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# Supporting Information



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**$Me_2Zn$ mediated Catalytic Enantioselective Reformatsky Reaction with Ketones.**

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General: $^{1}H$ NMR spectra were recorded on Varian 200 MHz or Varian 300 MHz spectrometers. chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (deuterochloroform: δ 7.27 ppm). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz). $^{13}C$ NMR spectra were recorded on a Varian 50 MHz, Varian 75 MHz or Varian 100 MHz spectrometers with complete proton decoupling. $^{19}F$ spectra were recorded with Varian VXR spectrometer at 282.208 MHz. $^{19}F$ spectra were referenced to $CFCl_3$ as the external standard. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard (deuterochloroform: δ 77.0 ppm). Mass spectra were performed at an ionizing voltage of 70 eV. Chromatographic purification was made with 240-400 mesh silica gel. Analytical gas chromatography (GC) was performed on a Hewlett-Packard HP 6890 gas chromatograph, with a flame ionization detector and split-mode capillary injection system, using a Crosslinked 5% PH ME Siloxane (30 m) column or a Megadex5 chiral (25 m) column. Analytical high performance liquid chromatograph (HPLC) was performed on a HP 1090 liquid chromatograph equipped with a variable wavelength UV detector (deuterium lamp 190-600 nm), using a Daicel Chiralcel™ OD column (0.46 cm I.D. x 25 cm) (Daicel Inc.). HPLC grade isopropanol and hexane were used as the eluting solvents. LC were obtained with HPLC Agilent

technologies HP1100 series, equipped with a diode array detector. Only a pre-column was used for purifying the products. The binary mobile phase consisted in (A) water (B) acetonitrile in isocratic conditions (A)20% (B)80% with a flow rate of 0.3 ml/min. The Mass detector consists in a Hewlett Packard 1100 MSD series, equipped with an API-ES interface and single quadrupole. The API-ES conditions for analysis in positive mode were performed with drying gas flow: x l/min, nebulizer pressure: x psgi, drying gas temperature: x °C, capillary voltage: x V, fragmentor: x V. All the reactions were carried out under a nitrogen atmosphere in flame-dried glassware, using standard inert techniques to introduce reagents and solvents. All ketones were purified prior to use. All the other commercially obtained reagents were used as received. $Me_2Zn$ 2M in toluene (Fluka) was used for all the reactions. Anhydrous diethyl ether and *t*butylmethyl ether were purchased from Fluka. All racemic or *quasi* racemic β alkoxyesters were prepared by Cl Mn(Salen)catalyzed Reformatsky reaction, run in toluene at 70°C temperature.

**General procedure for the Enantioselective Reformatsky reaction**

To a stirred solution of ClMn(Salen) (0.04mmol) in *t*BuOMe(5mL) at room temperature, ketone (0.2mmol) and iodoacetate (0.4mmol), were added. Then the flask was immersed in an oil bath an maintained at 100°C for 2 min. $Me_2Zn$ (0.4mmol) was added drop-wise. The brown homogeneous solution was stirred for 2-3 hours at reflux temperature, then cooled down to room temperature. The reaction was quenched with a saturated solution of $NaHCO_3$, then filtered over glass septum. The organic phase was separated, and the aqueous phase extracted with diethyl ether (2x 2mL). The combined organic phases were dried over $Na_2SO_4$ and evaporated under reduced pressure to give an oil purified by flash chromatography (eluant: cyclohexane: diethylether 70:30-90:10)

**General procedure for the enantioselective Reformatsky reaction in the presence of 4-phenyl pyridine N-oxide.**

To a stirred solution of ClMn(Salen) (0.04mmol) in *t*BuOMe(5mL), 4-phenyl pyridine N-oxide (0.05mmol) was added and the mixture was stirred at room temperature for 1 hour. The ketone (0.2mmol) and iodoacetate (0.4mmol) were added to the flask and the brown solution was stirred for 5 minutes. $Me_2Zn$ (0.4mmol) was added drop-wise by syringe. The mixture immediately become heterogeneous, and some precipitate was formed. The brown, heterogeneous solution was stirred for 24-120 hours at room temperature. The reaction was quenched with a saturated solution of $NaHCO_3$ then filtered over glass septum. The organic phase was

separated and the aqueous phase extracted with diethyl ether (3x 2mL). The combined organic phases were dried over $Na_2SO_4$ and evaporated under reduced pressure to give an oil purified by flash chromatography (eluant: cyclohexane :diethylether 70:30-90:10)

**Table 1**

**Table 1**.[a] Enantioselective Reformatsky reaction acetophenone with ethyl iodoacetate performed in the presence of different M(Salen) metal complexes

| Entry[a] | M(Salen) | Ee [%][b] |
|---|---|---|
| 1[c] | Co(Salen) | - |
| 2[c] | Co(Salen)OAc | - |
| 4[c] | Co(Salen)OTs | - |
| 4[c] | Co(Salen)$SbF_6$ | - |
| 5 | Al(Salen)Cl | 6 |
| 6 | Sn(Salen) | 0 |
| 7 | O=Ti(Salen) | 0 |
| 8 | O=V(Salen) | 0 |
| 9 | Cu(Salen) | 0 |
| 10 | Zn(Salen) | 20(*S*) |
| 11 | Ti(Salen)$Cl_2$ | 0 |
| 12 | Mn(Salen)Cl | **43(*R*)** |
| 13 | Cr(Salen)Cl | 0 |

[a] All the reactions were carried out at RT for 3-24 hours with acetophenone (0.2mmol), ethyl iodoacetate (0.4mmol) and $Me_2Zn$ (0.4mmol) in $Et_2O$ (5mL), in the presence of 20mol% of M(salen) metal complex. Reaction stirred 24 hours given complete conversion. [b] Determined by HPLC analysis on the crude reaction mixture. [c] No reaction occurs.

**Table 2.** Enantioselective Reformatsky reaction of acetophenone mediated by ClMn(Salen) (Scheme 1, M = MnCl) in different solvents.

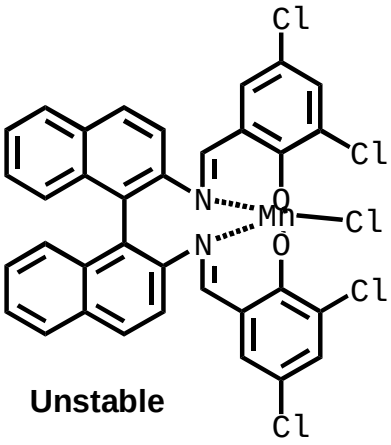
| Entry[a] | Solvents | T [°C] | Time, h | Yield [%][b] | Ee[c] |
|---|---|---|---|---|---|
| 1 | $Et_2O$ | RT | 24 | 95 | 43(*R*) |
| 2[d] | $CH_2Cl_2$ | RT | 24 | 95 | 0 |
| 3 | Toluene | RT | 24 | 95 | 0 |
| 4 | *t*BuOMe | RT | 24 | 95(89) | 44(*R*) |
| 5 | DME | RT | 24 | 0 | |
| 6 | Dioxane | RT | 24 | 0 | |
| 7 | $Et_2O$ | Reflux | 3 | 95 | 54(*R*) |
| 8 | Toluene | Reflux | 3 | 95(89) | 0 |
| 9 | Ethylacetate | Reflux | 3 | 40 | 14(*R*) |
| 10 | *t*BuOMe | Reflux | 3 | 95(90) | 63(*R*) |
| 11[d] | *t*BuOMe | Reflux | 3 | 58 | 62(*R*) |
| 12 | Chlorobenzene | Reflux | 3 | 80 | 0 |
| 13 | DME | Reflux | 3 | 0 | |
| 14 | Dioxane | Reflux | 3 | 0 | |

[a] All the reactions were performed at the indicated temperature using 2 equiv. ethyl iodoacetate and 2 equiv. of $Me_2Zn$ (for experimental details see supporting information). (*R*,*R*)-Cl(Mn(Salen) was used in 20mol%. [b] Conversion was evaluated by the HPLC analysis of the crude reaction mixture. Isolated yields in parenthesis. [c] Determined by chiral HPLC analysis (Chiralcel OD column). Absolute configuration *R* by correlation to the literature data.[1] [d] 10% of the (*R*,*R*)-ClMn(Salen) was used.

