Tetrahedron Vol. 40, No. 8, pp. 1401 to 1407, 1984
Printed in Great Britain.

0040-4020/84 $3.00 + .00
Pergamon Press Ltd.

ASYMMETRIC SYNTHESIS USING ENANTIOMERICALLY PURE 2-(*p*-ANISYLSULFINYL)-2-CYCLOALKENONES

GARY H. POSNER,* LEAH L. FRYE and MARTIN HULCE
Department of Chemistry, The Johns Hopkins University, Baltimore, MD 21218, U.S.A.

(*Received in USA* 13 *April* 1983)

Abstract—Conjugate additions of many organometallic reagents to 2-(*p*-anisylsulfinyl)-2-cycloalkenones, **2**, proceed with much greater diastereoselectivity than additions to the corresponding 2-(*p*-tolylsulfinyl)-2-cycloalkenones, **7**. Complexation of **2** with zinc dibromide followed by addition of various Grignard reagents lead, after reductive removal of the sulfoxide, to 3-substituted cycloalkanones of higher optical purity than those obtained from **7**. Addition of methyltitanium triisopropoxide to 2-(*p*-anisylsulfinyl)-2-cyclohexenone, **2b**, in the absence of zinc dibromide, proceeds with virtually complete asymmetric induction.

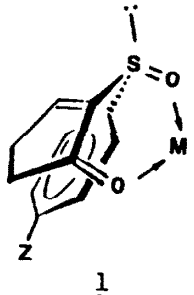
Recently we have shown that organometallic conjugate additions to some enantiomerically pure 2-(*p*-tolylsulfinyl)-2-cycloalkenones proceed with high asymmetric induction leading to a wide variety of 3-substituted cycloalkanones of high enantiomeric purity.[1-4] Since such chiral carbocycles are valuable synthons and in some cases important natural products, we now have improved our methodology by designing an even more effective series of 2-(arylsulfinyl)-2-cycloalkenones. We therefore describe here our synthesis of 3-substituted cyclopentanones and cyclohexanones from the corresponding enantiomerically pure 2-(*p-anisyl*sulfinyl)-2-cycloalkenones with a much higher degree of stereocontrol than previously reported with 2-(*p-tolyl*sulfinyl)-2-cycloalkenones. Furthermore, we report an improved method for the preparation of (S_S)-(−)-menthyl *p*-methoxybenzenesulfinate, the necessary precursor to our desired sulfoxides.

RESULTS AND DISCUSSION

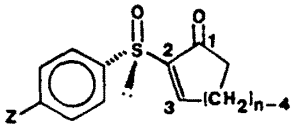
On the basis of our previously proposed chelate model,[1] **1** (Z=CH_3), in which a chiral β-ketosulfoxide acts as a bidentate ligand that coordinates with a metal ion, M, we expected that a stronger electron donating group Z on the aromatic moiety of the sulfoxide would increase the Lewis basicity of the sulfinyl oxygen. We reasoned that this enhancement in Lewis basicity would result in a more rigid and conformationally stable coordination complex or chelate that consequently would result in an increase in the diastereoselectivity observed during organometallic conjugate addition to the enone sulfoxide. A good indicator of the ability of an aromatic substituent to donate electrons is its Hammett σ constant. As the σ_{para} value for Me is −0.17 but the σ_{para} value for OMe is −0.37, we chose to synthesize 2-(*p*-anisylsulfinyl)-2-cycloalkenones **2a** and **2b** to test our hypothesis.

The first step in the preparation of **2** is to obtain optically pure (S_S)-(−)-menthyl *p*-methoxybenzene sulfinate, **3**. The synthesis of **3** has been reported previously in the literature, however six successive recrystallizations were required to obtain diastereomerically pure **3** and no final chemical yield was reported.[5,6] We have found that by modifying the reported reaction procedure, beautifully crystalline *diastereomerically pure* **3** can be crystallized directly from the crude reaction product with ease.

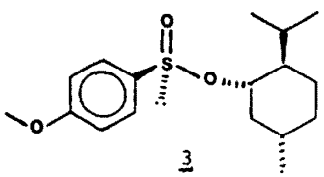
With **3** in hand, 2-(*p*-anisylsulfinyl)-2-cycloalkenones, **2**, were prepared in a manner analogous to the corresponding *p*-tolylsulfoxides **7**[1], eqn (1). Reaction of the appropriate 2-bromo-2-cycloalkenone ethylene ketal, **4**, with n-butyllithium at −78° as described by Branca and Smith[7] gives the vinyllithium species **5**. Transfer of **5** to a solution of **3** in THF at −78° *via* a precooled cannula, followed by protic work up gives the corresponding ketal sulfoxide **6** with inversion of configuration at S.[5]



