12092-47-6; 1,4-diiodobutane, 628-21-7.

Supplementary Material Available: Table III, crystal data; Table IV, details of crystallographic analyses; Table V, atomic parameters for 7; Table VI, anisotropic thermal parameters for 7; Table VII, bond lengths in 7; Table VIII, bond angles in 7; Table IX, atomic parameters for 9; Table X, anisotropic thermal parameters for 9; Table XI, bond lengths in 9; Table XII, bond angles in 9; Table XIII, atomic parameters for 15; Table XIV, anisotropic thermal parameters for 15; Table XV, bond lengths in 15; Table XVI, bond angles in 15 (15 pages). Ordering information is given on any current masthead page.

Rhodium Chiral Monophosphine Complex Catalyzed Hydrogenations of Terpenic and α-(Acylamino)-Substituted Acrylic Acids

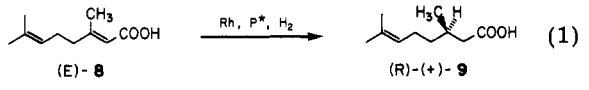
Donald Valentine, Jr.,* Katharine K. Johnson, Witta Priester, Ruen C. Sun, Katherine Toth, and Gabriel Saucy

Chemical Research Department, Hoffmann-La Roche, Inc., Nutley, New Jersey 07110

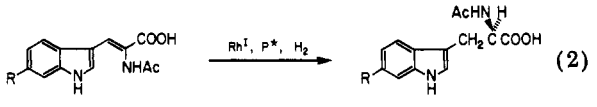
Received February 1, 1980

Four phosphines, 1–4, in which chiral menthyl or neomenthyl groups are ligated to chiral phosphorus, menthyldiphenylphosphine (5), neomenthyldiphenylphosphine (6), and (2-phenyl-2-methoxyethyl)diphenylphosphine (14), were used to form soluble rhodium catalysts for the enantioselective hydrogenations of 3,7-dimethylocta-2,6-dienoic acid (geranic acid, 8) and α-(acetylamino)-6-methylindole-3-acrylic acid (10). Under mild conditions (23 °C, 3 atm of H_2), the catalysts Rh-1 (containing (S_P)-menthylmethylphosphine), Rh-6, and Rh-14 catalyzed the hydrogenation of (*E*)-8 to optically active 3,7-dimethyloct-6-enoic acid (citronellic acid) in ca. 65–70% enantiomeric excess (ee). Very modest enantioselectivities were observed in hydrogenations of 10. The mechanism of Rh-6-catalyzed hydrogenations of 8 is discussed, and attempts to optimize this reaction for fast rates are described.

The preceding paper described our synthesis of the phosphines 1–4, which are characterized by ligation of chiral menthyl and neomenthyl moieties to chiral phosphorus.[1] This paper describes the use of these phosphines to form soluble rhodium-complex catalysts for the enantioselective hydrogenation reactions 1 and 2. Our study

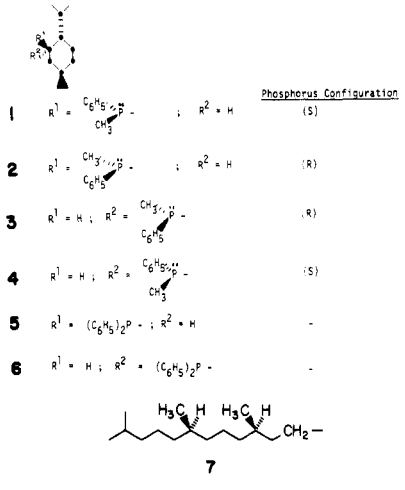


(E)-8 (R)-(+)-9 (1)



(Z)-10 (R=CH3) (R)-(-)-11 (R=CH3)
(Z)-12 (R=Cl) (R)-(-)-13 (R=Cl) (2)

of reaction 1 was part of an effort to find efficient ways to prepare the chiral moiety 7 which is found in several important natural products such as α-tocopherol (vitamin E) and phylloquinone (vitamin K_1).[2] Substrates such as 8 were potentially available as byproducts of existing technical syntheses of vitamins A and E and were considered to be possibly attractive precursors to 7. Hydrogenations of the related substrates, α- and β-methylcinnamic acids, catalyzed by rhodium complexes of 6, had been reported to give chiral carboxylic acid products in as high as 60% ee.[3] Reaction 1 was therefore subjected to detailed study by using both 1–6 and chiral diphosphines to form soluble rhodium hydrogenation catalysts. The results with rhodium catalysts containing 1–6 are presented in this paper. The results obtained by using rhodium diphosphine complex catalysts are described in the following paper.[4]



7

Our interest in reaction 2 was prompted by the potential value of 6-methyltryptophans as nonnutritive sweeteners. In this case also, both 1–6 and chiral diphosphines were studied. The results obtained by using rhodium–diphosphine complex catalysts were much better and have been reported elsewhere in detail.[5]

* To whom correspondence should be addressed at Catalytica Associates, Inc., 3255 Scott Boulevard, Suite 7E, Santa Clara, CA 95051.

(1) Valentine, D., Jr.; Blount, J.; Toth, K. *J. Org. Chem.*, preceding paper in this issue.

(2) Other approaches to the total synthesis of pure diasteromeric tocopherols have recently been reported: (a) Chan, K. K.; Cohen, N.; De Noble, J. P.; Specian, A. C., Jr.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3497–3404; (b) Cohen, N.; Eichel, W. F.; Lopresti, R. J.; Neukom, C.; Saucy, G. *Ibid.* **1976**, *41*, 3505–3511. (c) *Ibid.* **1976**, *41*, 3512–3515; (d) Chan, K. K.; Specian, A. C., Jr.; Saucy, G. *Ibid* **1978**, *43*, 3435–3440; (e) Leuenberger, H. G. W.; Boguth, W.; Barner, R.; Schmid, M.; Zell, R. *Helv. Chim. Acta* **1979**, *62*, 455–463; (f) Schmid, M.; Barner, R. *Ibid.* **1979**, *62*, 464–473; (g) Zell, R. *Ibid.* **1979**, *62*, 474–480.

(3) Morrison, J. D.; Burnett, R. E.; Aguiar, A. M.; Morrow, C. J.; Phillips, C. *J. Am. Chem. Soc.* **1971**, *93*, 1301–1303.

