenation of **2** in the presence of pyridine or piperidine again showed **2** to be the precursor of the other products. The presence of the catalyst modifier supresses the formation **4**, **7**, and **8**. Thus, simple alkene hydrogenation is inhibited by these nitrogen bases. This is reasonable in view of the known poisoning of palladium catalysts by nucleophiles.[5,9,11,25]

Piperidine has the further effect of enhancing the hydrogenolysis of **5** to produce **6**, which becomes the major product. However, prolonged hydrogenation of **1** does not change the 54:44 ratio of **6**/**5**. Furthermore, when pure **5** is hydrogenated in the presence of piperidine, no reaction occurs. In the absence of piperidine, **5** is smoothly converted to **7** without any formation of **6**. This anomolous behavior can be explained by the mechanism shown in Scheme II. In the presence of either pyridine or piperidine, k_1, k_4, and k_7 are dramatically decreased. Pyridine has no effect on k_5, whereas piperidine increases k_5 to the extent that **6** becomes the major product. We propose that piperidine is simultaneously inhibiting k_4 and enhancing k_5, while assuring that **5** can not be readsorbed on the catalyst surface ($k_3 \sim 0$). Thus, the ratio of **5**/**6** is determined by the relative rates of hydrogenolysis (k_5) and desorption from the catalyst surface (k_{-3}). Since piperidine prevents the adsorption of **5** onto the catalyst surface, **6** can only be formed when **5** is produced from **2** directly on the catalyst surface. Piperidine also prevents **6** from being readsorbed ($k_6 = 0$). Thus, prolonged hydrogenation does not change the **5**/**6** ratio. In the absence of piperidine, k_4 is much larger than k_5 so that **6** is a minor product. Alternate explanations are possible. For example, piperidine could be decreasing, but to different extents, the concentration of **5** adsorbed at the specific catalyst sites responsible for hydrogenation and hydrogenolysis.

Scheme II



These nitrogen bases also have a marked effect on the rate of hydrogen uptake. In all cases, the slope from a plot of equivalents of hydrogen uptake vs. time remained constant for at least 0.5 equiv of hydrogen uptake. These initial slopes are given in Table I for varying concentrations of pyridine and piperidine. Pyridine retards the rate for all concentrations, and piperidine enhances the rate at low concentration while retarding the rate at high concentration. It is not clear what interpretation should be given this result.

Several reaction variables have been studied. The substrate/catalyst ratio was varied from 5:1 (by weight) to 30:1 without any significant change in the product ratio (Table II). The inhibitor/catalyst ratio was varied over a small range, again without any significant change in product ratios. The product curves were essentially superimposable on the curves of Figures 3 and 4 when 200 μL of inhibitor was used rather than 50 μL.

Table I. Initial Rate of Hydrogen Uptake[a]

Nitrogen base	Amount	Initial rate[b]
Pyridine	50 μL	1.0
	200 μL	0.7
	500 μL	0.6
	5 mL	0.3
	15 mL	0.1
Piperidine	50 μL	1.9
	200 μL	1.8
	500 μL	1.6
	5 mL	0.9
	15 mL	0.7
None		1.5

[a] Each run contained a total volume of 30 mL of solvent (absolute ethanol plus nitrogen base), 5 mg of 10% Pd/C, and 75 mg of **1**. They were carried out at 25 °C and 1 atm of hydrogen pressure. [b] Slope of equivalents of H_2 uptake vs. time through the first 0.5 equiv of hydrogen uptake.

Experimental Section

General. Analytical gas chromatography (GC) was performed on a Perkin-Elmer Model 810 (hydrogen flame detector) chromatograph using temperature programming. Preparative GC was performed on a Varian Aerograph A-90-P (thermal conductivity detector) chromatograph. The analytical column was 10 ft × ⅛ in 15% FFAP on 60–80 mesh Chromosorb W; preparative columns were 10 ft × ¼ in 15% FFAP or 15% Carbowax 20 M on 60–80 mesh Chromosorb W. Percent composition data were estimated by peak areas (uncorrected). Anhydrous magnesium sulfate was used for all drying operations. Nuclear magnetic resonance (NMR) spectra were determined on a Varian Associates A-60 spectrometer. Infrared (IR) spectra were determined on a Perkin-Elmer Model 137 spectrophotometer. Melting points were measured with a Thomas-Hoover capillary melting point apparatus and are uncorrected.