**Table 3.** Enantioselective Reformatsky reaction of acetophenone mediated by ClMn(Salen) in the presence of different additives.

| Entry[a] | Additives | T [°C] | Time, h | Yield [%][b] | Ee[c] |
|---|---|---|---|---|---|
| 1 | 2,6-di*t*Butylpyridine | Reflux | 1.5 | 20 | 38(*R*) |
| 2 | N-Methylimidazole | Reflux | 1.5 | 85 | 13(*R*) |
| 3 | $Ph_3PO$ | Reflux | 1.5 | 60 | 21(*R*) |
| 4 | 4-PhPyridine-N-Oxide | Reflux | 1.5 | 50 | 66(*R*) |
| 5[d] | 4-PhPyridine-N-Oxide | Reflux | 0.75 | 60 | 59(*R*) |
| 6 | Pyridine-N-Oxide | Reflux | 1.50 | 50 | 52(*R*) |
| 7[e] | $CH_3CN$ | Reflux | 1.5 | 90 | 51(*R*) |
| 8 | $Ph_3PO$ | RT | 24 | 90 | 38(*R*) |
| 9 | 4-PhPyridine-N-Oxide | RT | 24 | 84 | 63(*R*) |
| 10[f] | 4-PhPyridine-N-Oxide | RT | 12 | 82 | 57(*R*) |
| 11[g] | Sieves 4Å | RT | 24 | 95 | 54(*R*) |

[a] All the reactions were performed at the indicated temperature using 2 equiv. ethyl iodoacetate and 2 equiv. of $Me_2Zn$ (for experimental details see supporting information), in the presence of 25mol% of additives. Cl(Mn(Salen) was used in 20mol%. [b] Conversion evaluated by HPLC analysis of the crude reaction mixture. [c] Determined by chiral HPLC analysis (Chiralcel OD column). [d] Commercially available ClMn(Salen) was employed [e]150mol% of anhydrous $CH_3CN$ was used as an additive [f] 3 equivalents of $Me_2Zn$ and 3 equivalents iodoacetate were employed in this reaction. [g] 400mg of Sieves 4Å were employed in the reaction.

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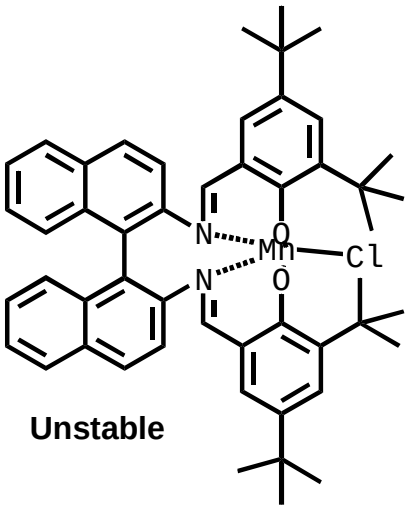


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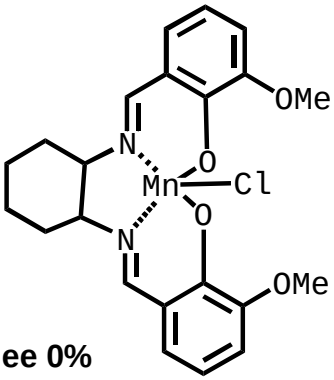
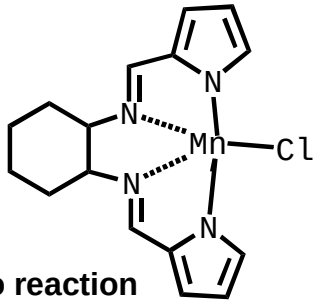
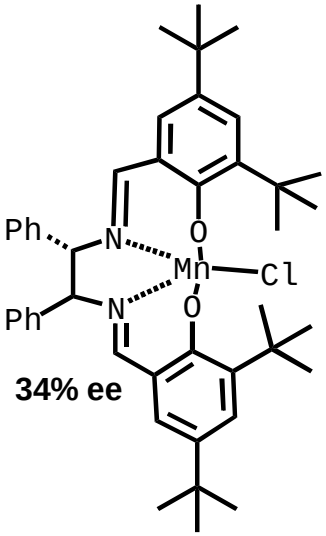


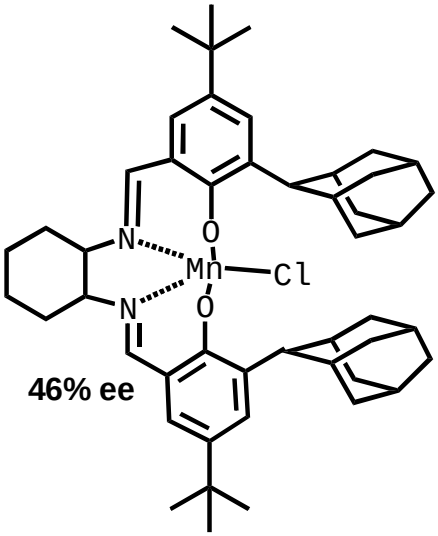

**ee 0%**




**No reaction**

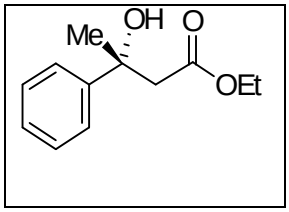



**34% ee**




**46% ee**

**(*R*) Ethyl-3-hydroxy-3–phenylbutyrate**




$C_{12}H_{16}O_3$ Fw = 208.25

$[\alpha]_D$ = -8.69 (c, 0.46 EtOH). Lit.[1] (*S*) Ethyl-3-hydroxy-3–phenylbutyrate

$[\alpha]_D$ = +3.05 (neat), Optical purity 38%.

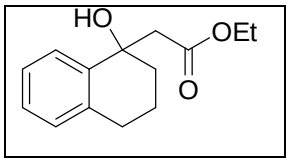
$^1$H NMR ($CDCl_3$, 300 MHz) δ: 1.69 (t, 3H, J = 7.2Hz); 1.58 (s, 3H); 2.92 (AB, 2H, J = 15.9Hz); 4.11 (q, 2H, J = 7.2Hz); 4.44 (s, 1H); 7.27 (dt, 1H, J = 1.2, 7.8Hz); 7.37 (dt, 2H, J = 1, 7.5Hz); 7.49 (dd, 2H, J = 1.5, 8.4Hz).

