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N,S-DIMETHYL-S-PHENYLSULFOXIMINE

A REAGENT FOR THE OPTICAL RESOLUTION OF KETONES

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Abstract—The addition of the α-lithio derivative of (+)- or (−)-N,S-dimethyl-S-phenylsulfoximine to selected *dl*-ketones was carried out at −78° in tetrahydrofuran followed by acid quench at that temperature to produce mixtures of diastereomeric β-hydroxysulfoximines. The optically-active diastereomers were chromatographically separated on silica gel. The purified diastereomers were thermolyzed at *ca.* 130° to produce optically-active ketones and the optically-active sulfoximine which could be recycled.

Ketones are key substances in organic synthesis and represent an important class of biologically interesting molecules. Methods for the optical activation of ketones are rather limited.[1] Approaches which have been used include (1) modification of the CO functionality (e.g. reduction to alcohol)[2] to permit classical resolution, (2) utilization of CO-specific resolving agents such as "menthydrazide",[1] (3) resolution by chromatography using optically activated stationary phases,[3] and (4) asymmetric synthesis.[4] In this paper we provide the details of a ketone resolution technique based on the reversible addition of an optically pure sulfoximine **1** to selected chiral ketones **2** (Scheme 1).[5]

Ideal successes with this sulfoximine-mediated resolution scheme require that the following conditions be met:

(1) Diastereoface selective addition of the sulfoximine reagent to the CO group.

(2) Facile separation of the diastereomeric β-hydroxysulfoximines **3**.

(3) Efficient regeneration of the ketone **2** and resolving reagent **1**.

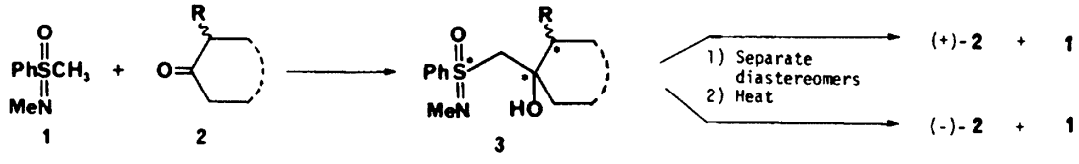
A discussion of each of the above factors as they pertain to the scheme at hand follows.

Addition. The non-stereoselective addition of resolved sulfoximine to a chiral *dl*-ketone will result in four optically active diastereomeric β-hydroxysulfoximines **3** which will greatly complicate the separation procedure. Ideally complete diastereoface selectivity should prevail as it would result in only two diastereomers. The two classes of ketones that are most likely to exhibit good diastereoface selectivity are substituted cycloalkanones and open-chain ketones bearing chelating substituents nearby the CO.

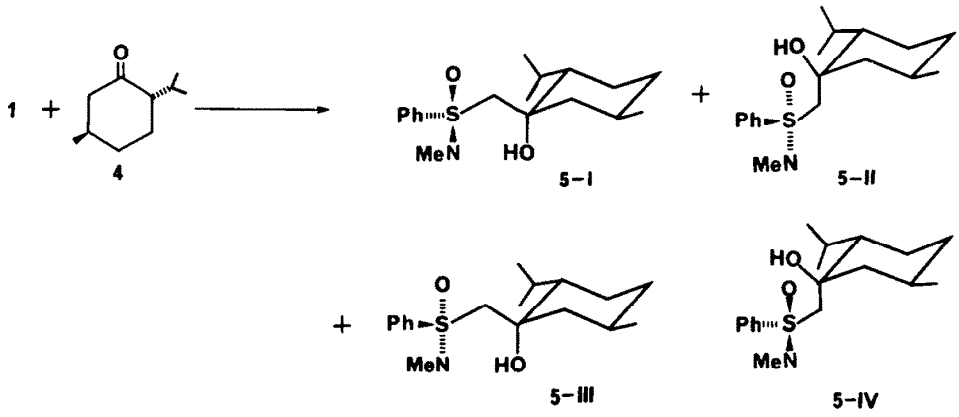
The stereoselectivity of the addition of nucleophiles to ketones can result from thermodynamic control, if the addition is reversible, or kinetic control, if the addition is irreversible. An investigation into the nature of the addition of *dl*-sulfoximine **1** to *l*-menthone (**4**) provides insight into the nature of the additions in question (Scheme 2). Analysis of the mixture from the addition carried out and quenched at −78° revealed that three diastereomers, **5**-I, **5**-II and **5**-III, were produced in a ratio of 5:1:4. (Throughout this paper the appended Roman numerals will refer to the order of elution of the various diastereomers from silica gel columns with I indicating the faster eluting diastereomer.)

The stereoselectivity at sulfur was determined by the rotation of the regenerated sulfoximine from the thermolysis of the purified diastereomers. Diastereomer **5**-I produced (−)-(*R*)-**1** while the other two gave the enantiomeric sulfoximine. The stereochemistry of the carbinol C was determined by Raney Ni hydrogenolysis of the C–S bond and comparison of the products with those known to be obtained by the addition of methylmagnesium iodide to menthone[6] (Scheme 3).