(4) Valentine, D., Jr.; Sun, R. C.; Toth, K. *J. Org. Chem.*, following paper in this issue.

0022-3263/80/1945-3698$01.00/0

Table I. Hydrogenations of 8 in Methanol[a]

% E in substr[g]	phosphine	mol % catal	base (amt)[b]	T, °C	rate[c]	% conv	% enantiomeric excess of 9 (confign)
95	6	0.5	M (0.1)	23	2.4	100	69 (R)[e]
98	6	0.7	A (1.1)	20	2.4	100	79 (R)[f]
98	6	0.3	M (0.1)	60	8[d]	100	35 (R)[e]
98	6	0.3	M (0.1)	60	8[d]	100	44 (R)[e]
06	6	1.1	M (0.1)	0	0.2	50	63 (S)[e]
90	5	1.8	M (0.1)	23	1.0	100	11 (S)[f]
96	3	1.4	M (0.1)	23	2.0	100	43 (R)[e]
96	4	1.6	M (0.1)	23	1.0	100	19 (S)[f]
87	2	0.7	M (0.1)	23	3.0	100	45 (R)[f]
95	1	1.1	M (0.1)	23	1.0	100	62 (S)[e]
95	(S)-14	0.5	M (0.1)	23	5.0	93	62 (S)[e]
95	(R)-14	0.7	M (0.1)	23	4.0	100	65 (R)

[a] All reactions at 23 °C used $P_{init}(H_2)$ of 2.72 atm. Chloride was present in all hydrogenations except the one using 2. At 60 °C, the initial $P(H_2)$ was ca. 20 atm. [b] Moles of base/moles of substrate. M = $NaOCH_3$; A = $(C_2H_5)_3N$. [c] Turnovers per hour. [d] Minimum value. [e] Enantiomeric excess determined by NMR. [f] Optical purity. [g] The substrate was compound 8 in all cases.

Results

Substrates (*E*)-8 and (*Z*)-8 were prepared by oxidation of the corresponding citral isomers (geranial and neral, respectively) with silver oxide. Recrystallization of (*E*)-8 from hexane at ca. −78 °C gave material which was ≥98% (*E*)-8 as a low-melting waxy solid. Purification of (*Z*)-8 by repeated vacuum distillation gave a light yellow oil assaying as 94% *Z* isomer. Measurements of these *E* to *Z* isomer ratios were made by using $Eu(fod)_3$-perturbed NMR spectroscopy with analysis of the C_3 methyl group signals.[6] The α-(acetylamino)acrylates (*Z*)-10 and (*Z*)-12 were obtained as the pure *Z* isomers as described previously.[5] These substrates were pure enough to allow hydrogenations with typical rhodium diphosphine complex catalysts at catalyst levels of 0.01 mol %.

Syntheses of the ligands 1–6 have been described.[1,3,7] Catalysts containing the new phosphine 14 were also studied; this ligand was prepared by using reaction 3. Both (*R*)-14 and (*S*)-14 were prepared.

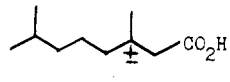
$$C_6H_5C^*(OCH_3)HCO_2H \xrightarrow[\text{2. TsCl, py}]{\text{1. LiAlH}_4} \xrightarrow[\text{3. LiP(C}_6\text{H}_5\text{)}_2\text{, THF}]{} C_6H_5C^*(OCH_3)HCH_2P(C_6H_5)_2 \quad (3)$$

14

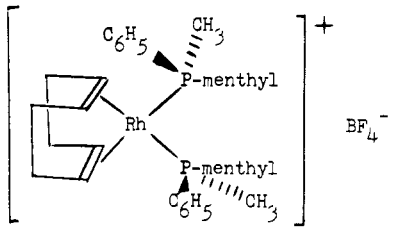
Hydrogenations of 8. Hydrogenations of 8 catalyzed by soluble rhodium complexes of 1–6 and 14 were studied in basic methanol solutions at 23 °C and 2–4 atm of dihydrogen. The results of these experiments are summarized in Table I. The identity and the enantiomeric excess (ee) of 9 obtained in these hydrogenations were established by NMR.[8] The most enantioselective hydrogenations of 8 were observed by using rhodium complexes of 1, 6, and 14, all of which converted 8 to an ca. 65–70% ee of 9. This may be compared with the ca. 75% ee of (*R*)-(+)-citronellal obtained from Java citronella oil and the ca. 84% ee of the same aldehyde obtained from β-pinene.[8] The practical use of these hydrogenations was and is limited by their very slow rates—in no case exceeding about ten turnovers per hour at 23 °C—and the present lack of any effective method to obtain pure 9 enantiomers from *R*/*S* enantiomer mixtures. A number of attempts were made, therefore, to increase the rates of hydrogenations of 8 in the hope that eventually use of very mild conditions to obtain high enantioselectivities would be possible.

Most of the rate-improvement studies were carried out by using the Rh-6 catalyst system, which gave marginally better rates and enantioselectivities than were obtained with Rh-1 or Rh-14. Rates given in Table I are very approximate. These hydrogenations are quite slow and subject to artifacts.

Using Rh-6 catalysts prepared by the combination in situ of 6 with $[Rh(1,5\text{-c-Oct})(Cl)]_2$[9] (1,5-c-Oct = 1,5-cyclooctadiene), we studied the effects of added bases on hydrogenations of 8 in methanol under mild conditions. Both sodium methoxide and triethylamine were used. We assumed that when less base than substrate was added, quantitative formation of $Na^+(O_2CR)^-$ or $[(C_2H_5)_3NH]^+(O_2CR)^-$ occurred. In Rh-6-catalyzed hydrogenations of 8 to which no base was added, the catalyst rapidly decomposed. The insoluble rhodium-containing products catalyzed rapid hydrogenation of 8 to the racemic, fully saturated acid 15. When 0.1–0.5 equiv (compared



15



16

to substrate) of sodium methoxide or triethylamine was added to the system, the catalysts remained soluble, and only 9 was obtained. The rate of hydrogenation increased somewhat with increasing base concentration and was about twice as fast when 0.5 equiv of base was used as compared to the case where 0.1 equiv was used. Use of more than 0.5 equiv of sodium methoxide led to catalyst decomposition. Hydrogenations containing as much as 1.1

