$C_{20}H_{28}O_4$ 332.1988, found 332.1960.

2-(5-Oxo-2,6,6-trimethyl-1-cyclohexenyl)-1-(1-methyl-4-oxo-2-cyclohexenyl)ethanone (19). The ketal **18** (183 mg, 0.55 mmol) was stirred 3 h at 45 °C in 4 mL of a 1:1 v/v mixture of THF and water in presence of *p*-toluenesulfonic acid (104 mg, 0.55 mmol). NMR analysis of aliquots allowed monitoring of the reaction. After 3 h, all the starting ketal has disappeared. The mixture was then diluted with Et_2O (20 mL) and washed with $NaHCO_3$ (saturated, 20 mL). The aqueous layer was extracted with Et_2O (20 mL) and the combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered, and evaporated to give pure deketalized product **19** (141.4 mg, 89.1%) as a colorless oil: IR (thin film) 2968.8, 2927.7, 2871.4, 1712.6, 1682.7, 1605.6, 1463.4, 1415.0, 1377.7, 1323.2, 1228.6, 1091.9, 1032.7, 1018.5, 807.1 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS) ∂ 1.047 (s, 3 H), 1.054 (s, 3 H), 1.45 (s, 3 H), 1.53 (s, 3 H), 1.96 (ddd, J = 13.2, 10.5, 5.2 Hz, 1 H), 2.40–2.49 (m, 4 H), 2.50–2.63 (m, 3 H), 3.36 (br s, 2 H), 6.08 (d, J = 10.2 Hz, 1 H), 7.04 (dd, J = 10.2, 1.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) ∂ 20.00, 24.13, 24.16, 25.06, 31.38, 32.47, 34.62, 35.80, 38.76, 47.28, 49.87, 128.61, 129.30, 131.64, 151.79, 198.07, 206.62, 214.11; MS m/z 41 (28), 43 (19), 53 (20), 55 (18), 67 (17), 79 (19), 81 (50), 110 (100), 123 (53), 136 (5), 151 (8), 288 (20); HRMS calcd for $C_{18}H_{24}O_3$ 288.1725, found 288.1716.

Preparation of Dione 20. 1. Preparation of 1-[5,5-(Ethylenedioxy)-2,6,6-trimethyl-1-cyclohexenyl]-1-hydroxy-3-methyl-3-buten-2-one. To a solution of potassium bis(trimethylsilyl)amide (KHMDS, 66 mg, 0.33 mmol, 3 equiv) in THF (anhydrous, 2 mL) cooled to −78 °C under nitrogen was added a solution of the enone **16** (29 mg, 0.11 mmol, 1 equiv) in THF (3 mL). After 15 min, a solution of *N*-(phenylsulfonyl)-phenyloxaziridine (86 mg, 0.33 mmol, 3 equiv) was added to the green solution which was then decolored. The reaction was stirred for 30 min at −78 °C before being quenched with a saturated solution of ammonium chloride (2 mL) and warmed to room temperature. The mixture was diluted with Et_2O (10 mL), washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated under reduce pressure. Flash chromatography of the residue (EtOAc/hexanes, 1:2) gave 26.7 mg of the hydroxy enone (87%): IR (neat, thin film) 3447.1, 2884.8, 1664.0, 1607.4, 1571.0, 1451.4, 1376.5, 1298.2, 1208.8, 1162.5, 1136.6, 1087.3, 1058.9, 1034.0, 949.5 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS) ∂ 1.05 (s, 3 H), 1.21 (s, 3 H), 1.63 (s, 3 H), 1.68–1.86 (m, 2 H), 1.96 (d, J = 0.7 Hz, 3 H), 2.19 (t, J = 6.6 Hz, 2 H), 3.89–4.00 (m, 4 H), 4.15 (br s, 1 H), 5.08 (s, 1 H), 5.77 (br s, 1 H), 6.07 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) ∂ 18.83, 20.23, 22.98, 23.95, 26.54, 31.62, 43.74, 65.01, 74.56, 111.82, 125.95, 133.68, 135.87, 141.43, 204.31; MS m/z 41 (100), 43 (32), 69 (32), 86 (58), 107 (100), 121 (70), 149 (43), 167 (35), 211 (82), 252 (3), 280 (20); HRMS calcd for $C_{16}H_{24}O_4$ 280.1675, found 280.1676.

