ENANTIO- AND DIASTEREOSELECTIVE REDUCTIVE ALDOL REACTIONS WITH IRIDIUM-PYBOX CATALYSTS.

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Supplementary Material

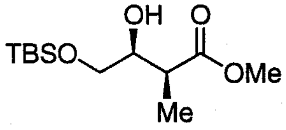
General. Infrared spectra were recorded on a Nicolet Magna 560 spectrometer, ν_{max} in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). ^1H NMR spectra were recorded on Varian Gemini (300 MHz) and Bruker (400 MHz) spectrometers. Chemical shifts are reported in ppm 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 preformed on a Hewlett-Packard 6890 Series chromatograph equipped with a CTC Analytics Combi PAL autosampler by Leap Technologies (Carrboro, NC), a split mode capillary injection system, a flame ionization detector and an Astec G9809-18 (Chiraldex-GTA) column with 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. All metals and phosphine ligands were purchased from Strem Chemical Company. All other reagents were purchased from either Lancaster or Aldrich Chemical Companies.

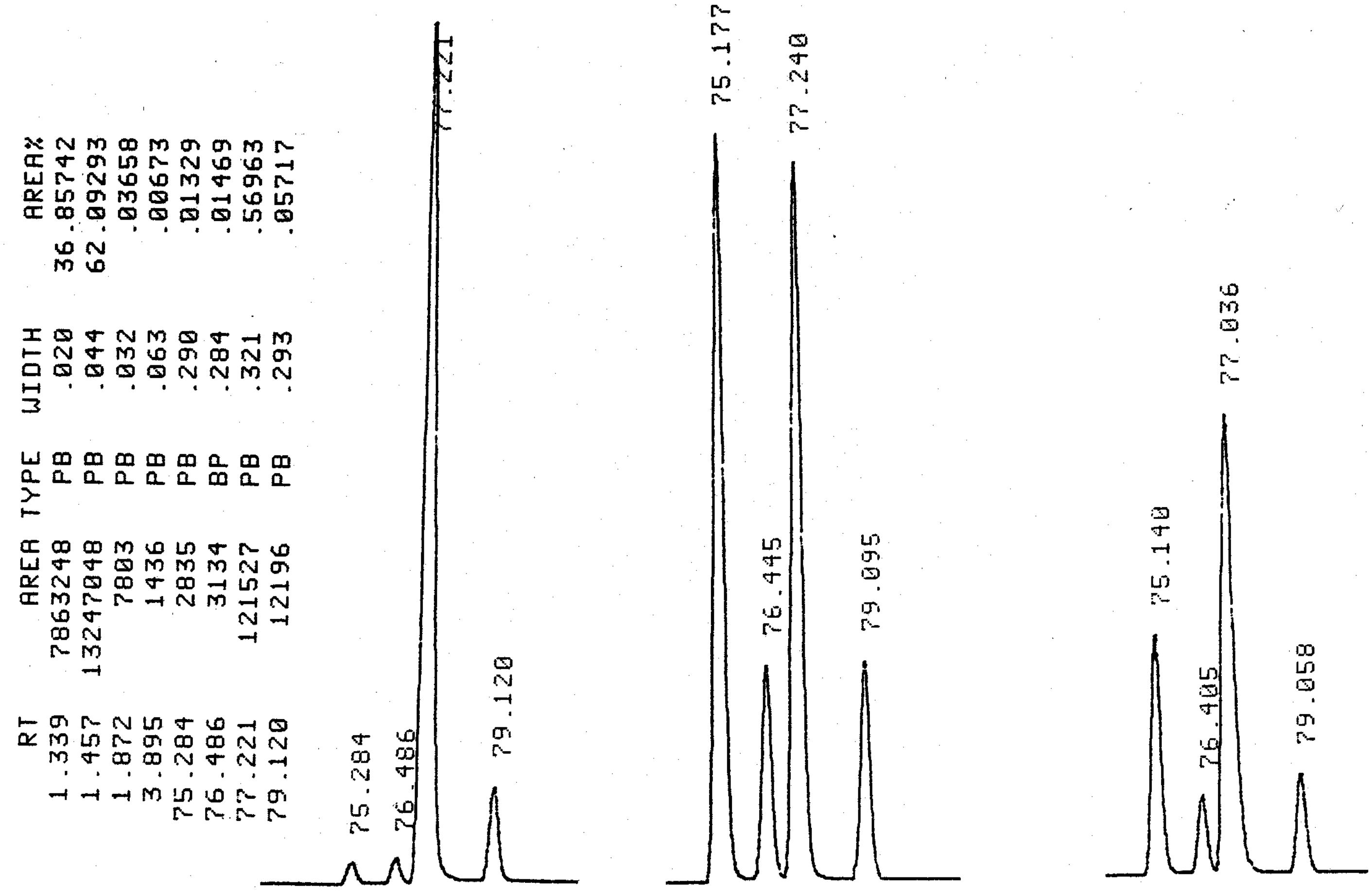
Representative procedure for catalytic reductive aldol reaction. A 10 mL flame-dried round bottom flask was charged with 20.0 mg of chloro(1,5-cyclooctadiene)iridium (I) dimer (0.03 mmol), 35.0 mg (0.089 mmol) of indane-pybox (derived from 1S,2R-aminoindanol; Davies, I. W.; Gerena, L.; Lu, N.; Larsen, R. D.; Reider, P. J. *J. Org. Chem.* **1996**, *61*, 9629) and 850 μL of dichloroethane. The resulting solution was stirred at room temperature for one hour. After one hour 644 μL of dichloroethane and 207 μL of diethylmethylsilane (1.43 mmol) were added to the mixture and the reaction vessel was stirred for 30 minutes. Next, 1.7 mL of stock benzaldehyde/methyl acrylate solution (0.7 M in aldehyde and 0.84 M in acrylate, 1.19 mmol aldehyde, 1.43 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 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 (10:1 then 8:1 hexanes:ethyl acetate) to yield 131 mg (0.6 mmol, 49 % yield) of Methyl (*2S, 3S*)-4-Benzyloxy-3-hydroxy-2-methylbutanoate (94% ee).