(5) Hengartner, U.; Valentine, D., Jr.; Johnson, K. K.; Larscheid, M. E.; Pigott, F.; Scheidl, F.; Scott, J. W.; Sun, R. C.; Townsend, J. M.; Williams, T. H. *J. Org. Chem.* **1979**, *44*, 3741–3747.
(6) Schoffner, J. P. *J. Am. Chem. Soc.* **1974**, *96*, 1599–1601.
(7) Morrison, J. D.; Masler, W. F. *J. Org. Chem.* **1974**, *39*, 270–272.
(8) Valentine, D., Jr.; Chan, K. K.; Scott, C. G.; Johnson, K. K.; Toth, K.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 62–66.
(9) Chatt, J.; Venanzi, L. *J. Chem. Soc.* **1957**, 4735–4741.

equiv of triethylamine remained homogeneous but were neither faster nor more enantioselective than those containing 0.5 equiv of the amine.

The generation of Rh-6 catalyst from 6 and $[Rh(1,5\text{-c-Oct})(Cl)]_2$ provides a chloride ligand. The possibility that halide was an inhibitor was tested. Added NaCl and NaBr produced if anything a slight rate enhancement. Added NaI quenched the hydrogenation. Hydrogenations of 8 were also slow in halide-free systems in which the catalyst was obtained by the combination of 6 with either $[Rh(1,5\text{-c-Oct})(CH_3CO_2)]_2$ or $[Rh(1,5\text{-c-Oct})(CH_3COCHCOCH_3)]$.[10] Hydrogenations of 8 catalyzed by Rh-2 delivered as the cationic complex 16[1] were also slow. Many attempts to make complexes analogous to 16 but containing instead 1, 6, or 14 failed.[11] Finally, catalysts Rh-6 prepared from $[Rh(1,5\text{-c-Oct})(Cl)]_2$ and 6 were treated with silver tetrafluoroborate. The hydrogenations of 8 catalyzed by the resulting, presumably chloride-free, Rh-6 complexes were slow.

With Rh-6 it was found that the rates of 8 hydrogenations were similar whether the P/Rh ratio was 2 or 3.[13] Use of P/Rh ratios lower than 2 led to rapid catalyst decompositions.[14] To test the possibility that the observed slow rates were due to dimerization of the catalyst,[15] we decreased the concentration of Rh-6 in steps by a factor of 10. The rate of hydrogenation of 8 decreased proportionally with catalyst concentration, and, eventually, at ca. 0.75 wt % of catalyst, hydrogen uptake ceased before 1 equiv of dihydrogen had been absorbed.

Increasing the temperature at which hydrogenations of 8 were carried out led to substantial rate increases with an accompanying reduction in the ee of the 9 which was obtained. Thus, at 60 °C and 20 atm of H_2 with 0.15 wt % of catalyst, both Rh-1 and Rh-6 catalyzed complete hydrogenations of 8 to (S)-(−)-9 in 49% ee and to (R)-(+)-9 in 44% ee, respectively.

Some other aspects of the Rh-6-catalyzed hydrogenations of 8 were noteworthy. (1) Hydrogenations of (E)-8 proceeded without isomerization: the 8 recovered from incomplete hydrogenations was pure E isomer within the limits of detection. (2) Consistent with eq 1, hydrogenation of (Z)-8 catalyzed by Rh-6 gave (S)-(−)-9 in 62% ee. Also, hydrogenations of E/Z isomer mixtures gave enantiomers of 9 in ratios which were predicted from the (E)-8/(Z)-8 isomer ratio and the ee's of 9 obtained in hydrogenations of the separate 8 isomers. (3) All of the hydrogenations of 8 with rhodium catalysts containing 1–6 or 14—whether halide free or not—were water white or very light yellow during the reaction, consistent with the catalyst existing primarily in the dihydridorhodium(III) form. (4) Attempts to increase the concentration of 8 significantly, e.g., to 50 wt % solutions in methanol, led to catalyst decompositions.

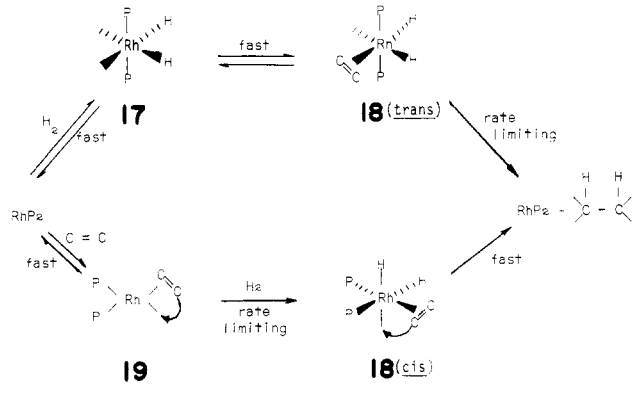
Hydrogenations of 10 and 12. Hydrogenations of 10 and 12 catalyzed by rhodium complexes of 1–6 and 14 in methanol solutions, with and without added base, were slow and gave only modest enantioselectivities for 11 and 13 enantiomers. Our results are summarized in Table II. The catalysts containing 1–6 and 14 gave slower rates than $Rh\text{–}P(C_6H_5)_3$ catalysts and slower rates and much lower enantioselectivities than were observed[5] by using typical rhodium chiral diphosphine complex catalysts. These reactions were not studied in detail.

