RHODIUM-CATALYZED ENANTIOSELECTIVE REDUCTIVE ALDOL REACTION.

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Supplementary Material

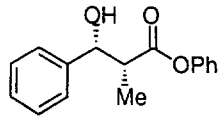
General. Infrared spectra were recorded on a Nicolet Magna 560 spectrometer, ν_{max} in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). ^1H NMR spectra were recorded on Varian Gemini (300 MHz) and Bruker (400 MHz) spectrometers. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: 7.24 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz) and assignment. ^{13}C NMR were recorded on a Varian Gemini 300 (75 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard ($CDCl_3$: 77.0 ppm). Microanalyses were preformed by Robertson Microlit.

Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on Sigma silica gel 60 (SiO_2, 230-400 mesh). Thin layer chromatography was performed on EM Science 0.25 mm silica gel 60 plates. Visualization was achieved with phosphomolybdic acid in ethanol, potassium permanganate in water, or vanillin in sulfuric acid, each followed by heating. Analytical gas-liquid chromatography (GLC) was performed on a Hewlett-Packard 6890 Series chromatograph equipped with a split mode capillary injection system, the indicated chiral GLC column, a flame ionization detector and using helium as the carrier gas.

All reactions were conducted in oven and flame dried glassware under an inert atmosphere of dry nitrogen. Dichloroethane was sequentially washed with concentrated H_2SO_4, water, aqueous Na_2CO_3, and water, then dried with $MgSO_4$ and fractionally distilled from CaH_2. Chloro(1,5-cyclooctadiene)rhodium (I) dimer and (*R*)-BINAP were purchased from Strem Chemical Company. All other reagents were purchased from either Lancaster or Aldrich Chemical Companies.

Representative procedure for catalytic reductive aldol reaction. A 10 mL flame-dried round bottom flask was charged with 10.0 mg of chloro(1,5-cyclooctadiene)rhodium (I) dimer (0.02 mmol), 33.0 mg (R)-BINAP (0.053 mmol) and 500 μL of dichloroethane. The resulting solution was stirred at room temperature for one hour. After one hour, 481 μL of dichloroethane and 174 μL of diethylmethylsilane (0.97 mmol) were added to the mixture and the reaction vessel stirred for 30 minutes. Next, 1.15 mL of stock benzaldehyde/phenyl acrylate solution (0.70 M in aldehyde and 0.84 M in acrylate, 0.81 mmol aldehyde, 0.97 mmol acrylate) was added dropwise to the solution. The vessel was then sealed and allowed to stir for 24 hours. Solvent was then evaporated from the reaction and 1 mL each of THF, MeOH, and 4N HCl were added. This mixture was stirred at room temperature for an additional 30 minutes. Ethyl acetate was then used to extract the product (3 x 7 mL). The combined organic layers were washed with a saturated aqueous sodium bicarbonate solution (2 x 20 mL), dried over $MgSO_4$, and filtered. The solvent was removed by rotary evaporation to yield crude product which was purified *via*

flash chromatography (9:1 then 5:1 hexanes:ethyl acetate) to yield 151 mg (0.59 mmol, 73 % yield) of a 1.5:1 ratio of (*2R,3R*)-3-hydroxy-2-methyl-3-phenylpropionic acid phenyl ester (87%ee) and (*2R,3S*)-3-hydroxy-2-methyl-3-phenylpropionic acid phenyl ester (32% ee), respectively.



