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for the Preparation
of Organic Compounds

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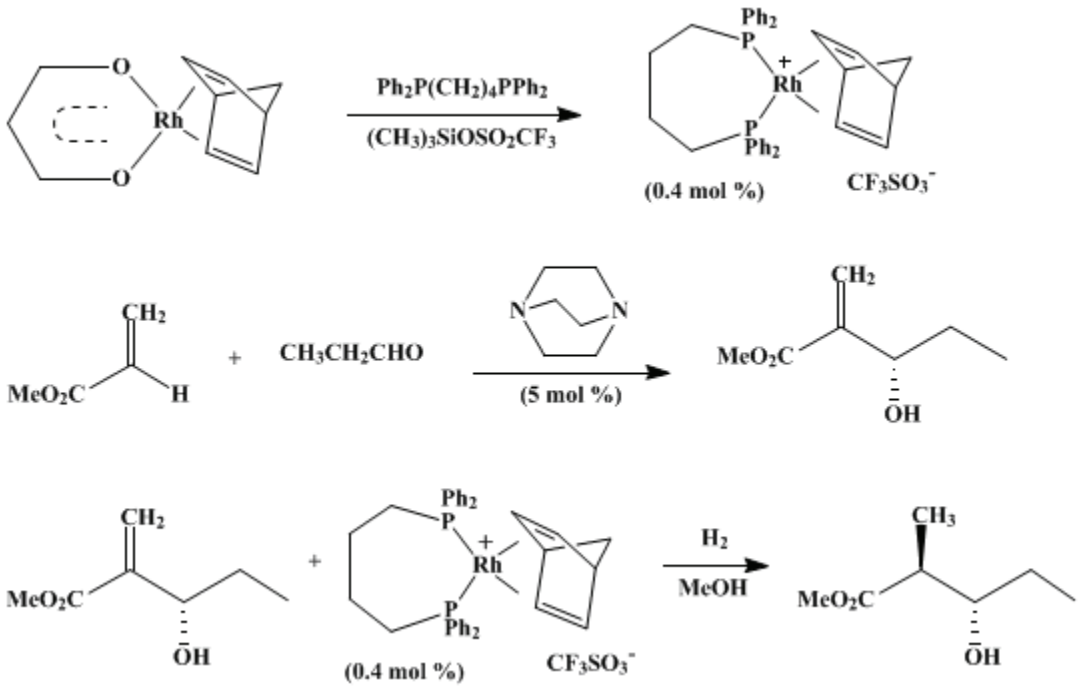
DIRECTED HOMOGENEOUS HYDROGENATION: METHYL *anti*-3-HYDROXY-2-METHYLPENTANOATE

[Pentanoic acid, 3-hydroxy-2-methyl-, methyl ester, (*R, *R**)-(±)-]**



Submitted by John M. Brown, Phillip L. Evans, and Alun P. James[1].
Checked by Ulrike Eggert, H. M. R. Hoffmann, and Ekkehard Winterfeldt.

1. Procedure

A. *Bicyclo[2.2.1]hepta-2,5-diene 1,4-bis(diphenylphosphino)butanerhodium trifluoromethanesulfonate* **1.** A 250-mL, two necked, round-bottomed flask, equipped with a septum, two-way stopcock used as a gas inlet and outlet, and a magnetic stirrer, is charged with a solution of bicyclo [2.2.1]hepta-2,5-diene-2,4-pentanedionatorhodium (117.6 mg, 0.4 mmol) (Note 1) in dry tetrahydrofuran (2.5 mL) under a gentle stream of argon. Trimethylsilyl trifluoromethanesulfonate (97.8 mg, 0.44 mmol) (Note 2) is added in one portion by microsyringe via the septum, resulting in a color change from yellow to orange. Solid 1,4-bis(diphenylphosphino)butane (170.4 mg, 0.4 mmol) (Note 3) is added all at once, with removal and immediate replacement of the septum cap. The color of the solution darkens to a deep orange-red, and precipitation of an orange solid occurs over 1–2 min. Dry 30–40 petroleum ether (10 mL) is added with vigorous stirring. The mixture is allowed to settle, and the solvent is removed first by syringe and finally under reduced pressure with an oil pump. Argon is admitted and the catalyst is dried and stored under argon (Note 4) and (Note 5).