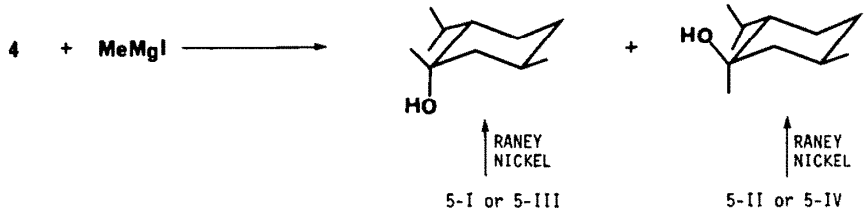
Treatment of each diastereomer with n-BuLi at −78° in tetrahydrofuran (THF), followed by quenching with acid resulted in quantitative recovery of the diastereomer unchanged. In contrast, treatment of each diastereomer with n-BuLi at 0° in THF followed by acid quench resulted in epimerization at the carbinol C and production of substantial amounts of sulfoximine and ketone. Diastereomer **5**-I gave rise to a new diastereomer (**5**-IV) resulting from the addition of (*R*)-**1** from the axial direction. Likewise, at 0°, **5**-II produces some **5**-III. This provides further proof that **5**-II and **5**-III differ only by being epimeric at the



Scheme 1



Scheme 2



Scheme 3

carbinol C. The production of sulfoximine **1** and menthone probably results from the enolization of the menthone by the lithiosulfoximine.

The above results indicate that addition of the lithiosulfoximine is kinetically controlled at −78°, that addition, at least to 2-substituted cyclohexanones, occurs preferentially from the equatorial direction, and that only one stereochemical combination of sulfoximine and ketone is sufficiently favorable to allow any axial addition to compete. The factors which influence the stereoface selectivity of irreversible nucleophilic additions to CO groups have been the subject of much debate during the past several decades:[7] discussion of these factors is beyond the scope of the present paper. The indication that significant enolization of ketones by the lithiosulfoximine reagents can occur at 0° provides an explanation for the generally higher yields of adducts which obtain when the addition and quench is carried out at lower temperatures.

During the course of our studies of the stereochemistry of addition of sulfoximine **1** to 2-substituted cyclohexanones we found that the ^{13}C NMR chemical shift of the S-methylene C was a consistent and reliable indicator of the stereochemistry of the adduct (Table 1). This is in accord with the general principle that all sterically crowded C's are found at higher field than similar C atoms not spacially crowded (steric compression shift).[8] In most cases, the stereochemical results presented in Table 1 were corroborated by Raney Ni desulfurization of the adduct to the known tertiary methyl carbinols.

As anticipated no problems were encountered in the addition of sulfoximine **1** to a variety of bicyclic ketones. With these envelope shaped molecules, nucleophiles generally add quite cleanly to the exo face of the CO. In each case that we examined in the present study only two diastereomers were formed.

As implied in the introductory remarks the addition of sulfoximine **1** to acyclic ketones would not be expected to occur with significant diastereoface selectivity. Still has shown, however, that the addition of alkylmagnesium reagents to acyclic α-alkoxy ketones proceeds with high diastereoface selectivity as a result of "chelation control". He has proposed that chelation of the Mg by the O atoms results in a stereochemically defined 5-membered ring.[9] A nucleophile would then be expected to approach the CO from the least hindered face. The addition of the Mg derivative of sulfoximine **1**, prepared by treatment of **1** with MeMgBr, to benzoin methyl ether resulted in the production of only two diastereomers, albeit in modest yield (40%). Higher yields of adducts were realized when the lithio reagent was employed, but the reaction produced three diastereomers.

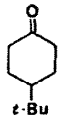
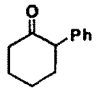
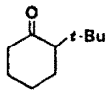
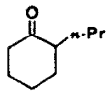
Separation of diastereomers. The success of the sulfoximine-mediated resolution of ketones depends on the chromatographic separation of the diastereomeric β-hydroxysulfoximines. Silica gel chromatography proved to be the most effective method for the separation of the diastereomers on both an analytical and preparative scale. An examination of the chromatographic data tabulated in Table 2 suggests two structural factors which seem to influence the chromatographic behavior of the adducts **3**. These factors are:

(1) Steric accessibility of the polar sulfoximine nitrogen and hydroxy groups on the diastereomers facilitate separation.

(2) Substitution proximate to the carbinol carbon improves chromatographic differentiation.

From a practical point of view, for the separation

Table 1. ^{13}C NMR chemical shifts of the S-methylene carbon of diastereomers 3 resulting from addition of 1 to various cyclohexanones 2

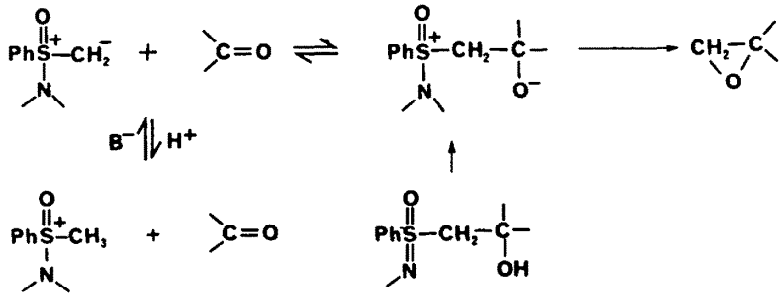
ketone	diastereomer no.[a]	chemical shift of methylene ppm[b]	direction of addition
	I	64.3	equatorial
	II	58.1	axial
	III	65.5	equatorial
	I	66.2	equatorial
	II	60.4	axial
	I	66.0	equatorial
	II	57.9	axial
	III	65.2	equatorial
	I	64.1	equatorial
	II	57.0	axial
	III	65.5	equatorial
	I	57.6	axial
	II	63.6	equatorial
	III	63.4	equatorial

[a] The numbers I, II, and III refer to the elution order of the diastereomers from silica gel. [b] Ppm downfield from tetramethylsilane in $CDCl_3$.

of gram-scale quantities of diastereomeric hydroxysulfoximines an α value greater than 1.3 is desirable. In Table 2, four of the ketone adducts (Entries 1–4) do not meet this requirement. Each of these ketones are bicyclic systems. The hydroxyl group resulting from the addition of the resolving agent from the exo face lies in the endo cavity of the adduct and is less accessible for interaction with the silica gel.