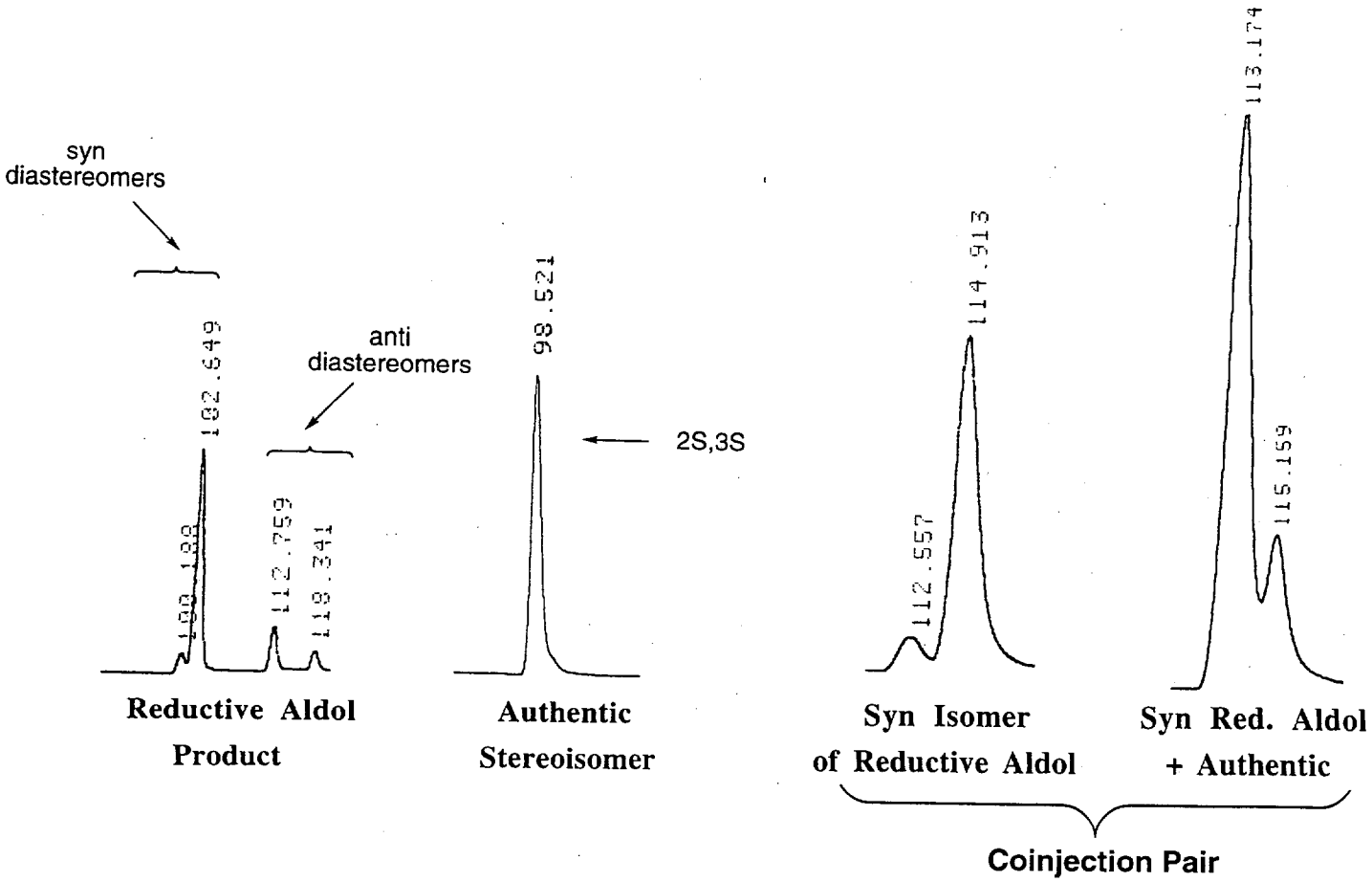
(*2R,3R*)-3-hydroxy-2-methyl-3-phenylpropionic acid phenyl ester. IR (neat) 3489 (br, s), 3032 (s), 2939 (s), 1756 (s), 1593 (m), 1193 (s) cm^{-1}; ^1H NMR: δ 6.86-7.45 (10H, m, aromatic), 5.15 (1H, d, J=5.1 Hz, ArC**H**OH), 3.05 (1H, dq, J=5.1, 7.2 Hz, CH_3C**H**), 2.70 (1H, broad s, O**H**), 1.32 (3H, d, J=7.3 Hz, CHC**H**$_3$); ^{13}C NMR: δ 174.0, 150.5, 141.5, 129.5, 128.5, 128.0, 126.3, 126.1, 121.5, 74.4, 47.2, 11.9. Anal. Calc'd for $C_{16}H_{16}O_3$: C, 74.98 ; H, 6.29. Found: C, 74.77; H, 6.11.

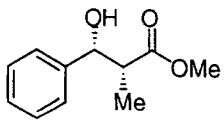
^1H NMR of the *anti* diastereomer: δ 6.86-7.45 (10H, m, aromatic), 4.87 (1H, d, J=8.6 Hz ArC**H**OH), 3.05 (1H, m, CH_3C**H**), 1.17 (3H, d, J=7.0 Hz, CHC**H**$_3$).

Proof of Stereochemistry. Stereochemical ratios were determined in comparison to authentic racemic materials prepared by lithium enolate aldol reaction (Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066-1081). Relative stereochemistry determined in comparison to ^1H NMR reported for the syn aldol adduct (Ishihara, K.; Maruyama, T.; Mouri, M.; Gao, Q.; Furuta, K.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3483). Absolute stereochemistry established in comparison to authentic 2S,3S isomer prepared through the use of a chiral auxillary (M.T. Crimmins and K. Chaudhary, *Organic Letters*, **In Press**).

Chiral GLC (β-dex, Supelco) analysisof reductive aldol product:

Note: Coinjection Pair Analyzed With Slightly Different GC Carrier Flow Rate.