2. Preparation of 1-[5,5-(Ethylenedioxy)-2,6,6-trimethyl-1-cyclohexenyl]-3-methyl-3-butene-1,2-dione (20). Swern oxidation (same conditions as for the preparation of compound **14**) of the resulting hydroxy enone (85 mg, 0.3 mmol) gave after flash chromatography (EtOAc/hexanes 1:4) the dione **20** (58 mg, 69%) as a yellow oil: IR (neat, thin film) 2980.0, 2957.7, 2883.8, 1668.7, 1454.4, 1378.0, 1259.9, 1213.0, 1137.4, 1110.6, 1042.9 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS) ∂ 1.18 (s, 6 H), 1.67 (s, 3 H), 1.82 (t, J = 6.7 Hz, 2 H), 1.94 (dd, J = 1.4, 0.9 Hz, 3 H), 2.30 (br t, J = 6.7 Hz, 2 H), 3.95–4.02 (m, 4 H), 6.10 (dq, J = 0.7, 0.9 Hz, 1 H), 6.20 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) ∂ 17.18, 21.40, 22.88, 26.34, 31.67, 42.07, 65.10, 111.17, 131.23, 138.44, 139.54, 139.68, 193.76, 197.76; MS m/z 41 (88), 43 (28), 45 (30), 67 (32), 69 (30), 87 (29), 137 (50), 181 (30), 209 (100), 278 (18); HRMS calcd for $C_{16}H_{22}O_4$ 278.1518, found 278.1515.

1-[5,5-(Ethylenedioxy)-2,6,6-trimethyl-1-cyclohexenyl]-2-(1-methyl-4-oxo-2-cyclohexenyl)-1,2-ethanedione (21). In a base-washed NMR tube with a screwable Teflon joint was placed a solution of enone **20** (48 mg, 0.172 mmol) and diene (0.69 mmol, 4 equiv) in deuterated benzene (0.5 mL), and the solution was heated to 80 °C. After 3 h, NMR analysis showed that the reaction was complete. The same workup as described for the preparation of enone **18** gave enone **21** as a yellow oil (56.7 mg, 95%): IR (neat, thin film) 2922.9, 2852.6, 1684.9, 1456.0, 1380.1, 1228.1, 1137.1, 1103.1, 1049.1, 992.3, 825.2 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS) ∂ 1.03 (s, 3 H), 1.09 (s, 3 H), 1.47 (s, 3 H), 1.55 (s, 3 H), 1.82 (m, 2 H), 1.97 (dt, J = 13.6, 8, 8 Hz, 1 H), 2.25 (m, 2 H), 2.46 (m, 2 H), 2.60 (m, 1 H), 3.92–4.02 (m, 4 H), 6.00 (d, J = 10.2 Hz, 1 H), 7.27 (dd, J = 10.2, 1.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) ∂ 20.92, 22.25, 23.38, 25.22, 26.34, 30.66, 32.59, 34.38, 42.01, 47.98, 65.06, 65.11, 110.75, 129.32, 135.73, 136.37, 151.04, 196.32, 197.91, 198.14; MS m/z 41 (20), 55 (25), 67 (28), 81 (27), 86 (23), 87 (25), 95 (20), 137 (40), 181 (28), 209 (100), 346 (18); HRMS calcd for $C_{20}H_{26}O_5$ 346.1780, found 346.1792.