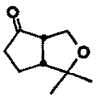
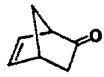
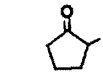
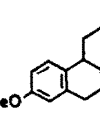
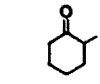
Studies are in progress in our laboratories aimed at delineating more clearly the effect of structural variation of the ketone and sulfoximine on the chromatographic separability of the adducts.

Regeneration of ketones. We have previously shown that betaines of the type shown in Scheme 4 revert to the sulfonium ylide and carbonyl compound.[10] Under appropriate conditions recombination can occur and can ultimately lead to the production of oxiranes in a typical sulfonium ylide reaction (Scheme 4). If the ylide is trapped by protonation the sulfonium salt and CO component can be quantitatively isolated. The prerequisite betaine can be generated by an alternate mode involving electrophilic activation at the sulfoximine N by a reagent such as trimethyloxonium tetrafluoroborate. In effect the same reaction pathway could be initiated thermally in the case of β-hydroxysulfoximines by the transfer of the OH proton to the sulfoximine N. Following proton transfer, reversion to the CO component and ylide would occur. In this case the ylide could self-quench by tautomerization to the sulfox-



Scheme 4

Table 2. Chromatographic data on diastereomers 3 resulting from the addition of sulfoximine 1 to ketones 2

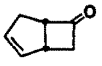
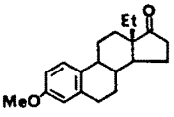
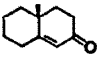
ketones 2	diastereomer 3 & retention time no.	(min)[a]	separation factor α^b	solvent % EtOAc in hexane
	I	2.3	1.09	80
	II	2.5		
	I	1.4	1.21	60
	II	1.7		
	I	2.4	1.25	50
	II	3.0		
	I	4.8	1.25	25
	II	6.0		
	I	2.3	2.0	15
	II	4.7		
	III (minor)	6.2		
	I	2.2	2.31	30
	II (minor)	2.7		
	III	5.1		
	I	1.6	3.31	25
	II	5.3		
	I	3.3	3.5	10
	II (minor)	3.9		
	III	11.2		
	I	2.7	3.96	25
	II (minor)	6.7		
	III	10.7		
	I	2.3	4.1	20
	II (minor)	2.9		
	III	9.5		
	I	3.0	4.4	15
	II (minor)	3.3		
	III	13.1		
	I	1.4	4.8	25
	II (minor)	2.3		
	III	6.3		

[a] HPLC using a duPont Zorbax Sil 5-6 μm steel column, 4.6 mm x 25 cm with a flow rate of 2 mL/min. Solvent front appeared at 1.7 min; the retention times shown are adjusted (actual retention time minus 1.7 min). [b] Separation factor α as used here is the ratio of adjusted retention times of the two major diastereomers.

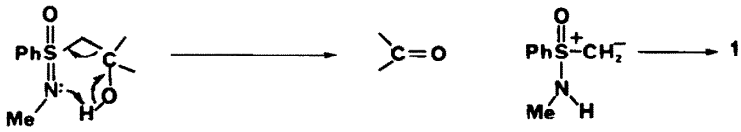
imine (Scheme 5). The exposure of purified optically-active β-hydroxysulfoximine diastereomers to temperatures in excess of 80° efficiently results in the production of their precursors with the ketone now in optically-active form.

The results of the sulfoximine-mediated resolution of ketones are listed in Table 3. The success of the resolution procedure depends on the stability of the ketone towards racemization during the thermolysis and workup procedures (see below). The β-hydroxysulfoximines were not recrystallized prior to their thermolysis; in the absence of racemization,

Table 3. Results of the sulfoximine-mediated ketone resolutions

ketone	addition yield, %	diastereomers no.	diastereomers yield, %[a]	thermolysis yield, %	[α] (temp(°C),concn,solv), deg.[b] Observed	[α] (temp(°C),concn,solv), deg.[b] Literature[c]
	86	I	56	93	+36.0(24.5,1,MeOH)[e]	
		II	12	98	-35.3(24.5,1,MeOH)[e]	
		III	20	73	-35.4(24.5,1,MeOH)[e]	
	98	I	37	94	+112.5(26,0.6,PhH)	+114.7(25,.45,PhH)
		II	16	81	-59.3(26,0.6,PhH)	
		III	29	88	-112.0(26,0.6,PhH)	
	98	I	49	89	+26.5(27,2,$CHCl_3$)	
		II	9			
		III	33	88	-27.5(27,2,$CHCl_3$)	-29.5(27,2,$CHCl_3$)
	95	I	18			
		II	31	35	-26.9(25,1.8,MeOH)	-27.9(25,1.8,MeOH)
		III	18			
	90	I	40			+592 (ns,ns,$CHCl_3$)
		II	32	50[d]	-1135.7(28,0.7,$CHCl_3$)[f]	
	98	I	25	80	-64.3(25,0.6,$CHCl_3$)	
		II	23	98	+59.6(25,1.3,$CHCl_3$)	
	96	I	48	48	+106.4(25,1,1:1 MeOH/$CHCl_3$)	
		II	37	61	-104.4(25,1,1:1 MeOH/$CHCl_3$)	-102.5 (25,1,1:1 MeOH/$CHCl_3$)
	91	I	42	98	-207.0(24,1,EtOH)[e]	
		II	21	84	+208.3(24,1,EtOH)[e]	+25(ns,1,EtOH)
	98	I	38	96	+52.8(19,0.6,PhH)	+50.9(15,0.6,PhH)
		II	8			
		III	31	93	-51.5(20,0.6,PhH)	
	76	I	15	88	-23.8(28,0.7,toluene)	
		II				
		III	21	88	+4.0((28,1,toluene)	+4440(28,0.7,toluene)