All products were identified by independent synthesis as described below, with the exception of **8**, which was identified by direct comparison with a sample obtained from the Aldrich Chemical Co. All chemicals used were reagent grade. Microanalyses were performed by Chemalytics, Inc., Tempe, Ariz.

Analytical Hydrogenation Procedure. A semimicro atmospheric pressure apparatus was employed.[26] A 50-mL Erlenmeyer flask equipped with a magnetic stirrer and side-arm addition tube was charged with 5 mg of palladium on charcoal (Engelhard Industries) followed by the addition of 10 mL of absolute ethanol along with any catalyst modifier (50 μL of pyridine or piperidine). The flask was evacuated and filled with hydrogen three times to eliminate air. The catalyst was then reduced by stirring at atmospheric pressure for 15 min. A solution of 75 mg of substrate in 10 mL of absolute ethanol was added via the side arm followed by an additional 10 mL of absolute ethanol. The mixture was hydrogenated at atmospheric pressure.

After an appropriate uptake of hydrogen, the flask was evacuated. The solution was filtered to remove the catalyst, 150 mL of water was added, and the resulting mixture was extracted with two 25-mL portions of ether. The combined ether extracts were washed first with 25 mL of 5% hydrochloric acid (if pyridine or piperidine was used) and then with 50 mL of saturated sodium bicarbonate. The solution was *not* dried since it was found that drying agents adsorbed a significant amount of product. The ether solution was then analyzed directly by analytical GC. The equivalents of hydrogen uptake agreed to within 5% of that calculated from the GC analyses.

2,5-Diacetoxy-2,5-dimethyl-3-hexyne (1). A mixture of 360 mL of pyridine, 100 g (0.7 mol) of 2,5-dimethylhex-3-yne-2,5-diol, and 214 g (2.1 mol) of acetic anhydride was heated at 85 °C with stirring for 50 h. The mixture was cooled, poured onto 1500 mL of cold water, and extracted with three 200-mL portions of 30–60 °C petroleum ether. The combined petroleum ether extracts were washed with three 100-mL portions of 5% HCl, 200 mL of 5% sodium carbonate, and three 200-mL portions of water and dried. Removal of the petroleum ether by rotary evaporation followed by fractional distillation gave 155 g (96%) of **1**: bp 63–65 °C (1 mm) [lit.[27] bp 106–107 °C (18 mm)]; IR (neat) 5.75, 6.82, 6.95, 7.35, 7.79, 8.03, 8.37, 8.80, 9.83, 10.40, 10.51, 11.52, 12.00, 12.59 μm; NMR (CCl_4) δ 3.18 (12 H, s), 3.90 (6 H, s).

***cis*-2,5-Diacetoxy-2,5-dimethyl-3-hexene (2).** A solution of 60 g (0.27 mol) of **1**, 0.25 mL of synthetic quinoline, 0.52 g of 5% palladium on barium sulfate, and 250 mL of methanol was hydrogenated at room temperature for 3 h using a Paar hydrogenation apparatus. The hydrogen pressure was maintained at 30 psig. The catalyst was removed by filtration, the filtrate was added to 800 mL of cold water, and the resulting mixture was extracted with three 150-mL portions of 30–60 °C petroleum ether. The combined extracts were washed with 50 mL of 5% hydrochloric acid and 50 mL of water and then dried. Removal of the solvent by rotary evaporation followed by fractional distillation gave 51.4 g (85%) of **2**: bp 110–112 °C (13 mm) [lit.[25] bp 112 °C (14 mm)]; IR (neat) 5.75, 6.04, 6.78, 6.85, 6.95, 7.30, 7.95, 8.12, 8.40, 8.75, 9.75, 10.52 μm; NMR (CCl_4) δ 1.58 (12 H, s), 1.94 (6 H, s), 5.29 (2 H, s).

