SIMPLE METAL-ALKOXIDES AS EFFECTIVE CATALYSTS FOR THE HETERO ALDOL-TISHCHENKO REACTION

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Supplementary Material

General. Infrared (IR) spectra were recorded on a Nicolet Magna 560 spectrophotometer, 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 AC200 (200 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, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), integration, 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 (deuterochloroform: δ 77.0 ppm). Microanalyses were performed by either E & R Microanalytical Laboratory (Parsippany, NJ) or Robertson Microlit Laboratories (Madison, NJ).

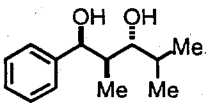
Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on Sigma silica gel 60 (SiO_2, 230-400 mesh). Thin layer chromatography was performed on EM Science 0.25 mm silica gel 60 plates. Visualization was achieved with phosphomolybdic acid in ethanol 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 and a flame-ionization detector. Diastereomeric ratios were determined by GLC with a Hewlett-Packard 1701 (30m x 0.3mm) column with helium as the carrier.

All reactions were conducted in oven and flame-dried glassware under an inert atmosphere of dry nitrogen. Tetrahydrofuran was distilled from sodium metal/benzophenone ketyl. Diethyl ether was dried by filtration through activated alumina.[1] Isobutyraldehyde was distilled from anhydrous calcium sulfate prior to use. n-Butyllithium was purchased from Aldrich and titrated against 2,6-di-*tert*-butyl-4-methylphenol with 1,10-phenanthroline as indicator. Dibutylmagnesium was purchased from Aldrich and titrated against 2-butanol with N-phenyl-1-naphthylamine as indicator. Magnesium isopropoxide was prepared by dropwise addition of dibutyl magnesium to isopropanol in ether. Lithium isopropoxide (*in situ*) was prepared by addition of n-butyllithium to isopropanol in ether. LiOiPr, $Ca(OMe)_2$ and NaOtBu were purchased from Aldrich. $La(OiPr)_3$, $Cu(OiPr)_2$, $Zn(OtBu)_2$, $Zr(OtBu)_4$ and $Yb(OiPr)_3$ were purchased from Alfa Inorganics. $Sm(OiPr)_3$ and $Al(OtBu)_3$ were purchased from Strem. All other reagents were purchased from Aldrich and distilled prior to use.

Procedure for catalytic aldol-Tishchenko reactions (and subsequent hydrolysis) with metal alkoxides (Table 1). A 25 mL flame-dried flask was charged with 0.6 mmol of metal alkoxide (0.2 equivalents) under nitrogen at room temperature and diluted with 0.5 ml of diethyl ether. To the solution was added 0.40 mL of propiophenone (3.0 mmol, 1.0 equivalent) with stirring. After 10 minutes, 0.55 mL of isobutyraldehyde (6.0 mmol, 2.0 equivalents) was added dropwise, with stirring. The reaction was quenched after 15 hours by addition of 20 mL 0.5 M HCl and extracted with 60 mL of diethyl ether. The solvent was removed *in vacuo* and the crude material dissolved in 5 mL methanol and 600 mg NaOH added. After stirring at room temperature for 12 hours, the solution was diluted with 30 mL brine and extracted with 60 mL of ethyl acetate. Product yields were determined via ^{1}H NMR of the crude material after addition of an internal standard (benzyl benzoate). Diastereomer ratios were obtained via GLC analysis in comparison to authentic diastereomers (*vide infra*).