[a]After chromatography, % yield of pure diastereomer. [b]Concentration given in g/100mL; ns=not specified. [c]See literature citations under individual compounds in experimental section. [d]Low yield due to loss of volatile ketone. [e]Sulfoximine of 99% ee was employed; rotations of ketones are not adjusted. [f]Sulfoximine of 95% ee was employed; rotations are not adjusted.



Scheme 5

the optical rotation of the ketones should reflect the optical purity of the starting sulfoximine provided that chromatographic separation was complete.

The thermolysis of β-hydroxysulfoximines which resulted in the production of volatile ketones was accomplished by placing the purified diastereomer without solvent in a Kuglerohr apparatus under vacuum at a preset oven temperature; the ketone distilled as it formed. Diastereomers resulting in the production of non-volatile ketones were thermolyzed in a refluxing solvent or by heating them neat under an argon atmosphere for a brief period. The latter method is preferable. Separation of the sulfoximine and the ketone was accomplished by extraction of the sulfoximine into aqueous mineral acid or aqueous copper(II) nitrate or by percolation through a silica gel column which retained the sulfoximine. The sulfoximine can be recovered in all cases in unchanged optical purity and recycled. Several of the ketones in Table 3 warrant special mention.

Although 2-*t*-butylcyclohexanone has not been previously reported in optically active form, the optical purity of our sample is assumed to be *ca* 98% or better. This assumption is based on the criteria that the precursor hydroxysulfoximines were shown to be pure compounds by analytical HPLC and by ^1H and ^{13}C NMR and the consistency of the observed rotation of the two enantiomers. One might anticipate that for steric reasons this ketone would not readily racemize. The rotation of bicyclo[3.2.0]hept-5-en-one has not been previously reported although it has been prepared in optically active form by enantioselective reduction by yeast and reoxidation.[11] The very high volatility of this ketone made purification of small amounts of material difficult and the discrepancies of the rotations reported in Table 3 are believed to reflect chemical rather than optical purity.

The optical purity of 2-phenylcyclohexanone was found to depend on the condition employed during the thermolysis. Thermolysis at 150° with distillation of the ketone followed by chromatographic removal of the sulfoximine resulted in a 96% yield of ketone of 78% optical purity. In control experiments it was shown that neither distillation of the ketone at 150° (25 mm Hg) nor chromatography on silica gel had an effect on its optical purity. However, when the ketone was distilled in the presence of an equimolar amount of sulfoximine its optical purity significantly decreased (78% to 68%). It appears that in the case of this rather sensitive ketone, the sulfoximine is a sufficient base to catalyze racemization. By dropping the temperature and pressure to 110° and 1 mm Hg the products distilled as they formed and the results was 2-phenylcyclohexanone of *ca* 97% optical purity. The more sensitive 2-phenylcyclopentanone was almost completely racemized under all conditions conducive to thermolysis of the prerequisite hydroxysulfoximine.

CONCLUSION

The method herein described can be applied to the resolution of a variety of ketones. The method is best suited to those ketones which exhibit high diastereoface selectivity in the addition of sulfoximine reagent. A significant advantage inherent in the method is the rapidity with which the ultimate success of a resolution can be predicted. Chromatographic examination (TLC or HPLC on silica gel) of small-scale addition of racemic **1** to racemic ketone,[12] optically-pure **1** to racemic ketone, or racemic **1** to an optically pure ketone will reveal the number and separability of the various diastereomers. The method has reciprocity and a number of ketones, particularly *l*-menthone, have been used to resolve *dl*-**1**. Results of these and related studies will be presented in a future paper.

EXPERIMENTAL

General procedure for the preparation of β-hydroxysulfoximines

A soln of n-BuLi in n-hexane (10 mmol, 1.6 M) was added to a soln of N,S-dimethyl-S-phenylsulfoximine[13] (1.7 g, 10 mmol) in dry THF (35 mL) maintained at 0°. After stirring at room temp for 15 min, the yellow soln was cooled to −78° and the ketone (10 mmol) in dry THF (10 mL) was added over 5 min. The mixture was allowed to stir for 45 min at −78°. The cold mixture was poured into a mixture of diethyl ether (50 mL) and saturated NH_4Cl aq (25 mL). The mixture was shaken vigorously and the layers were separated. The aqueous layer was extracted twice with 10-mL portions of diethyl ether and the combined organic layers were dried over $MgSO_4$, filtered and concentrated on a rotary evaporator.

The diastereomeric hydroxysulfoximines resulting from addition of sulfoximine to chiral ketones will be referred to throughout the experimental section as follows: diastereomer I—the fastest moving diastereomer on silica gel, diastereomer II—the second fastest moving diastereomer, etc.

Chromatography of β-hydroxysulfoximines

Analytical TLC was performed on silica gel plates (0.25 mm, EM Reagents). Flash chromatography[14] was effected using Silica Gel 60 (230–400 mesh, EM Reagents). Medium pressure liquid chromatography (MPLC) was performed with the above silica gel using various sizes of Michel–Miller columns (Ace Glass) and Milton Roy pumps with flow rates up to 50 mL/min. Analytical HPLC was accomplished using a Varian Associates Model 5000 HPLC with a duPont Zorbax Sil 5–6 μm steel column (4.6 mm × 25 cm).

