General Method for Asymmetric Synthesis of α-Methylsulfinyl Ketones: Application to the Synthesis of Optically Pure Oxisuran and Bioisosteres

H. El Ouazzani,[†] N. Khiar,*[,†,‡] I. Fernández,*[,†] and F. Alcudia[†]

Departamento de Química Orgánica y Farmacéutica, Facultad de Farmacia, Universidad de Sevilla, 41071 Seville, Spain, and Instituto de Investigaciones Químicas, C.S.I.C., Isla de la Cartuja, Seville, Spain

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The first asymmetric synthesis of oxisuran [**1**, (methylsulfinyl)methyl 2-pyridyl ketone], a synthetic immunosuppressive drug, is described. Both enantiomers were efficiently synthesized, in optically pure form, using DAG methodology for the key condensation step. Attempts to couple metal enolates of aryl methyl ketones with chiral sulfinyl compounds led to some epimerization at sulfur. This loss of chirality was circumvented by reacting the α-lithio derivatives of the *N*,*N*-dimethylhydrazones derived from these ketones with either the (*R*)- or the (*S*)-methanesulfinate of diacetone D-glucose, to yield the corresponding α-(methylsulfinyl)methylhydrazones, with complete inversion of chirality at sulfur. Hydrolysis of the resulting hydrazones with copper(II) chloride gave **1** in optically pure form. The generality of the method was demonstrated by the preparation of the optically active oxisuran analogs, **2**−**4**, in which the pyridyl moiety was replaced by phenyl, furyl, and thienyl moieties, respectively. The optical purities of these products were determined by proton NMR spectroscopy, using chiral shift reagents, following conditions established by the study of racemic mixtures of the *β*-keto sulfoxides.

Introduction

The use of optically pure sulfoxides as chiral controllers in highly asymmetric syntheses is now a reliable method, as shown by the large number of publications and monographs which appear each year.[1] In the rich chemistry of sulfoxides, *β*-keto sulfoxides occupy a place of prominence[2] as a result of Solladie's work on their stereoselective reduction which can afford either diastereoisomer under appropriate conditions.[3] The synthesis of chiral *β*-keto sulfoxides is generally achieved by the condensation of an α-sulfinyl anion (generally the (−)-(*R*)-*p*-tolyl methylsulfinyl anion) and an ester[4] (Scheme 1). However, neither cyclic *β*-keto sulfoxides nor other *β*-keto sulfoxides with a chiral methylsulfinyl group (Figure 1, compounds **A** and **B,** respectively) are accessible in this way.

To access these kinds of molecules, a straightforward route is the Andersen-type reaction of an enolate, or an enolate-like species, with a chiral nonracemic sulfinate ester. This idealized picture is complicated by the finding

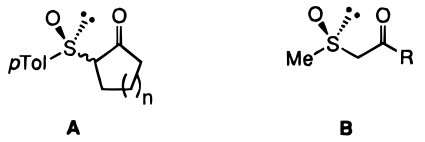
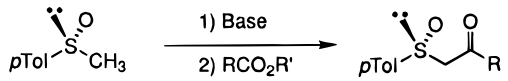


Figure 1.

Scheme 1



that this reaction occurs with epimerization at the sulfinyl sulfur. In the case of compounds of type **A** (Figure 1), this problem has been solved either by using an acid-catalyzed reaction of an enol silyl ether of a cyclic ketone with optically active menthyl *p*-toluenesulfinate,[5] or by using a magnesium enolate instead of the lithium enolate of a cyclic ketone with (−)-(*S*)-*O*-menthyl *p*-toluenesulfinate.[6] In the case of type **B** compounds, there is an additional challenge due to the chiral methyl sulfoxide, as in the classical Andersen synthesis where *O*-menthyl methanesulfinates cannot be obtained in optically pure form.[7] This explains the lack, until now, of methods leading to *β*-keto sulfoxides bearing a chiral nonracemic methylsulfinyl group.

In this paper we report a general method for the synthesis of *β*-keto sulfoxides of type **B**, making use of the DAG (diacetone D-glucose) methodology recently developed by us.[8] As an application, we report the first

† Universidad de Sevilla.

‡ Instituto de Investigaciones.