$^{13}$C NMR ($CDCl_3$, 75 MHz) δ: 13.95; 30.63; 46.38; 60.69; 72.71; 124.42; 126.80; 128.19; 146.79; 172.68.

GCMS: 208(1); 193(59); 163(5); 147(9); 131(3); 121(100); 115(3); 105(62); 91(10); 77(23); 65(3); 60(2); 51(7).

HPLC analysis OD: isocratic, flux 0.5mL/m (hexane: *i*-PrOH) 99:1. TM: 10.96 min; tm: 14.20 min. ee 66%.

**1-(Hydroxy-1,2,3,4-tetrahydronaphtalen-1-yl)-acetic acid ethyl ester**




$C_{14}H_{18}O_3$ Fw = 234.29

$[\alpha]_D$ = +11 (c 5.5, $CHCl_3$)

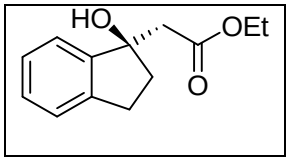
$^1$H NMR ($CDCl_3$, 300 MHz) δ: 1.32 (t, 3H, J = 6.9Hz); 1.89-1.79 (m, 1H); 2.17-1.95 (m, 3H); 2.86 (AB, 2H, J = 15.3Hz); 2.94-2.91 (m, 2H); 4.02 (brs, 1H); 4.24 (q, 2H, J = 6.9Hz); 7.11-7.10 (m, 1H); 7.30-7.24 (m, 2H); 7.62-7.59 (m, 1H).

$^{13}$C NMR ($CDCl_3$, 75 MHz) 14.11; 19.95; 29.40; 36.27; 46.041; 60.75; 71.07; 126.28; 126.33; 127.33; 128.82; 136.42; 140.56; 172.49.

GCMS: 146(65); 131(18); 118(100); 113(1); 104(3); 98(1); 90(72); 77(2); 63(4); 51(15).

HPLC analysis OD: isocratic, flux 0.5mL/m (hexane: *i*-PrOH) 98.5:1.5. TM: 14.22 min; tm: 20.63 min. ee 86%.

**(*R*)-1-(Hydroxy-indan-1-yl)-acetyc acid ethyl ester**




$C_{13}H_{16}O_3$ Fw = 220.26

$[\alpha]_D$ = +4.2 (c 2.6, $CHCl_3$)

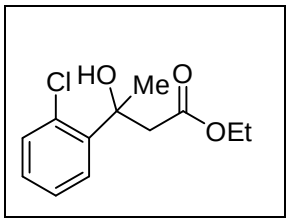
$^1$H NMR ($CDCl_3$, 300 MHz) δ: 1.32 (t, 3H, J = 7.2Hz); 2.32 (t, 2H, J = 7.2Hz); 2.74 (AB, 1H, J = 15.9Hz); 2.95-2.84 (m, 1H); 2.93 (AB, 1H, J = 15.9Hz); 3.14-3.04 (m, 1H); 3.87(brs, 1H); 4.25 (q, 2H, J = 7.2Hz); 7-28-7.20 (m, 3H); 7.39-7.37 (m, 1H).

$^{13}$C NMR ($CDCl_3$, 75 MHz) δ: 14.24; 29.47, 40.40: 44.10; 60.93; 81.17; 122.97; 125.06; 126.88; 128.57; 136.30; 142.84; 172.20.

GCMS: 220(1); 202(47); 191(1); 175(4); 163(1); 157(8); 145(2); 133(100); 115(11); 103(10); 91(7); 77(10); 76(3); 63); 51(3).

HPLC analysis OD: isocratic, flux 0.8mL/m (hexane: *i*-PrOH) 95:5. TM: 14.90 min; tm: 16.31 min. ee 84%.

**Ethyl-3-(2-chlorophenyl)-3-hydroxy-butanoate**




$C_{12}H_{15}ClO_3$ Fw = 242.69

$[\alpha]_D$ = -1.6 (c 2.5, $CHCl_3$)

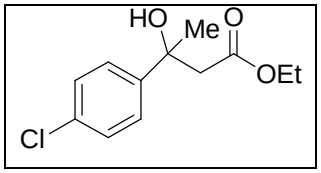
$^1$H NMR ($CDCl_3$, 300 MHz) δ: 1.13 (t, 3H, J = 6.9Hz); 1.76 (s, 3H); 2.98 (AB, 1H, J = 16.2Hz); 3.61 (AB, 1H, J = 16.2Hz); 4.06 (q, 2H, J = 6.9Hz); 4.72, (s, 1H); 7.26-7.20 (m, 1H); 7.39-7.32 (m, 2H); 7.92 (td, 1H, J = 1.5, 8.1Hz).

$^{13}$C NMR ($CDCl_3$, 75 MHz) δ: 13.88; 27.15; 43.72; 60.69; 73.05; 126.93; 127.99; 128.54; 130.40; 131.14; 142.89; 172.92.

GCMS: 229(8); 227(15); 207(65); 197(2); 181(11); 163(10); 155(100); 139(79); 131(6); 111(11); 105(6); 91(14); 77(13); 60(10); 51(9).

HPLC analysis OD: isocratic, flux 0.5mL/m (hexane: *i*-PrOH) 99:1. TM: 16.81 min; tm: 22.40 min. ee 84%.

**Ethyl-3-(4-chlorophenyl)-3-hydroxy-butanoate**




$C_{12}H_{15}ClO_3$ Fw = 242.69

$[\alpha]_D$ = -6.8 (c 5, $CHCl_3$)

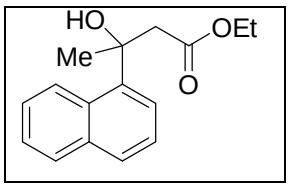
$^1$H NMR ($CDCl_3$, 300 MHz) δ: 1.91 (t, 3H, J = 6.9Hz); 1.55 (s, 3H); 2.81(AB, 1H, J = 15.9Hz); 2.97 (AB, 1H, J = 15.9Hz); 4.10 (q, 2H, J = 6.9Hz); 4.47 (s, 1H); 7.32 (AA',BB', 2H, J = 9Hz); 7.42 (AA',BB', 2H, J = 9Hz).

$^{13}$C NMR ($CDCl_3$, 75 MHz) δ: 13.97; 30.61; 46.14; 60.86; 72.44; 126.01; 128.31; 132.64; 154.43; 172.53,

GCMS: 229(13); 227(40); 197(3); 181(6); 155(100); 139(54); 125(2); 111(10); 101(2); 91(4); 75(7); 60(3); 51(3).

HPLC analysis OD: isocratic, flux 0.5mL/m (hexane: *i*-PrOH) 97:3. TM: 11.98 min; tm: 14.44 min. ee 85%.