1-(5-Oxo-2,6,6-trimethyl-1-cyclohexenyl)-2-(1-methyl-4-oxo-2-cyclohexenyl)-1,2-ethanedione (22). The ketal **21** (56 mg, 0.16 mmol) was treated with *p*-toluenesulfonic acid (30 mg, 0.16 mmol) at 60 °C for 21 h in a THF/water mixture (1:1 vol, 2 mL), and the reaction was monitored by NMR analysis of aliquots. The same workup as for **19** gave after flash chromatography (EtOAc/hexanes, 1:4) 2 fractions, remaining starting ketal (5 mg) and tetrone **22** (35.4 mg, 0.117 mmol, 73.3%, 79.4% based on starting material recovery), as a yellow oil: IR (thin film) 2971.6, 2930.1, 1680–1720, 1461.8, 1379.4, 1230.8, 1210.1, 1127.0, 1033.7, 874.5, 827.8, 803.6 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS) ∂ 1.17 (s, 3 H), 1.23 (s, 3 H), 1.58 (s, 3 H), 1.60 (s, 3 H), 2.02 (ddd, J = 13.4, 10, 5.7 Hz, 1 H), 2.40–2.57 (m, 4 H), 2.58–2.68 (m, 3 H), 6.04 (d, J = 10.2 Hz, 1 H), 7.25 (dd, J = 10.2, 1.1 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) ∂ 21.47, 24.07, 25.02, 25.18, 31.29, 32.51, 34.34, 34.97, 46.07, 48.02, 129.61, 135.77, 138.37, 150.64, 195.04, 197.90, 198.13, 211.80; CIMS (CH_4) m/z 165 (100), 303 (79), 304 (20); HRMS calcd for $C_{18}H_{23}O_4$ (M + H) 303.1596, found 303.1586.

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Supplementary Material Available: ^1H and ^{13}C NMR spectra of **2–16** and **18–22** (41 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Kinetic Resolution of a Racemic Sulfide by Enantioselective Sulfoxide Formation†

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The asymmetric epoxidation and kinetic resolution of allylic alcohols has been described by Sharpless.[1] This oxidation is catalyzed by a chiral titanium complex and is best carried out under anhydrous conditions. Kagan[2] reported that when this catalyst is prepared with 1 equiv of water it is useful for the conversion of prochiral sulfides into enantiomerically-enriched sulfoxides. Anhydrous conditions were shown to be less effective for this transformation. Kinetic resolution of a racemic sulfide could be possible using this water-modified complex. While several reports on the use of these conditions for the synthesis of chiral sulfoxides have appeared in the literature,[3] none have described a kinetic resolution of the sulfide starting material.[4]

(±)5-[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]-methyl]-4-thiazolidinone (**6**) is a novel antioxidant which has been shown to be protective against acetic acid-induced colitis in rats (an animal model of inflammatory bowel disease).[5] A method for producing each individual enantiomer of thiazolidinone **6** was required to allow for comparative efficacy, pharmacokinetic, and toxicological

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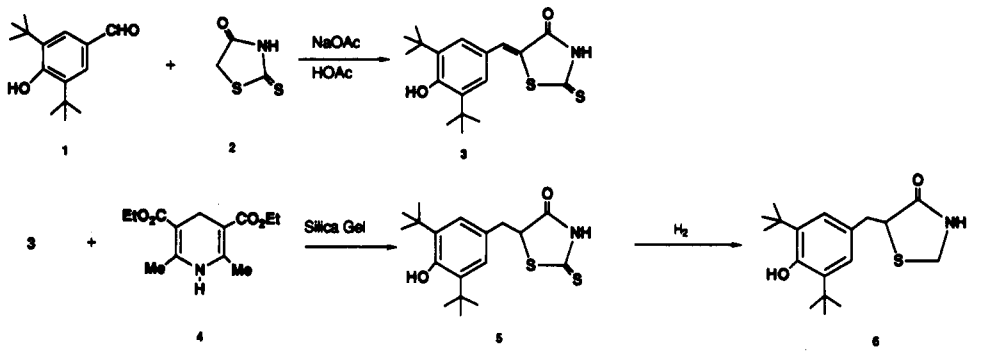
Scheme I



Scheme II

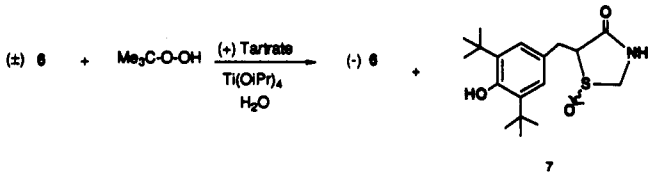


Table I. The Effect of Varying Molar Equivalents of TBHP on Kinetic Resolution

entry	equiv of TBHP	reactn[a] compln (%)	ee (NMR) (%)	ee (HPLC) (%)
1	0.6	60	65	67
2	0.75	70	82	86, 89[b]
3	0.85	79	>86[c]	93, 94[b]

[a] Based on isolated yields of starting material and products. [b] Duplicate runs. [c] Limit of detection of minor enantiomer is 7%.

studies as a part of the compound's development as a clinical candidate. The increasing realization that enantiomers may have vastly different pharmacological properties have made this a necessity when developing a potential therapeutic agent.