Methyl (2*S*, 3*S*)-4-(tert-Butyldimethylsilyoxy)-3 hydroxy-2 methylbutanoate. IR (neat) 3477 (br s), 2945 (s) 2858 (s), 1741 (s), 1465 (m), 1244 (s), 1106 (s), 835 (s) cm^{-1}; ^{1}H NMR (400 MHz) 3.87 (1H, m, **CH**OH), 3.68 (3H, s, C(O)OC**H**$_3$), 3.61 (1H, dd, J = 4.7, 10Hz, TBSOC**H**H), 3.55 (1H, dd, J = 6.0, 10.1 Hz, TBSOCH**H**), 2.65 (1H, s, O**H**), 2.63 (1H, m, **CH**CH$_3$), 1.21 (3H, d, J=7.1 Hz, CHC**H**$_3$), 0.88 (9H, s, (C**H**$_3$)$_3$CSi), 0.05 (6H, S, (C**H**$_3$)$_2$Si). ^{13}C NMR: δ 175.9, 72.4, 64.6, 52.0, 41.9, 26.0, 18.4, 12.4, -5.2 (2 carbons). Anal. Calc'd for $C_{12}H_{26}O_4Si$: C, 54.92; H, 9.99 Found: C, 55.09, H 9.95.

Proof of Configuration: Determination of stereochemical ratios was accomplished through chiral GLC analysis in comparison to non-selective aldol adducts prepared according to the method of Heathcock *et al.* (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 the major stereoisomer was established by GLC in comparison to authentic material (Evans, D. A.; Bartoli, J; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127-2129).

Chiral GLC (β-dex 120, Supelco) analysis of reductive aldol reaction product.



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 75.284     2835  PB    .290    .01329
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 77.221   121527  PB    .321    .56963
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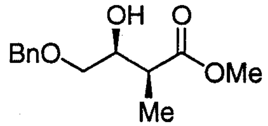
Reductive Aldol