**3-Hydroxy-3-naphtalen-3-yl-butyric acid ethyl ester**



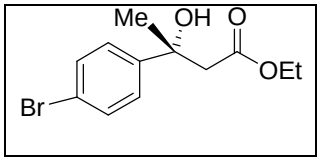

$C_{16}H_{18}O_3$ Fw = 258.31

$[\alpha]_D$ = -17.9 (c 3.8, $CHCl_3$)

$^1$H NMR ($CDCl_3$, 300 MHz) δ: 1.21 (t, 3H, J = 7.2Hz); 1.91 (s, 3H); 3.02 (AB, 1H, J = 16.2Hz); 3.47 (AB, 1H, J = 16.2Hz); 4.16 (q, 2H, J = 7.2Hz); 4.75 (s, 1H); 7.81 (d, 1H, J = 8.1Hz); 7.42 (t, 1H J = 7.8Hz); 7.59-7.48 (m, 3H); 7.90 (dd, 1H, J = 2.1,7.5Hz); 8.86 (d, 1H, J = 8.1Hz).

$^{13}C$ NMR ($CDCl_3$, 75 MHz) δ: 14.00; 29.78; 46.17; 60.79; 74.51; 122.71; 124.65; 125.15; 125.38; 126.84; 128.79; 129.09; 130.89; 134.91; 141.34; 173.02.
GCMS: 258(24); 243(13); 213(2); 171(100); 155(57); 127(39); 115(10); 77(5); 63(3).
HPLC analysis OD: isocratic (hexane: *i*-PrOH) 99:1. tm: 39.87 min; TM: 42.39 min. ee 82%.

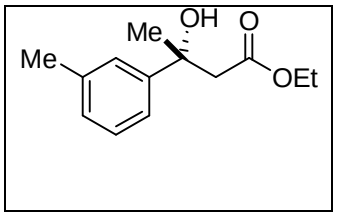
**(*R*)-1-Ethyl-3-(4-bromophenyl)-3-hydroxy-butanoate**




$C_{12}H_{15}BrO_3$ Fw = 287.14
$[\alpha]_D$ = -9.7 (c 2, $CHCl_3$)

$^1H$ NMR ($CDCl_3$, 300 MHz) δ: 1.91 (t, 3H, J = 6.9Hz); 1.55 (s, 3H); 2.82 (AB, 1H, J = 15.9Hz); 2.98 (AB, 1H, J = 15.8Hz); 4.10 (q, 2H, J = 6.9Hz); 4.47 (s, 1H); 7.36 (AA',BB', 2H, J = 9Hz); 7.42 (AA',BB', 2H, J = 9Hz).
$^{13}C$ NMR ($CDCl_3$, 75 MHz) δ: 14.27; 30.78; 46.38; 61.16; 72.78; 121.10; 126.70; 131.58, 146.27; 172.82.
GCMS: 288(3); 286(3); 273(39); 271(39); 201(100); 199(100); 183(50); 181(50); 155(10);153(10); 146(1); 131(4); 115(9); 91(8); 77(11); 60(6); 51(5).
HPLC analysis OD: isocratic, flux 0.5mL/m (hexane: *i*-PrOH) 95:5. TM: 11.18 min; tm: 12.64 min. ee 80%.

**(*R*)-1-Ethyl-3-(3-methylphenyl)-3-hydroxy-butanoate**




$C_{13}H_{18}O_3$ Fw = 222.28
$[\alpha]_D$ = -11 (c 0.9, $CHCl_3$)

$^1H$ NMR ($CDCl_3$, 300 MHz) δ: 1.18 (t, 3H, J = 7.5Hz); 1.57 (s, 3H); 2.39 (s, 3H); 2.82 (AB, 1H, 16.8Hz); 3.01 (AB, 1H,

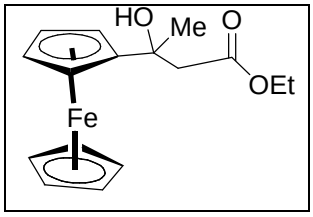
J = 16.8Hz); 4.11 (q, 2H, J = 7.5Hz); 4.40 (s, 1H); 7.10-7.07 (m, 1H); 7.28-7.25 (m, 2H); 7.32 (s, 1H).

$^{13}C$ NMR ($CDCl_3$, 75 MHz) δ: 13.96; 21.56; 30.63; 46.36; 60.65; 72.66; 121.42; 125.18; 127.53; 128.07; 137.75; 146.89; 172.72.

GCMS: GCMS: 222(4); 210(10); 207(70); 189(1); 177(5); 161(6); 147(1); 135(100); 119(73); 105(6); 91(35); 89(6); 77(7); 65(8); 51(3).

HPLC analysis OD: isocratic, flux 0.5mL/m(hexane: *i*-PrOH) 99:1. TM: 15.03 min; tm: 17.08 min. ee 81%.

**Ethyl-3-ferrocenyl-3-hydroxy-butanoate**




$C_{16}H_{20}FeO_3$ Fw = 316.17

$[\alpha]_D$ = -15 (c 0.8, $CHCl_3$)

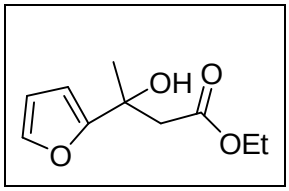
$^{1}H$ NMR ($CDCl_3$, 300 MHz) δ: 1).1.35(t, 3H, J = 6,)Hz); 1.63(s, 3H); 2,74(AB, 2H, J = 15,3Hz); 3,54 (s, 1H); 4.20-4.1(m, 3H); 4.25(s, 5H).

$^{13}C$ NMR ($CDCl_3$, 50 MHz) δ: 14.47; 29.02; 48.01; 60.84; 65.72; 66.44; 68.1; 68.97; 70.00; 98.13; 172.25.

GCMS: 298(100); 270(10); 253(10); 233(65); 205(11); 189(73); 165(3); 159(15); 122(10); 121(53); 95(5); 78(10); 56(20).

HPLC analysis OD: isocratic, flux 0.5mL/m (hexane: *i*-PrOH 94:6). tm: 15.63 min; TM: 17.22 min. ee 57%.

**3-Furan-3-yl-3-hydroxy-butyric acid ethyl ester**




$C_{10}H_{14}O_4$ Fw = 198.21

$[\alpha]_D$ = -4.5 (c 3.8, $CHCl_3$)

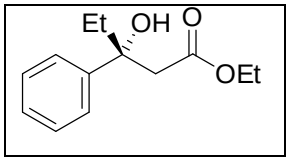
$^{1}$H NMR ($CDCl_3$, 300 MHz) δ: 1.26 (t, 3H, J = 7.2Hz); 1.62 (s, 3H); 2.75 (AB, 1H, J = 15.9Hz); 3.02 (AB, 1H, J = 15.9Hz); 4.17 (q, 2H, J = 7.2Hz); 4.42 (s, 1H); 6.28 (dd, 1H, J = 0.6, 3.9Hz); 6.34-6.33 (m, 1H); 7.36-7.33 (m, 1H).

$^{13}$C NMR ($CDCl_3$, 75 MHz) δ: 14.03; 19.12; 27.65; 44.39; 60.82; 104.56; 110.15; 141.53; 158.41; 172.36.

GCMS: 198(10); 183(11); 153(7); 137(9); 111(100); 77(6); 53(3).

HPLC analysis OD: isocratic isocratic, flux 0.5mL/m (hexane: *i*-PrOH) 98:2. tm: 20.26 min; TM: 26.71 min. ee 40%.