***trans*-2,5-Diacetoxy-2,5-dimethyl-3-hexene (3).** Using a literature procedure,[17] 20.5 g (0.14 mol) of 2,5-dimethylhex-3-yne-2,5-diol was reduced by lithium aluminum hydride to 14.1 g of crude product, which was shown by NMR analysis to be 63% *trans*-2,5-dimethyl-3-hexene-2,5-diol[28] and 37% reactant. The crude sample was acetylated by the same procedure used in the preparation of **1**. This crude product was separated by preparative GC to give a pure sample of **3**: mp 73–74 °C; IR (CCl_4) 5.75, 7.30, 8.00, 8.84, 9.75 μm; NMR (CCl_4) δ 1.48 (12 H, s), 1.92 (6 H, s), 5.84 (2 H, s).

Anal. Calcd: C, 63.14; H, 8.83. Found: C, 62.90; H, 8.75.

2,5-Dimethyl-2,5-diacetoxyhexane (4). Using the procedure described for the synthesis of **1**, 25 g (0.17 mol) of 2,5-dimethylhexane-2,5-diol, 150 mL of pyridine, and 38.4 g (0.38 mol) of acetic anhydride gave 34 g (87%) of **4**: bp 120–121 °C (20 mm) [lit.[29] bp 117–118 °C (19 mm)]; IR (neat) 5.75, 6.55, 6.85, 7.28, 7.90, 8.15, 8.96, 9.70 μm; NMR (CCl_4) δ 1.40 (12 H, s), 1.78 (4 H, s), 1.92 (6 H, s).

2,5-Dimethyl-2-hexene (6). To 0.5 g (0.0038 mol) of 2,5-dimethyl-2-hexanol was added 10 g of pyridine and 0.8 g of phosphorous oxychloride. The mixture was stirred at 25 °C for 12 h and then at 100 °C for 1.5 h, cooled, and poured into 4 g of ice. To the resulting mixture was added 100 mL of water, and the solution was extracted with three 20-mL portions of pentane. The combined pentane extracts were washed with two 25-mL portions of 5% hydrochloric acid and two 20-mL portions of saturated sodium bicarbonate and dried. The solvent was removed by rotary evaporation to give 0.2 g of crude product. NMR analysis indicated that the sample was 60% 2,5-dimethyl-1-hexene and 40% **6**.[30]

2,5-Dimethyl-2-acetoxy-4-hexene (5). The sample isolated from the hydrogenation of **1** gave NMR and IR data identical to that published by Bly.[31] The sample was further identified by its reduction to 2,5-dimethyl-4-hexen-2-ol.

2,5-Dimethyl-4-hexen-2-ol. A 2.34-g (0.0138 mol) sample of **5** was dissolved in 50 mL of anhydrous ether and slowly added to a stirred slurry of 1.60 g of lithium aluminum hydride in 50 mL of anhydrous ether. After the addition was complete, the mixture was refluxed for

Table II. Effect of Substrate/Catalyst Ratio[a]

1, mg	Catalyst, mg	Equiv of H_2	1/catalyst	Products, % 1	2	3	4	5	6	7	8
152.9	5.5	1.19	27.8	9.3	60.3	6.9	5.4	14.3	1.4	2.3	0
103.5	5.3	1.24	19.5	4.2	61.8	7.3	6.4	16.7	0.8	2.8	0
80.1	5.0	1.29	16.0	8.0	56.5	3.6	8.7	18.4	2.4	2.4	0
71.8	5.8	1.61	12.5	0.6	32.8	13.5	11.5	33.3	3.8	4.0	0
79.9	10.1	1.67	7.9	0	36.0	8.0	14.6	30.8	5.0	5.6	0
72.7	5.1	2.04	14.3	0	9.5	7.4	14.5	48.6	7.9	11.1	1.0
51.1	5.0	1.96	10.2	1.5	18.5	3.9	15.5	40.4	9.3	10.1	0.8
53.3	10.2	2.06	5.2	0	12.7	8.1	14.9	45.6	9.5	8.4	0.8

[a] All runs contained 30 mL of absolute ethanol as solvent and were run at 25 °C and 1 atm of hydrogen pressure.