Racemic

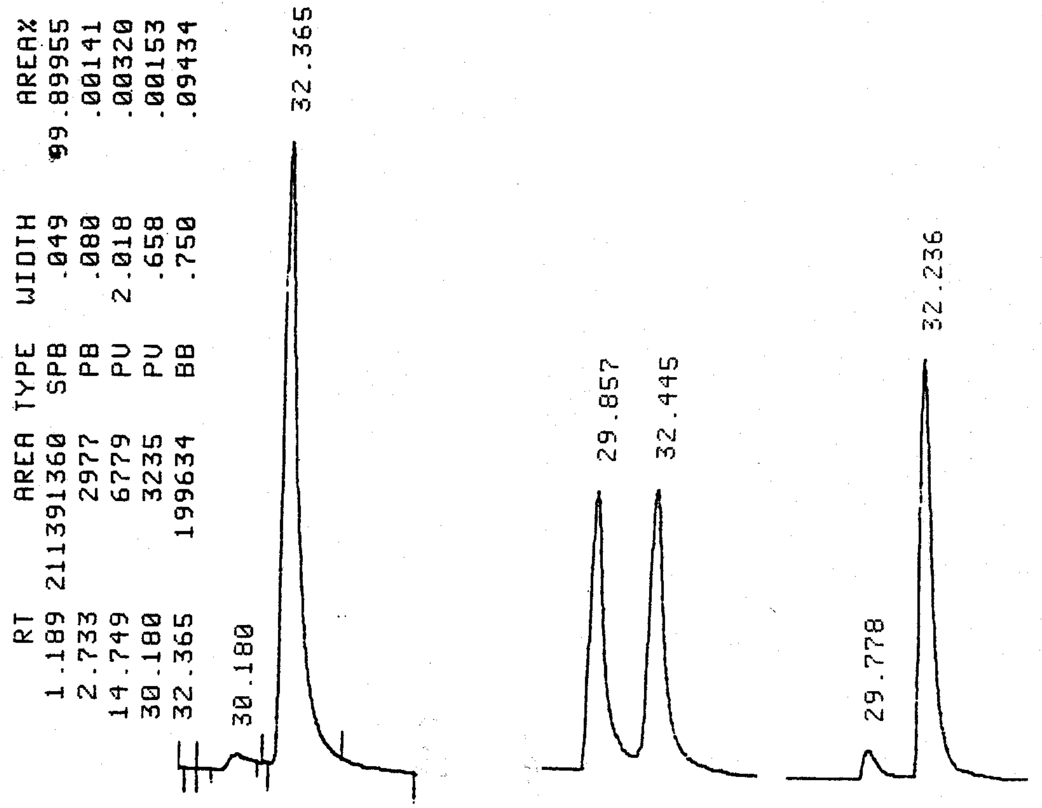
Coinjection
Racemic + Reductive Aldol



Methyl (2*S*, 3*S*) 4-Benzyloxy-3-hydroxy-2-methylbutanoate. IR (Neat) 3462 (br, s), 3032 (m), 2950 (s), 1961 (w), 1869 (w), 1731 (s) 1203 (s), 1101 (s). ^{1}H NMR δ 7.34 (5H, m, Ar), 4.55 (2H, s, Ar$\mathbf{CH_2}$O), 4.07 (1H, m, **CH**OH), 3.67 (3H, s, C(O)OC$\mathbf{H_3}$), 3.53 (1H, dd, J=1.9, 8Hz, BnOC**H**H), 3.48 (1H, dd, J= 3.4, 7.0Hz, BnOCH**H**), 2.72 (1H, d, J=4.8 Hz, **OH**), 2.70 (1H, m, **CH**CH$_3$), 1.22 (3H, d, J=7.2, CHC$\mathbf{H_3}$). ^{13}C NMR: δ 175.8, 138.0, 128.7, 128.04, 128.00, 73.7, 71.8, 71.1, 52.0, 42.2, 12.2. Anal. Calc'd for $C_{12}H_{18}O_4$: C 65.53; H 7.61 Found: C 65.31, H 7.51.

Proof of Configuration: The diastereomer ratio was determined by ^{1}H NMR (300MHz). The major *syn* reductive aldol product was separated by chromatography and it's enantiomeric purity determined by chiral GLC analysis in comparison to racemic *syn* 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) followed by separation of *syn* and *anti* isomers on silica gel. The relative configuration was established by comparison to reported ^{1}H NMR spectra (Buisson, D.; Henrot, S.; Larcheveque, M.; Azerad, R. *Tetrahedron Lett.* **1987**, *42*, 5033-5036). Absolute configuration of each diastereomer was established by GLC comparison to the authentic stereoisomer (Evans, D. A.; Bartroli, J; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127-2129).