General procedures for the thermolysis of β-hydroxysulfoximines

Method A (Volatile ketones): The hydroxysulfoximine was added to a flask fitted with a Kuglerohr collection tube and attached to a vacuum line. The collection tube was cooled to −78° and the apparatus was placed in a Kuglerohr oven preheated to the desired temp (usually 130°). The products distilled as they were formed and were separated by extraction of the N,S-dimethyl-S-phenylsulfoximine into aqueous 6N H_2SO_4, aqueous copper(II) nitrate, or by percolation through silica gel.

Method B (Non-volatile ketones): The hydroxysulfoximine was refluxed in 2-BuOH until TLC analysis indicated complete thermolysis. The solvent was removed on the rotary evaporator and the sulfoximine and ketone were separated as described under Method A.

Method C (Non-volatile ketones): The hydroxysulfoximine, in a Kuglerohr tube under an argon atmosphere, was placed in an oven preheated to 130° until thermolysis was complete (5–10 min). Workup was completed as described under Method A.

Resolution of 2-t-Butylcyclohexanone

The addition of (+)-(S)-N,S-dimethyl-S-phenylsulfoximine (1) (1.0 g, 5.85 mmol, 99% ee)[13] to 2-t-butylcyclohexanone (0.9 g, 5.85 mmol,) yielded a mixture of diastereomers (1.63 g, 86%). Analytical HPLC (10% EtOAc in n-hexane, 2 mL/min) revealed three diastereomers: diastereomer I, 5.1 min, 61%; diastereomer II, 5.8 min, 22%; diastereomer III, 13.5 min, 17%. MPLC with elution with 8% EtOAc in hexanes yielded 1.3 g of a mixture of diastereomer I and II and 0.33 g of pure diastereomer III. Rechromatography of the mixture using 49% dichloromethane/49% n-hexane/2% EtOAc gave 0.92 g of diastereomer I and 0.21 g of diastereomer II.

Diastereomer I: m.p. 123–125°; ^{13}C NMR ($CDCl_3$) δ 66.09 (S-CH_2); $[\alpha]_D^{25} = +57.8°$ (*c*, 1.0, EtOH); (Found C 67.06 H 8.81. Calc for $C_{18}H_{29}NO_2S$: C 66.87 H 8.98%).

Diastereomer II: m.p. 121–122°; ^{13}C NMR ($CDCl_3$) δ 57.89 (S–CH_2); $[\alpha]_D^{24.5} = +45.9°$ (*c*, 0.95, EtOH); (Found C 66.81 H 8.96. Calc for $C_{18}H_{29}NO_2S$: C 66.87 H 8.98%).

Diastereomer III: m.p. 87–88°; ^{13}C NMR ($CDCl_3$) δ 65.16 (S–CH_2); $[\alpha]_D^{24.5} = +12.6°$ (*c*, 1.56, EtOH); (Found C 66.69 H 9.04. Calc for $C_{18}H_{29}NO_2S$: C 66.87 H 8.98%).

Thermolysis of the above diastereomers using Method A and separation of the products by flash chromatography gave optically active 2-t-butylcyclohexanone. From diastereomer I: 93%; $[\alpha]_D^{24.5} = +36.0°$ (*c*, 1.0, MeOH). From diastereomer II: 98%; $[\alpha]_D^{24.5} = -35.3°$ (*c*, 1.0, MeOH). From diastereomer III: 73%; $[\alpha]_D^{24.5} = 35.4°$ (*c*, 1.0, MeOH). Spectroscopic data and chromatographic behavior of the optically active samples were identical to those of the racemic ketone.

Resolution of 2-phenylcyclohexanone

The addition of (+)-S-1 (1.7 g, 10 mmol, 95% ee) to 2-phenylcyclohexanone (1.7 g, 10 mmol) yielded a mixture of diastereomers (3.4 g, 98%). Analytical HPLC (20% EtOAc in n-hexane, 2 mL/min) revealed three diastereomers: diastereomer I, 4.0 min, 57%; diastereomer II, 4.6 min, 25%; diastereomer III, 11.2 min, 18%. MPLC with 10% EtOAc in n-hexane gave 1.0 g of pure diastereomer III and 2.2 g of a mixture of I and II. Rechromatography of the mixture using 24% dichloromethane/73% n-hexane/3% EtOAc yielded 1.3 g of pure diastereomer I, 0.57 g of II, and 0.23 g of a mixture of the two.

Diastereomer I: m.p. 109–111°; ^{13}C NMR ($CDCl_3$) δ 64.1 (S–CH_2); $[\alpha]_D^{26} = +66.3°$ (*c*, 1.0, $CHCl_3$). (Found: C 70.17 H 7.28. Calc for $C_{20}3H_{25}NO_2S$: C 69.95 H 7.31%).

Diastereomer II: m.p. 173–174°; ^{13} CNMR ($CDCl_3$) δ 57.0 (S–CH_2); $[\alpha]_D^{26} = +93.1°$ (*c*, 1.0, $CHCl_3$). (Found: C 69.79 H 7.28. Calc for $C_{20}H_{25}NO_2S$: C 69.95 H 7.31%).