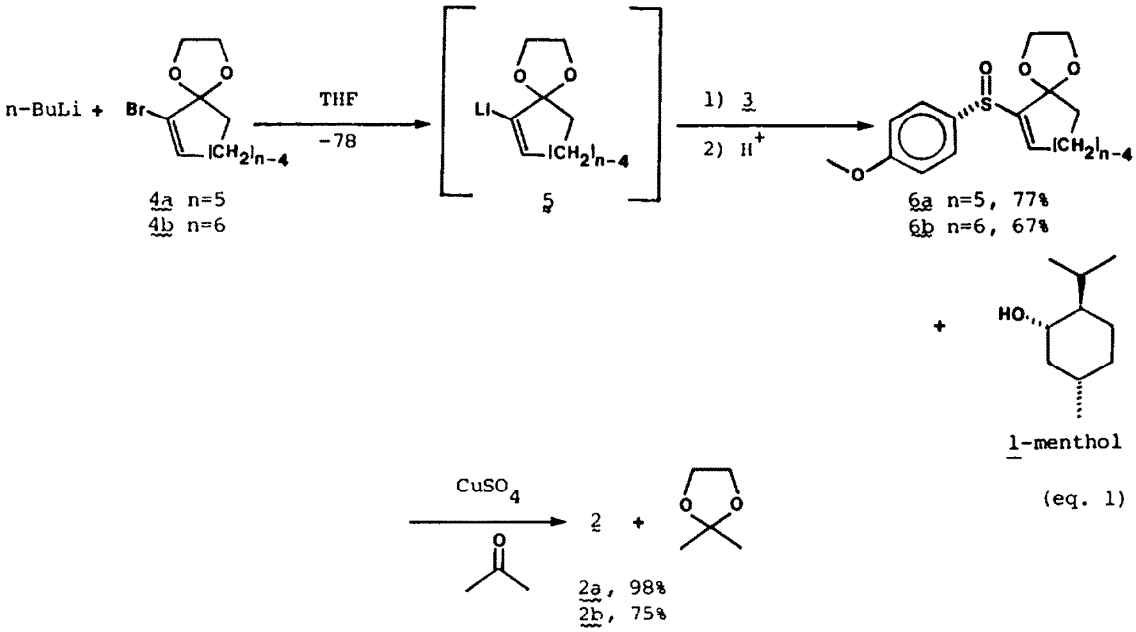
1



Z=OCH_3 **2a** n=5, **2b** n=6
Z=CH_3 **7a** n=5, **7b** n=6

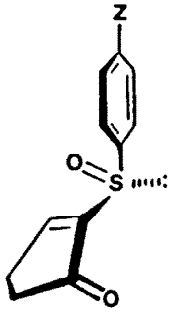


3



Deketalization is accomplished by copper(II) sulfate-mediated transketalization using acetone as the solvent,[1-4] giving the desired 2-(*p*-anisylsulfinyl)-2-cycloalkenones **2a** and **2b** in 76 and 50% yields, respectively. Both of these sulfinylcycloalkenones are crystalline compounds which are stable at refrigerator temperatures for at least several months. The original source of chirality for the entire synthetic sequence, l-menthol, is easily recoverable during chromatographic isolation of the ketal sulfoxides **6**.

When **2a** is in THF solution with no metallic cations present, the most likely orientation of the molecule is such that the dipoles of the ketone and sulfoxide are in opposite directions,[8] **1'** (Z = OCH_3). Upon the addition of zinc dibromide to **2a** in THF, significant changes are observed in both the ^{13}C and ^1H NMR spectra suggesting pronounced conformational and/or electronic changes. For instance, vinylic carbon 3 shifts 2.14 ppm downfield with the addition of zinc dibromide. This is consistent with the expected reduction of electron density at carbon 3 upon coordination of the β-ketosulfoxide with a metal cation.

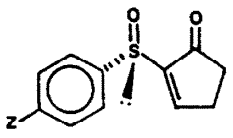


1'

As expected, based on chelate model **1** (Z = OCH_3), organometallic conjugate additions occurred from that diastereotopic face of the enone opposite to the bulky *p*-anisyl group, the Pro-R face, resulting in (*R*)-3-substituted cycloalkanones after reductive cleavage of the sulfinyl group. In all cases we studied, the diastereoselectivity of the conjugate addition to **2** is greater than that seen with the *p*-tolylsulfoxides **7**. For example, enantiomerically pure **2a** undergoes complex formation with zinc dibromide and then asymmetric conjugate addition with various Grignard reagents followed by reductive removal of the chiral sulfinyl group, producing (*R*)-(+)-3-substituted cyclopentanones **8** (eqn (2); Table 1). Conjugate addition of dineopentylcoppermagnesium chloride to **2a** ultimately leads to **8d** with a 3-fold increase in the ratio of *R* to *S* over that from **7a**, without the use of an additional complexing ion (Table 1). The enantiomeric purity of the resultant 3-substituted cyclopentanones, **8**, was determined by specific rotation and/or by preparation of the corresponding diastereomeric ketals **9**, eqn (3). The ratio of *R*:*S* at the 3-position of the ketal **9** then can be determined by ^{13}C NMR.[9]

Likewise, enantiomerically pure **2b** undergoes zinc-mediated asymmetric Grignard conjugate additions, affording (*R*)-(+)-3-substituted cyclohexanones, **10**, with greater diastereoselectivity than those from **7b** (eqn (4); Table 2). Virtually complete asymmetric induction was observed during methyltitanium triisopropoxide[10,11] conjugate addition to **2b** in the absence of zinc dibromide (Table 2). Thus, by using 2-(*p*-anisylsulfinyl)-2-cycloalkenones in conjunction with "bulky" organometallic reagents, even the smallest alkyl group, a methyl group, may be added in conjugate manner with extremely high and reliable asymmetric induction and in excellent isolated chemical yield.