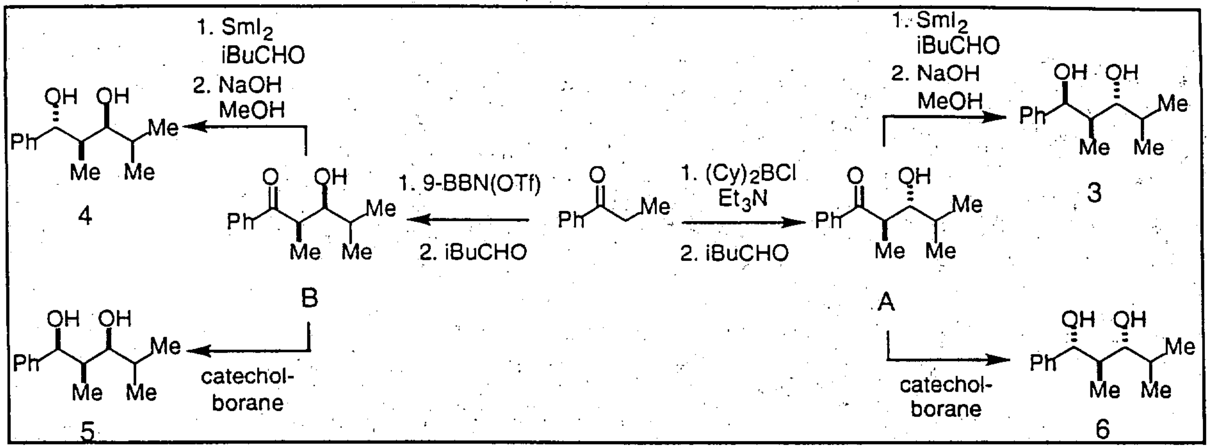
Representative procedure for catalytic aldol-Tishchenko reaction (Table 2). A 25 mL flame-dried flask was charged with 35 μL (0.45 mmol) of freshly distilled isopropanol and 0.5 mL of diethyl ether under nitrogen. To the solution was added 103 μL of n-BuLi (4.35 M in hexanes, 0.45 mmol) dropwise at room temperature, with stirring. 400 μL of propiophenone (3.0 mmol), was then added dropwise and the mixture allowed to stir for 10 minutes. Next, 820 μL of isobutyraldehyde (9.0 mmol) was added dropwise over a period of 10 minutes. The mixture was allowed to stir for 14 hours and was quenched by addition of 25 mL 0.5 M HCl and extracted with 60 mL of diethyl ether. The ether layer was washed with brine, dried with anhydrous $MgSO_4$ and concentrated *in vacuo* to yield a pale yellow oil. The crude material was directly dissolved in a solution of 20 mL methanol and 10 mL 25% NaOH and heated to reflux for 3 hours. The resulting mixture was concentrated in vacuo, redissolved in ethyl acetate and washed with brine. After drying with $MgSO_4$, concentration and purification by silica gel chromatography (3:1 hexanes/ethyl acetate) yielded 453 mg of **3** (73% yield).