Diastereomer III: m.p. 170–171°; ^{13}C NMR ($CDCl_3$) δ 65.5 (S–CH_2); $[\alpha]_D^{26} = +37.4°$ (*c*, 1.0, $CHCl_3$). (Found: C 69.42 H 7.49. Calc for $C_{20}H_{25}NO_2S$: C 69.95 H 7.31%).

Diastereomer I (0.8 g, 2.4 mmol) under a vacuum of 1 torr was placed in a Kugelrohr oven preheated to 110° The products distilled over after 5 min. The distillate was dissolved in n-pentane (30 mL) and washed with saturated aqueous copper(II) nitrate soln (2 × 20 mL) and water (10 mL).

The n-pentane layer was dried over $MgSO_4$ and the solvent was removed under vacuum at room temp to provide (+)-2-phenylcyclohexanone (0.38 g, 94%) as a white crystalline solid; m.p. 41–42°; $[\alpha]_D^{24} = +112.5°$ (*c*, 0.5, benzene) (lit.[15] m.p. 38–39°; $[\alpha]_D^{24} = +114.7°$ (*c*, 0.5, benzene).

Diastereomers II and III were thermolyzed in like manner but were purified by flash chromatography using 20% EtOAc in n-hexane. The ketone from II, obtained in 81% yield, had m.p. 37-39° and $[\alpha]_D^{24} = -59.3°$ (*c*, 0.6, benzene). The ketone from III, obtained in 88% yield, had m.p. 38–39° and $[\alpha]_D^{24} = -112°$ (*c*, 0.6, benzene).

Resolution of menthone

The condensation of *dl*-menthone and (+)-(S)-1 was effected in 98% yield on a 10 mmol scale. Analytical HPLC (15% EtOAc in n-hexane, 2 mL/min) revealed three diastereomers: diastereomer I, 3.0 min, 50%; diastereomer II, 3.3 min, 10%; diastereomer III, 13.1 min, 40%. MPLC with 10% EtOAc in n-hexane gave 1.1 g of pure diastereomer III and 2.3 g of a mixture of I and II. Rechromatography of the mixture using 49% dichloromethane/49% n-hexane/2% EtOAc yielded 1.6 g of pure diastereomer I, and 0.6 g of diastereomer II.

Diastereomer I: m.p. 147–149°; ^{13}C NMR ($CDCl_3$) δ 64.3 (S–CH_2); $[\alpha]_D^{25} = +66.5°$ (*c*, 1.0, $CHCl_3$).

Diastereomer II: m.p. 120–122°; ^{13}C NMR ($CDCl_3$) δ 58.1 (S–CH_2); $[\alpha]_D^{25} = +0.87°$ (*c*, 1.0, $CHCl_3$).

Diastereomer III: m.p. 113–115°; ^{13}C NMR ($CDCl_3$) δ 65.5 (S–CH_2); $[\alpha]_D^{25} = +53.5°$ (*c*, 1.0, $CHCl_3$).

Diastereomer I, upon thermolysis at 140°, gave menthone (89%) with $[\alpha]_D^{27} = +26.5°$ (*c*, 2.0, $CHCl_3$). Diastereomer III gave the enantiomer (91%) with $[\alpha]_D^{27} = -27.5°$ (*c*, 2.0, $CHCl_2$). Menthone obtained in our laboratories from the oxidation of menthol had $[\alpha]_D^{27} = -29.5°$ (*c*, 2.0, $CHCl_3$).

Resolution of 2-propylcyclohexanone

The addition of (−)-(R)-1 (99% ee) to 2-propylcyclohexanone (10 mmol) gave a mixture of diastereomers in 95% yield. Analytical HPLC (25% EtOAc in n-hexane) revealed diastereomer I (3 min, 25%), diastereomer II (4 min, 50%) and diastereomer III (8 min, 25%). MPLC with 10% EtOAc in hexanes separated the diastereomers on a preparative scale.

Diastereomer I: m.p. 47–49°; ^{13}C NMR ($CDCl_3$) δ 57.6 (S–CH_2); (Found: C 65.85 H 8.56. Calc for $C_{17}H_{27}NO_2S$: C 66.04 H 8.74%).

Diastereomer II: m.p. 87–89°; $[\alpha]_D^{24.5} = -73.6°$ (*c*, 1.0, $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 63.6 (S–CH_2); (Found: C 66.15 H 8.74. Calc for $C_{17}H_{27}NO_{23}S$: C 66.04 H 8.74%).

Diastereomer III: m.p. 80–81°; ^{13}C NMR ($CDCl_3$) δ 63.4 (S–CH_2); (Found: C 65.91 H 8.72. Calc for $C_{17}H_{27}NO_2S$: C 66.04 8.74%).

Diastereomer II (0.8 g, 2.6 mmol) was subjected to a vacuum of 15 torr and placed in a Kuglerohr oven preheated to 90°. The distillate was dissolved in n-pentane and the soln was extracted with copper(II) nitrate soln. Completion of the workup yielded (−)-2-propylcyclohexanone (0.125 g, 35%) as a colorless liquid; $[\alpha]_D^{25} = -26.9°$ (*c*, 1.8, MeOH) (lit.[16] $[\alpha]_D^{25} = -27.9°$ (*c*, 1.8, MeOH). The low yield was a result of loss of product due to high volatility.

Resolution of bicyclo[2.2.1]hept-5-en-2-one

The addition of (+)-(S)-1 (1.7 g, 10 mmol), 95% ee) to bicyclo[2.2.1]hept-5-en-2-one (1.08 g, 10 mmol) have 2.5 g (90%) of a 1:1 mixture of diastereomers (HPLC) with 45% EtOAc in n-hexane: 4.8 min and 5.2 min). MPLC with 30% EtOAc in hexanes gave 1.1 g of pure I, 0.87 g of pure II along with 0.51 g of a mixture of the two.