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



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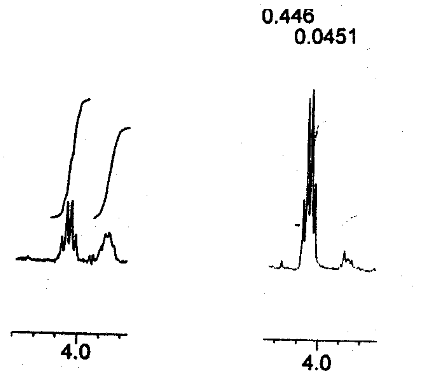
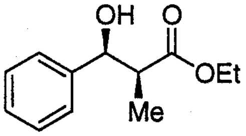
reductive aldol   racemic   authentic (2S,3S)

^{1}H NMR analysis of diastereomer ratio:



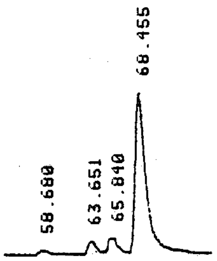
syn/anti mixture   reductive aldol



Ethyl (2*S*,3*S*)-3-Phenyl-3-hydroxy-2-methylpropionate. IR (neat) 3462 (br s), 2982 (m), 1724 (s), 1465 (m), 1185 (s) cm^{-1}; ^{1}H NMR (300 MHz) δ 7.24-7.33 (5H, m, Ar), 5.07 (1H, dd, J=4.2, 3.3 Hz, CHOH), 4.11 (2H, q, J= 7.2 Hz, $\mathbf{CH_2}CH_3$), 2.96 (1H, d, J=3.3 Hz, **OH**), 2.76 (1H, dq, J= 4.2, 7.2 Hz, $\mathbf{CH}CH_3$), 1.19 (3H, t, J=7.2 Hz, $CH_2\mathbf{CH_3}$), 1.11 (3H, d, J= 7.2 Hz, $CH\mathbf{CH_3}$). ^{13}C NMR: δ 175.6, 141.3, 128.1, 127.3, 125.9, 73.6, 60.7, 46.4, 14.1, 10.9. Anal. Calc'd for $C_{12},H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.35, H 7.68.

Proof of Configuration: Determination of stereochemical ratios was accomplished through chiral GLC analysis in comparison to non-selective aldol adducts prepared according to the method of Heathcock *et al.* (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 ^{1}H NMR spectra (Ishihara, K.; Maruyama, T.; Mouri, M.; Gao, Q.; Furuta, K.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3483-3491). Absolute configuration of the diastereomer was established by GLC comparison to the authentic stereoisomer (Taylor, S. J.; Duffey, M. O.; Morken, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 4528-4529).

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



Reductive aldol product

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21.580        3003   VB    1.390       .32115
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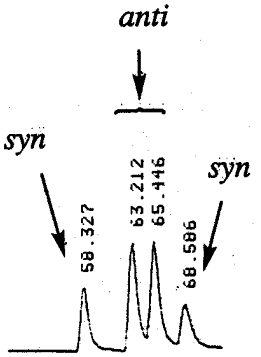
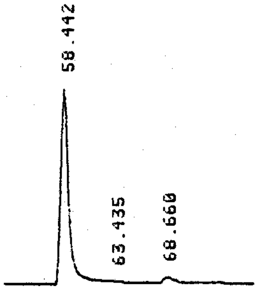
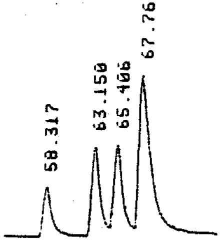