Inspection of the structure of thiazolidinone 6 reveals no acidic or basic functional group which one could utilize in the preparation of a diastereomeric salt which might be fractionally crystallized and subsequently converted back to thiazolidinone 6. While possible routes to chiral 6 involving asymmetric synthesis could be devised, their development could prove to be time consuming. Since large quantities of racemic 6 were available, the possibility of an expedient kinetic resolution was explored.

The synthesis of 6 is shown in Scheme I. 3,5-Di-*tert*-butyl-4-hydroxybenzaldehyde (1) was condensed with rhodanine (2) to give benzylidene rhodanine 3.[6] Reduction of the double bond of 3 was accomplished using the Hantzsch ester 4[7,8] to provide benzylrhodanine 5. Desulfurization of 5 via hydrogenation yielded 6. The overall yield of 6 from 1 was 45%.

Table II. The Effect of Water on Kinetic Resolution

entry	catalyst ratio Ti:tartrate:H_2O	equiv of TBHP	reactn compln[a] (%)	ee (NMR) (%)	ee (HPLC) (%)
1	1:2:1	0.6	60	65	67
4	1:2:0.5	0.6	60	64	64
5	1:2:0	0.6	62	61	62

[a] Based on isolated yields of starting material and products.

Table III. The Effect of a Different Tartrate Ester on Kinetic Resolution[a]

entry	tartrate	equiv of TBHP	reactn compln[a] (%)	ee (NMR) (%)	ee (HPLC) (%)
1	(+)-diisopropyl-tartrate	0.6	60	65	67
6	(+)-diethyltartrate	0.6	60	60	ND[b]

[a] Based on isolated yields of starting material and products. [b] ND, not done.

The oxidation of racemic sulfide 6 with less than 1 equiv of *tert*-butyl hydroperoxide (TBHP) in the presence of the water-modified Sharpless reagent allows recovery of enantiomerically-enriched starting material after isolation from the corresponding sulfoxide 5 (Scheme II). The (+)-enantiomer of 6 reacts faster than the (−) enantiomer in the presence of the catalyst prepared with (+)-tartrate. This results in the recovery of (−)-6. Conversely, the resolution employing (−)-tartrate yields (+)-6, with analogous results. Enantiomeric excesses (ee) of the unreacted sulfide resulting from varying degrees of reaction completion are found in Table I. If the reaction is continued to near 80% completion, 94% ee is obtained. Crystallization of the purified starting material results in precipitation of racemic 6, thereby enhancing the ee of the material in the mother liquor.

Kagan[9] has reported that the enantioselective oxidation of *p*-tolyl methyl sulfide is dependent on the amount of water present in the reaction medium, with a 2:1:1 ratio of tartrate–titanium–water being optimal. Under anhydrous conditions, this oxidation proceeds slower with a dramatic drop in ee. This is in contrast to the deleterious effect water has on the asymmetric epoxidation of allylic alcohols.[1] The kinetic resolution of (±)-6 is affected only slightly, if at all, by a 50% reduction in the amount of water in the catalyst. Interestingly, under anhydrous conditions, the reaction does proceed more slowly (28 h vs 6 h), but with only a small decrease in ee (Table II).

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Diethyl tartrate was compared to diisopropyl tartrate to examine the effect of the steric bulk of the chiral tartrate ligand on the enantioselectivity of the oxidation. Diisopropyl tartrate was found to be slightly superior, increasing the ee by 5% at 60% reaction completion (Table III).