Table II. Hydrogenations of 10 and 12 in Methanol[a]

substr	phosphine	% catal	reaction time[c]	% conv	product optical purity, % (confign)
12	5	0.2	48 h	0	
12	6	0.2	48 h	0	
10	6	1.0	240 h	55	*d*, *e*
10	6	1.0[b]	168 h	29	*d*
10	3	1.1	18 h	100	19 (*S*)
10	4	1.1	84 h	100	37 (*R*)
10	1	0.5	72 h	100	23 (*R*)
10	2	0.5	72 h	100	33 (*S*)
12	(*S*)-14	1.5	72 h	100	33 (*R*)
10	CAMP[f]	0.2	36 h	100	67 (*S*)
10	DIOP[g]	0.2	30 min	100	72 (*R*)
10	$P(C_6H_5)_3$	0.2	2 h	100	0

[a] Except for 2, the catalysts were prepared by mixing 4 mol of phosphine with 1 mol of $[Rh(1,5\text{-c-Oct})(Cl)]_2$. Phosphine 2 was delivered as the complex 16. P_{init} = 2.72 atm; T = 23 °C. We used 10 wt % solutions of substrate in methanol. [b] Triethylamine (0.5 mol/mol of 8) was added. [c] Time until H_2 uptake ceased or total reaction time when no H_2 was absorbed. [d] Not determined. [e] The catalyst decomposed and rhodium precipitated. [f] (*R*)-(−)-Cyclohexyl-*o*-anisylmethylphosphine. [g] (4*R*, 5*R*)-*trans*-Bis(diphenylphosphinomethyl)-1,3-dioxalane.

Scheme I



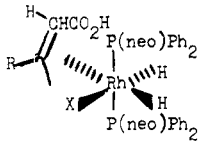
Discussion

Chiral phosphines used in this work to form rhodium complex hydrogenation catalysts[16] allow trans P–Rh–P coordination, and their rhodium(I) complexes are, therefore, expected to add H_2 under mild conditions to give 17 and to catalyze olefin hydrogenations by the "hydrogen route" shown in Scheme I (top).[17–19] The "olefin route"[20] shown in Scheme I (bottom) is expected only with catalysts where H_2 addition to $Rh(I)P_2$ is disfavored, allowing the rhodium(I)–substrate complex 19 to be formed.[21] The

(10) Cramer, R. *J. Am. Chem. Soc.* **1964**, *86*, 217–222.
(11) For example, the reaction of 6 with K_2PtCl_4 in xylene gave only yellow *trans*-dichlorobis(neomenthyldiphenylphosphine)platinum(II). Typical alkyldiarylphosphines afford both the *cis*- and *trans*-PtL_2Cl_2 isomers under these conditions.[12]
(12) Hartley, F. R. *Organomet. Chem. Rev., Sect. A* **1970**, *6*, 106.
(13) In some earlier work with alkyldiaryl- and especially dialkylarylphosphines dependence of hydrogenation rate on the P/Rh ratio was observed. Review: James, B. R. "Homogeneous Hydrogenation"; Wiley: New York, 1973; pp 204 ff.
(14) Cf.: Nagy-Magos, Z.; Vastag, S.; Heil, B.; Marko, L. *Transition Met. Chem. (Weinheim, Ger)* **1978**, *3*, 123–126.
(15) Dimerization of "$Rh(P(C_6H_5)_3(Cl)$" has been reported. Osborne, J. A.; Jardine, F. H.; Young, J. F.; Wilkinson, G. *J. Chem. Soc. A* **1966**, 1711–1732.
(16) Reviews: Valentine, D., Jr.; Scott, J. W. *Synthesis* **1978**, 329–353; Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1978**, *10*, 175–261.
(17) Halpern, J.; Okamoto, T.; Zahariev, A. *J. Mol. Catal.* **1976**, *2*, 65–68.
(18) Halpern, J. *Trans. Am. Crystallogr. Assoc.* **1978**, *14*, 59–69.
(19) Halpern, J.; Chan, A. S. C.; Riley, D. P.; Pluth, J. J. *Adv. Chem. Ser.* **1979**, *No. 173*, 16–26.
(20) Halpern, J.; Riley, D. P.; Chan, A. S. C.; Pluth, J. J. *J. Am. Chem. Soc.* **1977**, *99*, 8057–8059.

reaction which determines the rate and enantioselectivity of the hydrogenation of 8 catalyzed by Rh-1, -6, and -14 complexes is, therefore, conversion of 18 (trans) to products. This might, in principle, occur by stepwise hydride transfer, as has been proposed by Halpern et al. in the case of "$Rh(PPh_3)_3(Cl)$"-catalyzed[19] cyclohexene hydrogenation, or by rate-limiting isomerization to 18 (cis), whose collapse to products is then rapid.[26] Our data are in slightly better agreement with the former possibility.

The best catalysts found for the enantioselective hydrogenation of 8 were Rh-1, Rh-6, and Rh-14, which contain ligands of rather diverse structures. The kinetic features of these hydrogenations were very similar. All of the hydrogenations were very slow and rather insensitive to the reaction parameters except for temperature. Specifically, the concentrations of carboxylate and halide had little influence on rate, and there were several solvent systems, e.g., methanol, toluene, and their mixtures, which gave similar results. These observations are consistent with a rate-limiting collapse of 20, which is 18 (trans) for the



20

case of Rh-6-catalyzed hydrogenation of 8. The sixth ligand, X, is either provided by bidentate coordination of substrate (or its anion) by halide or by a second substrate (or anion). The ready availability of a sixth ligand might be expected to impede formation of five-coordinated intermediates whose collapse to products or isomerization would be expected to be rapid. Isomerization of 20 to a cis P–Rh–P isomer might be relatively favored thermodynamically by reducing the steric bulk of the ligand. However, the most bulky ligand, 6, gave the fastest Rh–phosphine catalyst for hydrogenations of 8. This provides mild suggestive evidence that it is hydride transfer and not isomerization of 20 which is rate limiting.

Hydrogenations of 10 and 12 catalyzed by Rh complexes of 1–6 and 14 have no practical importance because of slow rates and low enantioselectivities. The mechanisms are of some potential interest, however. It might be expected that a substrate such as 10, capable of strong bonding to rhodium(I), might favor formation of 19 over oxidative addition of H_2, leading to 17. The ligands PPh_3 and CAMP (CAMP = cyclohexyl-*o*-anisylmethylphosphine) both catalyze relatively fast hydrogenations of 10. In the case of CAMP, it is believed on the basis of NMR and dihydrogen uptake studies that oxidative addition of H_2 to $[Rh(CAMP)_2]^+$ is not thermodynamically favored.[25] Formation of 19 should then be possible. In the case of PPh_3, oxidative addition of H_2 to $[Rh(PPh_3)_2]^+$ is thermodynamically favorable, but strong bonding of 10 may make formation of 19 at least competitive with formation of 17. Formation of 19, which requires cis P–Rh–P geometry, may be more difficult when the very bulky ligands 1–6 are present. In this circumstance, the olefin route becomes very slow and/or is replaced by the hydrogen route.