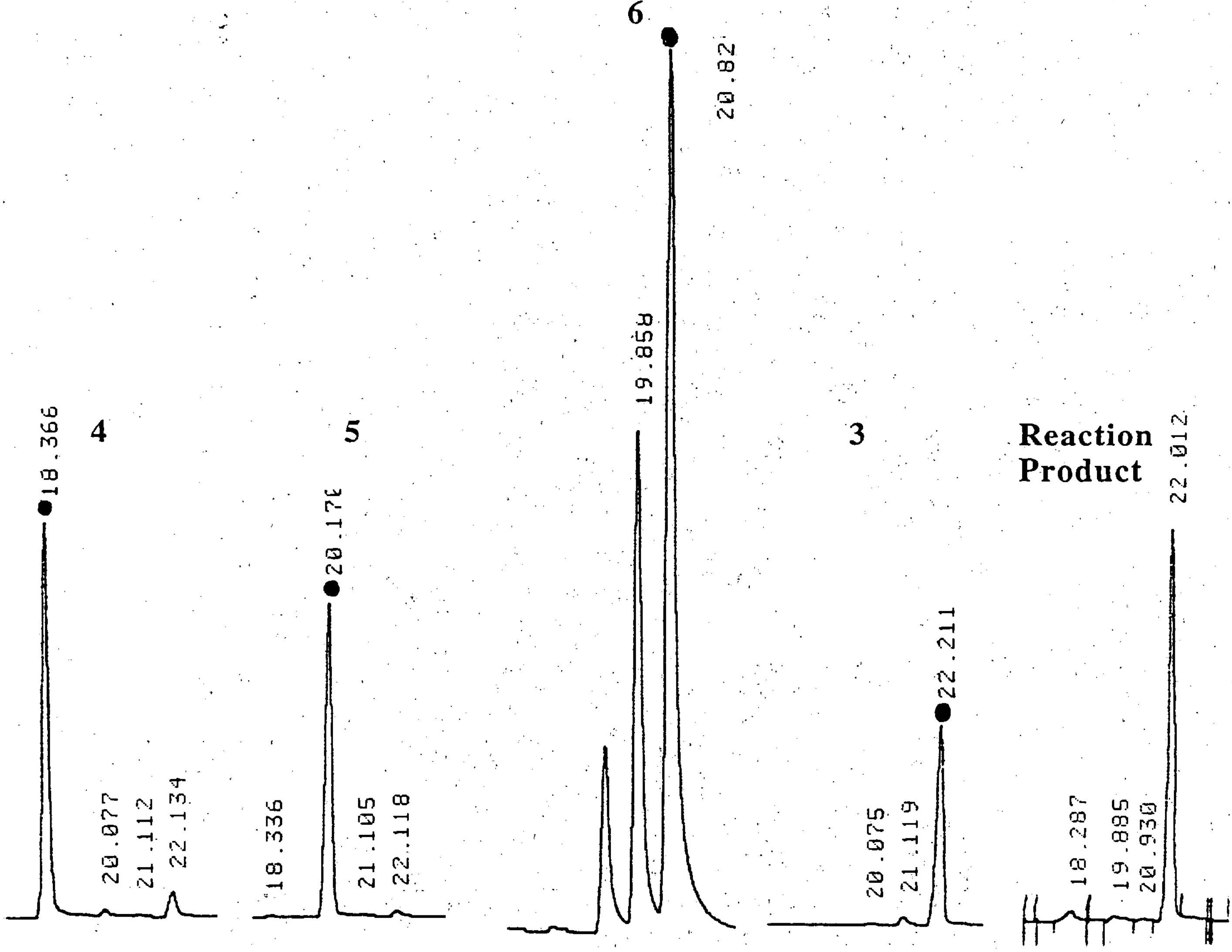
***(1S, 2R, 3R)* and *(1R, 2S, 3S)* 1-Phenyl-2,4-dimethylpentane-1,3-diol (3).** IR (KBr): 3336 (br, s), 2964 (s), 2874 (m), 1451 (m), 1062 (w) cm^{-1}; ^{1}H NMR: δ 7.20-7.40 (5H, m, phenyl), 5.21 (1H, t, J=3.0 Hz, PhCHOH), 3.38 (1H, q, J=5.7 Hz, iPrCHOH), 3.25 (1H, d, J=3.4 Hz, OH), 2.45 (1H, d, J=4.9 Hz, OH), 1.90-2.15 (2H, m), 1.05 (3H, d, J=3.4 Hz, $CH_3CH\mathbf{CH_3}$), 1.02 (3H, d, J=3.5 Hz, $\mathbf{CH_3}CHCH_3$), 0.85 (3H, d, J=6.8 Hz, $CH\mathbf{CH_3}$); ^{13}C NMR: δ 143.1, 128.0, 126.8, 125.9, 80.4, 74.3, 40.7, 30.8, 19.6, 17.3, 11.1. Anal Calc'd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.21; H, 9.95. Characterization is in agreement with literature values.[2]

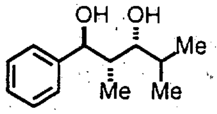
■ **Proof of Stereochemistry**. Determination of product configuration was accomplished though comparison with all four independently prepared diastereomers (**C-F,** see below). Stereoselective aldol reactions were performed with propiophenone and isobutyraldehyde according to the method of Brown[3] to provide both *anti* (**A**) and *syn* (**B**) aldol adducts. Subsequent samarium-catalyzed Evans-Tishchenko[4] reductions followed by alkaline hydrolysis resulted in the formation of diastereomers **3** and 4, whereas a directed catechol borane[5] reduction yielded diastereomers **5** and **6**. Comparison of both ^{1}H NMR and GLC of the four authentic stereoisomers with the compound obtained from catalytic aldol-Tishchenko reaction reveals major product configuration and stereoisomer ratios.