Kinetic resolution of other racemic sulfides by this method should be possible when one considers the substrate diversity reported for the asymmetric sulfoxide formation.[3]

Experimental Section

General Methods. Compounds 3 and 4 were prepared by published procedures.[6,7] Toluene and dichloromethane were distilled from calcium hydride. Titanium tetraisopropoxide, (+)-diisopropyl tartrate, and (+)-diethyl tartrate were distilled under high vacuum. The *t*-Bu hydroperoxide in isooctane was obtained from Aldrich and titrated.[1c] Pellet 4-Å molecular sieves obtained from Red Bird Service were activated by heating in a vacuum oven at 110 °C for at least 16 h. Silica gel 60 (finer than 230 mesh) was obtained from E. Merck and activated by heating under vacuum at 50 °C for 4 h. Preparative chromatography was performed on a Waters Associates Prep LC/System 500A. NMR spectra were obtained at 300 MHz. Trifluoroanthranylethanol was obtained from Aldrich.

5-[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]-methyl]-2-thioxo-4-thiazolidinone (5). To a stirred suspension of 3[6] (41.94 g, 120 mmol) in toluene (1.8 L) was added diethyl 2,6-dimethyl-1,4-dihydro-3,5-pyridinedicarboxylate (4)[7] (39.51 g, 156 mmol) and activated silica gel 60 (120 g). The mixture was heated to 80 °C for 22 h, and then the warm suspension was filtered. The filter cake was rinsed with ethyl acetate. The combined filtrate and rinse were evaporated to dryness. The evaporation residue was redissolved in ethyl acetate and extracted with five portions of 1 N HCl. The ethyl acetate layer was dried over Na_2SO_4 and evaporated to yield 5 (42.6 g, 100%) as a yellow solid: mp 178–179 °C; ^1H NMR ($CDCl_3$) δ 9.05 (s, 1 H), 7.03 (s, 2 H), 5.22 (s, 1 H), 4.58 (dd, J = 3, 9 Hz, 1 H), 3.51 (dd, J = 3, 15 Hz, 1 H), 3.09 (dd, J = 9, 15 Hz, 1 H), 1.45 (s, 18 H); FD MS 351 (M^+). Anal. Calcd for $C_{18}H_{25}NO_2S_2$: C, 61.50; H, 7.17; N, 3.98. Found: C, 61.60; H, 7.21; N, 4.14.

5-[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]-methyl]-4-thiazolidinone (6). Hydrogenation of 5 (32.3 g, 92 mmol) in EtOH (2.3 L) in the presence of 5% Pd/C (110 g) under 500 psi of H_2 for 20 h at 120 °C yielded, after filtration and evaporation of solvent, crude 6. Crystallization with CH_2Cl_2 and trituration with hot hexane resulted in pure 6 (14.6 g, 49.5% yield) as white crystals: mp 149–152 °C; ^1H NMR ($CDCl_3$) δ 7.16 (s, 1 H), 7.11 (s, 2 H), 5.15 (s, 1 H), 4.25 (d, J = 9 Hz, 1 H), 4.07 (d, J = 9 Hz, 1 H), 3.93 (dd, J = 3, 6 Hz, 1 H), 3.35 (dd, J = 3, 14 Hz, 1 H), 2.93 (dd, J = 6, 14 Hz, 1 H), 1.4 (s, 18 H); FD MS 321 (M^+). Anal. Calcd for $C_{18}H_{27}NO_2S$: C, 67.25; H, 8.47; N, 4.36. Found: C, 67.05; H, 8.54; N, 4.61.

(−)-5-[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]-methyl]-4-thiazolidinone [(−)6]. To a stirred suspension of 4-Å molecular sieves (1.05 g) in CH_2Cl_2 (25 mL) were added titanium tetraisopropoxide (0.45 mL, 1.5 mmol), (+)-diisopropyl tartrate (0.63 mL, 3.0 mmol), and deionized water (27 μL, 1.5 mmol), respectively. The suspension was allowed to stir at rt for 20 min before addition of thiazolidinone (±)-6 (0.80 g, 2.5 mmol). After dissolution of the sulfide, the reaction was cooled to −20 °C and 2.57 M *t*-Bu hydroperoxide solution in isooctane (0.58 mL, 1.5 mmol) was added. The reaction was stirred at −20 °C for 6 h, at which time the molecular sieves were removed by filtration. The filtrate was quenched by pouring into a stirred 50-mL solution prepared from citric acid monohydrate (3.3 g), ferrous sulfate heptahydrate (9.9 g), and deionized water. Stirring was continued for 30 min, and then the layers were left to separate. The aqueous layer was extracted with an equal volume of CH_2Cl_2. The original CH_2Cl_2 layer and the CH_2Cl_2 extract were combined and dried over Na_2SO_4. Evaporation of the solvent followed by NMR analysis of a $CDCl_3$ solution of the residue showed a 40/60 ratio of 6 to its sulfoxide products, 7 (80/20 mixture of diastereomers). The evaporation residue was chromatographed on silica gel. Elution with 6 L of a 10%–50% ethyl acetate in hexane gradient yielded (−)-6 (0.29 g, 36% recovery) as a white foam: mp 144–146 °C; $[\alpha]^{20}_D$ −56.99° (*c* 1.0, MeOH). Anal. Calcd for $C_{18}H_{27}NO_2S$: C, 67.25; H, 8.47; N, 4.36. Found: C, 67.31; H, 8.55; N, 4.12.