Experimental Section

General Procedures. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are not corrected. Spectral measurements were taken by members of the Physical Chemistry Department of Hoffmann-La Roche. ^1H NMR spectra were recorded on Varian A-60, HA-100, and XL-100 instruments in the continuous-wave mode. ^{31}P NMR spectra were obtained on a Varian XL-100 spectrometer in the Fourier transform mode at 40.5 MHz. Chemical shifts are reported in parts per million downfield from internal tetramethylsilane for ^1H nuclei and from external phosphoric acid for ^{31}P nuclei. Infrared spectra were obtained on a Beckman IR-9 or Digilab FTS-14 spectrometer. Ultraviolet spectra were recorded on a Cary Model 14 spectrophotometer. Mass spectra were obtained on a JEOLCO OISG or CEC 21-110 instrument.

(*E*)-3,7-Dimethylocta-2,6-dienoic Acid ((*E*)-8). To a mechanically stirred solution of 82 g (0.482 mol) of silver nitrate in 125 mL of water was added over a period of 1–2 min a solution of 38.5 g of sodium hydroxide (0.96 mol) in 60 mL of water and 100 mL of methanol. When the precipitate had become granular in appearance and the reaction mixture was at 35–40 °C, 23.3 g (0.153 mol) of geranial [(*E*)-3,7-dimethylocta-2,6-dienal] was added at a rate sufficient to cause the reaction temperature to increase to and remain at 55 °C. The reaction mixture was stirred for 45 min at 55–56 °C, cooled, and filtered through Celite. The solids and the reaction flask were washed with 450 mL of 2:1 (v/v) methanol/water. The combined washings and filtrate were acidified with 30% sulfuric acid and extracted three times with ether. The combined ether extracts were concentrated under reduced pressure. The crude acid was dissolved in 1 N NaOH and extracted twice with ether. The aqueous layer was then acidified with 10% hydrochloric acid and extracted three times with ether. The ether extracts were washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The crude oil was twice distilled in a Kugelrohr apparatus to give 21.4 g (83%) of 3,7-dimethylocta-2,6-dienoic acid: bp 80 °C (0.05 mm); NMR ($CDCl_3$) δ 1.58, 1.65 (2 s, 6, $(CH_3)_2C=$), 2.12 (m, 7, $CH_3=$ and CH_2CH_2), 5.05 (br m, 1, =CH), 5.67 (=$CHCO_2H$).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.68; H, 9.69.

The *E*/*Z* isomer ratio of the acid as prepared above was determined to be 13:1 by $Eu(fod)_3$-perturbed NMR spectroscopy; 50 mg of the acid and 15 mg of $Eu(fod)_3$ were dissolved in 0.35 mL of $CDCl_3$, and 0.005 mL of tetramethylsilane was added. These solutions gave NMR spectra in which the C_3 methyl resonances of the *E* and *Z* isomers of 8 were observed at δ 2.60 and 2.05, respectively. Integration gave the *E*/*Z* isomer ratio.

Samples of (*E*)-8 used in hydrogenation studies were purified by low-temperature crystallizations. For example, 3,7-dimethylocta-2,6-dienoic acid, with *E*/*Z* isomer ratio of 10:1 (16.4 g), was dissolved in 150 mL of hexane at 25 °C and then cooled in dry ice/acetone for 2 h. The fine white crystals which formed were recovered by filtration at −40 °C and then redissolved in hexane. The hexane solution was concentrated under reduced pressure, and the residue was vacuum distilled to give 10.5 g of

(21) The most common case is the diphosphine ligand which can only give cis P–Rh–P coordination geometry. Cis oxidative addition of H_2 to such a species cannot occur without coordination of hydride trans to phosphorus, a presumably unfavorable geometry. Diphosphines capable of trans P–Rh–P coordination geometry have been shown to give rhodium complexes which do readily add H_2.[22,23] On the other hand, the monophosphine CAMP[24] (CAMP = cyclohexyl-*o*-anisylmethylphosphine) forms Rh^I complexes to which addition of H_2 does not seem to be thermodynamically favored under mild conditions, perhaps because the *o*-methoxy substituent coordinates to Rh.[25]

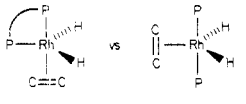
(22) Descotes, G.; Lafont, D.; Sinou, D. *J. Organomet. Chem.* **1978**, *150*, C14–C15.

(23) Brown, J. M.; Chaloner, P. A.; Descotes, G.; Glaser, R.; Lafont, D.; Sinou, D. *J. Chem. Soc., Chem. Commun.* **1979**, 611–612.

(24) Knowles, W. S.; Sabacky, M. J.; Vineyard, B. D. *Adv. Chem. Ser.* **1974**, *No. 132*, 274.

(25) Brown, J. M.; Chaloner, P. A.; Nicholson, P. M. *J. Chem. Soc., Chem. Commun.* **1978**, 646.

(26) Rapid conversion of 18 (cis) to products would be expected since two hydrogens and an olefin may occupy an octahedral face, in a position for synchronous or rapid stepwise hydride transfer. The slower conversion of 18 (trans) may reflect the fact that in this intermediate the two hydrogens and the olefin are coordinated along the meridian of the octahedron. Also, formation of a five-coordinate intermediate from 18 (cis) would result in closer proximity of the two hydrogens and the olefin than in the corresponding intermediate obtained from 18 (trans), i.e.:



an ca. 17:1 mixture of *E* and *Z* isomers of 8 according to the $Eu(fod)_3$-perturbed NMR spectrum. A similar experiment in which 26.5 g of 3,7-dimethylocta-2,6-dienoic acid with an *E*/*Z* isomer ratio of ca. 7.5:1 was recrystallized from 250 mL of hexane gave 10.35 g of 8 with an *E*/*Z* isomer ratio of 22:1.