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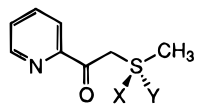
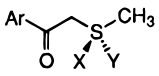


OXISURAN

X	Y	Compound
••	O	(S)-**1**
O	••	(R)-**1**



OXISURAN BIOISOSTERS

Ar	X	Y	Compound
Ph	••	O	(S)-**2**
Ph	O	••	(R)-**2**
2-Furyl	••	O	(S)-**3**
2-Furyl	O	••	(R)-**3**
2-Thienyl	••	O	(S)-**4**
2-Thienyl	O	••	(R)-**4**

Figure 2.

asymmetric synthesis of both *R* and *S* isomers of oxisuran and various related bioisosteres **2**−**4** where the pyridine ring has been replaced by another aromatic ring (benzene, furan, thiophene) (Figure 2).

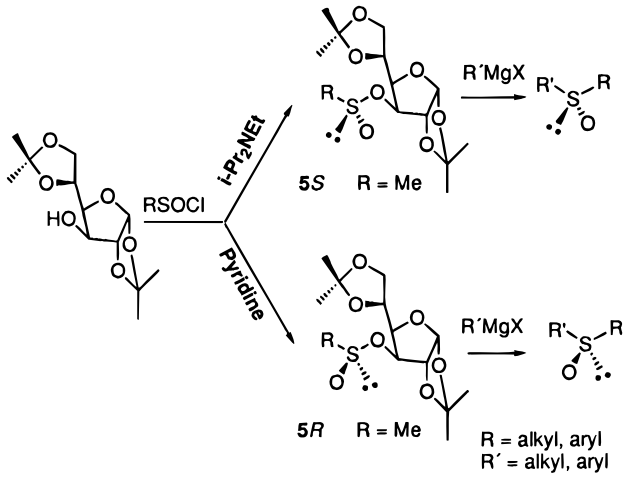
Results and Discussions

Oxisuran **1**, (methylsulfinyl)methyl 2-pyridyl ketone, is a synthetic immunosuppressive drug that is used in organ and tissue transplants to suppress cell-mediated immunity, as well as to promote graft acceptance without inhibiting humoral antibody formation.[9] It is not cytotoxic and it is antiinflammatory. It has been shown that oxisuran undergoes three reactions in its biotransformation: two are reductive and one is oxidative.[10] All the oxisuran metabolites have been shown to possess immunosuppressive activity. Despite the interest in these drugs, little is understood of their mechanism of action. For this reason, their synthesis, as well as that of some of their bioisosteres in optically pure form, is of great interest.

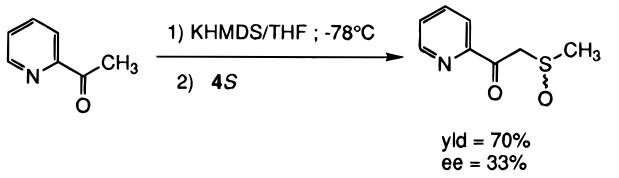
Great efforts have been made toward the synthesis and conformational analysis of racemic oxisuran and analogs.[11] These studies have permitted the determination of a pathway which explains the stereoselectivity observed in the reduction of β-keto sulfoxides with DIBALH.[12a] The conformational behavior of diastereomeric β-hydroxy sulfoxides has permitted the establishment of an empirical method for the determination of their configuration, based mainly on ^{1}H and ^{13}C NMR spectroscopy.[11b] The same conclusions have been reached recently using molecular mechanics force fields (MMX).[13]

In order to get both isomers of oxisuran in optically pure (op) form, an efficient method for chiral methylsulfinyl delivery is necessary. The widely used Andersen

Scheme 2. The DAG Methodology for the Synthesis of Optically Pure Sulfoxides



Scheme 3



method does not fulfil this requirement since the menthyl methanesulfinates are oils,[7] and thus cannot be obtained in op form. Recently, we have introduced the "DAG methodology"—a cheap, general, and powerful method—for the synthesis of both isomers of alkane- and arenesulfinates. It has been shown for the first time that the stereochemical outcome of the reaction between a secondary alcohol and a sulfinyl chloride depends not only on the chiral alcohol but also on the nature of the base used. Thus, with the same inducer of chirality, DAG, simply changing the base from pyridine to *i*-Pr$_2$NEt affords optically pure *(S)*-sulfinates instead of the *(R)* diastereoisomers (Scheme 2). Using DAG and *i*-Pr$_2$NEt is equivalent to using Py and changing the inducer of chirality from the cheap and commercially available DAG to the diacetone derivative of expensive, nonnatural (−)-L-glucose, making this method superior to all the other routes developed for the synthesis of op sulfinates.[8,14]