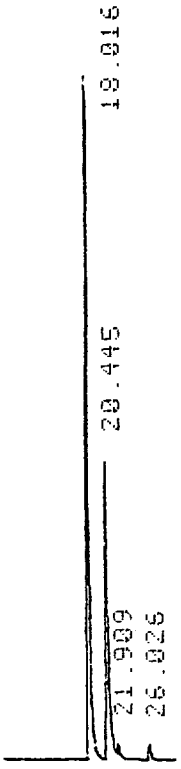




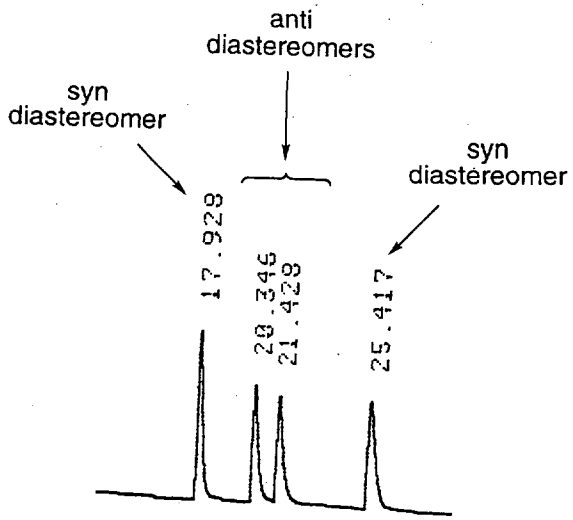
(2*R*,3*R*)-3-hydroxy-2-methyl-3-phenylpropionic acid methyl ester. IR (KBr) 3450 (br, s) 3085 (s), 2940 (s) 1900 (w) 1720 (s), 1230 (s) cm^{-1}; ^1H NMR: δ 7.20-7.40 (5H, m, $C_6\mathbf{H_5}$), 5.08 (1H, broad t, J=3.8 Hz, ArC**H**OH), 3.65 (3H, s, O$C\mathbf{H_3}$), 2.93 (1H, d, J=3.09 Hz, O**H**), 2.77 (1H, m, $CH_3C\mathbf{H}$), 1.11 (3H, d, J=7.12 Hz, CHC$\mathbf{H_3}$) ; ^{13}C NMR: δ 176.2, 141.4, 128.3, 127.4, 125.9, 73.6, 51.9, 46.3, 10.7. Anal. Calc'd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C 67.85, H 7.04.

Proof of Stereochemistry. Determination of stereochemical ratios was accomplished through chiral GLC analysis in comparison to non-selective aldol adducts prepared according to the method of Heathcock (Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066-1081). The relative configuration was established by comparison to reported ^1H NMR spectra (Itoh, T.; Kuroda, K.; Tomosada, M.; Takagi, Y. *J. Org. Chem.* **1991**, *56*, 797-804). Absolute configuration of each diastereomer was established by comparison of the optical rotation of each purified diastereomer to that reported in the literature (Gennari, C.; Colombo, L.; Bertolini, G.; Schimperna, G. *J. Org. Chem.* **1987**, *52*, 2754).

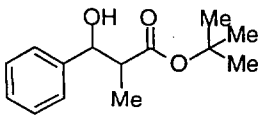
Chiral GLC (Chiraldex-GTA, Alltech) analysis of reductive aldol reaction product and racemic mixture of diastereomers:



Reductive Aldol Product



Authentic Stereoisomer Mixture

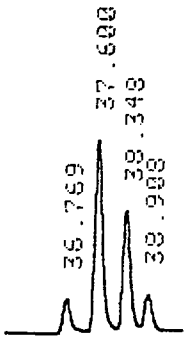


3-hydroxy-2-methyl-3-phenylpropionic acid *tert*-butyl ester. . IR (neat) 3458 (br, s), 3061 (s) 2978 (s), 1946 (w), 1883 (w), 1723 (s), 1453 (s), 1147 (s), 1024 (s), 695 (s) cm-1 ; 1H NMR 7.26-7.37 (5H m, aromatic), 5.02 (1H, dd, J= 2.5, 4.3 Hz, ArC**H**OH), 3.13 (1H, d, J= 3.1 Hz, O**H**), 2.7 (1H, m, CHC**H**CH3), 1.4 (9H, s, OC(C**H3**)3), 1.11 (3H, d, J= 7.2 Hz, CHC**H3**) 13C NMR 175.6, 141.8, 128.4, 127.6, 126.4, 81.3, 74.1, 47.3, 28.1, 11.3. Anal. Calc'd for C14H20O3: C, 71.16; H, 8.53 Found: C, 70.90; H, 8.25.