When the reaction was taken to 70% completion using (−)-diisopropyl tartrate (+)-6 was recovered as a white foam: mp 144–146 °C; $[\alpha]^{20}_D$ +70.41° (*c* 1.0, MeOH); ee 84% (HPLC). Anal. Calcd for $C_{18}H_{27}NO_2S$: C, 67.25; H, 8.47; N, 4.36. Found: C, 66.95; H, 8.22; N. 4.26.

5-[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]-methyl]-4-thiazolidinone 1-Oxide (7). Continued elution of the silica gel column with 4 L of 50% 2-propanol in hexane yielded 7 (0.46 g, 55%). Isomer A: mp 182–184 °C; ^1H NMR ($CDCl_3$) δ 7.02 (s, 2 H), 6.02 (s, 1 H), 5.23 (s, 1 H), 4.05 (dd, J = 3, 12 Hz, 1 H), 3.63 (m, 2 H), 3.37 (dd, J = 5, 14 Hz, 1 H), 3.09 (dd, J = 8, 14 Hz, 1 H), 1.43 (s, 18 H); FD MS 337 (M^+). Anal. Calcd for $C_{18}H_{27}NO_3S$: C, 64.06; H, 8.06; N, 4.15. Found: C, 63.84; H, 8.09; N, 4.12. Isomer B: mp 177–181 °C; ^1H NMR ($CDCl_3$) δ 7.16 (s, 2 H), 7.04 (s, 1 H), 5.19 (s, 1 H), 4.32 (s, 2 H), 3.46 (dd, J = 3, 12 Hz, 1 H), 3.37 (dd, J = 3, 15 Hz, 1 H), 3.17 (dd, J = 12, 15 Hz, 1 H), 1.45 (s, 18 H); FD MS: 337 (M^+). Anal. Calcd for $C_{18}H_{27}NO_3S$: C, 64.06; H, 8.06; N, 4.15. Found: C, 63.88; H, 8.12; N, 4.29.

Determination of Enantiomeric Excess. Two methods were used to determine the ee of the resolved thiazolidinone 6. HPLC on a Chiracel OJ column using 15% 2-propanol in hexane as mobile phase results in t_R = 4.9 min for (−)-6 and t_R = 5.8 min for (+)-6 using 280-nm UV detection. NMR spectroscopy of a $CDCl_3$ solution of 6 treated with the chiral shift reagent trifluoroanthranylethanol results in an enantioselective shifting of the peak at δ 4.25. Good agreement of these two methods was seen in all cases (see tables).

Syn/Anti Diastereoselectivity in the Reduction of α-Alkoxy Ketones by Tin Hydride Reagents

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The general problem of the stereocontrolled construction of acyclic materials has been a topic of intensive investigation. In recent years, considerable progress has been made in controlling the stereochemistry of the reaction of α-alkoxy carbonyl compounds by the interaction between an alkoxy group and Lewis acids.[1] Organotin compounds such as allylstannane play an important role in controlling the diastereoselectivity by the assistance of Lewis acids.[2]

In the reduction of α-alkoxy ketones, the selection of reducing agent to control the diastereoselectivity is difficult. Generally, the control is achieved by using oxygen substituents.[3] Fujita and Hiyama have reported unique reducing systems using silyl hydrides to control the diastereoselectivity for a single substrate.[4] However, the selectivity in such reactions using organotin hydrides has not been reported because of their radical manner.[5] We

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