**(*R*)-Ethyl-3-hydroxy-3–phenylpentanoate**




$C_{13}H_{18}O_3$ Fw = 222.28

$[\alpha]_D$ = -10 (c 0.8, $CHCl_3$).

$[\alpha]_D$ = +28.8 (c 0.2, benzene).(of the corresponding diol) Lit.[2] (*S*) 3–phenyl-1,3-pentanediol $[\alpha]_D$ = -32.3 (c 10, benzene). Optical purity 55%.

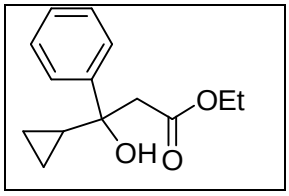
$^{1}$H NMR ($CDCl_3$, 300 MHz) δ: 0.812 (t, 3H, J = 7.2Hz); 1,13 (t, 3H, J = 7.5Hz); 1.84 (dq, 2H, J = 2.7, 7.5Hz); 2.91 (AB, 2H, J = 15.6Hz); 4.062 (q, 2H, J = 7.2Hz); 4.37 (s, 1H); 7.47-7.30 (m, 5H).

$^{13}$C NMR ($CDCl_3$, 75 MHz) δ: 7.76; 13.94; 35.90; 44.99; 60.65; 75.21; 125.14; 126.67; 128.03; 145.17; 172.92.

GCMS: 193(40); 177(5); 147(10); 135(15); 105(100); 91(7); 77(23); 65(3); 60(2); 57(14).

HPLC analysis OD: isocratic, flux 0.5mL/m (hexane: *i*-PrOH) 99:1. TM: 14.32 min; tm: 16.05 min. ee 53%.

**3-Cyclopropyl-3-hydroxy-3-phenyl-propionic acid ethyl ester**



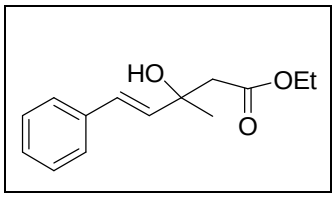

$C_{19}H_{23}NO_4$ Fw = 234.29

$[\alpha]_D$ = +24.1 (c 3.4 , $CHCl_3$)

GCMS: 234(3); 217(6); 206(35); 193(16); 170(1); 160(8); 147(60); 143(7); 118(90); 105(100); 91(17); 77(40); 55(4); 51(5).

HPLC analysis OD: isocratic, flux 0.5mL/m(hexane: *i*-PrOH) 99:1. tm: 12.46 min; TM: 13.37 min. ee 41%.

**Ethyl-3-hydroxy-3-methyl-5-phenyl-pent-4-enoate**




$C_{14}H_{18}O_3$ Fw = 234.29

$[\alpha]_D$ = +1.3 (c 2.5, $CHCl_3$)

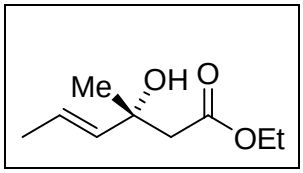
$^1$H NMR ($CDCl_3$, 300 MHz) δ: 1.28 (t, 3H, J = 6.9Hz); 1.47 (s, 3H); 2.80-2.69 (m, 2H); 4.12 (s, 1H); 4.19 (q, 2H, J = 6.9Hz); 6.32 (dd, 1H; J = 1.5, 16.2Hz); 6.69 (d, 1H, J = 16.2Hz); 7.42-7.30 (m, 5H).

$^{13}$C NMR ($CDCl_3$, 75 MHz) δ: 14.13; 28.43; 45.53; 60.78; 71,24; 126.46; 127.48; 127.83; 128.22; 128.49; 128.94; 134.73; 136.68; 172.49.

GCMS: 234(14); 216(9); 171(5); 147(100); 131(34); 103(14);77(10); 51(3).

HPLC analysis OD: isocratic, flux 0.5mL/m (hexane: *i*-PrOH) 95:5. TM: 15.87 min; tm: 19.72 min. ee 49%.

**(*R*)-Ethyl-3-hydroxy-3-methyl-hex-4-enoate**




$C_9H_{16}O_3$ Fw = 172.22

$[\alpha]_D$ = -10 (c 1.1, $CHCl_3$); Lit.[3] (*R*) Ethyl-3-hydroxy-3-methyl-hex-4-enoate $[\alpha]_D$ = -13.0 (c 1.3, $CHCl_3$).

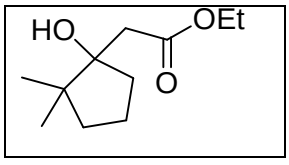
$^1$H NMR ($CDCl_3$, 300 MHz) δ: 1.26 (t, 3H, J = 7.2Hz); 1.30 (s, 3H); 1.68 (dd, 3H, J = 1.2, 6Hz); 2.53 (AB, 2H, J = 15.3Hz); 3.84 (brs, 1H); 4.16 (q, 2H, J = 7.2Hz); 5.55 (dd, 1H, J = 1,2, 15.3Hz); 5.66 (qq, 1H, J = 6.6, 15.3Hz).

$^{13}$C NMR ($CDCl_3$, 75 MHz) δ: 14.15; 17.57; 28.26; 45.54; 60.59; 70.75; 123.45; 136.33; 172.66.

GCMS: 172(3); 157 (18); 154 (2); 139(2); 127(5); 112(13); 85(100); 69(45); 60(5); 51(3).

HPLC analysis OD: isocratic, flux 0.5mL/m (hexane: *i*-PrOH, 202 and 206nm) 95:5. TM: 9.51 min; tm: 10.60 min. ee 75%%.

**3-(2,2-Dimethylciclopentyl)-3-hydroxy-butyric acid ethyl ester**




$C_{11}H_{20}O_3$ Fw = 228.32

$[\alpha]_D$ = +7.5 (c 2, $CHCl_3$)

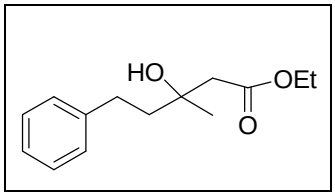
$^1$H NMR ($CDCl_3$, 300 MHz) δ: 0.88 (s, 3H); 1.02 (s, 3H); 1.32 (t, 3H, J = 6.9Hz); 1.93-1.63 (m, 5H); 1,48-1.43 (m, 1H); 2.46 (AB, 1H, J = 15.9Hz); 2.57 (AB, 1H, J = 15.9Hz); 3.48 (s, 1H); 4.21 (q, 2H, J = 6.9Hz).

$^{13}$C NMR ($CDCl_3$, 75 MHz) δ: 14.16; 19.07; 21.52; 25.05; 37.41; 38.71; 39.23; 45.15; 60.66; 81.68; 173.72.

GCMS: 200(1); 182(10); 168(3); 158(22); 157(18): 143(42); 130(100); 115(26); 108(37); 95(65); 88(20); 79(10); 69(39); 56(53); 51(2).

GC analysis: isotherm 120°C. TM: 17.68 min; tm: 18.27 min. ee 96%.