(*Z*)-3,7-Dimethylocta-2,6-dienoic Acid ((*Z*)-8). Neral [(*Z*)-3,7-dimethylocta-2,6-dienal] was oxidized by silver oxide in *water*.[27,28] Two Kugelrohr distillations of the crude product gave 3,7-dimethylocta-2,6-dienoic acid in 77% yield as a light yellow oil, bp 118 °C (0.01 mm). Analysis of the $Eu(fod)_3$-perturbed NMR spectrum indicated that the *E*/*Z* isomer ratio of the sample was 4:96: NMR ($CDCl_3$) δ 1.67 (2 s, 6, $(CH_3)_2C=$), 1.91 (s, 3, $CH_3C=$), 2.15, 2.62 (2 m, 4, CH_2CH_2), 5.11 (m, 1, $=CHCH_2$), 5.66 (s, 1, =CHCOOH).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.57. Found: C, 71.51; H, 9.82.

(*Z*)-α-(Acetylamino)-6-chloroindole-3-acrylic Acid (12). This substance was prepared by following Scheme I of ref 5: yellow crystals; mp 255 °C dec; NMR (Me_2SO-d_6) δ 2.18 (s, 3, $COCH_3$), 9.28 (br s, 1, NH), 11.85 (br s, 1, COOH). The corresponding 6-methyl derivative was prepared as previously described.[5]

Anal. Calcd for $C_{13}H_{11}ClN_2O_3$: C, 53.43; H, 4.31; N, 9.59; Cl, 12.13; H_2O, 4.61. Found: C, 53.57; H, 4.45; N, 9.78; Cl, 11.92; H_2O, 4.41.

(*S*)-(+)- and (*R*)-(−)-(2-Phenyl-2-methoxyethan-1-yl)diphenylphosphine (14). (*S*)-(+)-2-Methoxy-2-phenylacetic acid [$[\alpha]^{25}_{5461}$ +175° (*c* 0.69, C_2H_5OH); mp 62–64 °C (lit.[29] $[\alpha]^{20}_{5461}$ +172.6° (*c* 0.494, C_2H_5OH); mp 65–66 °C); 45 g, 0.271 mol] in 500 mL of ether was added dropwise under argon with vigorous stirring to the mixture of 13.5 g (0.383 mol) of lithium aluminum hydride in 570 mL of ether at a rate fast enough to maintain reflux. Reflux was maintained for 30 min after the addition had been completed. The reaction was then allowed to cool to 23 °C when it was hydrolyzed by dropwise addition of 550 mL of 10% sulfuric acid. The aqueous layer was extracted with ether (3 × 500 mL). The ether layers were combined, washed with 200 mL of 10% sulfuric acid and then 200 mL of water, and dried over $MgSO_4$. The dry ether layer was filtered and then concentrated on a rotary evaporator under aspirator suction. Distillation of the residue through a short, packed column gave 37.3 g (90%) of (*S*)-(+)-2-methoxy-2-phenylethanol:[30] bp 78 °C (1–2 mm); $[\alpha]^{25}_D$ +126° (*c* 2.57, C_2H_5OH).

Anal. Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 71.55; H, 7.98.

(*S*)-(+)-2-Methoxy-2-phenylethanol (15.2 g) was stirred for 3.5 h under argon at 0 °C with a solution of 20.0 g of *p*-toluenesulfonyl chloride in 350 mL of pyridine and then refrigerated (ca. −5 °C) overnight. The resulting mixture was hydrolyzed by slow addition of small pieces of ice over ca. 1 h. The pyridine hydrochloride dissolved, and the tosylate precipitated. Addition of ice was continued until no more precipitate appeared to be forming. The tosylate was recovered by filtration, washed with a little water, and vacuum dried (23 °C, 1 mm, 18 h). The yield of white crystalline tosylate was 24 g (80%): mp 56–57 °C; $[\alpha]^{25}_D$ +92.6° (*c* 3.04, C_6H_6); NMR ($CDCl_3$) δ 2.43 (s, 3, CH_3Ar), 3.21 (s, 3, CH_3O), 4.07 (d, 2, *J* = 4 Hz, CH_2O), 4.43 (m, 1, CH), 7.35 (m, 7, Ar H), 7.88 (m, 2, Ar H).

Anal. Calcd for $C_{16}H_{18}O_4S$: C, 62.72; H, 5.92; S, 10.47. Found: C, 62.91; H, 5.98; S, 10.45.

A solution of the (*S*)-(+)-tosylate (7.6 g, 0.024 mol) in 25 mL of tetrahydrofuran was added dropwise at 0 °C to a rapidly stirred solution of lithium diphenylphosphide (0.0248 mol) in 20 mL of tetrahydrofuran. The resulting light orange solution was stirred for 10 min at 0 °C and then hydrolyzed with 25 mL of deoxygenated brine. The mixture was extracted with ether. The organic layers were dried over sodium carbonate, filtered under argon, and concentrated under reduced pressure. The oily residue was distilled in a Kugelrohr apparatus to give (*S*)-(+)-14 as a colorless oil: bp 140 °C (0.02 mm); $[\alpha]^{25}_D$ +44.4° (*c* 5.35, $CHCl_3$).

Anal. Calcd for $C_{21}H_{21}OP$: C, 78.73; H, 6.61; P, 9.73. Found: C, 78.65; H, 6.58; P, 9.44.

The enantiomer, (*R*)-(−)-14, was obtained similarly: colorless oil; $[\alpha]^{25}_D$ −43.44° (*c* 5.13, $CHCl_3$); NMR ($CDCl_3$) δ 2.26–2.76 (8 d in ca. 1:1:3:3:3:3:1:1 ratio, 2, $CH_{pro}(R)H_{pro}(S)PPh_2$, $J_{H_{pro}(R)H_{pro}(S)}$ = 14 Hz, $J_{H_{pro}(R)H_a}$ = 8 Hz, $J_{H_{pro}(S)H_a}$ = 6 Hz, $J_{H_{pro}(R)P}$ = 2 Hz, $J_{H_{pro}(S)P}$ = 1.5 Hz), 3.13 (s, 3, OCH_3), 4.12 (m, 1, CH_3OCHa, J_{H_aP} = 5.5 Hz), 7.2–7.5 (m, 15, 3 C_6H_5).

Anal. Found: C, 78.18; H, 6.63; P, 10.19.