B. *Methyl 3-hydroxy-2-methylenepentanoate.* A 250-mL, round-bottomed flask is charged with methyl acrylate (50.0 mL, 0.556 mol), propionaldehyde (60.0 mL, 0.832 mol), and 1,4-diazabicyclo [2.2.2]octane (3.0 g, 26.8 mmol) (Note 6). After the solution is stirred briefly to ensure complete dissolution, the flask is stoppered and set aside at ambient temperature for 7 days. The reaction mixture is then dissolved in dichloromethane (150 mL) and washed with 1 *M* hydrochloric acid (100 mL), and the organic layer is separated and dried over anhydrous magnesium sulfate. Solvent is removed under reduced pressure after filtration and the residue is fractionated through a 12-in. vacuum-jacketed Vigreux column. The main fraction boiling at 54°C (0.1 mm) is collected as a water-white liquid to afford 57 g (71%) of condensation product (Note 7). Care must be taken in the distillation to avoid

contamination by high-boiling impurities that may inactivate the catalyst.

C. *Methyl dl-anti-3-hydroxy-2-methylpentanoate.* Freshly distilled methyl 3-hydroxy-2-methylenepentanoate (14.4 g, 0.1 mol) is added to the biphosphinorhodium catalyst (catalyst/substrate ratio 1/250) (Note 8) in the flask from Step A. Methanol [40 mL, distilled from $Mg(OMe)_2$] is added. The apparatus is sealed with a rubber septum, the side arm is connected to a burette line, and the apparatus is then transferred to a dry ice/2-propanol bath. The vessel is evacuated to 1 mm 3 times and filled with hydrogen (Note 9) each time, the burette being partially filled on the last occasion. The mixture is warmed to near-ambient temperature and transferred to a water bath at 12° ± 2°C (Note 10). When thermal equilibration is complete, the stirrer is started so as to create a deep vortex in the reaction solution, which darkens to a brick-red color with rapid uptake of hydrogen. The burette is recharged with hydrogen as necessary, and gas absorption occurs steadily until the reaction is complete, when ca. 2.5 L of hydrogen has been consumed (Note 11). Completion of reaction can be readily checked by addition of 50 μL of methyl 3-hydroxy-2-methylenepentanoate to the reaction solution by microsyringe, leading to a perceptible burst of gas absorption. At this stage the flask is disconnected from the hydrogen line and flushed with argon and the contents are transferred to a 250-mL, round-bottomed flask. Solvent is removed at ambient temperature on a rotary evaporator, and the residue is dissolved in diethyl ether (40 mL) and 30–40 petroleum ether (150 mL). The mixture is filtered through a small plug of silica (60 μm, Merck flash chromatography grade) that effectively retains the residual rhodium catalyst (Note 1). Solvents are removed on a rotary evaporator, and the colorless product (Note 12) is distilled in a Kugelrohr apparatus, bp 50°C (~ 0.5 mm). The yield of methyl *dl-anti*-3-hydroxy-2-methylpentanoate is 13.3 g (91%), chemically and stereochemically pure by ^{13}C NMR (Note 13).

This procedure may be adapted for kinetic resolution of the reactant, employing an optically active biphosphinorhodium catalyst (Note 13).