Preparation of Authentic Stereoisomers of 3.



GLC chromatograms of authentic ***3-6*** *and that from the catalytic aldol-Tishchenko reaction:*

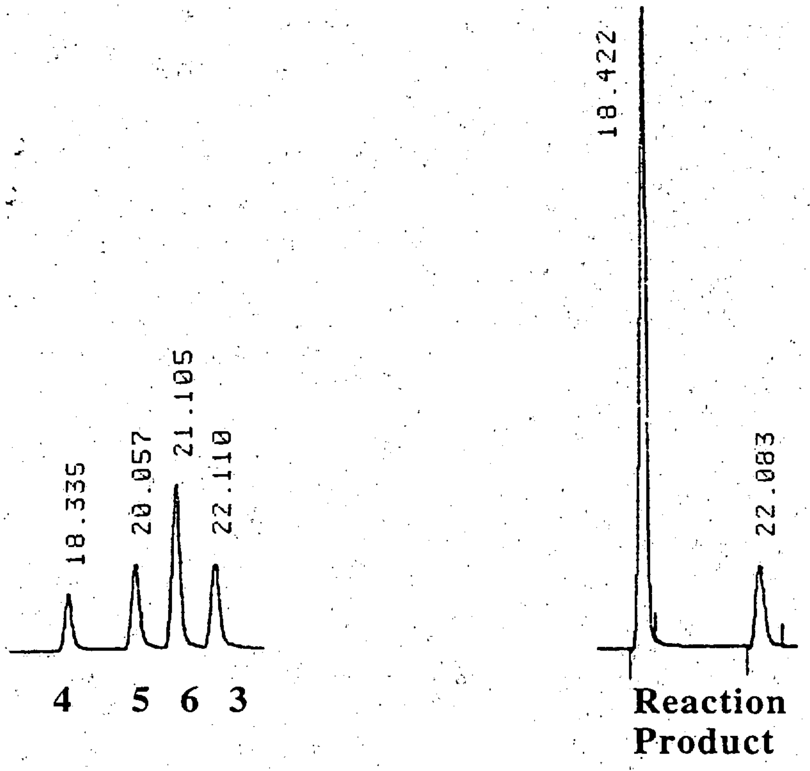


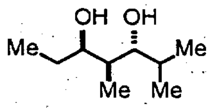


(1S, 2S, 3R) and (1R, 2R, 3S) **1-Phenyl-2,4-dimethylpentane-1,3-diol (4)**. IR (KBr): 3239 (br, s), 2964 (s), 2874 (m), 1457 (s), 1056 (s) cm^{-1}; ^{1}H NMR: δ 7.10-7.30 (5H, m, phenyl), 4.64 (1H, t, J=6.0 Hz, PhCHOH), 3.33 (1H, d, J=5.0 Hz, OH), 3.25 (1H, ddd, J=9.3, 4.1, 1.6 Hz, iPrCHOH), 2.46 (1H, d, J=4.4 Hz, OH), 1.89 (1H, m, $CHCH_3$), 1.57 (1H, m, $CH(CH_3)_2$), 0.88 (3H, d, J=6.9 Hz, CH_3CHCH_3), 0.83 (3H, d, J=6.6 Hz, CH_3CHCH_3), 0.61 (3H, d, J=6.8 Hz, $CHCH_3$); ^{13}C NMR: δ 144.0, 128.2, 127.1, 126.0, 78.1, 76.4, 40.6, 31.2, 19.8, 18.7, 10.2. Anal Calc'd for $C_{13}H_{20}O_2$: C, 74.9; H, 9.68. Found: C, 74.94; H, 9.97.