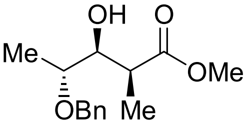
Racemic



Authentic (2*R*,3*R*)-enantiomer

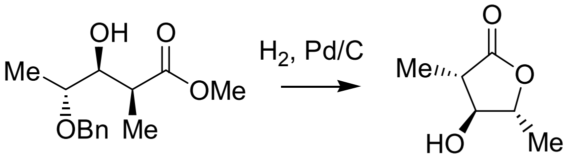


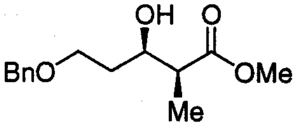
Red. aldol + Racemic coinjection



Methyl (*2S,3S,4R*) 4- Benzyloxy 3- hydroxy-2-methylpentanoate. IR (Neat) 3418 (br, s), 2938 (m), 1738 (s), 1455 (s). ^{1}H NMR (300Hz) δ 7.31 (5H, m, Ar), 4.71 (1H, d, J=11.7 Hz, ArC**H$_2$**O), 4.41 (1H, d, J=11.7 Hz, ArC**H$_2$**O), 3.88 (1H, dd, J=5.1, 6.6 Hz, C**H**OH), 3.64 (3H, s, C(O)OC**H$_3$**), 3.46 (1H, m, BnOC**H**), 2.78 (1H, dq, J=5.1, 7.2 Hz, C**H**CH$_3$), 2.50 (1H, br, O**H**), 1.25 (3H, d, J=6.0, BnOCHC**H$_3$**), 1.16 (3H, d, J=7.2, CHC**H$_3$**). ^{13}C NMR: δ 176.3, 138.1, 128.3, 127.7, 127.6, 74.9, 74.0, 70.6, 51.7, 41.0, 15.2, 11.8. Anal. Calc'd for $C_{14}H_{20}O_4$: C 66.64; H 7.93 Found: C 66.60, H 7.71.

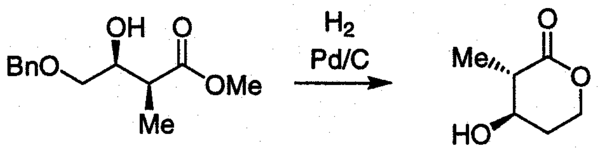
Proof of Configuration: ^{1}H NMR showed only one diastereomer of the crude reductive aldol product. This diastereomer was converted to the derived γ-lactone (Ewing, W. R.; Bhat, K. L.; Joullie, M. M. *Tetrahedron.* **1986,** *42*, 5863-5868) by hydrogenolysis of the benzyl ether which resulted in spontaneous cyclization to the lactone (below). The configuration of the derived γ-lactone was determined by comparison to that reported in the literature (Chen, S.-Y.; Joullie, M. M. *J. Org. Chem.* **1984**, *49*, 2168-2171).



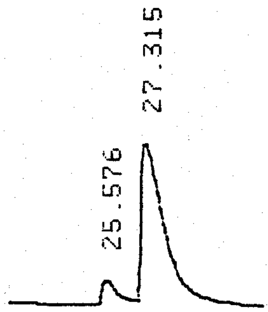


Methyl (*2S,3R*) 5-Benzyloxy-3-hydroxy-2-methylpentanoate. IR (Neat) 3489 (br, s), 2950 (s), 1738 (s), 1455 (s). ^{1}H NMR (300Hz) δ 7.20 (5H, m, Ar), 4.40 (2H, s, ArCH_2O), 3.96 (1H, m, **CH**OH), 3.57 (3H, s, C(O)OCH_3), 3.56 (2H, m, BnOCH_2), 2.43 (1H, m, **CH**CH_3), 1.53-1.75 (2H, m, $CH_2$$CH_2$OBn), 1.09 (3H, d, J=7.1 Hz, CHCH_3). ^{13}C NMR: δ 176.0, 138.0, 128.5, 127.8, 127.8, 73.5, 71.3, 68.8, 52.0, 45.1, 33.9, 11.8. Anal. Calc'd for $C_{14}H_{20}O_4$: C 66.64; H 7.93. Found: C 66.5, H 8.00.

Determination of Stereoisomer Ratio: Determination of diastereomer ratio was determined by ^{1}H NMR analysis. Determination of enantiomer ratio (*syn isomer*) was accomplished by chiral GLC analysis of the derived δ-lactone prepared by hydrogenolysis of the reductive aldol adduct followed by spontaneous lactonization (see below). Analyses were performed in comparison to racemic adducts prepared according to the method of Heathcock *et al.* (Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066-1081).



Chiral GLC analysis (Chiraldex-GTA, Alltech; analysis performed on δ-lactone) of the reductive aldol reaction product and racemic syn diastereomer:



Reductive Aldol

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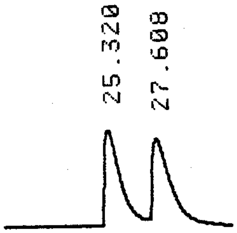
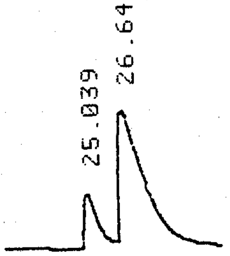