2. Notes

1. The starting material for complex preparation is $RhCl_3 \cdot 3\ H_2O$, obtained as a loan from Johnson Matthey Co. Rhodium-containing reaction residues are collected for return. The synthesis of bicyclo[2.2.1]hepta-2,5-diene-2,4-pentanedionatorhodium has been described by Wilkinson,[2] and later by Green,[2] and may be carried out by the following modification: $RhCl_3 \cdot 3\ H_2O$ (0.68 g, 2.58 mmol) was dissolved in 90% ethanol (10 mL) and stirred with freshly distilled bicyclo[2.2.1]hepta-2,5-diene (1.95 mL) for 2 days under argon. The yellow precipitate was filtered, dried, and dissolved in tetrahydrofuran (10 mL) to which was added sodium 2,4-pentanedionate (0.314 g, 2.58 mmol) in one portion. The suspension was stirred vigorously for 4 hr and filtered and solvent was removed from the filtrate under reduced pressure. The resulting complex [530 mg, 70%, mp 172–175°C (lit.[2] 175–177°C)] is sufficiently pure to use, but may be sublimed under reduced pressure if desired. Alternatively, catalysts may be purchased from Chemical Products, Johnson Matthey Co., Royston, Cambridgeshire, England.
2. This toxic and corrosive reagent (Aldrich Chemical Company, Inc.) was transferred directly from the septum-sealed commercial sample.
3. This reagent was obtained from the Strem Chemical Company, Inc.
4. If it is desired to isolate and store the catalyst, an alternative procedure, preferred by the submitters, may be used. A 25-mL Schlenk tube is used as a reaction flask. After addition of the petroleum ether, the resulting orange suspension is filtered by centrifugation in a Craig tube and dried under argon. The bright-orange solid (0.26–0.28 g), mp 211–212°C (dec), is indefinitely stable when stored in a −20°C freezer under argon.
5. Earlier work on directed hydrogenation used tetrafluoroborate salts.[3,4] Triflate salts seem superior in keeping properties, and their preparation is easy and convenient.
6. Methyl acrylate, 99% (stabilized with 200 ppm hydroquinone monomethyl ether); propionaldehyde, 97%; and 1,4-diazabicyclo[2.2.2]octane were purchased from the Aldrich Chemical Company, Inc. and used as supplied.
7. The Michael-induced condensation reaction between acrylates and aldehydes[5] is dramatically accelerated by high pressure, cutting the reaction time from several days to a few minutes.[6]
8. The submitters used a 1 : 500 catalyst/substrate ratio (H_2 uptake ca. 40 mL/min), but the checkers used the higher ratio to speed up the hydrogen uptake. If an accurate rate of hydrogen uptake is crucial to a user, the lower ratio may be preferred.

9. Hydrogen of 99.99% purity, supplied by the British Oxygen Company, was employed.
10. The diastereoselectivity of reduction increases with decreasing temperature, and the conditions chosen represent a compromise between rate and specificity.
11. On one occasion the submitters added an extra 15.0 g of starting material to the reaction vessel at this point. Hydrogenation proceeded to completion (i.e., 1000 turnovers, in total) but slowed appreciably in the latter stages of reaction.
12. The submitters fractionated the product through a short Vigreux column, collecting the main fraction boiling at 65°C (1 mm). The ^{13}C NMR spectrum of the bulk reaction product is as follows: ($CDCl_3$) δ: 8.89 (CH_3CH), 13.19 (CH_3CH_2), 26.41 (CH_2), 44.21 (OCH_3), 50.79 (CH-CO), 73.73 (CH-O), 175.63 (C=O). The *syn* isomer exhibits resonances at ($CDCl_3$) δ: 9.10, 13.19, 28.33, 44.21, 50.94, 71.53; it may be prepared by $Pd/C/H_2$ reduction of the starting material and separation of the diastereomers of product by preparative GLC (OV 225, 15', 150°C).
13. When (*R,R*)-1,2-bis(*o*-anisylphenylphosphino)ethanerhodium triflate (DIPAMPRh$^+$) was used as catalyst,[7] 5.0 g of starting material was hydrogenated with 0.1 g of catalyst in methanol at 0°C to 65% reaction (ca. 6 hr). Workup and isolation by preparative GLC (OV 225, 15', 150°C) gave 2.0 g of 2*R*,3*R*-(−)-methyl 3-hydroxy-2-methylpentanoate, $[\alpha]_{587}^{20}$ −6.4° (chloroform, *c* 4), and 0.8 g of recovered *S*-(−)-methyl 3-hydroxy-2-methylenepentanoate, $[\alpha]_{587}^{20}$ −20.3° (chloroform, *c* 2). The optical purity of the former is 57 ± 2% by chiral shift NMR [$Eu(hfc)_3$] and the latter is ≥97% optically pure. This represents an enantiomer rate ratio of 13 : 1.

