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).

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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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Asymmetric and Regioselective Hydrogenation of Piperitenone by Homogeneous Rhodium Complexes

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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

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Table I. Hydrogenation of Piperitenone

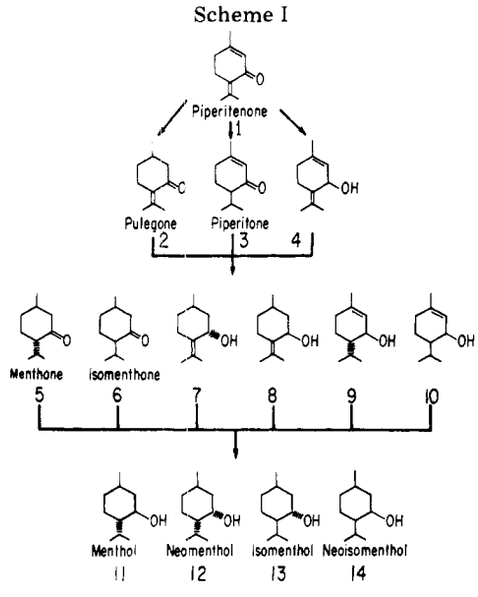
Run No.	Ligand[a]	Solvent	Temp, °C	Press, psig	Conversion, %	Time, h	Product selectivity[b] Pulegone, %	Piperitone, %	Menthones,[c] %	Minor peaks, %	Pulegone, % ee.
1	(+)-15	DMF[d]	80	180	96	18	74	4	22	<3	(−) 33
2	(+)-15	DMF	60	180	94	22	88	3	9	<3	(−) 33
3	(+)-15	DMF	40	180	74	20	92	3	5	<3	(−) 28
4	(+)-15	DMF	80	120	82	6	85	8	7	<3	(−) 27
5	(+)-15	DMF	60	120	88	19	89	4	7	<3	(−) 31
6	(+)-15	DMF	60	325	53	20	76	10	10	4 % menthols	(−) 20
7	(+)-15	DMA[d]	60	180	62	21	51	18	26	5	(−) 15
8	(+)-15	MeOH	80	180	86	2.5	59	26	15	<3	(−) 25
9	(+)-15	MeOH	60	180	84	3.0	68	21	11	<3	(−) 26
10	(+)-15	MeOH	40	180	50	4.0	78	16	6	<3	(−) 12
11	(+)-15	MeOH	80	120	72	3.0	61	30	9	<3	(−) 38
12	(+)-15	MeOH	60	120	48	4.0	71	23	6	<3	(−) 23
13	(+)-15	MeOH	40	120	37	6.5	74	21	5	<3	(−) 6
14	(+)-15	MeOH	80	60	NA[e]		64	25	11	<3	(−) 26
15	(+)-15	MeOH	60	60	62	6.0	68	24	8	<3	(−) 24
16	(−)-16	DMF	60	180	45	22	73	10	17	<3	(+) 2
17	(−)-21	DMF	100	180	32	20	47	25	6	22	(−) 2
18	(−)-21	DMF	80	180	44	20	62	25	13	<3	(−) 6
19	(+)-17	DMF	60	180	55	22	75	10	15	<3	(−) 28
20	(+)-17	DMF	60	120	42	21	67	14	9	10	(−) 31
21	(+)-18	DMF	60	180	18	22	51	25	12	12	(−) 11
22	19[g]	DMF	60	180	8	22	48	38	9	5	Too little
23	20[g]	DMF	60	180	28	20	77	10	10	3	(−) 19
24	(−)-21	MeOH	80	180	76	18	19	47	19	15[f]	(−) 7
25	(+)-22	MeOH	40	180	—	6.5	Very little reaction				Too little
26	(+)-23	MeOH	60	120	52	3.0	25	40	32	3	(−) 2

[a] See list of ligands. All added as $[Rh(diolefin)L_2]BF_4$ complex except run 23 in which we added 2L/Rh as $[Rh(NBD)Cl]_2$. [b] All based on area percent by GC on Carbowax 20 M or Carbowax 400. In cases where the minor impurities constituted <3% of the peak area, the major peaks were normalized to 100%. [c] Total menthone and isomenthone. [d] DMF = dimethylformamide; DMA = dimethylacetamide. [e] NA = not available. [f] 7% menthols, 8% others. [g] Sign of rotation not identified.

the pulegone stage is fully retained on further reduction.[3]

The established ability of homogeneous rhodium catalysts to effect selective hydrogenations as well as asymmetric hydrogenations provided the basis for our decision to investigate the utility of these catalysts first. It had been previously established by Schrock and Osborn[2c] that rhodium catalysts need approximately 1% water in the system to reduce ketones whereas olefin reduction can be conducted in the absence of water, so that we expected the ketonic portion of **1** to survive hydrogenation in anhydrous solvents. Also, it is well known that a variety of rhodium-catalyzed reactions proceed more rapidly on unsubstituted olefins than on highly substituted olefins.[2b,d] Thus, we had good grounds for expecting to achieve our objective of the formation of a predominance of **2** over **3**.