Racemic

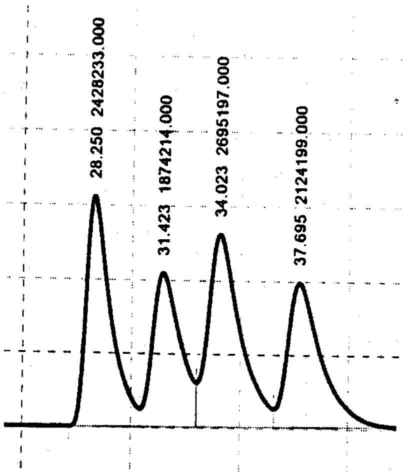


Coinjection

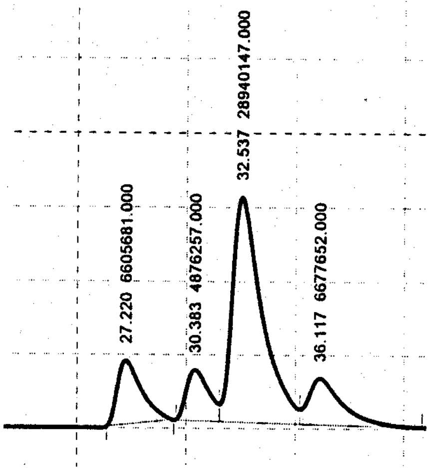
Racemic+Reductive Aldol

Proof of Configuration: Absolute configuration of the major diastereomer was established by HPLC comparison to the authentic stereoisomer (Evans, D. A.; Bartroli, J; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127-2129).

Chiral HPLC (Chiralcel-OD, Daicel, derived p-chlorobenzyl esters) analysis of reductive aldol reaction product, Evans Aldol product and racemic mixture of diastereomers:

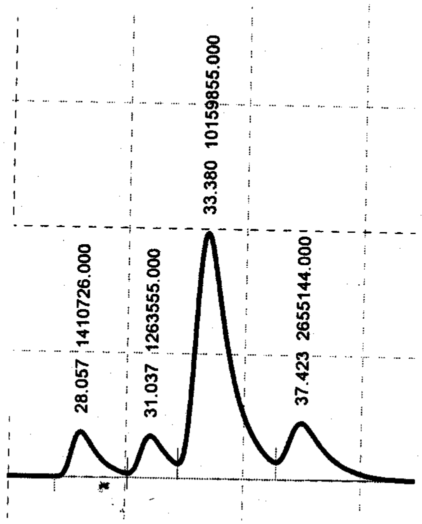


Racemic

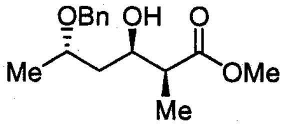


Coinjection

Authentic (2S,3R)+Racemic



Reductive Aldol



Methyl (*2S,3R,5S*)-5-Benzyloxy-3-hydroxy-2-methylhexanoate. IR (Neat) 3483 (br, s), 2970 (s), 1730 (s), 1456 (s). ^{1}H NMR (300Hz) δ 7.13-7.24 (5H, m, Ar), 4.50 (1H, d, J=11.6 Hz, ArC**H**$_2$O), 4.32 (1H, d, J=11.6 Hz, ArC**H**$_2$O), 4.04 (1H, m, C**H**OH),), 3.75 (1H, m, BnOC**H**), 3.57 (3H, s, C(O)OC**H**$_3$), 2.90 (1H, br, O**H**), 2.40 (1H, dq, J=4.9, 7.1 Hz, C**H**CH$_3$), 1.55 (1H, m, C**H**$_2$CHOBn), 1.43 (1H, m, C**H**$_2$CHOBn), 1.14 (3H, d, J=6.3 Hz, BnOCHC**H**$_3$), 1.08 (3H, d, J=7.1, CHC**H**$_3$). ^{13}C NMR: δ 176.2, 138.6, 128.5, 127.9, 127.7, 72.6, 70.9, 69.0, 51.9, 45.1, 40.6, 19.7, 11.9. Anal. Calc'd for $C_{14}H_{20}O_4$: C 67.64; H 8.33 Found: C 68.01, H 8.30.

Proof of Configuration: 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). Absolute configuration of the major diastereomer was established by GLC comparison to the authentic stereoisomer (Evans, D. A.; Bartroli, J; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127-2129).