3. Discussion

α-Substituted β-hydroxy esters are the formal product of an ester enolate aldol condensation. High *anti*-stereoselectivity in the reaction requires the lithium enolate of a reasonably bulky aryl ester and a sterically demanding aldehyde. The condensation between 2,6-dimethylphenyl propionate and 2-methylpropanal has been described in *Organic Syntheses*,[8] under conditions where the product is formed with 98% *anti*-selectivity. Recently the condensation of *E*-silylketene acetals derived from *N*-methylephedrine esters with aldehydes mediated by titanium(IV) chloride has been shown to occur with good *anti*-selectivity and in high ee.[9]

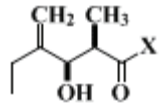
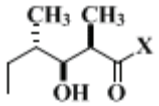
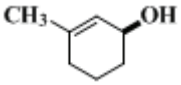
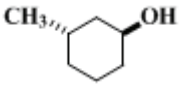
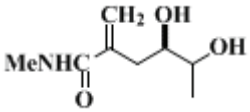
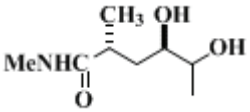
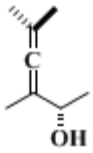
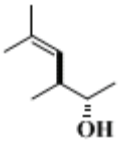
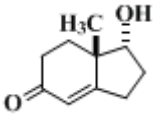
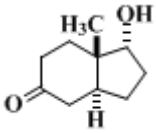
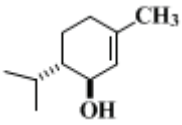
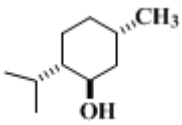
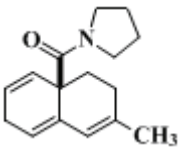
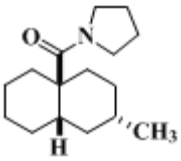
Alternatively, the *anti*-α-alkyl-β-hydroxy ester structure may be obtained by alkylation of the dianion of a β-hydroxy ester, which occurs with ≥95% stereoselectivity.[10] Since the starting materials are available in moderate to high optical purity by yeast reduction of β-keto esters,[11,12] this constitutes an asymmetric synthesis.[13]

The present procedure involving homogeneous catalysis is operationally simple and takes advantage of the easy availability of 2-(1'-hydroxyalkyl)acrylic esters. A two-step procedure involving kinetic resolution of the racemic starting material with an optically active hydrogenation catalyst, followed by a further reduction with an achiral catalyst, leads to diastereomerically pure products in ≥97% ee.

Directed hydrogenation is applicable to olefins that are α'-disubstituted or trisubstituted with a polar functional group at an adjacent chiral center.[14] The latter must be capable of sustained coordination to the metal during the catalytic cycle, thereby exerting stereochemical control on hydride transfer to carbon. The presence of an electron-withdrawing group at the α'-position enhances both the reaction rate and stereoselectivity, making 2-(1'-hydroxyalkyl)acrylates highly suitable substrates for the reaction. The polar group is most commonly -OH, but CO_2Me, $CONR_2$, NHCOR, and $NHCO_2R$ have all been used. Other substituents, including OMe, OCOR, and NH_2, are much less effective. For acyclic cases where the reactant possesses conformational flexibility, cationic rhodium complexes derived from the seven-ring chelate of 1,4-bis(diphenylphosphino)butane have proved most effective. With cyclic reactants, cationic iridium catalysts of the type introduced by Crabtree and Morris[15] have generally been more successful, and the procedure is more tolerant of steric bulk in the reactant olefin. A series of examples is collected in Table I.