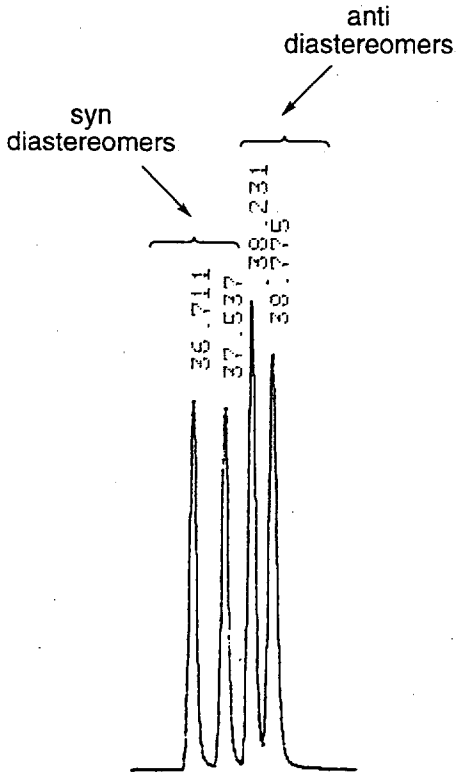
1H NMR of the *anti* diastereomer: 7.26-7.37 (5H, m, aromatic), 4.7 (1H, dd, J= 4.9, 8.0 Hz C**H**OH), 3.23 (1H, d, J= 4.9 Hz, O**H**) 2.7 (1H, m, CHC**H**CH3) 1.44 (9H, s, OC(C**H3**)3) 1.02 (3H, d, J= 7.2 Hz CHC**H3**)

The identitiy of this compound and the relative configuration of the stereoisomers was established by comparison to those reported in the literature (Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066-1081). Absolute stereochemistry of the reaction product was not established.

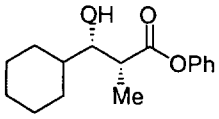
Chiral GLC (Chiraldex-GTA, Alltech) analysis of reductive aldol reaction product and racemic mixture of diastereomers:



Reductive Aldol Product



Authentic Stereoisomer Mixture

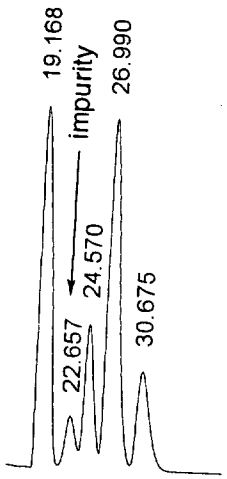


(*2R,3S*)-3-cyclohexyl-3-hydroxyl-2-methylpropionic acid phenyl ester. IR (neat) 3505 (br, m), 2926 (s), 2852 (m), 1755 (s), 1493 (m), 1196 (s) cm^{-1}; ^1H NMR: δ 6.95 - 7.27 (5H, m, aromatic), 3.67 (1H, dd, J=8.1, 3.7 Hz, C**H**OH), 2.80 (1H, dq, J=3.8, 7.1 Hz, CH_3C**H**), 1.98 (1H, br, O**H**), 1.20 (3H, d, J=7.1 Hz, $CHCH_3$), 0.83-1.75 (11H, m, cyclohexyl); ^{13}C NMR: δ 175.1, 150.6, 129.5, 126.0, 121.6, 41.9, 40.6, 29.4, 26.6, 26.3, 26.1, 10.4. Anal. Calc'd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.22; H, 8.41.

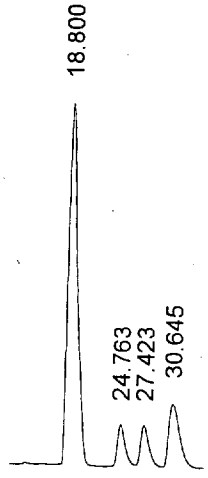
^1H NMR of the *anti* diastereomer: δ 6.95 - 7.27 (5H, m, aromatic), 3.40 (1H, t, J=5.9 Hz C**H**OH), 2.80 (1H, m, CH_3C**H**), 1.98 (1H, br, O**H**), 1.25 (3H, d, J=7.1 Hz, $CHCH_3$), 0.83-1.75 (11H, m, cyclohexyl).

Proof of Stereochemistry. Stereochemistry was determined in comparison to authentic racemic materials prepared by lithium enolate aldol reaction (Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066-1081). Identity of *syn* and *anti* stereoisomers was established through analysis of the coupling constant between carbinol proton and the proton at the α-carbon (typically ~3 Hz for the *syn* isomer and ~9 Hz for the *anti* isomer). In addition, after conversion of the major diastereomer to the derived methyl ester, relative stereochemistry was established in comparison to literature data (syn: Hofstraat, R. G.; Scheeren, H. W.; Nivard, R. J. F. *JCS Perkin 1*, **1985**, 561; anti: Harada, T.; Kurokawa, H.; Kagamihara, Y.; Tanaka, S.; Inoue, A.; Oku, A. *J. ORg. Chem.* **1992**, *57*, 1412). Absolute configuration of the *syn* isomer was established by measurement of optical rotation of the derived methyl ester ($[\alpha]^{25}_D$ -6.23, c=1.25, CH_2Cl_2) in comparison to literature value (*2R,3S*:: $[\alpha]^{25}_D$ -6.17, c=1.1, CH_2Cl_2; Drewes, S. E.; Malissar, D. G. S.; Roos, G. H. P. *Tetrahedron Asymm.* **1992**, *3*, 515).