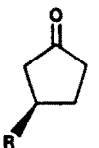
Thus we have developed further a general method of reproducibly preparing many 3-substituted cycloalkanones of high enantiomeric purity *via* conjugate additions to our 2-(*p*-anisylsulfinyl-2-cycloalkenones,



2a Z=OCH_3
7a Z=CH_3

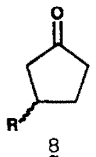
1) Chelating Agent
2) R-Met

Al/Hg



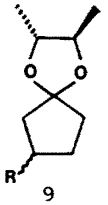
8

(eq. 2)



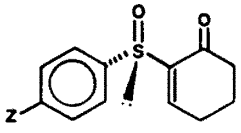
8

HO OH
TsOH/benzene



9

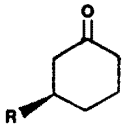
(eq. 3)



2b Z=OCH_3
7b Z=CH_3

1) Chelating Agent
2) R-Met

Al/Hg



10

(eq. 4)

Table 1.

Product Number	R-Met	Chelating Agent	Z=OCH_3 Chemical Yield (%)	Z=OCH_3 Ratio (R:S)	Z=CH_3 Chemical Yield (%)	Z=CH_3 Ratio (R:S)
8a	CH_3CH_2MgCl	$ZnBr_2$	83[a]	8.3:1[b]	90	4.4:1[b]
8b	$(CH_3)_2CHMgCl$	$ZnBr_2$	74[a]	8.8:1[b,c]	67	6.7:1[b]
8c	$(CH_3)_3CCH_2MgCl$	$ZnBr_2$	69	14.4:1[b]	32	1.4:1[b,c]
8d	$((CH_3)_3CCH_2)_2CuMgCl$	—	99	7.0:1[b]	99	2.2:1[b,c]
8e	$CH_2=CHCH_2MgCl$	$ZnBr_2$	60	5.1:1[b]	80	3.5:1[b]
8f	p-$CH_3C_6H_4MgBr$	$ZnBr_2$	86	5.5:1[c]	89	3.8:1[c]

a: Chemical yield determined by GLPC.

b: Optical purity determined by specific rotation.

c: Optical purity determined by ^{13}C NMR of diastereomeric ketals.

Table 2.

Product Number	R-Met	Chelating Agent	Z=OCH_3 Chemical Yield (%)	Z=OCH_3 Ratio (R:S)	Z=CH_3 Chemical Yield (%)	Z=CH_3 Ratio (R:S)
10a	$CH_3Ti(OCH(CH_3)_2)_3$	—	85	≥49.0:1[b,c]	85[a]	14.4:1[b,c]
10b	CH_3MgBr	$ZnBr_2$	41	2.4:1[b]	51	2.1:1[b,c]
10c	$(CH_3)_2CHMgCl$	$ZnBr_2$	52	3.9:1[c]	62	3.3:1[c]

a: Chemical yield determined by GLPC.

b: Optical purity determined by specific rotation.

c: Optical purity determined by ^{13}C NMR of diastereomeric ketals.

2. The resultant chiral carbocycles are valuable synthons in the synthesis of natural products, examples of which are being pursued in our laboratories. Further work on the modification of the aryl group of the sulfoxide to enhance the diastereoselection of the conjugate additions also is in progress.

EXPERIMENTAL

M. and b.ps are uncorrected. IR spectra were recorded with a Perkin–Elmer 599B spectrometer in the solvent indicated. Proton NMR spectra were recorded with a Varian CFT-20 or Bruker WM.300 spectrometer operating at 80 or 300 MHz, respectively. Carbon NMR spectra were recorded with a Varian CFT-20 spectrometer operating at 20 MHz. All NMR spectra were obtained in the solvent indicated and reported in units of ppm downfield from TMS. Mass spectra were performed by the Middle Atlantic Mass Spectrometry Laboratory, Baltimore, MD. Optical rotations were recorded with a Perkin–Elmer 141 variable-wavelength polarimeter using 1-dm quartz window cells in the indicated solvent. Microanalyses were performed by Galbraith Laboratories, Inc. Gas–liquid phase chromatography (GLPC) data were obtained with a Varian Aerograph Series 1200 gas chromatograph with a carrier gas (He) flow rate of 22 mL/min and equipped with a 10 ft. × 1/8 in. column packed with 5% FFAP on Chromosorb W and a flame ionization detector.

Tetrahydrofuran (THF) and diethyl ether were distilled from sodium benzophenone ketyl prior to use. The following reagents were purchased from Aldrich Chemical Company: 2-chloropropane, allyl chloride, 4-bromotoluene, thionyl chloride, l-menthol, 2-cyclopentenone, 2-cyclohexenone, ethylene glycol, titanium(IV) chloride, titanium(IV) isopropoxide, and (*R, R*)-(−)-2,3-butanediol. Sodium *p*-methoxybenzenesulfinate was purchased from Parrish Chemical Co. Anhyd $CuSO_4$. Cu_2I_2, neopentylchloride and anhyd $ZnBr_2$ were purchased from Alfa-Ventron. Alkyllithium reagents were purchased from Aldrich Chemical Co. as solns in the solvent indicated: MeLi (diethyl ether) and n-BuLi (hexane); they were titrated with anhyd diphenylacetic acid prior to use.[12] MeMgCl (THF) and allylmagnesium chloride (THF) were purchased from Aldrich Chemical Co. All other Grignard reagents were prepared by the usual methods in THF except neopentylmagnesium chloride which was prepared in diethyl ether. Preparative TLC plates, Silica Gel H Uniplates and Uniplate-T Taper Plate were purchased from Analtech. The 2-bromo-2-cycloalkenone ethylene ketals, **4**, were prepared as described in the literature.[1,7] The preparations and reactions of the 2-(*p*-tolylsulfinyl)-2-cycloalkenones, **7**, were strictly analogous to those of the 2-(*p*-anisylsulfinyl)-2-cycloalkenones, **2**.[1-4]

Preparation of (S$_s$)-(−)-*menthyl* p-*methoxybenzenesulfinate*, **3**.