Diastereomer I: a gum, ^{13}C NMR ($CDCl_3$) δ 66.3 (S–CH_2).

Diastereomer II: m.p. 85–85.5°; ^{13}C NMR ($CDCl_3$) δ 64.9 (S–CH_2); $[\alpha]_D^{25} = -63.8°$ (*c*, 1.2, $CHCl_3$); (Found: C 65.11 H 6.73. Calc for $C_{15}H_{19}NO_2S$: C 65.00 H 6.86%).

Diastereomer II (0.75 g, 2.7 mmol) at 15 torr pressure was placed in a Kugelrohr oven preheated to 120°. After 5 min, the products which had collected were dissolved in diethyl

ether (50 mL). The soln was extracted with two 10-mL portions of 6N H_2SO_4 and one 10-mL portion of $NaHCO_3$ aq. The ether layer was dried over $MgSO_4$ and the solvent was removed at room temp under vacuum. The ketone was obtained as a low melting, volatile solid (m.p. < 25°)(0.14 g, 50%); $[\alpha]_D^{28} = -1135.7$ (*c*, 0.7, $CHCl_3$) (lit.[17] $[\alpha]_D^{28} = +592°$ ($CHCl_3$) for material believed to be 47% optically pure).

Resolution of bicyclo[3.2.1]*hept-2-en-6-one*

The addition of (+)-(S)-**1** (1.7 g, 10 mmol) to bicyclo[3.2.1]hept-2-en-6-one (1.08 g, 10 mmol) gave 2.7 g (98%) of a 1:1 mixture of diastereomers (HPLC with 60% EtOAc in n-hexane: 3.1 min and 3.4 min). MPLC with 30% EtOAc in n-hexane gave 0.68 g of pure I, 0.63 g of pure II along with 0.1.1 g of a mixture of the two.

Diastereomer I: m.p. 94–97°; $[\alpha]_D^{25} = -105.6°$ (*c*, 0.6, $CHCl_3$); (Found: C 65.09 H 7.02. Calc for $C_{15}H_{19}NO_2S$: C 65.00 H 6.86%).

Diastereomer II: a gum; $[\alpha]_D^{25} = -42.8°$ (*c*, 1.0, $CHCl_3$); (Found: C 64.91 H 6.95. Calc for $C_{15}H_{19}NO_2S$: C 65.00 H 6.86%).

Diastereomer I was thermolyzed at 130° and 25 torr and the ketone was isolated (80%) by flash chromatography as a clear liquid, $[\alpha]_D^{25} = -64.3°$ (*c*, 0.64, $CHCl_3$). Diastereomer II under identical conditions gave the enantiomeric ketone (98%), $[\alpha]_D^{25} = +59.6°$ (*c*, 1.3, $CHCl_3$).

Resolution of 13-*ethyl*-3-*ethoxygona*-1,3,5(10)-*trien*-17-*one*

The addition of (−)-(R)-**1** (0.96 g, 5.6 mmol, 99% ee) to the *dl* form of the title ketone (1.7 g, 5.6 mmol) yielded a mixture of two diastereomers. Diastereomer I eluted in 3.3 min and diastereomer II in 7.0 min on HPLC with 25% EtOAc in n-hexane. Separation by MPLC with 17% EtOAc in hexanes resulted in 1.4 g of diastereomer I and 1.0 g of diastereomer II.

Diastereomer I: m.p. 146–147°; $[\alpha]_D^{24} = +18.2°$ (*c*, 0.64, acetone); (Found: C 71.94 H 7.78. Calc for $C_{28}H_{37}NO_3S$: C 71.91 H 7.97%).

Diastereomer II: m.p. 152–153°; $[\alpha]_D^{26} = -54.8°$ (*c*, 1.0, acetone); (Found: C 71.88 H 8.04. Calc for $C_{28}H_{37}NO_3S$: C 71.91 H 7.97%).

Diastereomer I (1.3 g, 2.8 mmol) was dissolved in 25 mL of 2-BuOH and refluxed (98°) overnight. The alcohol was removed with a rotary evaporator. The residue was dissolved in diethyl ether (75 mL) and extracted with 6N HSO_4 (2 × 20 mL) and then washed with 10 mL sat $NaHCO_3$ aq. The ether layer was dried over $MgSO_4$ and the ether removed to yield 0.72 g (86%) of crude product which was further purified by flash chromatography to give 0.40 g of the (+)-ketone as white crystals, m.p. 145–147°; $[\alpha]_D^{25} = +106.4°$ (*c*, 1.0, 50% MeOH in $CHCl_3$).

In a similar fashion diastereomer II gave (−)-ketone as white crystals (61%): m.p. 145–147°; $[\alpha]_D^{25} = -104.4°$ (*c*, 1.0, 50% MeOH in $CHCl_3$) {lit.[18] m.p. 146–148°; $[\alpha]_D^{25} = -102.5°$ (*c*, 1.0, 50% MeOH in $CHCl_3$)}

Resolution of 4a-*methyl*-4,4a,5,6,7,8-*hexahydro*-2(3H)-*napthalenone*

The addition of (+)-(S)-**1** (1.7 g, 10 mmol), 98% ee) to the title ketone (1.64 g, 10 mmol) yielded 3.0 g (91%) of a mixture. HPLC (15% EtOAc in n-hexane) revealed two major diastereomers eluting at 4.0 min and 6.4 min. MPLC of the mixture with 10% EtOAc in n-hexane resulted in 1.25 g of pure diastereomer I and diastereomer II which was contaminated with a slower eluting compound (not characterized). Recrystallization of this mixture from pentane/diethyl ether resulted in 0.63 g of pure diastereomer II.