Hydrogenation Procedures. The solvents used in the hydrogenations were methanol, toluene, and benzene, which were continuously distilled from magnesium (CH_3OH) or sodium–benzophenone (C_6H_6, C_7H_8) under argon and delivered to the reaction systems without exposure to air. Methanol purified by hydrogenation over Raney nickel gave equivalent results as a hydrogenation solvent. Triethylamine was distilled under argon. Commercial (i.e., Aldrich) sodium methoxide was used as received. Catalysts for the hydrogenations were typically delivered to the reactions as solutions prepared by dissolving the desired amounts of phosphine and $[Rh(1,5\text{-c-Oct})(Cl)]_2$[9] in deoxygenated methanol. The usual order of addition to the autoclave or pressure bottle was substrate, base, solvent, and catalyst solutions. Such reaction mixtures were flushed several times with hydrogen and stirred at ambient temperature until uptake of the theoretical amount of hydrogen had occurred (this was determined from the observed pressure drop in the vessel).

Recovery of the hydrogenated acids was done by mixing the reaction mixture with aqueous NaOH, extracting it with toluene, acidifying the aqueous layer with 30% sulfuric acid or 6 N hydrochloric acid, and extracting this with ether. The ether layers were combined, dried over $MgSO_4$, filtered, concentrated, and distilled in a Kugelrohr apparatus to give the crude acid hydrogenation product.

The acids obtained were analyzed by NMR to determine the extent of hydrogenation. Optical purities reported in this paper were determined by comparison of the $[\alpha]^{25}_D$ (*c* 5.0, $CHCl_3$) with that of the pure (*R*)-(+)-**9**, $[\alpha]^{25}_D$ +10.2° (*c* 5.0, $CHCl_3$).[8] Enantiomeric excess (ee) determinations were made by treating **9** with diazomethane in ether, isolating the resulting methyl ester of **9** and/or **15** by distillation, and analyzing its $Eu(dcm)_3$-perturbed[31] NMR spectrum.[8]

The following experiments illustrate typical procedures.

(*R*)-(+)-3,7-Dimethyloct-6-enoic Acid from (*E*)-3,7-Dimethylocta-2,6-dienoic Acid. A pressure bottle was equipped with a magnetic stirrer and charged with 1 g of 3,7-dimethylocta-2,6-dienoic acid (*E*/*Z* ratio of 17), 32 mg of $NaOCH_3$, and 170 mg of $NaClO_4$. The bottle was evacuated to 0.1 mm for 30 min and then charged with 6 mL of catalyst solution (241 mg of neomenthyldiphenylphosphine, 60 mg of μ,μ′-dichloro-bis(1,5-cyclooctadiene)rhodium(I), and methanol to make 25 mL). The system was then quickly flushed with hydrogen three times and sealed. The reaction was run at ambient temperature under an initial pressure of 2.5 atm of H_2 for 3 days. The pressure drop on the bottle gauge indicated uptake of 1 equiv of H_2. Workup by distillation afforded 0.85 g (85%) of (3*R*)-(+)-3,7-dimethyloct-6-enoic acid. The corresponding methyl ester had $[\alpha]^{25}_D$ +5.39° (*c* 5.01, $CHCl_3$) and was shown by NMR analysis (32 mg of ester, 170 mg of $Eu(dcm)_3$, 350 μL of CS_2, Me_4Si) to have a 5.93:1 ratio of *R* and *S* enantiomers (71.1% ee).

Hydrogenation of 3,7-Dimethylocta-2,6-dienoic Acid at 60 °C in an Autoclave. A stirring bar, 3.3 mg of μ,μ′-dichlorobis(1,5-cyclooctadiene)rhodium(I) (13.5 μmol of Rh), and 34.2 mg of neomenthyldiphenylphosphine (106 μmol, assuming 95% phosphine and 5% phosphine oxide) were added to a pressure bottle which was then evacuated and filled with argon. Distilled methanol (25 mL) was added via syringe, and the resulting yellow solution was stirred for 30 min under 3 atm of hydrogen. A solution of 840 mg of geranic acid (5.0 mmol, *E*/*Z* ratio of 22), 80 mg of $NaOCH_3$ (1.48 mmol), and 20 mL of distilled methanol was stirred for 15 min while a stream of argon was passed through it. The hydrogenated catalyst solution and the geranic acid solution were then transfered via cannula to a modified Parr

(27) "Organic Syntheses"; Wiley: New York, 1963; Collect. Vol. 4, p 919.

(28) Oxidation of neral using the procedure described for the oxidation of geranial gave an ca. 2:1 *E*/*Z* isomer mixture of 8.

(29) Neilson, D. G.; Peters, D. A. V. *J. Chem. Soc.* **1962**, 1519. Jacobus, J.; Raban, M.; Mislow, K. *J. Org. Chem.* **1968**, *33*, 1142–1145.

(30) Casey, J. P.; Lewis, R. A.; Mislow, K. *J. Am. Chem. Soc.* **1969**, *91*, 2789–2790.

(31) McCreary, M. D.; Wernick, D. L.; Lewis, D. W.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 1038–1047.

microreactor that had previously been evacuated and filled with argon. The reaction was stirred at 60 °C under 22 atm of H_2 for 24 h. The pale yellow reaction mixture was concentrated on a rotary evaporator and the residue partitioned between 10 mL of CH_2Cl_2 and 10 mL of 10% NaOH. The aqueous layer was separated and washed with ether (2 × 10 mL). The aqueous layer was then acidified with HCl and extracted with ether (3 × 10 mL). The combined ether extracts were washed with 5 mL of H_2O, dried over $MgSO_4$, and concentrated to yield 0.90 g of crude acid. Distillation in a Kugelrohr apparatus (100 °C, 0.5 mm) afforded 0.75 g (89%) of 3,7-dimethyloct-6-enoic acid: $[\alpha]^{25}_D$ +4.48° (c 4.9323, $CHCl_3$); 44% optical purity. The acid was converted to its methyl ester by using CH_2N_2. The ester had $[\alpha]^{25}_D$ +3.23° (c 5.0191, $CHCl_3$) and was shown by Eu(dcm)$_3$-perturbed NMR to have an R/S ratio (at the C_3 methyl) of 28/11 (44% ee).