A 3-neck 250 mL round bottom flask equipped with a reflux condenser, a drying tube, a pressure equalizing addition funnel and an overhead mechanical stirrer was charged with *p*-methoxybenzenesulfinic acid, sodium salt (10.2g, 52-3 mmol) and 40 mL anhyd diethyl ether. To this vigorously stirred suspension, $SOCl_2$ (17.5 mL, 240 mmol) was added at such a rate as to maintain a gentle reflux. After all the $SOCl_2$ was added, stirring was maintained overnight at room temp. The resultant slurry was filtered through a coarse sintered glass filter funnel and the filter cake was washed well with a total of 100 mL anhyd diethyl ether. The combined filtrates, in a l-neck 250 mL round bottom flask, were concentrated by rotary evaporation. The excess $SOCl_2$ was removed by azeotropic rotary evaporation with two 40 mL aliquots of anhyd diethyl ether. The resultant oil was diluted with 40 mL anhyd diethyl ether, l-menthol (8.2 g, 52.3 mmol) was added, and the flask equipped with a magnetic stirring bar, a pressure equalizing addition funnel, and a drying tube. The slurry was stirred until all the l-menthol was dissolved; the flask then was cooled to 0°. Pyridine (4.2 mL, 52.3 mmol) in 40 mL anhyd diethyl ether was added slowly to this vigorously stirred soln of l-menthol and *p*-methoxybenzenesulfinylchloride. Stirring was maintained and the mixture was allowed to warm to room temp overnight. 10% HClaq (150 mL) and 100 mL diethyl ether was added; the mixture was stirred until all the solid was dissolved and the flask contents were transferred to a 500 mL separatory funnel. The diethyl ether layer was removed and the aqueous layer was extracted with a total of 500 mL diethyl ether. The combined organic layers were dried over $MgSO_4$. Filtration, rotary evaporation, and vacuum drying gave 16.5 g of an off white, oily solid. Hot crystallization with diethyl ether gave with no further purification 7.9 g (47%) of **3** as rectangular, clear colorless crystals: m.p.110.0–110.5°, $[\alpha]_D^{25°} = -188.9°$(*c* 1.19, acetone); lit.[5] m.p. 106-108°, acetone/H_2O; $[\alpha]_D^{25°} = -189°$ (acetone). Spectral data are identical with those reported.[5,6]

Preparation of (S) - (+)-2-(p-*anisylsulfinyl*) - 2 - *cyclopentenone*, **2a**

A flame dried 2-neck 25 mL round bottom flask equipped with a serum cap, a pressure equalizing addition funnel with a gas inlet, and a magnetic stirring bar was flushed with argon and after cooling to room temp was charged with 9.0 mL anhyd THF and cooled to −78°. n-BuLi (5.2 mL, 1.6 M, 8.5 mmol) was added dropwise *via* the addition funnel. The addition funnel was rinsed with 2 ml anhyd THF. Freshly distilled[7] **4a**, (b.p. 38°/0.1 mm Hg, 1.6 g, 7.7 mmol) in 8.0 mL anhyd THF was added dropwise *via* the addition funnel. Stirring was continued at −78° for 90 min. This solution then was transferred under positive argon pressure *via* a coiled, dry ice/isopropanol bath-cooled cannula to a vigorously stirred soln of **3** (2.6 g, 8.5 mmol) in 65 mL anhyd THF at −78° in an oven dried, l-neck, 250 mL round bottom flask. Stirring was continued under argon at −78° for 15 min, after which the cold bath was removed and 20 mL of sat NaH_2PO_4 aq was poured into the reaction vessel. After the soln was warmed to room temp, the THF was removed by rotary evaporation. The crude mixture was diluted with 40 mL distilled water and extracted with 25 mL $CHCl_3$ and then 3 × 13 mL $CHCl_3$. The combined organic layers were dried over K_2CO_3; filtration and rotary evaporation gave a yellow oil with many clear, colorless crystals. The desired ketal sulfoxide **6a** (1.7 g, 77%) was isolated by medium pressure liquid chromatography (MPLC) (25 × 600 mm column, 240–400 mesh SiO_2, EtOAc, 6 mL/min, R_f 0.32) as an oil: ^{1}H NMR ($CDCl_3$, 80 MHz) δ 7.63 (d, J = 8.9 Hz, 2 H), 6.98 (d, J = 8.9 Hz, 2 H), 6.74 (t, J = 2.4 Hz, 1 H), 4.0–3.5 (m, 7 H), 2.6–2.3 (m, 2 H), 2.2–2.0 (m 2 H); IR ($CHCl_3$, cm^{-1}) 3000 (w), 2890 (w), 1594 (s), 1495 (s), 1255 (s), 1173 (s), 1090 (s), 1040 (s); mass spectrum (70 eV, *m/e*) 280 (M^+).