**3-Hydroxy-3-methyl-5-phenyl pentanoic acid ethyl ester**




$C_{14}H_{20}O_3$ Fw = 236.30

$[\alpha]_D$ = -0.2 (c 3, $CHCl_3$)

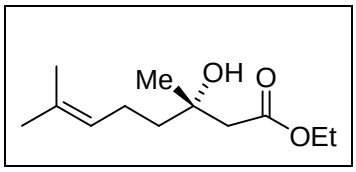
$^1$H NMR ($CDCl_3$, 300 MHz) δ: 1.31 (t, 3H, J = 6.9Hz); 1.36 (s, 3H); 1.91-1.93 (m, 2H); 2.57 (AB, 2H; J = 15.6Hz); 2.79-2,75 (m, 2H); 3.8 (brs, 1H); 4.24 (q, 2H, J = 6.9Hz); 7.31-7.23 (m, 3H); 7.36-7.34 (m, 2H).

$^{13}$C NMR ($CDCl_3$, 175 MHz) δ: 14.45; 26.96; 30.56; 44.13; 45.21; 60.99; 71.06; 126.07; 128.60; 128.69; 142.51; 173.30.

GCMS: 236(1); 221(2); 218(31); 189(1); 172(4); 157(2); 144(76); 131(100); 129(49); 115(4); 105(25); 91(100); 77(14); 65(15); 51(6).

HPLC analysis OD: isocratic, flux 0.5mL/m (hexane: *i*-PrOH) 95:5. TM: 14.70 min; tm: 16.83 min. ee 23%.

**(*S*)-Ethyl-3-hydroxy-3,7-dimethyloct-6-enoate**




$C_{12}H_{22}O_3$ Fw = 214.30

$[\alpha]_D$ = -0.5 (c 2., $CHCl_3$); Lit.[4] (*S*)-Ethyl-3-hydroxy-3,7-dimethyloct-6-enoate $[\alpha]_D$ = -1.9 (c 1.4, $CHCl_3$).

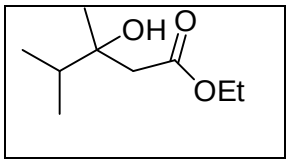
$^1$H NMR ($CDCl_3$, 300 MHz) δ: 1.25 (s, 3H); 1.28 (t, 3H, J = 7.2Hz); 1.56-1.50 (m, 2H); 1.61 (s, 3H); 1.68 (s, 3H); 2.06-2.04 (m, 2H); 2.52 (AB, 2H, J = 15.3Hz); 3.55 (brs, 1H); 4.18 (q, 2H, J = 7.2Hz); 5.07-5.11 (m, 1H).

$^{13}$C NMR ($CDCl_3$, 75 MHz) δ: 14.15; 17.57; 22.63; 25.65; 26.59; 41.81; 44.81; 60.61; 70.89; 124.03; 131.77; 173.05.

GCMS: 214 (1); 196(43); 181(5); 167 (6); 151(15); 135(5); 122 (63); 109(100); 93(21); 85(42); 69(72); 55(26); 51(12).

HPLC analysis OD: isocratic, flux 0.5mL/m (hexane: *i*-PrOH, 202 and 206nm) 93:7. TM: 8.1 min; tm: 8.75 min. ee 21%.

**3-Isopropyl-3-hydroxy-butyric acid ethyl ester**




$C_9H_{18}O_3$ Fw = 174.23

$[\alpha]_D$ = -2.75 (c 4, $CHCl_3$)

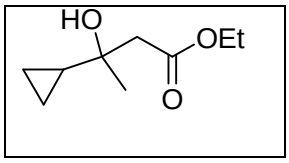
$^1$H NMR ($CDCl_3$, 300 MHz) δ: 0.96 (d, 3H, J = 6.6Hz); 1.01 (d, 3H, J = 6.6Hz); 1.20 (s, 3H); 1.32 (t, 3H, J = 7.2Hz); 1.79 (sept, 1H, J = 6.6Hz); 2.51 (AB, 2H, J = 15.6Hz); 3.62 (brs, 1H); 4.22 (q, 2H, J = 7.2Hz).

$^{13}$C NMR ($CDCl_3$, 75 MHz) δ: 14.15; 16.95; 17.65; 22.81; 37.39; 42.64; 60.61; 73.31; 173.48.

GCMS: 159(11); 157(1); 141(2); 131(100); 113(11); 103(27); 87(39); 85(72); 71(15); 61(4); 58(8).

GC analysis: Isotherm 95°C. TM: 20.12 min; tm: 20.64 min. ee 28%.

**3-Cyclopropyl-3-hydroxy-butyric acid ethyl ester**




$C_9H_{16}O_3$ Fw = 172.22

$[\alpha]_D$ = +1.7 (c 5.3, $CHCl_3$)

$^1$H NMR ($CDCl_3$, 300 MHz) δ: 0.50-0.32 (m, 4H); 0.95-0.87 (m, 1H); 1.26 (s, 3H); 1.32 (t, 3H; J = 7.2Hz); 2.56 (AB, 2H, J = 15Hz); 3.44 (s, 1H); 4.21 (q, 2H, J = 7.2Hz).

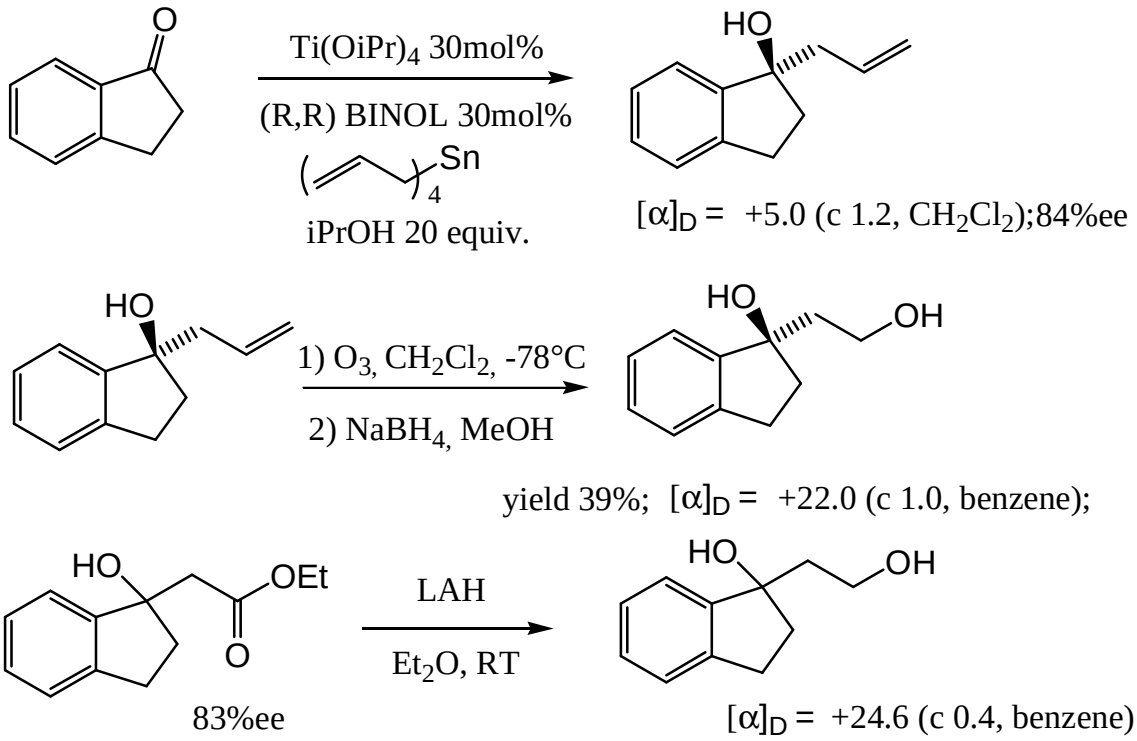
$^{13}$C NMR ($CDCl_3$, 75 MHz) δ: -0.63; 0.72; 14.15; 20.76; 27.00; 46.07; 60.65; 69.10; 173.00.