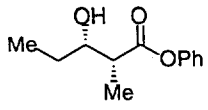
Chiral HPLC (Chiralcel-OJ, Daicel) of reductive aldol reaction product and racemic mixture of stereoisomer:



Mixture of Stereoisomers



Reductive Aldol Product



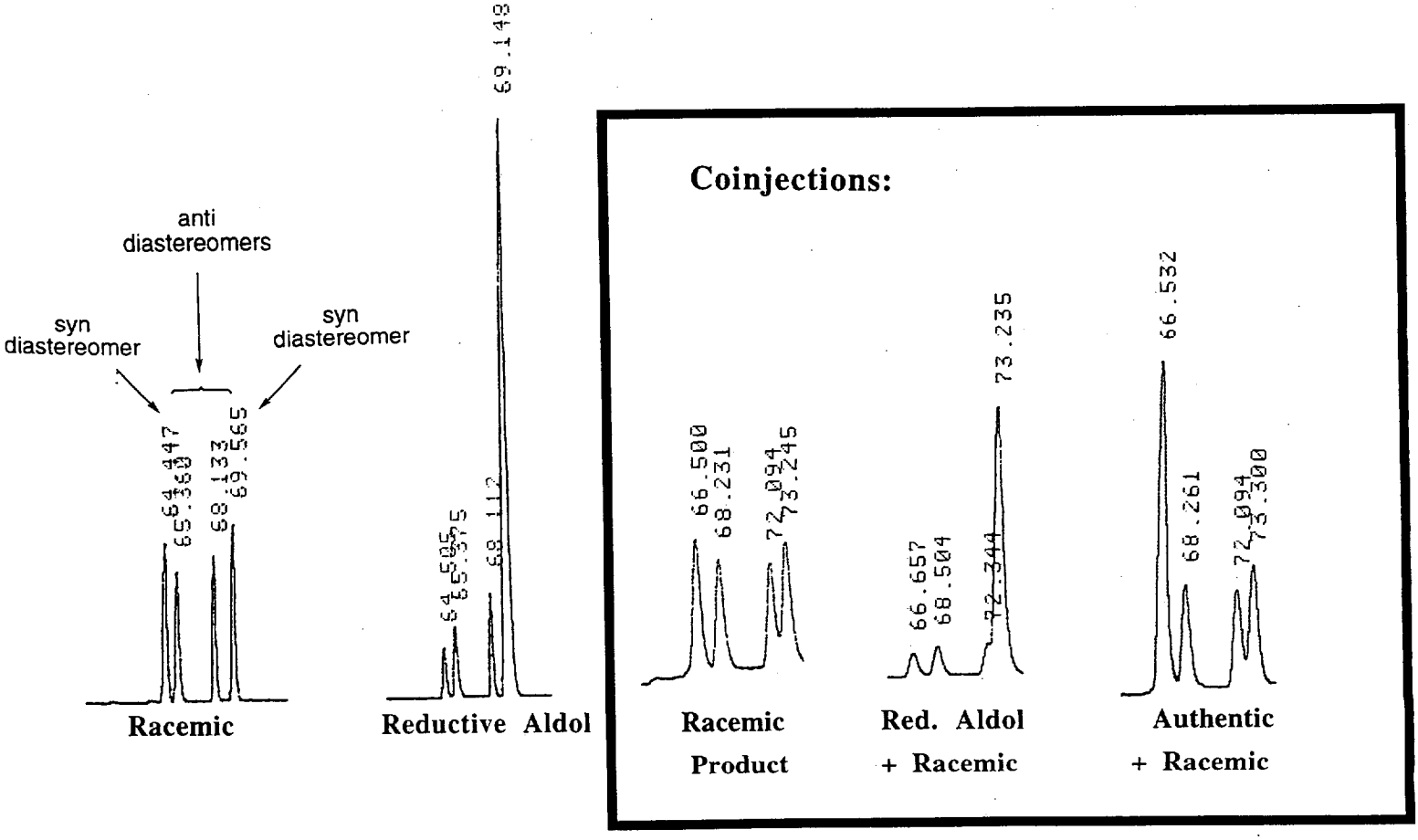
(2*R*,3*S*)-3-hydroxy-2-methylpentanoic acid phenyl ester. IR (neat) 3473 (br, s), 3068 (m), 2976 (s), 1742 (s), 1491 (s), 979 (s) cm^{-1}; ^1H NMR: δ 7.05 – 7.39 (5H, m, aromatic), 3.95 (1H, m, C**H**OH), 2.78 (1H, dq, J=3.9, 7.2 Hz $CH_3CHCHOH$), 2.42 (1H, d, J=4.8, O**H**), 1.47 - 1.71 (2H, m, CH_2CH_3), 1.32 (3H, d, J=7.2 Hz, $CHCH_3$), 1.01 (3H, t, J=7.4 Hz, CH_2CH_3); ^{13}C NMR: δ 174.7, 150.6, 129.5, 126.0, 121.6, 73.4, 44.4, 27.2, 11.0, 10.7. Anal. Calc'd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.31; H, 7.55.