A 100 mL Erlenmeyer flask equipped with a magnetic stirring bar charged with 12.5 g anhyd $CuSO_4$. The ketal sulfoxide **6a** in 36 mL reagent grade acetone was transferred to the flask; the flask was flushed with N_2 and tightly stoppered. The mixture was stirred at room temp for 24 hr, then the suspension was filtered and the $CuSO_4$ filter cake was washed thoroughly with acetone. Rotary evaporation gave spectroscopically pure **2a** (1.1 g, 92%) as a crystalline solid that was recrystallized from EtOAc CH_2Cl_2–hexanes: m.p. 120.5–121.5°; ^{1}H HMR (d_8-THF, 300 MHz) δ8.0065 (t, J = 2.758 Hz, lH), 7.6385 (dt, J = 8.926, 2.868 Hz, 2 H), 6.9851 (dt, J = 8.868, 2.867 Hz, 2 H), 3.7917 (s, 3 H), 2.814–2.564 (m, 2 H), 2.528–2.305 (m, 2 H); ^{1}H NMR (d_8 THF + 1.0 equiv. $ZnBr_2$, 300 MHz) δ8.1373 (t, J = 2.607 Hz, 1 H), 7.6828 (dt, J = 8.707, 2.908 Hz, 2 H), 7.0171 (dt, J = 8.864, 2.785 Hz, 2 H), 3.8081 (s, 3 H), 2.859-2.633 (m, 2 H), 2.551-2.333 (m, 2 H) ^{13}C NMR (d_8-THF, 20 MHz) δ189.69, 162.25, 161.91, 152.24, 130.70, 126.09, 114.06, 54.59, 35.78, 26.89; ^{13}C NMR (d_8-THF + 1.0

eq. $ZnBr_2$, 20 Hz) 190.09, 164.39, 162.65, 149.22, 130.07, 127.41, 114.45, 54.90, 35.75, 27.35. IR ($CHCl_3$, cm^{-1}) 3000 (w), 1710 (s), 1595 (s), 1495 (s), 1255 (s), 1040 (s); mass spectrum (70 eV, *m/e*) 236 (M^+), 188 (base); $[\alpha]_D^{25} = +141.0°$ (*c* 1.45, acetone); (Found: C,61.19; H, 5.35; S, 13.66%. Calc for $C_{12}H_{12}O_3S$: C, 61.00; H, 5.12; S, 13.57%).

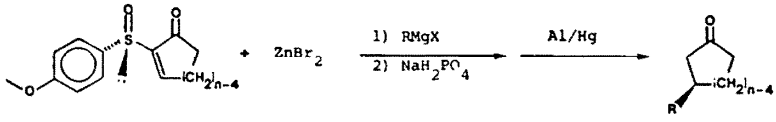
Preparation of (S)-(+)-2-(p-*anisylsulfinyl*-2-*cyclohexenone*, **2b**

The desired ketal sulfoxide, **6b**, was prepared in the same manner as **6a** except that **4b**, (1.5 g, 6.8 mmol) was used. The product **6b** (1.4 g, 67%) was isolated by MPLC (25 × 600 mm, 240–400 mesh SiO_2, EtOAc, 6 mL/min, R_f 0.36) as an oil: ^1H NMR ($CDCl_3$, 80 MHz) δ 7.61 (d, J = 8.8 Hz 2 H), 7.07–6.85 (m, 3 H), 4.05–3.29 (m, 7 H), 2.38–2.23 (m, 2 H), 1.90–1.70 (m, 4 H); IR ($CHCl_3$ cm^{-1}) 2980 (s), 2883 (w), 1590 (s), 1490 (s), 1230 (s), 1030 (s), 952 (s), 862 (s). Mass spectrum (70 eV, *m/e*) 294 (M^+). Ketal sulfoxide **6b** was deketalized by the same procedure as **6a** except the $CuSO_4$ was filtered off, the cake washed well with acetone, the filtrate rotary evaporated, acetone added and the soln resubmitted to fresh anhyd $CuSO_4$. This procedure was repeated 3 times over the period of one week. After the fourth filtration the cake was washed well with acetone, rotary evaporation and vacuum drying gave a yellow oil. The desired product **2b** (0.88 g, 75%) was isolated as a white crystalline solid by the addition of diethyl ether and filtration. The product was recrystallized from EtOAc–hexanes: m.p. 106.5–107°, ^1H NMR ($CDCl_3$, 80 MHz) δ 7.77–7.56 (m, 3 H); 6.94 (d, J = 8.9 Hz, 2 H), 3.82 (s, 3 H), 2.64–2.34 (m, 4 H), 2.17–1.95 (m, 2 H); IR ($CHCl_3$, cm^{-1}) 3000 (w), 1675 (s), 1590 (s), 1492 (s), 1230 (s), 1045 (s); mass spectrum (70 eV, *m/e*) 250 (M^+), 155 (base; $[\alpha]_D^{25} = +187°$ (*c* 1.46, acetone); (Found : C, 62.28; H, 5.87; S, 12. 89%. Calc for $C_{13}H_{14}O_3S$: C, 62.38; H, 5.64; S, 12.81%).