GCMS: 172(1); 157(91); 155(29); 144(4); 131(19); 127(9); 115(6); 111(23); 98(26); 86(6); 85(100); 69(50); 67(9); 56(9).

GC analysis Isotherm 95°C. TM: 9.93 min; tm: 10.85 min. ee. 86%.

**Determination of absolute configuration of the products derived from 1-indanone.**

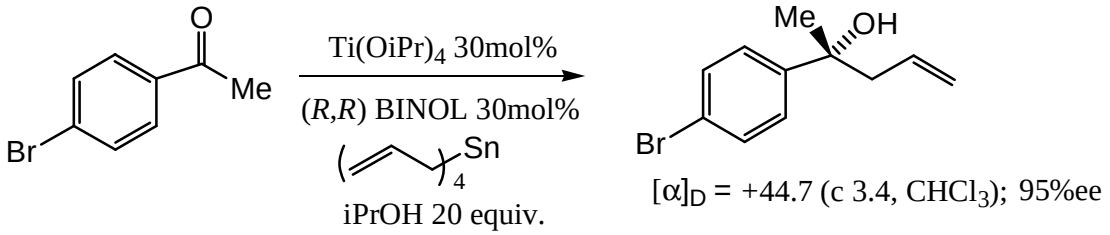
The absolute configuration was determined from the sign of optical rotation of the corresponding diol, obtained from the Reformatsky adduct by reduction, with the diol of established absolute configuration,[5] as follows.



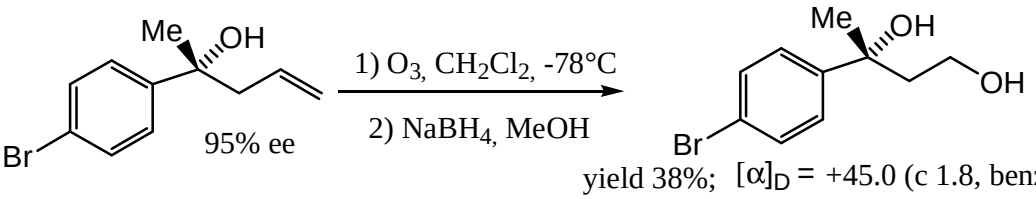

From the sign of optical rotation of the corresponding diol the absolute configuration of the Reformatsky adduct was deduced to be *R*.

**Determination of absolute configuration of the products derived from 4-bromoacetophenone.**

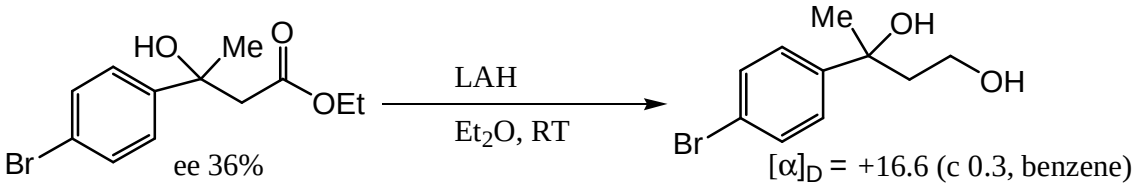
The absolute configuration was determined from the sign of optical rotation of the corresponding diol, obtained from the Reformatsky adduct by reduction, with the diol of established absolute configuration, as follows.




$[\alpha]_D$ = +44.7 (c 3.4, $CHCl_3$); 95%ee




yield 38%; $[\alpha]_D$ = +45.0 (c 1.8, benzene);

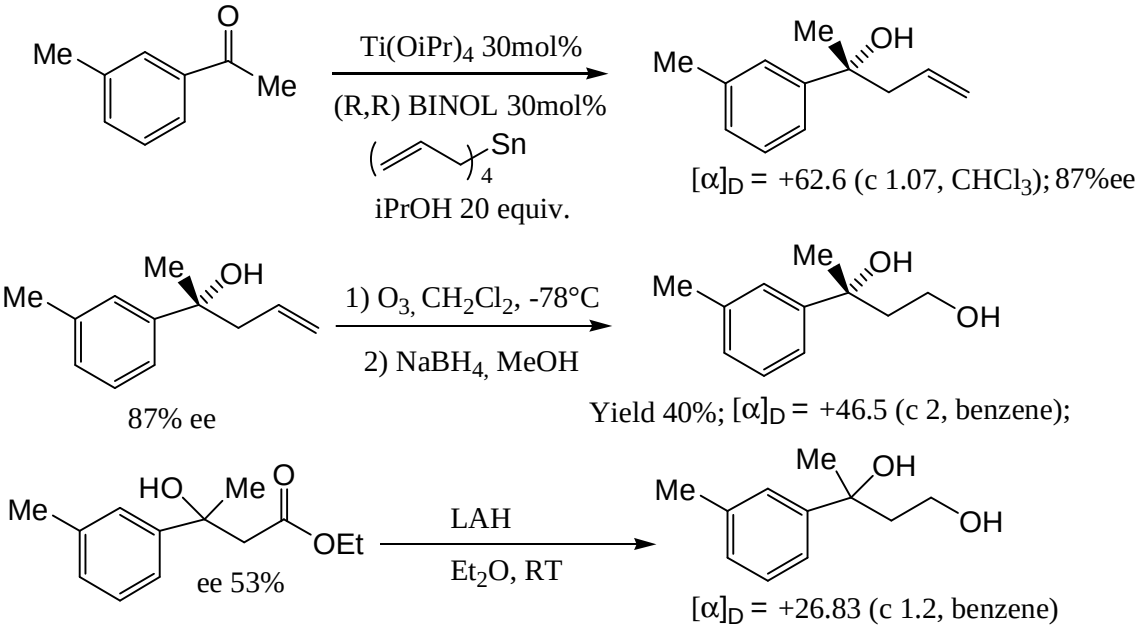



$[\alpha]_D$ = +16.6 (c 0.3, benzene)

From the sign of optical rotation of the corresponding diol the absolute configuration of the Reformatsky adduct was deduced to be ***R***.

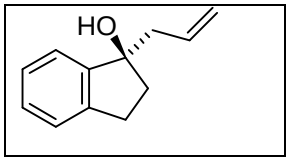
**Determination of absolute configuration of the product derived from 3-methylacetophenone.**

The absolute configuration was determined from the sign of optical rotation of the corresponding diol, obtained from the Reformatsky adduct by reduction, with the diol of established absolute configuration, as follows.




From the sign of optical rotation of the corresponding diol the absolute configuration of the Reformatsky adduct was deduced to be ***R***.