Diastereomer I: white crystals, m.p. 121–123°; ^{13}C NMR ($CDCl_3$) δ 62.4 (S–CH_2); $[\alpha]_D^{23.5} = -159.7°$ (*c*, 1.0, $CHCl_3$); (Found: C 68.58 H 8.32. Calc for $C_{19}H_{27}NO_2S$: C 68.49 H 8.10%).

Diastereomer II: white crystals, m.p. 153–154°; ^{13}C NMR ($CDCl_3$) δ 65.3 (S–CH_2); $[\alpha]_D^{23} = +102.4°$ (*c*, 1.0, $CHCl_3$); (Found: C 68.50 H 8.20. Calc for $C_{19}H_{27}NO_2S$: C 68.49 H 8.10%).

Diastereomer I (1.25 g, 3.8 mmol) was thermolyzed at 160° and 25 torr for 5 min. The distillate was dissolved in n-pentane and washed with 6N H_2SO_4 followed by $NaHCO_3$ aq. Optically active (−)-ketone (0.61 g, 98%) was obtained as a colorless liquid; $[\alpha]_D^{24} = -207.0°$ (*c*, 1.1, EtOH).

In a similar fashion diastereomer II (0.66 g, 0.2 mmol) yielded 0.27 g (84%) of the (+)-ketone; $[\alpha]_D^{24} = +208.3°$ (*c*, 1.0, EtOH) {lit.[19] $[\alpha]_D = +25°$ (*c*, 1.0, EtOH)}.

Resolution of 2-*methoxy*-1,2-*diphenylethanone*

The addition of (+)-(S)-**1** (99% ee) to 2-methoxy-1,2-diphenylethanone (benzoin methyl ether) on a 10 mmol scale gave a mixture of diastereomers (98% yield). HPLC (25% EtOAc in n-hexane) revealed three diastereomers: diastereomer I, 4.4 min, 50%; diastereomer II, 8.4 min, 10%; diastereomer III, 12.4 min, 40%. Separation by MPLC (12% EtOAc in n-hexane) afforded 1.5 g of diastereomer I, 0.3 g of diastereomer II, and 1.2 g of diastereomer III.

Diastereomer I: white crystals, m.p. 126–127.5°; $[\alpha]_D^{25} = +64.8°$ (*c*, 0.9, $CHCl_3$); (Found: C 69.93 H 6.17. Calc for $C_{23}H_{25}NO_3S$: C 69.85 H 6.32%).

Diastereomer II: white crystals, m.p. 151–152.5°; (Found: C 70.00 H 6.38. Calc for $C_{23}H_{25}NO_3S$: C 69.85 H 6.32%).

Diastereomer III: white crystals, m.p. 133–134°; $[\alpha]_D^{25} = +31.5°$ (*c*, 0.9, $CHCl_3$); (Found: C 69.56 H 6.51. Calc for $C_{23}H_{25}NO_3S$: C 69.85 H 6.32%).

Diastereomer I (1.3 g) was thermolyzed under an argon atmosphere at 105° for 8 min. The mixture was dissolved in diethyl ether (50 mL) and washed with 6N H_2SO_4 (10 mL) and water (2 × 10 mL). The ether layer was dried over $MgSO_4$ and concentrated to yield the resolved ketone (96%): m.p. 43–46°; $[\alpha]_D^{15} = +52.8°$ (*c*, 0.6, benzene) {lit.[20] $[\alpha]_D^{15} = +50.9°$ (*c*, 0.6, benzene)}.

In a like manner diastereomer III afforded the enantiomeric ketone: m.p. 44–45°; $[\alpha]_D^{20} = -51.5°$ (*c*, 0.6, benzene).

Resolution of 2-*phenylcyclopentanone*

The addition of (+)-(S)-**1** was achieved in 76% yield. HPLC (30% EtOAc in n-hexane) revealed diastereomers at 3.9 min (50%) 4.4 min (10%), and 6.8 min (40%). MPLC with 25% EtOAc in n-hexane afforded pure diastereomer III and a mixture of I and II. Recrystallization of the mixture from dichloromethane gave material which was 98% diastereomer I.

Diastereomer I: m.p. 120° (dec); $[\alpha]_D^{25} = -94.4°$ (*c*, 1.0, $CHCl_3$); (Found: C 69.36 H 6.88. Calc for $C_{19}H_{23}NO_2S$: C 69.32 H 6.99%).

Diastereomer III: m.p. 92–96°; $[\alpha]_D^{25} = -38.2°$ (*c*, 0.9, $CHCl_3$); (Found: C 69.45 H 7.18. Calc for $C_{19}H_{23}NO_2S$: C 69.32 H 6.99%).

Thermolysis of diastereomer I at 130° and 10 torr afforded (−)-2-phenylcyclohexanone as a low melting solid (m.p. *ca* 28°); $[\alpha]_D^{28} = -23.8°$ (*c*, 0.7, toluene). From diastereomer III, (+)-2-phenylcyclopentanone with $[\alpha]_D^{28} = +4°$ (*c*, 1.0, toluene) {lit.[21] $[\alpha]_D^{28} = +4440°$ (*c*, 0.7, toluene)} was obtained. Control experiments revealed that the sulfoximine produced in the thermolysis was sufficiently basic to catalyze the racemization of this sensitive ketone.

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