General method for the preparation (*R*)-3-*substituted cyclopentanones*, **8**, *via zinc dibromide-mediated Grignard addition*

A flame dried 1-neck 10 mL round bottom flask equipped with serum cap, argon needle inlet, and magnetic stirring bar and containing sulfoxide **2a** (0.083 g, 0.35 mmol) was flushed with argon. The sulfoxide was treated with a soln of $ZnBr_2$ in anhyd THF (0.21 mL, 1.7 M, 0.35 mmol). This soln was stirred at room temp for 15 min, then 1.75 mL anhyd THF was added and the flask cooled to −78°. The appropriate Grignard reagent (0.53 mmol, 1.5 eqn) was added slowly dropwise *via* a gas-tight syringe at the temps indicated in Table 3. After the given period of time, the reaction was warmed to −5° to −10° and was quenched with sat NaH_2PO_4aq. The THF was removed by rotary evaporation at 0° and the mixture was extracted well with diethyl ether. The combined diethyl ether layers were filtered through anhyd $MgSO_4$ and the diethyl ether was removed by rotary evaporation at −10°. The flask then was equipped with a magnetic stirring bar and placed in a −10° bath; ~15 mL of 0° THF–H_2O (9 : 1) was added and the soln treated with 10 equivs of freshly prepared aluminum amalgam.[13] The resultant mixture under argon was stirred with slow warming to room temp overnight; anhyd $MgSO_4$ was added, the slurry filtered through a fine sintered glass filter funnel, and the cake washed well with diethyl ether. The combined filtrates were rotary evaporated at −10° and the residue was dissolved in CH_2Cl_2 for chromatography. Preparative TLC (SiO_2, 20 × 20 cm preabsorbent taper plate, 10 : 0.6 benzene: diethyl ether) gave the corresponding 3-substituted cyclopentanone, **8**. Samples for specific rotation were purified further by Kugelrohr distillation (50°, 10 mm Hg, −78° receiving bulb). All rotations were obtained in $CHCl_3$. For the method of determination of enantiomeric purity and physical properties see *Determination of Enantiomeric Purity of* **8** *and* **10**. The purity of the products were determined by TLC (SiO_2, 10 : 0.6 benzene:diethyl ether) and GLPC.

Table 3.



Product Number	n	R	X	Reaction temperature(s) and time(s)	$[\alpha]_D^{25°}$ (c)[a]	R_f (Preparative TLC)	GLPC retention Time (temp, °C)
8a	5	CH_3CH_2	Cl	-78°C, 1 h	90.0° (0.67)	0.55	9.0 min (145°)
8b	5	$(CH_3)_2CH$	Cl	-78°C, 2.3 h & 0°C,30 min	147.8°[b] (0.87)	0.59	13.5 min (145°)
8c	5	$(CH_3)_3CCH_2$	Cl	-78°C, 1 h	130.5° (0.92)	0.64	22.8 min (142°)
8e	5	CH_2=$CHCH_2$	Cl	-78°C, 3 h	83.9° (0.67)	0.52	18.9 min (145°)
8f	5	p-$CH_3C_6H_4$	Br	-78°C, 2 h	–[c]	0.54	–[c]
10b	6	CH_3	Br	-78°C, 1.5 h	71.5°[d] (0.34)	0.56	22.2 min (120°)
10c	6	$(CH_3)_2CH$	Cl	-78°C, 2 h	–[c]	0.60	–[c]

a: Concentration units are g/100 mL. Chloroform was the solvent used for all specific rotations.

b: A temperature of 20°C was used for the rotation of 3-isopropylcyclopentanone.

c: Optical purity determined by diastereomeric ketals only.

d: A wavelength of 365 nm (Hg) was used instead of the D-line (Na) for the rotation of 3-methycyclohexanone.

Addition of dineopentylcoppermagnesium chloride to **2a**

An oven dried l-neck 10 mL round bottom flask equipped with a magnetic stirring bar, a serum cup and a gas needle inlet was charged with Cu_2I_2 (0.1106 g, 0.58 mmol). The reaction vessel then was flushed with argon, charged with 1.5 mL anhyd THF, cooled to −20° and neopentylmagnesium chloride (0.49 mL, 2.2 M, 1.1 mmol) added dropwise *via* a gas tight syringe. Stirring was continued at −20° for 30 min. The resultant grey-black slurry was transferred dropwise to a l-neck 25 mL round bottom flask containing **2a** (0.0850 g, 0.36 mmol) and 2.0 mL anhyd THF at −78° under argon *via* gas tight syringe and was stirred at −78° for 1 hr. The reaction was quenched at −78° with sat NH_4Claq and then warmed to 0°. The THF was removed by rotary evaporation at 0° and the mixture was extracted well with 0° diethyl ether. The ether extracts were filtered through anhyd $MgSO_4$ and the ether was removed by rotary evaporation at 0°. Reductive cleavage and work up were performed as above. The (*R*)-(+), **8d**, was isolated by preparative TLC (SiO_2, 20 × 20 cm preabsorbent taper plate, 10 : 0.6 benzene–diethyl ether, R_f 0.64) yielding 55 mg (99%) with $[\alpha]_D^{25°} = +112.5°$ (*c* 0.96, $CHCl_3$) and 75% ee (ratio of *R* to *S* = 7.0:1). The purity of **8d** was determined by TLC and GLPC (retention time 22.8 min at 142°).

General method for the preparation of (R)-3-*substituted cyclohexanones*, **10**, *via zinc dibromide-mediated Grignard addition*

The preparation of (*R*)-3-substituted cyclohexanones, **10**, *via* $ZnBr_2$-mediated Grignard addition was identical to that of 3-substituted cyclopentanones except that sulfoxide **2b** was used instead of **2a**. See Table 3 for temps, times, and chromatographic properties. Also, see *Determination Enantiomeric purity of* **8** *and* **10**.