Acknowledgment. We are grateful to Professors G. Whitesides and J. D. Morrison for many helpful discussions, to Dr. U. Hengartner for preparation of **10** and **12**, to Mr. W. Conradi for supplying neral and geranial, to Dr. T. Williams and R. Pitcher for NMR analyses, and to Dr. F. Scheidl for microanalytical services.

Registry No. (*E*)-**8**, 4698-08-2; (*Z*)-**8**, 4613-38-1; (*R*)-**9**, 18951-85-4; (*S*)-**9**, 2111-53-7; (*R*)-**9** methyl ester, 20425-48-3; (*S*)-**9** methyl ester, 56994-89-9; (*Z*)-**10**, 69203-27-6; D-**11**, 66920-63-6; (*Z*)-**12**, 74298-23-0; D-**13**, 56777-76-5; (*R*)-**14**, 74345-43-0; (*S*)-**14**, 60149-04-4; geranial, 141-27-5; neral, 106-26-3; (*S*)-2-methoxy-2-phenylacetic acid, 26164-26-1; (*S*)-2-methoxy-2-phenylethanol, 66051-01-2; (*S*)-2-methoxy-2-phenylethanol tosylate, 61825-54-5; μ,μ'-dichloro-bis(1,5-cyclooctadiene)rhodium(I), 12092-47-6; geranic acid, 459-80-3.

Enantioselective Hydrogenations of a Terpenic Acrylic Acid Catalyzed by Rhodium Complexes of Chiral Diphosphines

Donald Valentine, Jr.,* Ruen C. Sun, and Katherine Toth

Chemical Research Department of Hoffmann-La Roche, Inc., Nutley, New Jersey 07110

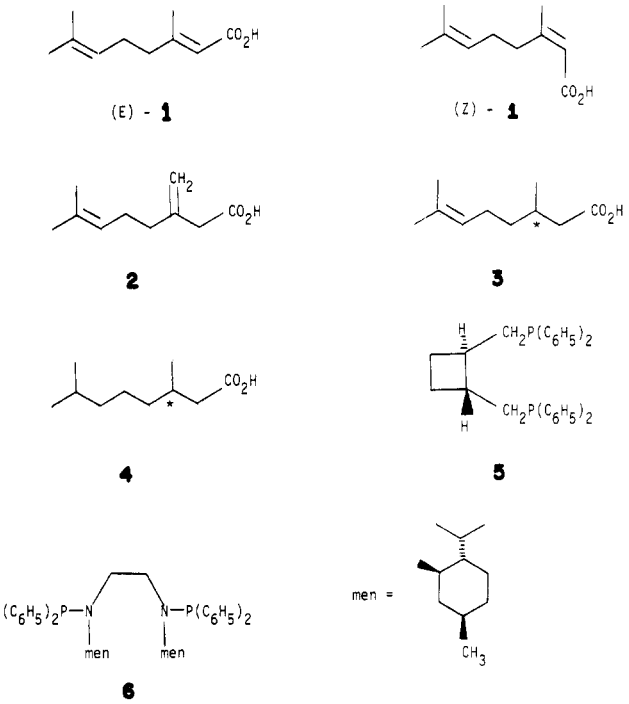
Received February 1, 1980

Hydrogenations of (*E*)-3,7-dimethylocta-2,6-dienoic acid ((*E*)-**1**) catalyzed by rhodium complexes of the chiral diphosphine (1*R*,2*R*)-bis[(diphenylphosphino)methyl]cyclobutane (**5**) in chloride-free methanol (23 °C, 2–3 atm of H_2) were rapid (~300 turnovers per hour) and gave (*S*)-(−)-3,7-dimethyloct-6-enoic acid ((*S*)-(−)-**3**) in ca. 40–42% ee. Under the same conditions, (*Z*)-**1** was converted to (*R*)-(+)-**3** in 45% ee. The Rh-**5**-catalyzed hydrogenation of (*E*)-**1** in chloride-free methanol was strongly promoted by triethylamine, with maximum rates of ca. 2500 turnovers per hour. The product enantiomeric excess was not changed by addition of triethylamine. A study of the amine-promoted hydrogenation of (*E*)-**1** is reported. It is concluded that the carboxylate anion of (*E*)-**1** complexes with rhodium more strongly than does the parent acid and that the resulting rhodium(I) substrate complex adds H_2 more rapidly in the deprotonated form.

In the preceding paper,[1] we described enantioselective hydrogenations of the terpenic acrylic acids (*E*)-**1** and (*Z*)-**1**, (see Chart I) catalyzed by rhodium complex catalysts containing chiral monophosphine ligands. This paper describes hydrogenations of the same substrates catalyzed by rhodium complexes of chiral diphosphines. We have also briefly studied enantioselective hydrogenations of **2**.

The main subject of this paper is the hydrogenation of (E)-**1** catalyzed by Rh-**5** in chloride-free methanol. In the absence of added base this hydrogenation has a modest rate (~300 turnovers per hour), and (*S*)-(−)-**3** is obtained in 40–42% ee. Addition of triethylamine in amounts less than the amount of substrate results in dramatic rate increases (~2500 turnovers per hour) without changing the enantioselectivity. The use of triethylamine in Rh-**5**-catalyzed hydrogenations of (*E*)-**1** was suggested by reports that addition of amine to some apparently similar hydrogenations resulted in increased enantioselectivities.[2] In the present case, consideration of the appropriate acid–base equilibria indicated that the added triethylamine was converted quantitatively to the ammonium salt of **1**.[3] A kinetic study described in this paper provides an explanation of the increased reactivity of the carboxylate anion compared to the parent acid **1** in the Rh-**5**-catalyzed hydrogenation.

Chart I



Results

We have studied the enantioselective hydrogenations of **1** and **2** catalyzed by soluble rhodium complexes of the chiral diphosphines **5**–**9**.[4a-e] Phosphines **5** and **6** were converted to the complexes **10**[4a] and **11**[4b] (Chart II).

*To whom correspondence should be addressed at Catalytica Associates, Inc., 3255 Scott Boulevard, Suite 7E, Santa Clara, CA 95051.

(1) Valentine, D., Jr.; Johnson, K. K.; Priester, W.; Sun, R.; Toth, K.; Saucy, G. *J. Org. Chem.*, preceding paper in this issue.

0022-3263/80/1945-3703$01.00/0