30 min. To the cooled mixture was added dropwise enough 5% sodium hydroxide to discharge the gray color. The mixture was filtered and dried, and the ether was removed by rotary evaporation to give 1.31 g (74%) of 2,5-dimethyl-4-hexen-2-ol. The spectral data was identical with that reported by Crandall.[32]

2,5-Dimethyl-2-acetoxyhexane (7). Using the procedure described for the synthesis of **1**, 1.0 g (0.0077 mol) of 2,5-dimethyl-2-hexanol, 0.87 g (0.0085 mol) of acetic anhydride, and 30 mL of pyridine gave 1.2 g (89%) of **7**: IR (neat) 1735, 1462, 1381, 1255, 1220, 1160, 1140, 1118, 1085, 1020, 945 cm^{-1}; NMR (CCl_4) δ 0.90 (6 H, d, J = 6 Hz), 1.1–1.8 (5 H, m), 1.40 (6 H, s), 1.91 (3 H, s).

Acknowledgment. We would like to thank the National Science Foundation (NSF–URP), the California State University, Los Angeles Foundation, and the National Institutes of Health, Research Grant RR08104, Minority Student Training for Biomedical Research (MBS), for support of this research.

Registry No.—**1**, 34106-07-5; **2**, 65149-96-4; **3**, 65149-97-5; **4**, 56323-20-7; **7**, 65149-98-6; 2,5-dimethylhex-3-yne-2,5-diol, 142-30-3; *trans*-2,5-dimethyl-3-hexene-2,5-diol, 927-81-1; 2,5-dimethylhexane-2,5-diol, 110-03-2; 2,5-dimethyl-2-hexanol, 3730-60-7.

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(1) (a) Portions of this work were presented at the 10th Western Regional Meeting of the American Chemical Society, San Francisco, Calif., Oct 16–18, 1974. (b) National Science Foundation Undergraduate Research Participant, Summer 1975. (c) MBS Trainee.
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Asymmetric and Regioselective Hydrogenation of Piperitenone by Homogeneous Rhodium Complexes

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Received July 19, 1977

Piperitenone (**1**) has been hydrogenated with homogeneous rhodium catalysts containing chiral phosphine ligands. The major product, pulegone (**2**), has been obtained in up to 38% optical purity. Piperitone (**3**), menthone (**5**), and isomenthone (**6**) were the predominant minor products.

Following the initial report of Knowles and Sabacky,[1a] the use of homogeneous transition metal catalysts for asymmetric synthesis has grown tremendously.[1] In addition, the ability of homogeneous transition metal catalysts to effect selective transformation of functional groups[2] has led to a recognition of the potential for such catalysts to operate on organic molecules in a highly specific manner.

Piperitenone (**1**) offers a unique challenge in selective hydrogenation due to the presence of two different olefinic bonds and one ketonic bond. Hydrogenation of either one or more of these unsaturated sites leads to the structures **2–10**, whereas complete reduction leads to the four diasteromeric alcohols of the menthol series **11–14**.

In addition, piperitenone is prochiral and thus offers the possibility for asymmetric synthesis of pulegone (**2**) and piperitone (**3**). Achievement of chirality at C_1 of **2** is particularly advantageous because the hydrogen atom at C_1 is not labile. Thus, whatever degree of chirality is attained in conducting an asymmetric hydrogenation of **1** to **2** is locked in on further reduction. Pulegone of high optical purity is thus the cornerstone of a direct synthesis of optically active menthol (**11**) since the configuration and enantiomeric excess obtained at

0022-3263/78/1943-1787$01.00/0