Preparation of (R)-(+)-*methylcyclohexanone*, **10a**, *via methyltitanium triisopropoxide conjugate addition*

A flame dried l-neck 10 mL round bottom flask equipped with serum cap, gas needle inlet, and a magnetic stirring bar was flushed with argon and charged with triisopropoxytitanium chloride[10,11] (0.75 mL, 1.4 Min THF, 1.1 mmol), then cooled to −78°. This soln then was treated with MeLi (0.75 mL, 1.4 M, 1.1 mmol) dropwise *via* a gas-tight syringe. the resultant soln was stirred at −78° for 15 min, and 1.0 mL anhyd THF was added slowly. To this bright yellow soln, sulfoxide **2b** (0.088 g, 0.35 mmol) in 1 mL anhyd THF was added dropwise. the soln was stirred at −78° for 1 hr, then was warmed to 0° and stirred for 2 hr; subsequent quenching with 0° 10% HClaq and rotary evaporation at 0° gave an aqueous concentrate. The remainder of the procedure was performed as described above to give (*R*)-(+)- **10a**, (32.2 mg, 82%). The sample for specific rotation was purified further by Kugelrohr distillation (40°, 10 mm Hg, −78° receiving bulb): $[\alpha]_{365}^{25°} = +171.0°$ (*c* 0.56, $CHCl_3$) with 97% ee. The product was pure by TLC (SiO_2, 10:0.6 benzene:diethyl ether, R_f 0.32) and GLPC (retention time 22.2 min, 120°). The diastereomeric ketal prepared from this 3-methylcyclohexanone had an optical purity of 96 ± 4% by ^{13}C NMR.

General procedure for the preparation of diastereomeric ketals, **9**

An oven dried 25 mL l-neck round bottom flask with stirring bar was charged with benzene, the appropriate 3-substituted cycloalkanone, 2 equivs of (*R*, *R*)-(−)-2,3-butanediol, and a catalytic amount of *p*-toluenesulfonic acid hydrate and equipped with an oven dried Dean-Stark trap with a condenser and N_2 inlet. The mixture was refluxed for 24 hr, allowed to cool to room temp, and the benzene removed by rotary evaporation. The residue was dissolved in pentane and washed with sat $NaHCO_3$aq and 5% $NaHSO_3$aq. The combined aqueous layers were back-extracted with pentane. The combined pentane layers were dried over K_2CO_3, filtered, and rotary evaporated. Preparative TLC (SiO_2, 20 cm × 20 cm × 100μ 175 : 1.5 benzene : ether, $R_f \sim 0.3$, the ketals have slightly higher R_fs than the ketones) gave the desired ketals, **9**. The optical purity of the diastereomeric ketals then was determined by ^{13}C NMR.[9]

Determination of enantiomeric purity of **8** *and* **10**

Compound **8a**. Enantiomeric purity of **8a** from **7a** was determined by ^{13}C NMR of the corresponding diastereomeric ketal: ^1H NMR (80 MHz, $CDCl_3$) δ 3.75–2.80 (m, 2 H), 2.50–1.20 (m, 15 H), 0.87 (t, J = 6 Hz, 3 H); IR ($CHCl_3$, cm^{-1}) 2980 (s), 1460 (m), 1380 (m), 1320 (m), 1105 (s); (Found: C, 71.91; H, 10.65. Calc for $C_{11}H_{20}O_2$: 71.70; H, 10.94). Relative integrations of the diastereotopic C resonances at 39.64 and 39.12 ppm in the ^{13}C NMR spectrum were used to determine the ratio of *R* : *S* at position 3. The enantiomeric purity of **8a** from **2a** was determined by specific rotation using $[\alpha]_D^{25°} = +116°$ ($CHCl_3$) for enantiomerically pure (*R*)-(+)-**8a** which was obtained by extrapolation of the ^{13}C NMR data.

Compound **8b**. $[\alpha]_D^{20°} = +186°$ ($CHCl_3$).[14]

Compounds **8c** and **8d**. Enantiomeric purity of **8c** and **8d** from **7a** were determined by ^{13}C NMR of the corresponding diastereomeric ketals: ^1H NMR (80 MHz, $CDCl_3$) δ 3.65–3.55 (m, 2 H), 2.20–1.05 (m, 15 H), 0.91 (s, 9 H); IR ($CHCl_3$, cm^{-1} 2950 (s), 1460 (w), 1366 (w), 1208 (w), 1110 (m), 975 (w), 918 (w); Found: C, 74.39; H, 11.49. Calcd for $C_{14}H_{26}O_2$: C, 74.29, H, 11.58%. Relative integrations of the diastereotopic resonances at 34.7384 and 34.2123 ppm in the ^{13}C NMR spectrum were used to obtain the ratio of *R*:*S* at position 3 of **8c** and **8d** from **7a**. The enantiomeric purity of **8c** and **8d** from **2a** was determined by specific rotation using an $[\alpha]_D^{25°} = +150.6°$ ($CHCl_3$) for enantiomerically pure (*R*)-(+)-**8c** which was obtained by extrapolation of the ^{13}C NMR data.