Chiral GLC (beta-DEX, Supelco) analysis of reductive aldol reaction product, Evans Aldol product and racemic mixture of diastereomers:

RT	AREA	TYPE	WIDTH	AREA%
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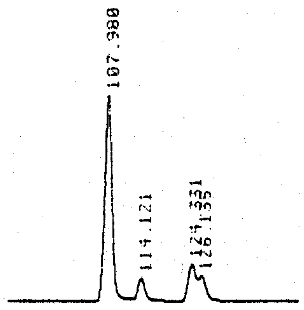
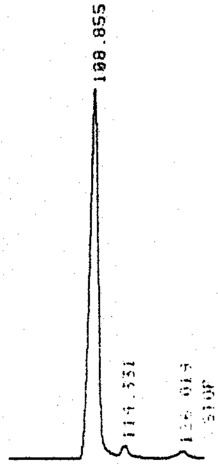
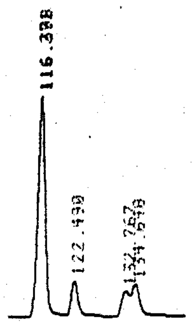
124.331	177841	PV	1.799	.21702
126.135	120905	VV	1.782	.14754



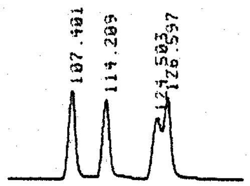
Reductive Aldol



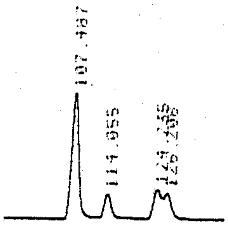
Authentic
(2S,3R)-enantiomer



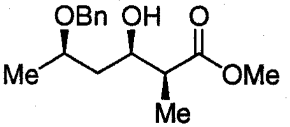
Authentic + Racemic



Racemic



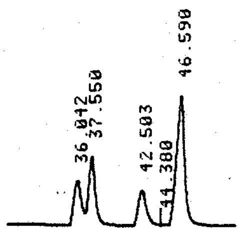
Red. Aldol + Racemic



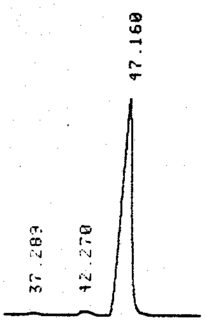
Methyl (*2S,3R,5R*)-5-Benzyloxy3-hydroxy-2-methylhexanoate. IR (Neat) 3482, (br, s), 2971 (s), 1730 (s), 1456 (s). ^{1}H NMR (300Hz) δ 7.13-7.24 (5H, m, Ar), 4.53 (1H, d, J=11.2 Hz, Ar**CH$_2$**O), 4.30 (1H, d, J=11.2 Hz, Ar**CH$_2$**O), 3.93 (1H, m, **CHOH**),), 3.70 (1H, m, BnOC**H**), 3.57 (3H, s, C(O)OCH$_3$), 2.90 (1H, br, **OH**), 2.40 (1H, dq, J=4.9, 7.1 Hz, **CH**CH$_3$), 1.39-1.69 (2H, m, **CH$_2$**CHOBn) 1.14 (3H, d, J=6.0 Hz, BnOCH**CH$_3$**), 1.07 (3H, d, J=7.1 Hz, CH**CH$_3$**). ^{13}C NMR: δ 176.3, 138.1, 128.3, 128.3, 127.6, 75.7, 72.0, 70.4, 51.7, 45.4, 41.0, 19.7, 11.8. Anal. Calc'd for $C_{14}H_{20}O_4$: C 67.64; H 8.33. Found: C 67.80, H 8.31.

Proof of Configuration: 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). Absolute configuration of the major diastereomer was established by GLC comparison to the authentic stereoisomer (Evans, D. A.; Bartroli, J; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127-2129).

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



Red. Aldol + Racemic



Authentic
(2S,3R)-enantiomer

```
    RT      AREA TYPE  WIDTH      AREA%
35.920     48556  PU     .796   4.87049
37.489   1261 81  VV     .826  12.65681
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46.780    416481  BB    1.008  41.77586
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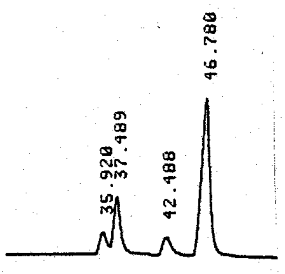
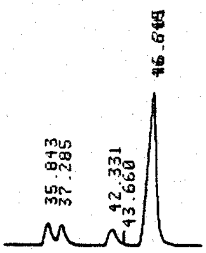
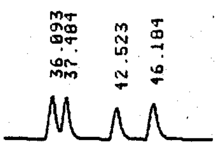


Reductive Aldol



Authentic + Racemic



Racemic