■ **Proof of Stereochemistry**. Stereochemical identity of the reaction product and stereochemical ratios were determined by comparison to authentic isomers of **1** prepared above.

GLC Chromatograms of 3-6 (combined) and that from the catalytic aldol-Tishchenko reaction:

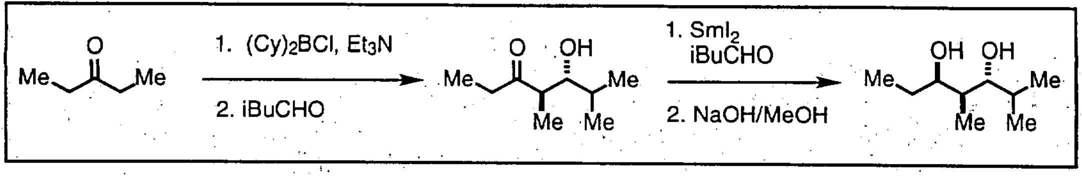




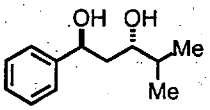
(3R, 4S, 5R) and (3S, 4R, 5S) **2,4-Dimethylheptane-3,5-diol (7)**. IR (neat) 3342 (br, s), 2967 (br, s), 2876 (m), 1464 (s), 1111 (m) cm^{-1}; ^{1}H NMR major diastereomer: δ 3.82 (1H, m, iPrCHOH), 3.30 (1H, q, J=5.6, 5.1 Hz, EtCHOH), 2.59 (1H, d, J=3.5 Hz, OH), 2.42 (1H, d, J=4.7 Hz, OH) 1.80 (2H, m), 1.49 (2H, m), 0.92 (12H, m); ^{13}C NMR: δ 79.9, 73.1, 36.4, 29.8, 25.8, 18.6, 16.5, 10.3, 9.7. Anal Calc'd for $C_9H_{20}O_2$: C, 67.45; H, 12.58. Found: C, 67.72; H, 12.67.

■ **Proof of Stereochemistry**. The configuration of the product was determined by comparison of the ^{13}C NMR of the reaction product (7) with that of authentic material. Authentic material was prepared by stereoselective *anti* aldol reaction between 3-pentanone and isobutyraldehyde, followed by Evans-Tishchenko reduction and subsequent methanolysis (below).

Preparation of Authentic 7.



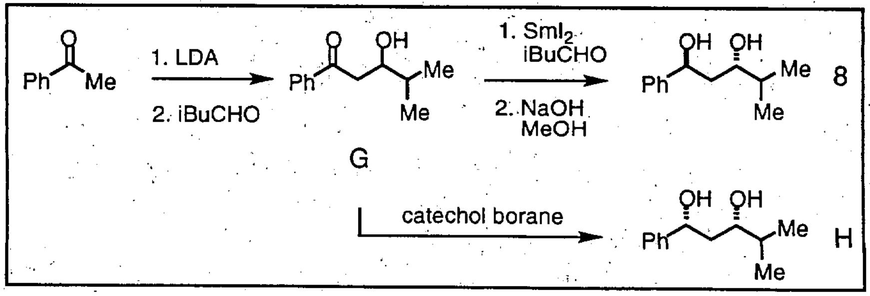
^{13}C δ (Authentic 7)	^{13}C δ (Product 7)
80.0 ppm	79.9 ppm
73.2	73.1
36.5	36.4
29.8	29.8
25.8	25.8
18.6	18.6
16.4	16.5
10.3	10.3
9.7	9.7