Scheme I



Results

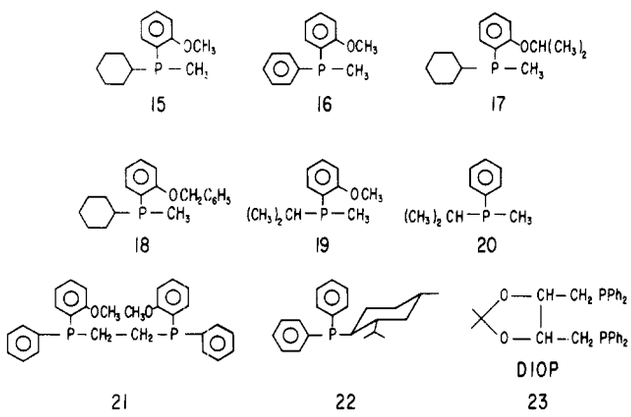
Our expections concerning the stability of the ketone bond were generally met as the amount of diastereomeric menthols or unidentified by-products was usually less than 3%.[4] The selectivity toward **2** vs. **3** normally resulted in an excess of **2** as expected (see Table I), but the ratio of **2** to **3** was quite dependent on reaction conditions. However, in methanol, the use of bidentate ligands **21** and **23** resulted in a predominance of product **3** (runs 24 and 26).

The majority of our runs were performed with the chiral ligand **15**, cyclohexylanisylmethylphosphine. In DMF, fairly long times (18–22 h) were usually required to achieve 70–96% conversion. High selectivity to pulegone (85–92%) could be obtained easily (runs 2–4) and the optical purity of the pulegone often reached 27–33% (runs 1–5). The use of DMA as solvent produced a drastic increase in piperitone content accompanied by a loss of pulegone optical purity (run 7 vs. run 2).

In methanol, the hydrogenations proceeded much more rapidly but the amount of piperitone produced increased five- to tenfold. The pulegone optical purity did not vary over a great range when the hydrogenations were run in DMF but did so to a greater extent in methanol. The highest optical purity, 38%, was obtained in methanol when the hydrogenation was run at 80 °C and 120 psi H_2 (run 11).

The use of a variety of other ligands was explored in DMF (ligands 16–21, runs 16–23) and in methanol (ligands 21–23, runs 24–26). In general, these offered pulegone of much lower

optical purity and with less selectivity than ligand **15**. Ligand **17**, the isopropyl ether analogue of ligand **15**, gave pulegone of optical purity comparable to that with **15** but the selectivity to pulegone was significantly reduced (runs 2 and 5 vs. runs 19 and 20). Of great interest was the result with the bidentate ligands **21**[5] and **23** in that piperitone was the predominant product with these ligands in methanol whereas pulegone had predominated in DMF. This may be one of the rare instances in homogeneous catalysis in which hydrogenation of a more-substituted double bond takes precedence over hydrogenation of a less-substituted double bond.



One interesting sidelight to this work concerned the composition of the menthones in regards to the ratio of menthone to isomenthone. The equilibrium ratio is well known to be ca. 70:30 in favor of menthone[6] and relatively pure menthone can be produced by oxidation of menthol[7] or equilibrative distillation of a menthone–isomenthone mixture.[8] We found that reduction of piperitenone in our catalyst system afforded a predominance of isomenthone except for run 17 at 100 °C and run 23 which contained chloride. In some cases, this predominance was only very slight but in methanol it often approached 80% of the mixture with ligand **15**. Run 9 afforded 82% isomenthone.

Experimental Section

All hydrogenations were carried out in glass Fisher-Porter aerosol compatibility tubes attached to a regulated gas manifold. Hydrogen was supplied from a small high-pressure reservoir through a regulator to maintain constant reactor pressure. Solvents were commercially available, nominally dry materials used without further purification. Piperitenone was initially prepared by the procedure of Beereboom[9] and later by that of ourselves.[10] Ligands chiral at phosphorus were supplied by W. S. Knowles,[11] generally in the form of the anionic complex.[12] Ligands **22** and **23** were purchased from Strem Chemicals. Product analyses were performed by GC on either Carbowax 20 M or Carbowax 400 columns. GC peak comparison followed by preparative GC and NMR was used for the determination of the pulegone, piperitone, and menthones peaks. Pulegone for determination of optical purity was obtained by preparative GC on a large FFAP column.

Run 11. Into a F-P tube containing a magnetic stirring bar were placed Rh(COD)(cyclohexylanisylmethylphosphine)$_2$BF$_4$ (44.8 mg, 0.06 mmol), methanol (20 mL), and piperitenone (4.5 g, 30 mmol). The mixture was bubbled with N_2 and the tube was attached to the gas manifold. Stirring was commenced and the whole apparatus was flushed four times with 120 psig H_2. The mixture was then pressurized to 120 psig H_2 and an 80 °C oil bath was brought up to surround the reaction tube. Gas uptake proceeded for 3 h at which time the rate of uptake had slowed to $\frac{1}{10}$ its original value. The oil bath was removed and the cooled system was vented. The mixture was concentrated on a rotary evaporatory to afford reaction concentrate for GC analysis.

Registry No.—**1**, 491-09-8; **2**, 89-82-7; **3**, 89-81-6; (+)-**15**, 35144-03-7; (−)-**16**, 65337-14-6; (+)-**17**, 65253-51-2; (+)-**18**, 65253-52-3; **19**, 65253-53-4; **20**, 36050-92-7; (−)-**21**, 55739-58-7; (+)-**22**, 65392-08-7; (+)-**23**, 37002-48-5; [Rh(NBD)Cl]$_2$, 12257-42-0; Rh, 7440-16-6; Rh(COD)(cyclohexylanisylmethylphosphine)$_2$BF$_4$, 65375-70-4.

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(11) We thank Dr. Knowles and his colleagues for a generous supply of the cationic complexes of these ligands.
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