Condensation of the potassium enolate of methyl 2-pyridyl ketone with (*S*)-methanesulfinate **5***S* gave the desired β-keto sulfoxide **1** in 70% yield (Scheme 3). Being aware that this condensation may occur with epimerization at the sulfinyl sulfur, we carried out a careful study of the optical purity of **1** by ^{1}H NMR using two types of chiral shift reagent: (−)-*N*-(3,5-dinitrobenzoyl)-α-phenylethylamine, developed by Kagan,[15] and the widely used Eu(hfc)$_3$.[16] Compound **1** was found to be scalemic, indicating that the direct condensation of the enolate of methyl 2-pyridyl ketone with op sulfinate occurred with some epimerization at the sufinyl sulfur (33% ee), and that an alternative route had to be found.

It has been reported that the condensation of α-lithio *N*,*N*-dimethylhydrazone with a chiral sulfinate occurs

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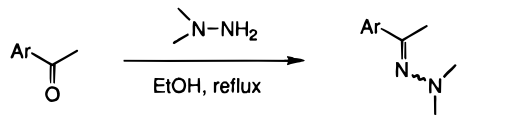
Scheme 4



Ar	Compound	Ar	Compound
2-Pyridyl	**6**	2-Furyl	**8**
Phenyl	**7**	2-Thienyl	**9**

Table 1. Yields and Specific Rotations of Sulfinyl Derivatives

	α-sulfinyl hydrazone			α-methylsulfinyl ketone		
hydrazone		yield (%)	$[\alpha]_D^{22}$ [b]		yield (%)	$[\alpha]_D^{22}$ [b]
6	**10*S***	90	−291	**1*S***	50	+33
6	**10*R***	86	+286	**1*R***	45	−32
7	**11*S***	90	−6	**2*S***	90	+63
14[a]	**16*S***	55[c]	--	**3*S***	60[d]	+75
15[a]	**17*S***	57[c]	--	**4*S***	47[d]	+59

[a] Silylated derivative at the 5 position of the aromatic ring. [b] $[\alpha]_D^{22}$ in ethanol. [c] *E*/*Z* mixture. [d] The yield corresponds to two steps.

with complete inversion at the sulfinyl sulfur, and further hydrolysis of the hydrazone fuction can lead to the corresponding β-keto sulfoxide without loss of the optical purity.[17] Thus, we decided to protect the starting ketones as *N*,*N*-dimethylhydrazone derivatives. Reaction of 2 equiv of the dimethylhydrazone **6**, obtained by a standard procedure[18] (Scheme 4) with 2 equiv of *n*-BuLi gave the corresponding α-lithio derivative which upon condensation with **5***R* and **5***S* methanesulfinate (Scheme 5) yielded optically pure sulfoxides **10***S* and **10***R*, respectively, in high yield (Table 1). In the same way, the condensation of 2 equiv of *n*-BuLi with 2 equiv of *N*,*N*-dimethylhydrazone **7**, with 1 equiv of methanesulfinate **5***S* led to the α-sulfinyl hydrazone **11***S*.

The configurational assignment of the obtained α-sulfinyl hydrazones **10***S*, **10***R*, and **11***S* was made by assuming that the condensation step occurs with complete inversion of configuration at the sulfinyl sulfur as has been shown for many Andersen-type reactions.[19]

Reaction of compounds **10***S* and **10***R* with copper chloride in aqueous tetrahydrofuran[20] led to the first synthesis of op **1***S* and **1***R* oxisuran, respectively (Scheme 5). Similarly, (*S*)-(methylsulfinyl)methyl phenyl ketone (**2**) was also obtained in op form from the corresponding α-sulfinyl hydrazone **11***S* in excellent yield (Scheme 5).