**(*R*)-1-Allyl-indan-1-ol**

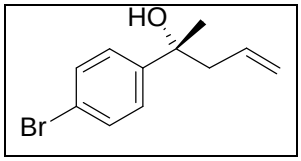



$[\alpha]_D$ = +5 (c 1.2, $CHCl_3$)

$^1$H NMR ($CDCl_3$, 300 MHz) δ: 2.16-2.07 (m, 1H); 2.41-2.33 (m, 1H); 2.56 (dd, 1H, J = 6.9, 13.8Hz); 2.68 (dd, 1H, J = 7.5, 13.8Hz); 2.91-2.80 (m, 1H); 3.09-2.99 (m, 1H); 5.25-5.17 (m, 2H); 5.95-5.83 (m, 1H); 7.31-7.26 (m, 3H); 7.39-7.36 (m, 1H).

HPLC analysis OD: flux 0.5mL/m (hexane: *i*-PrOH) from 97:3 to 93;7 in 15min. TM: 14.88 min; tm: 17.47 min. ee 84%.

**(*R*)-2-(4-Bromophenyl)-pent-4-en-2-ol**

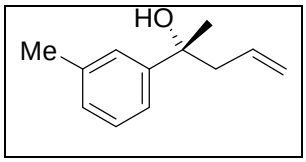



$[\alpha]_D$ = +44.76 (c 3.4, $CHCl_3$)

$^1$H NMR ($CDCl_3$, 300 MHz) δ: 1.56 (s, 3H); 2.10 (s, 1H); 2.51 (dd, 1H, J = 8.1, 13.8Hz); 2.69 (dd, 1H, J = 6.3, 13.8Hz); 5.21-5.14 (m, 2H); 5.66-5.57 (m, 1H); 7.35 (AA'BB', 2H, J = 8.7Hz); 7.50 (AA'BB', 2H, J = 8.7Hz).

HPLC analysis OD: HPLC analysis OD: isocratic, flux 0.5mL/m (hexane: *i*-PrOH) 97:3. tm: 16.40min; TM 17.25min. ee 95%

**(*R*)-2-(3-Methylphenyl)-pent-4-en-2-ol**

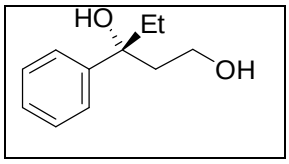



$[\alpha]_D$ = +62.06 (c 1.07, $CHCl_3$)

$^1$H NMR ($CDCl_3$, 300 MHz) δ: 1.49 (s, 3H); 2.41 (s, 3H); 2.55 (dd, 1H, J = 8.1, 13.5Hz); 2.69 (dd, 1H, J = 6.3, 13.5Hz); 5.23-5.15 (m, 2H); 5.72-5.61 (m, 1H); 7.13-7.09 (m, 1H); 7.27 (s, 1H); 7.33-7.28 (m, 2H).

HPLC analysis OJ: from 98:2 to 92:8 in 15min. TM: 12.77 min; tm: 13.45 min. ee 87%.

**(*R*)-3–Phenyl-pentane-1,3-diol**

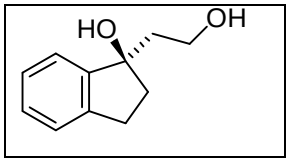



$[\alpha]_D$ = +28.8 (c 0.2, benzene)

$^1$H NMR ($CDCl_3$, 300 MHz) δ: 0.81 (t, 3H, J = 7.2Hz); 1.94(dq, 2H, J = 2.7, 7.2Hz); 2.08-2.01 (m, 1H); 2.27-2.18 (m, 1H); 3.20 (brs, 1H); 3.64-3.56(dt, 1H, J = 3.3, 10.8Hz); 3.82-3.75(m, 1H); 7.45-7.26(m, 5H).

$^{13}$C NMR ($CDCl_3$, 75 MHz) δ: 7.44; 36.20; 42.74; 60.30; 78.34; 125.38; 126.42; 128.51; 145.52.

**(*R*)-1-(2-Hydroxyethyl)-indan-1-ol**

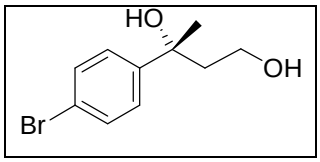



$[\alpha]_D$ = +24.64 (c 0.4, benzene)

$^1$H NMR ($CDCl_3$, 300 MHz) δ: 1.81 (dd, 1H, J = 3.9, 6.6Hz); 1.86 (dd, 1H, J = 3.9, 6.9Hz); 2.11-1.99 (m, 2H); 2.23 (dd, 1H, J = 3.9, 7.8Hz); 2.28 (dd, 1H, J = 4.2, 7.8Hz); 2.77-2.71(m, 1H); 2.94-2.86(m, 1H); 3.90-3.75(m, 2H); 7.18-7.15 (m, 3H); 7.33-7.26 (m, 1H).

$^{13}$C NMR ($CDCl_3$, 75 MHz) δ: 29.21; 40.20; 40.75; 60.42; 84.71; 123.09; 125.06; 126.76; 128.37; 142.47; 147.02.

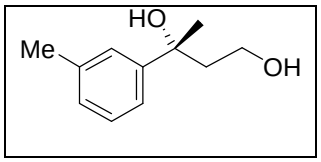
**(*R*)-3–(4-Bromophenyl)-butane-1,3-diol**




$[\alpha]_D$ = +16.6 (c 0.3, benzene)

$^{1}$H NMR ($CDCl_3$, 300 MHz) δ: 1.59 (s, 3H); 2.21-2.01 (m, 2H); ; 2.82 (brs, 1H); 3-65-3.57 (m, 1H); 3.88-3.81 (m, 1H); 7.33 (AA'BB', 2H, J = 8.4Hz); 7.49 (AA'BB', 2H, J = 8.4Hz).
$^{13}$C NMR ($CDCl_3$, 75 MHz) δ: 31.00; 43.71; 60.39; 75.56; 120.49; 126.75; 131.27; 146.65.

**(*R*)-3—(3-Methylphenyl)-butane-1,3-diol**




$[\alpha]_D$ = +26.83 (c 1.2, benzene)

$^{1}$H NMR ($CDCl_3$, 300 MHz) δ: 1.61 (s, 3H); 2.19-2.02 (m, 2H); 2.41 (s, 3H); 2.84 (brs, 1H); 3.66-3.58 (m, 1H); 3.85-3.78 (m, 1H); 7.15-7.07 (m, 1H); 7.26 (s, 1H); 7.33-7.30 (m, 2H).
$^{13}$C NMR ($CDCl_3$, 75 MHz) δ: 21.63; 31.02; 43.88; 60.38; 75.90; 121.75; 125.43; 127.29; 128.11; 137.78; 147.37.

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1 M. Guetté, J. Capillon, J.-P. Guettè, *Tetrahedron*, **1973**, *29*, 3659-3667.
2 S. Mitsui, Y. Kudo, *Tetrahedron* **1967**, *23*, 4271-4277.
3 I. Dyong, D. Glittemberg, *Chem. Ber.* **1977**, *110*, 2721-2728.
4 K. Y.-K. Chow, J. Bode, *J. Am. Chem. Soc.* **2004**, *126*, 8126-8127.
5 J. G. Kim, K. M. Waltz, I. F. Garcia, D. Kwiatowski, P. J. Walsh, *J. Am. Chem. Soc.* **2004**, *126,* 12580-12585, and ref. therein.