TABLE I
DIRECTED HOMOGENEOUS HYDROGENATION

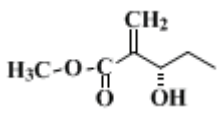
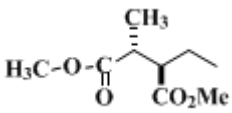
Reactant	Product	Catalyst[a] (mol%)	Selectivity

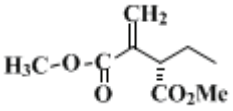
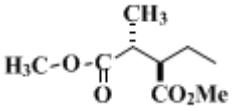
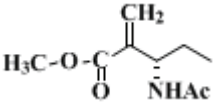
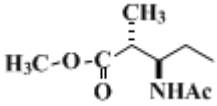
		A(>2)	93[4]
		A(20)	99.6[3c]
		A(2)	96[16]
		A(3)	97[16]
		B(20)	96[17]
		B(2.5)	99.7[18]
		B(5)	99.9[19]

[a]Catalyst A is complex **1** (see text); catalyst B is $(PCx_3)(py)(C_8H_{12})IrPF_6$.

Substituted acrylates (which resemble the enamide substrates employed in asymmetric hydrogenation)[16] may be deracemized by reduction with an optically active catalyst, especially DIPAMPRh$^+$. Selectivity ratios of 12 : 1–22 : 1 have been obtained for a variety of reactants; with compounds of reasonable volatility, separation of starting material and product may be effected by preparative GLC. Recovered starting material can then be reduced with an achiral catalyst to give the optically pure *anti* product. Examples of kinetic resolutions by this method are given in Table II. More recently very successful kinetic resolutions of allylic alcohols have been carried out with Ru(BINAP) catalysts.[13]

TABLE II
KINETIC RESOLUTIONS IN ACRYLATE HYDROGENATION[a]

Recovered reactant	Major product	% Reaction	Ee
		65	98[16]

		65	96[20]
		58	96[21]

[a] 1–4 mol % DIPAMPRh$^+$ in MeOH, usually at 0°C.

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

petroleum ether

H_2O

bicyclo[2.2.1]hepta-2,5-diene-2,4-pentanedionatorhodium

$RhCl_3 \cdot 3\ H_2O$

sodium 2,4-pentanedionate

2R,3R-(−)-methyl 3-hydroxy-2-methylpentanoate

S-(−)-methyl 3-hydroxy-2-methylenepentanoate

Pentanoic acid, 3-hydroxy-2-methyl-, methyl ester, (R^*, R^*)-(±)-

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

diethyl ether (60-29-7)

hydrogen (1333-74-0)

chloroform (67-66-3)

Propionaldehyde (123-38-6)

carbon (7782-42-5)

dichloromethane (75-09-2)

methyl acrylate (96-33-3)

lithium (7439-93-2)

magnesium sulfate (7487-88-9)

tetrafluoroborate (14874-70-5)

2-methylpropanal (78-84-2)

Tetrahydrofuran (109-99-9)

titanium(IV) chloride (7550-45-0)

argon (7440-37-1)

hydroquinone monomethyl ether (150-76-5)

bicyclo[2.2.1]hepta-2,5-diene

triflate

iridium (7439-88-5)

rhodium (7440-16-6)

1,4-diazabicyclo[2.2.2]octane (280-57-9)

Trimethylsilyl trifluoromethanesulfonate (27607-77-8)

2,6-dimethylphenyl propionate (51233-80-8)

E-silylketene

Methyl anti-3-hydroxy-2-methylpentanoate,
methyl dl-anti-3-hydroxy-2-methylpentanoate (100992-75-4)

1,4-bis(diphenylphosphino)butane (7688-25-7)

Methyl 3-hydroxy-2-methylenepentanoate (18052-21-6)

biphosphinorhodium

N-methylephedrine (42151-56-4)

Bicyclo[2.2.1]hepta-2,5-diene 1,4-bis(diphenylphosphino)butanerhodium tri-fluoromethanesulfonate

(R,R)-1,2-bis(o-anisylphenylphosphino)ethanerhodium triflate