With regard to the asymmetric synthesis of compounds **3** and **4**, condensation of the corresponding *N*,*N*-dimethylhydrazones **8** and **9** with methanesulfinate **5***S* as before did not lead to the desired α-sulfinyl hydrazone. In both cases the reaction gave a mixture of products having the methylsulfinyl group on the heterocyclic ring (Scheme 6). The major regioisomer came from the attack of the anion at the 5 position of the heterocycle. This result, which indicated that the proton at position 5 was more acidic than the methyl proton in compounds **8** and **9**, made necessary the protection of this position before condensation with the sulfinates. This protection was accomplished by quenching the intermediate anion with trimethylsilyl chloride, giving the silylated derivatives **14** and **15** in 70% yield in both cases. Addition of *n*-BuLi at −78 °C in THF led to the desired α-lithio *N*,*N*-dimethylhydrazone and thus the condensation of **5***S* afforded the optically pure α-sulfinyl hydrazones **16***S* and **17***S* , respectively (Scheme 7).

Reaction of α-sulfinyl hydrazones **16***S* and **17***S* with copper chloride[17] gave the silylated β-keto sulfoxides **18***S* and **19***S*, which upon treatment with TBAF in THF gave op (*S*)-(methylsulfinyl)methyl 2-furyl ketone (**3***S*) as well as (*S*)-(methylsulfinyl)methyl 2-thienyl ketone (**4***S*, Scheme 7) in excellent yields (Table 1).

Besides their interest as immunosuppressive drugs, the op β-keto sulfoxides obtained so far are also interesting in that their stereoselective reduction can lead to both isomers of the corresponding β-hydroxy sulfoxides, also known to have some immunosuppressive activities (in racemic form). Moreover β-keto sulfoxide **3***S* is a valuable chiral intermediate in asymmetric synthesis, as the furyl group can easily be converted to many other functionalities.[21]

Determination of the Optical Purities of the β-Keto Sulfoxides. The optical purity of the final sulfoxides was demonstrated by ^{1}H NMR using two types of chiral shift reagents, Eu(hfc)$_3$ and (−)-*N*-(3,5-dinitrobenzoyl)-α-phenylethylamine, under preestablished conditions on racemic samples. The racemic compounds **1**−**4** were easily synthesized by condensation of dimethylsulfinyl anion with the corresponding esters.

In all the cases studied, the inexpensive Kagan's amide[15] has been shown to be superior to the expensive and widely used Eu(hfc)$_3$,[16] which generally gave poor peak separation. The enantiomeric excess can be measured either with the singlet of the methyl peak or on the B part of the AB system of CH_2−S*. All the β-keto sulfoxides prepared in this work were shown to be optically pure, as no trace of the other isomer could be detected in any case. Thus, from these results we can affirm that condensation of the α-sulfinyl hydrazones **6**, **7**, **14**, and **15** with (*S*)- and (*R*)-methanesulfinate of DAG, **5***S* and **5***R*, occurs with inversion of configuration at the sulfinyl sulfur and with no concomitant epimerization.

In conclusion, in this work we have reported for the first time the asymmetric synthesis of both isomers (1*S*)- and (1*R*)-oxisuran in optically pure form. Additionally, various optically pure bioisosteres of oxisuran **2***S*, **3***S*, and **4***S* have also been obtained in good overall yields. In this work we make use of the recently developed DAG methodology, a powerful method for the synthesis of dialkyl chiral sulfoxides, especially when both isomers of the sulfoxide are needed. We suggest that this method is superior to other available methods for the synthesis of such sulfoxides. The use of *N*,*N*-dimethylhydrazones as starting material solves the problem of the epimerization at the sulfinyl sulfur observed in the direct condensation of the metal enolate of the starting ketone with the chiral sulfinate. This route is thus a general approach to both isomers of methylsulfinyl ketones in optically pure forms.