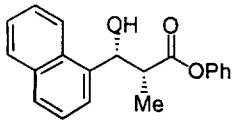
^1H NMR of the *anti* diastereomer: δ 7.05 – 7.39 (5H, m, aromatic), 3.72 (1H, m, CHOH), 2.76 (1H, m, $CH_3CHCHOH$), 2.48 (1H, d, J=6.8 Hz, O**H**), 1.47 - 1.71 (2H, m, CH_2CH_3), 1.34 (3H, d, J=7.3 Hz, $CHCH_3$), 1.02 (3H, t, J=7.4 Hz, CH_2CH_3).

Proof of Stereochemistry. Stereochemistry was determined in comparison to authentic racemic materials prepared by lithium enolate aldol reaction (Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066-1081) and also in comparison to authentic 2S,3R isomer prepared through the use of a chiral auxillary (M.T. Crimmins and K. Chaudhary, *Organic Letters*, **In Press**).

Chiral GLC (Chiraldex-GTA, Alltech, GC of derived acetate esters):

Note: Coinjection Set Analyzed Under Slightly Different GC Flow Rate



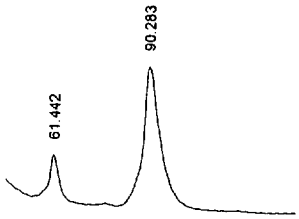


(2*R*,3*R*)-3-(1-naphthyl)-3-hydroxy-2-methylpropionic acid phenyl ester. IR (neat) 3498 (br, s), 3057 (m), 2986 (m), 1753 (s), 1496 (s), 902 (s) cm^{-1}; ^1H NMR: δ 7.01 – 8.33 (12H, m, aromatic), 6.11 (1H, d, J=3.4 Hz, C**H**OH), 3.32 (1H, dq, J=3.7, 7.1 Hz, CH_3C**H**), 2.86 (1H, s, O**H**), 1.28 (3H, d, J=7.1 Hz, $CHCH_3$); ^{13}C NMR: δ 174.5, 150.8, 136.8, 134.0, 130.1, 129.7, 129.4, 128.6, 126.6, 126.2, 125.9, 125.6, 124.4, 122.9, 121.7, 70.7, 45.2, 10.7. Anal. Calc'd for $C_{12}H_{16}O_3$: C, 78.41; H, 5.92. Found: C, 78.06; H, 6.01.

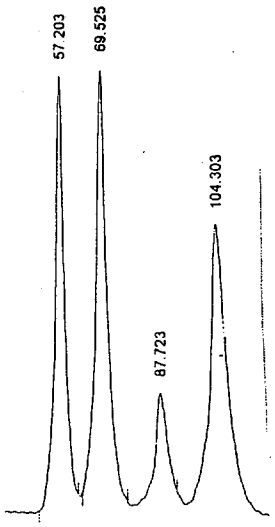
^1H NMR of the *anti diastereomer*: δ 7.01 – 8.33 (12H, m, aromatic), 5.64 (1H, d, J=8.2 Hz, C**H**OH), 3.45 (1H, m , CH_3C**H**), 3.16 (1H, broad s, O**H**), 1.23 (3H, d, J=7.2 Hz, $CHCH_3$).

Proof of Stereochemistry. Stereochemistry was determined in comparison to authentic racemic materials prepared by lithium enolate aldol reaction (Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066-1081) and also in comparison to authentic 2S,3S isomer prepared through the use of a chiral auxillary (M.T. Crimmins and K. Chaudhary, Organic Letters, **In Press**).

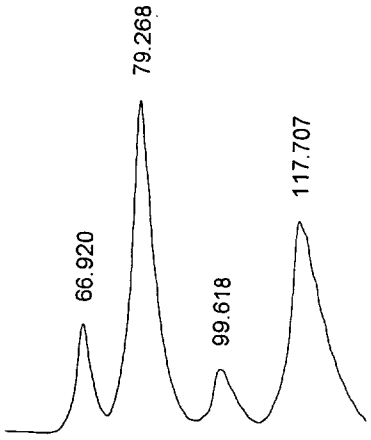
Chiral HPLC (Whelk-O 2, Regis) analysis of reductive aldol reaction product and racemic mixture of stereoisomers:



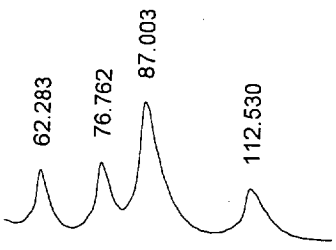
Authentic 2S,3S



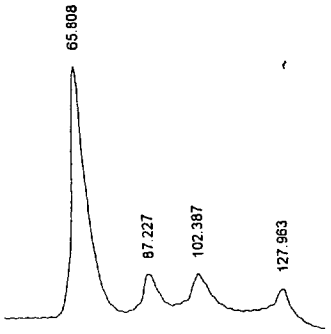
Red. Aldol + Racemic



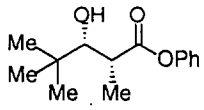
Racemic



Authentic + Racemic



Reductive Aldol



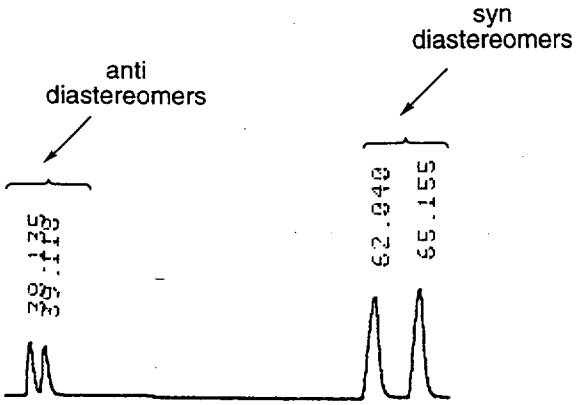
(*2R,3R*)-3-hydroxy-2,4,4-trimethylpentanoic acid phenyl ester. IR (neat) 3457 (br, m), 2950 (s), 1737 (s), 1486 (s), 1194 (s) cm^{-1}; ^1H NMR: δ 7.04 – 7.39 (5H, m, aromatic), 3.79 (1H, t, J=4.83 Hz, C**H**OH), 2.93 (1H, dq, J=4.7, 7.1 Hz CH_3CH),), 2.03 (1H, d, J=5.1 Hz, O**H**), 1.38 (3H, d, J=7.1 Hz, CHC**H**$_3$), 1.00 (9H, s, (C**H**$_3$)$_3$C); ^{13}C NMR: δ 175.9, 151.0, 129.9, 126.3, 121.8, 78.5, 41.7, 36.2, 26.9, 13.6. Anal. Calc'd for $C_{12}H_{16}O_3$: C, 71.68 ; H, 9.22. Found: C, 72.02; H, 9.02.

Characterization of the *anti* diastereomer: IR (neat) 3518 (br, m), 3053 (m), 2930 (s), 1731 (s), 1265 (s) cm^{-1}; ^1H NMR: δ 6.98 – 7.36 (5H, m, aromatic), 3.36 (1H, d, J=9.0 Hz, O**H**), 3.20 (1H, dd, J=9.6, 2.2 Hz, C**H**OH), 2.93 (1H, dq, J=2.2, 7.3 Hz CH_3CH), 1.45 (3H, d, J=7.3 Hz, CHC**H**$_3$), 0.93 (9H, s, (C**H**$_3$)$_3$C); ^{13}C NMR: δ 175.9, 150.2, 129.6, 126.2, 121.4, 82.9, 39.0, 30.0, 26.6, 18.5.

Proof of Stereochemistry. Stereochemistry was determined in comparison to authentic racemic materials prepared by lithium enolate aldol reaction and also in comparison to authentic 2S,3S isomer prepared through the use of a chiral auxillary (M.T. Crimmins and K. Choudhary, unpublished). Relative stereochemistry was also confirmed by ^1H NMR analysis of the derived pyrrolidine amide (pyrrolidine neat, 12hr) in comparison to literature values (Fujita, M.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 5405).

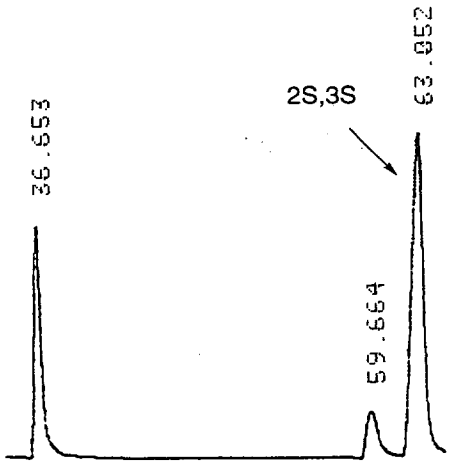
Chiral GLC analysis (Chiraldex GTA, Alltech) of reductive aldol product:

Note: Coninjections analyzed with slight different carrier flow rate



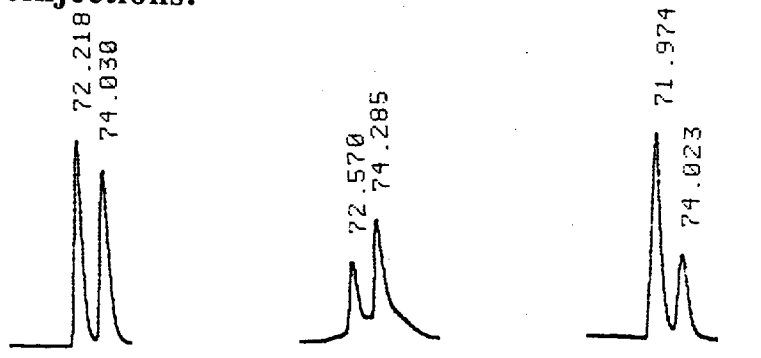
Mixture of Stereoisomers

Reductive Aldol Product

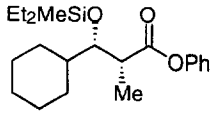


Authentic Stereoisomer

Coinjections:



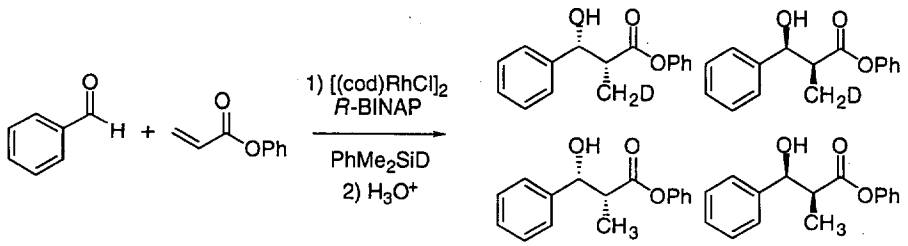
Racemic Syn | **Authentic Syn + Racemic Syn** | **Red. Aldol + Racemic Syn**

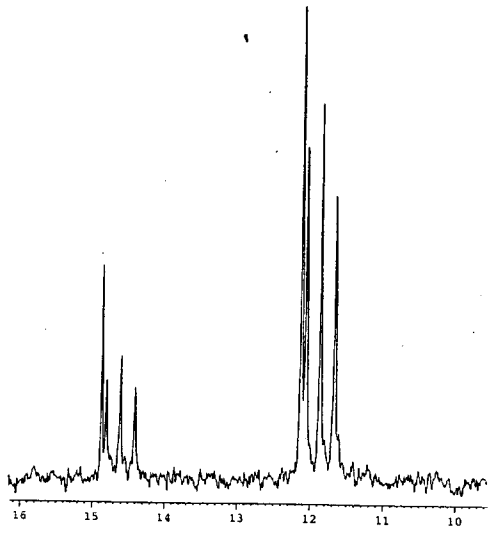


(*2R,3R*)-3-cyclohexyl-3-diethytlmethylsiloxy-2-methylpropanoic acid phenyl ester. . IR 2930 (s), 2852 (m), 1755 (s), 1450 (m) cm^{-1}; ^1H NMR: δ 7.04 - 7.39 (5H, m, aromatic), 3.88 (1H, t, J=5.4 Hz, **CH**OSi), 2.85 (1H, m, CH_3**CH**), 1.27 (3H, d, J=7.0 Hz, CH**CH$_3$**), 1.00-1.90 (11H, m, cyclohexyl), 0.94 (6H, m, **CH$_3$**CH_2Si), 0.60 (4H, m, CH_3**CH$_2$**Si), 0.10 (3H, s, **CH$_3$**Si) ; ^{13}C NMR: δ 173.8, 150.6, 129.3, 125.5, 121.3, 77.8, 43.4, 42.8, 30.2, 28.1, 26.6, 26.5, 25.5, 12.8, 7.3, 7.2, 7.1, -3.7. HR EI-MS exact mass calcd for $C_{21}H_{34}O_3Si$ $[M-CH_3]^+$ 347.2042, found 347.2044.

Proof of Stereochemistry. Stereochemical ratio and configuration of the major product was determined by GLC analysis of the derived β-hydroxy ester as described above.

Reductive Aldol Reaction with PhMe$_2$SiD. The general procedure was followed except that phenyldimethylsilyldeuteride (Brookhart, M.; Grant, B. E. *J. Am. Chem. Soc.* **1993**, *115*, 2151) was used in place of diethylmethyl silane. ^{13}C NMR analysis of the C2 methyl groups shows partial deuteration for each diastereomer.





Methyl Region of ^{13}C NMR

Exchange of Si-D and Acrylate β-H. Treatment of phenyl acrylate with phenyldimethylsilyldeuteride for 24 hours in the presence of catalytic [(cod)RhCl]2-(*R*)-BINAP, followed by removal of solvent and examination of the ^{1}H NMR shows indicates incorporation of deuterium at the β-position of the acrylate (see olefinic region of ^{1}H NMR below).