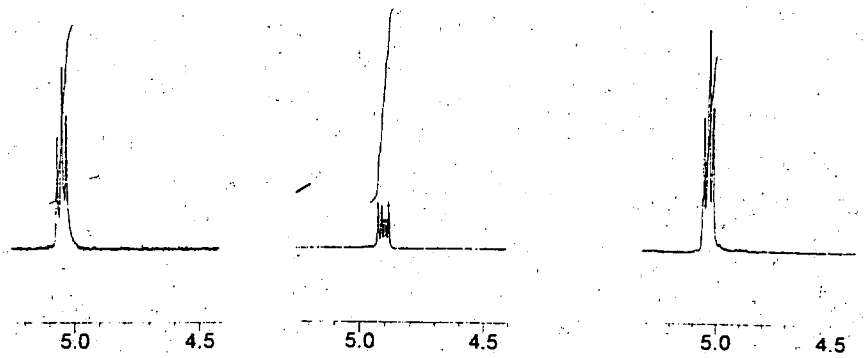
***(1S,3R)* and *(1R,3S)* 1-Phenyl-4-methylpentane-1,3-diol (8).** IR (KBr): 3435 (br, s), 3313 (br, s), 2952 (s), 1401 (m), 1015 (s) cm^{-1}; ^{1}H NMR: δ 7.20-7.40 (5H, m, phenyl), 5.04 (1H, br t, J=5.5 Hz, PhC**H**OH), 3.58 (1H, q, J=6.0 Hz, CH_2C**H**OH), 2.73 (1H, br s, O**H**), 2.08 (1H, br s, O**H**), 1.85 (2H, t, J=5.7 Hz, **C**$\mathbf{H_2}$), 1.66 (1H, m, **C**$\mathbf{H}$$(CH_3)_2$), 0.89 (3H, d, J=7.1 Hz, $\mathbf{CH_3}$), 0.86 (3H, d, J=7.1 Hz, $\mathbf{CH_3}$); ^{13}C NMR: δ 144.7, 128.4, 127.3, 125.5, 73.8, 71.8, 41.6, 33.7, 18.5, 17.7. Anal Calc'd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.38; H, 9.42. Characterization is in agreement with literature values.[6]

■ **Proof of Stereochemistry.** Determination of product configuration was accomplished through comparison with independently prepared *syn* and *anti* diastereomers. Aldol condensation between acetophenone and isobutyraldehyde afforded β-hydroxy ketone **G**. Catechol borane reduction provided *syn* diol **H** while the *anti* diol **8** was obtained from a samarium-catalyzed Evans-Tishchenko reduction followed by alkaline hydrolysis. ^{1}H NMR analysis of the reaction product in comparison to the authentic stereoisomers indicates the tandem aldol-Tishchenko reaction proceeds with >95:5 anti:syn stereoselectivity.

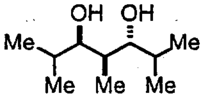
*Preparation of Authentic Stereoisomers of **8**.*



^{1}H NMR comparison of authentic 8, H and aldol-Tishchenko reaction product:

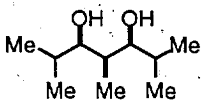
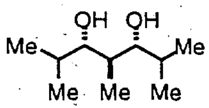
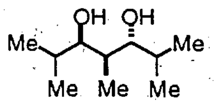