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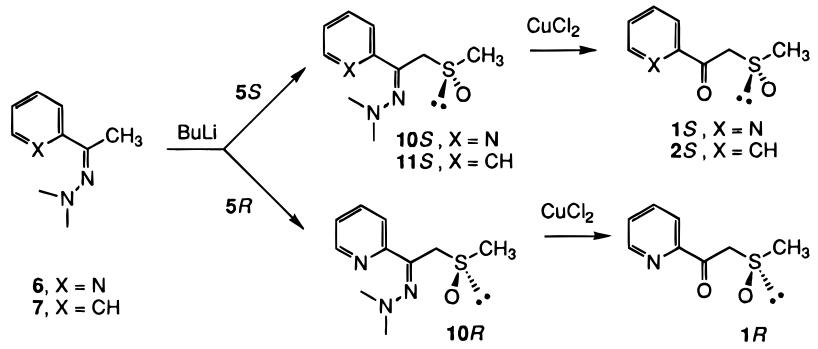
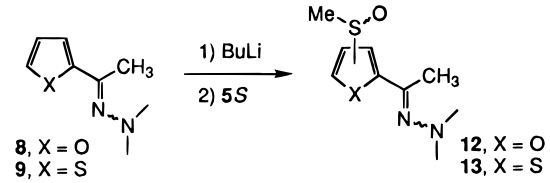
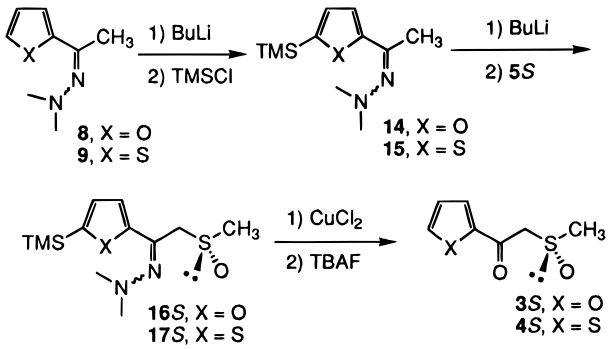
Scheme 5



Scheme 6



Scheme 7



Experimental Section

General methods were previously reported.[8a]

Scalemic α-Methylsulfinyl Ketones from Direct Condensation of Aryl Methyl Ketones with Optically Pure DAG Methanesulfinates. General Procedure. To a solution of the corresponding aryl methyl ketone (10 mmol, 2 equiv) in THF (30 mL) was added a solution of the base, LDA or potassium bis(trimethylsilyl)amide (KHMDS), (10 mmol, 2 equiv) at −78 °C. After 30 min, a solution of optically pure DAG methanesulfinate, **5***R* or **5***S*, (1.61 g, 5 mmol) in THF (20 mL) was added at −78 °C. The mixture was stirred for a further 30 min, then quenched with saturated NH_4Cl solution (40 mL), and extracted with EtOAc (2 × 30 mL) and CH_2Cl_2 (2 × 30 mL). The organic layer was dried over Na_2SO_4 and evaporated under vacuum. The crude was purified by flash chromatography on silica gel using EtOAc/CH_3OH (30/1).

Methyl Aryl Ketone *N,N*-Dimethylhydrazones. General Procedure. A solution of the corresponding ketone (20 mmol) and 4.56 mL of *N,N*-dimethylhydrazine (60 mmol, 3 equiv) in EtOH (30 mL) was refluxed overnight. Evaporation of the mixture under vacuum yielded, quantitatively, the corresponding *N,N*-dimethylhydrazones that were used in the following step without further purification.

Methyl 2-pyridyl ketone *N,N*-dimethylhydrazone (6): ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3H), 2.61 (s, 6H), 7.13−7.20 (m, 1H), 7.54−7.63 (m, 1H), 7.94−7.98 (m, 1H), 8.49−8.53 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.6, 47.1, 120.6, 123.5, 136.0, 148.4, 156.5, 161.2; HRMS mass exact calcd for $C_9H_{13}N_3$ 163.1107, found 163.1108.

Methyl phenyl ketone *N,N*-dimethylhydrazone (7): ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3H), 2.63 (s, 6H), 7.35−7.39 (m, 3H), 7.72−7.77 (m, 2H); HRMS mass exact calcd for $C_{10}H_{14}N_2$ 162.1154, found 162.1146.