Compound **8e**. Enantiomeric purity of **8e** from **7a** was determined by ^{13}C NMR of the diastereomeric ketals: ^1H NMR (80 MHz, $CDCl_3$) δ 6.2–5.5 (m, 1 H), 5.3–4.8 (m, 2 H): 3.8–3.3 (m, 2 H), 2.5–1.1 (m, 15 H); IR ($CHCl_3$, cm^{-1}) 2975 (s), 1640 (w), 1440 (w), 1377 (w), 1318 (m), 1105 (s), 960 (w), 915 (m); Found: c, 73.56; H 10.23% Calc for $C_{12}H_{20}O_2$: C, 73.43: H, 10.27%. Relative integrations of the diastereotopic carbon resonances at 44.2670 and 43.9418, 40.0919 and 39.9010, or 29.9909 and 29.5508 ppm in the ^{13}C NMR spectrum were used to determine the ratio of *R*:*S* at position 3. The enantiomeric purity of **8e** from **2a** was determined by specific rotation using an $[\alpha]_D^{25°} = +125.4°$ ($CHCl_3$) for enantiomerically pure **8e** which was obtained by extrapolation of the ^{13}C NMR data.

Compound **8f**. Enantiomeric purity was determined from the diastereomeric ketals: ^1H NMR (80 MHz, $CDCl_3$) δ 7.10 (s, 4 H), 3.80-3.45 (m, 2 H), 3.45-2.92 (m, 1 H), 2.50-1.50 (m, 9 H), 1.40-0.91 (m, 6 H); IR ($CHCl_3$, cm^{-1} 2960 (s), 1515 (m), 1320 (m), 1100 (s), 980 (w), 915 (w), 820 (m); Found: C, 77,88; H, 9.01. Calc for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00%. Relative integrations of the diastereotopic carbon resonances at 42.62 and 43.08 ppm in the ^{13}C NMR spectrum were used to determine the ratio of *R*:*S* at position 3.

Compounds **10a** and **10b**. Enantiomeric purity was determined by specific rotation, $[\alpha]_{365°}^{25°} = +175.5°$ ($CHCl_3$, Aldrich Chemical Company).

Compound **10c**. Enantiomeric purity was determined from the diastereomeric ketals: ^1H NMR (80 MHz, $CDCl_3$) 3.90-3.50 (m, 2 H), 2.0-1.09 (m, 16 H), 0.85 (d, J = 6 Hz, 6 H); IR ($CHCl_3$, cm^{-1}) 2930 (s), 1450 (m), 1375 (m), 1100 (s); (Found: C, 73.28; H,11.48. Calc for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39%). Relative integrations of the diastereotopic C resonances at 23.26 and 22.86, 41.37 and 40.85, or 40.66 and 39.68 ppm in the ^{13}C NMR spectrum where used to determined the ratio of *R*:*S* at position 3.

Note added in proof: the very high enantiomeric purity of our synthetic (*R*)-3-methylcyclohexanone shown in Table 2 has been confirmed by Prof. V. Schurig and Dr. R. Weber

(University of Tubingen, West Germany) using complexation gas chromatography; using a 37-m Pyrex glass capillary column with nickel(II) bis[(1*R*)-3-(heptafluorobutyryl)-camphorate] as the chiral stationery phase, they have determined an enantiomeric purity of 97.1 ± 1% (68:1 ratio of enantiomers). We gratefully acknowledge their help.

Acknowledgements—Financial support from the National Science Foundation (CHE79-15161) is gratefully acknowledged. We thank The Johns Hopkins NMR facility and T. P. Kogan for WM-300 spectral data. We also thank the Middle Atlantic Mass Spectrometry Laboratory and C. A. Lisek for mass spectra.

REFERENCES

[1]G. H. Posner, J. P. Mallamo, K. Miura, *J. Am. Chem. Soc.* **103**, 2886 (1981).
[2]G. H. Posner, J. P. Mallamo, K. Miura and M. Hulce, *J. Org. Chem.* **46**, 5244 (1981).
[3]G. H. Posner, J. P. Mallamo, M. Hulce and L. L. Frye, *J. Am. Chem. Soc.* **104**, 4180 (1982).
[4]G. H. Posner, J. P. Mallamo, K. Miura and M. Hulce, *Asymmetric Carbon-Carbon Bond Formation Using Enantiomerically Pure Vinylic Sulfoxides*, in *Assymetric Reactions and Processes in Chemistry* (Edited by E. L. Eliel and S. Otsuka), pp. 139-154. American Chemical Society: Washington, D. C. (1982).
[5]K. K. Andersen, W. Gaffield, N. E. Papanikdaou, J. W. Foley and R. I. Perkins, *J. Am. Chem. Soc.* **86**, 5637 (1964).
[6]H. F. Herbrandson and R. T. Dickerson, Jr., *J. Am. Chem. Soc.* **81**, 4102 (1959).
[7]S. J. Branca and A. B. Smith III, *J. Am. Chem. Soc.* **100**, 7767 (1978).
[8]B. M. Trost, T. N. Salzmann and K. Hiroi, *J. Am. Chem. Soc.* **98**, 4887 (1976).
[9]H. Hiemstra and H. Wynberg, *Tetrahedron Letters* 2183 (1977).
[10]B. Weidmann, L. Wilder, A. G. Olivero, L. D. Maycock and D. Seebach, *Helv. Chim. Acta* **64**, 357 (1981).
[11]M. T. Reetz, R. Steinbach, J. Westermann and R. Peta, *Angew. Chem.* Int. Ed. Engl. **19**, 1011 (1980).
[12]W. G. Kofron and L. M. Baclawski *J. Org. Chem.* **41**, 1879 (1976).
[13]E. J. Corey L. O. Weigel, A. R. Chamberlin, H. Choand and D. H. Hua, *J. Am. Chem. Soc.* **102**, 6613 (1980).
[14]Y.-R. Naves, *Bull. Soc. Chim. France* 1372 (1958).