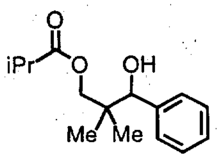
8 **H** **Reaction Product**



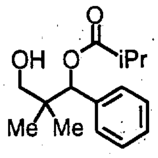
***(3R,5R) and (3S, 5S)* 2,4,6-Trimethylheptane-3,5-diol (9).** IR(neat): 3333 (br,s), 2954 (m), 1473(m), 987 (m) cm^{-1}. ^{1}H NMR: δ 3.49 (1H, d, J=9.3 Hz, $CH(CH_3)_2C\mathbf{H}OH$), 3.19 (1H, dd, J=8, 3.5 Hz, $CH(CH_3)_2C\mathbf{H}OH$), 2.55 (1H, d, J=3.3 Hz, $CHO\mathbf{H}$), 2.35 (1H, d, J=1.9Hz, $CHO\mathbf{H}$), 1.87 (2H, m, $(CH_3)_2C\mathbf{H}CHOH$), 1.66 (1H, m, $CHOHC\mathbf{H}(CH_3)CHOH$), 0.99 (9H, m, CH_3's), 0.85 (3 H, d, J= 6.6 Hz, $\mathbf{CH_3}$), 0.80 (3H, d, J= 6.6 Hz, $\mathbf{CH_3}$). ^{13}C NMR: δ 82.2, 77.4, 34.4, 31.2, 31.1, 19.9, 19.3, 19.0, 18.8, 10.6. Anal Calc'd for $C_{10}H_{22}O2$: C, 68.92; H, 12.72. Found: C, 68.98; H, 13.08.

■ **Proof of Stereochemistry**. The configuration of the major product was established by comparison with reported ^{1}H NMR resonances.[7] Notably, only the anti-syn adduct exhibits distinct resonances for each of the two carbinol protons; due to symmetry, the carbinol protons in the syn-syn and anti-anti stereoisomers are enantiotopic.

			Reaction Product
syn,syn-9	***anti,anti-9***	***syn,anti-9***	
3.2 - 3.4 ppm 2H, dd, J=9, 2 Hz	3.5 ppm 2H, dd, J=8, 2 Hz	3.40 ppm 1H, d, J=9 Hz	3.49 ppm 1H, d, J=9.3 Hz
		3.23 ppm 1H, dd, J=8, 4 Hz	3.19 ppm 1H, dd, J=8.0, 3.5 Hz



1-Hydroxy-1-phenyl-2,2-dimethylprop-3-yl Isobutanoate (1). IR (neat): 3500 (br, s), 2973 (br, s), 2877 (s), 1717 (s), 1050 (m) cm^{-1}; ^{1}H NMR: δ 7.20-7.35 (5H, m, phenyl), 4.55 (1H, d, J=3.3 Hz, PhC**H**OH), 4.19 (1H, d, J=11.1 Hz, **CH**$_a$H$_b$OR), 3.74 (1H, d, J=11.1 Hz, CH$_a$**H**$_b$OR), 2.60 (1H, m, **CH**(CH$_3$)$_2$), 2.37 (1H, d, J=3.3 Hz, **OH**) 1.20 (6H, d, J=7.2 Hz, CH(**CH**$_3$)$_2$), 0.92 (3H, s, **CH**$_3$), 0.84 (3H, s, **CH**$_3$); ^{13}C NMR: δ 177.3, 141.1, 127.7, 127.6, 127.5, 70.5, 39.2, 34.2, 21.4, 18.4, 19.1, 19.0. Anal Calc'd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.21; H, 9.17.



3-Hydroxy-2,2-dimethyl-1-phenylprop-1-yl Isobutanoate (2). IR (neat): 3447 (br, s), 2972 (s), 2876 (m), 1734 (s), 1048 (m) cm^{-1}; ^{1}H NMR: δ 7.24-7.36 (5H, m, phenyl), 5.78 (1H, s, PhC**H** OR), 3.40 (1H, dd, J=6.9, 4.5 Hz, **CH**$_a$H$_b$OR),), 3.22 (1H, dd, J=8.4, 3.0 Hz, CH$_a$**H**$_b$OH), 2.62 (1H, m, **CH**-(CH$_3$)$_2$), 2.29 (1H, dd, J=4.8, 3.3 Hz, OH), 1.20 (3H, d, J=6.9 Hz), 1.17 (3H, d, J=7.2 Hz), 0.87 (3H, s), 0.85 (3H, s); ^{13}C NMR: δ 176.8, 137.6, 127.8, 127.7, 69.0, 40.1, 34.4, 21.5, 19.3, 19.1, 18.9. Anal. Calc'd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.84; H, 8.73.

References

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