Methyl 2-furyl ketone *N,N*-dimethylhydrazone (8): ^{1}H NMR ($CDCl_3$) (mixture of *Z*/*E* isomers) δ [2.11/2.17] (s, 3H), [2.39/2.45] (s, 6H), [6.22/6.31] (dd, *J* = 3.4, 1.8 Hz/3.5, 1.8 Hz, 1H), 6.49 (dd, *J* = 3.4, 0.5 Hz, 1H), [7.26/7.30] (dd, *J* = 1.8, 0.4 Hz/1.8, 0.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.6, 20.4, 46.1, 46.4, 109.9, 110.4, 111.1, 115.9, 141.4, 142.8, 146.6, 150.1, 151.6, 152.8.

Methyl 2-thienyl ketone *N,N*-dimethylhydrazone (9): ^{1}H NMR ($CDCl_3$) (mixture of *Z*/*E* isomers) δ [2.31/2.38] (s, 3H), [2.45/2.55] (s, 6H), 6.92−7.01 (m, 1H), 7.22−7.26 (m, 1H), 7.40−7.48 (m, 1H); HRMS mass exact calcd for $C_8H_{12}SN_2$ 168.0719, found 168.0728.

Silylation of Hydrazones 8 and 9. General Procedure. To a solution of *N,N*-dimethylhydrazone **8** or **9** (6 mmol, 1 equiv) in THF (50 mL) was added 4.5 mL of *n*-BuLi 1.6 M in hexane (7.2 mmol, 1.2 equiv) at −78 °C. After 30 min, 1.38 mL of trimethylsilyl chloride (10.8 mmol, 1.8 equiv) was added, and the stirring was continued for 1 h at −78 °C. The solution was then quenched with saturated NH_4Cl solution (40 mL) and extracted with EtOAc (2 × 40 mL) and CH_2Cl_2 (3 × 40 mL). The organic layer was dried over Na_2SO_4 and evaporated under vacuum. The crude product was purified by flash chromatography using Et_2O/hexane (1/3) as an eluent.

Methyl 5-(trimethylsilyl)-2-furyl ketone *N,N*-dimethylhydrazone (14): yield 70%; ^{1}H NMR ($CDCl_3$) (mixture of *Z*/*E* isomers) δ 0.25 (s, 9H), [2.27/2.32] (s, 3H), [2.52/2.57] (s, 6H), [6.60/6.70] (d, *J* = 3.3 Hz, 1H), [6.73/7.40] (d, *J* = 3.3 Hz, 1H).

Methyl 5-(trimethylsilyl)-2-thienyl ketone *N,N*-dimethylhydrazone (15): yield 70%; ^{1}H NMR ($CDCl_3$) (mixture of *Z*/*E* isomers) δ [0.29/0.32] (s, 9H), [2.33/2.39] (s, 3H), [2.48/2.57] (s, 6H), [7.13/7.14] (d, *J* = 3.5/3.7, 1H), [7.29/7.59] (d, *J* = 3.5/3.7, 1H); HRMS mass exact calcd for $C_{11}H_{20}N_2SiS$ 240.1108, found 240.1114.

(α-Methylsulfinyl)hydrazones. General Procedure. To a solution of the *N,N*-dimethylhydrazone (7.75 mmol, 2.5 equiv) in THF (25 mL), at −78 °C, was slowly added a solution of *n*-BuLi 2.5 M in hexane (3.1 mL, 7.75 mmol). After 30 min a solution of (−)- or (+)-DAG methanesulfinate, **5***S* or **5***R*, (1 g, 3.1 mmol) in THF (15 mL) was added at −78 °C. The mixture was stirred for a further 30 min, then quenched with saturated NH_4Cl solution (40 mL), and extracted with EtOAc (2 × 25 mL) and CH_2Cl_2 (2 × 25 mL). The organic layer was dried over Na_2SO_4 and evaporated under vacuum. The crude product was purified by flash chromatography on silica gel using EtOAc/CH_3OH (20/1) as an eluent.

(−)-(*S*) and (+)-(*R*)-(methylsulfinyl)methyl 2-pyridyl ketone *N,N*-dimethylhydrazone (10*S* and 10*R*): IR (KBr, cm^{-1}) 1571, 1021; ^{1}H NMR ($CDCl_3$) δ 2.63 (s, 3H), 2.69 (s, 6H), 4.55 (AB system, *J* = 12.1Hz, Δν = 14.4 Hz, 2H), 7.21−7.28 (m, 1H), 7.61−7.70 (m, 1H), 8.01−8.06 (m, 1H), 8.50−8.54 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 39.5, 47.8, 53.0, 120.8, 124.1, 136.3, 148.1, 154.2, 155.1. **(−)-10*S*:** yield: 90%; $[\alpha]^{22}_D$ −291 (c 1.0, EtOH); HRMS mass exact calcd for $C_{10}H_{15}N_3SO$ 225.0938, found 225.0947. **(+)-10*R*:** yield 86%; $[\alpha]^{22}_D$ +289 (c 1.4, EtOH).

(−)-(*S*)-(Methylsulfinyl)methyl phenyl ketone *N,N*-dimethylhydrazone (11): yield 90%; mp 106−108 °C; IR (KBr, cm^{-1}) 1600, 1036; ^{1}H NMR ($CDCl_3$) δ 2.56 (s, 6H), 2.60 (s, 3H), 4.35 (AB system, *J* =12.9 Hz, Δν = 19.0 Hz, 2H), 7.35−

7.42 (m, 3H), 7.74−7.79 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 39.1, 47.3, 54.6, 127.0, 128.5, 130.4, 136.0, 160.0; HRMS mass exact calcd for $C_{11}H_{16}N_2OS$ 224.0980, found 224.1006; $[\alpha]^{22}_D$ −6 (*c* 0.9, EtOH).

(*S*)-(Methylsulfinyl)methyl 5-(trimethylsilyl)-2-furyl ketone *N*,*N*-dimethylhydrazone (16): yield 55%; IR (KBr, cm^{-1}) 1040, 843; ^{1}H NMR ($CDCl_3$) (Mixture of *Z*/*E* isomers) δ [0.26/0.27] (s, 9H), [2.54/2.58] (s, 6H), [2.57/2.62] (s, 3H), [4.16/4.27] (AB system, J = 12.8 Hz, $\Delta\upsilon$ = 78.6 Hz/J = 12.5 Hz, $\Delta\upsilon$ = 15.4 Hz, 2H), [6.64/6.70] (d, J = 3.4 Hz, 1H), [6.90/7.30] (d, J = 3.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −1.8, −1.7, 38.8, 39.2, 46.8, 47.5, 53.9, 59.7, 111.4, 117.3, 121.6, 121.8, 143.7, 149.2, 151.1, 154.5, 162.0, 163.7; HRMS mass exact calcd for $C_{12}H_{22}N_2SiSO_2$ 286.1170, found 286.1152.

(*S*)-(Methylsulfinyl)methyl 5-(trimethylsilyl)-2-thienyl ketone *N*,*N*-dimethylhydrazone (17): yield 57%; IR (KBr, cm^{-1}) 1578, 1250, 1024, 841; ^{1}H NMR ($CDCl_3$) (mixture of *Z*/*E* isomers) δ [0.29/0.31] (s, 9H), [2.52/2.53] (s, 6H), [2.63/2.69] (s, 3H), [4.15/4.30] (AB system, J = 13.1 Hz, $\Delta\upsilon$ = 61.4 Hz/J = 12.7 Hz, $\Delta\upsilon$ = 20.7 Hz, 2H), [7.15/7.17] (d, J = 2.5 Hz, 1H), [7.46/7.61] (d, J = 2.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −0.4, −0.3, 38.9, 46.7, 47.3, 54.3, 60.7, 126.2, 128.0, 130.2, 132.3, 132.7, 134.1, 145.4, 148.9, 152.3, 154.8; HRMS mass exact calcd for $C_{12}H_{22}N_2SiS_2O$ 302.0942, found 302.0965.

α-Methylsulfinyl Ketones from α-Sulfinyl Hydrazones. General Procedure. To a solution of the α-sulfinyl hydrazone (1.0 mmol) in THF (15 mL) was added $CuCl_2$ (0.188 g, 1.1 mmol) in 0.02 N phosphate buffer (7 mL; pH 7).

In the case of compound **1*S*** and **1*R***, after the mixture was stirred for 2 h, the solvent was removed under vacuum and the residue was treated with a saturated solution of EDTA (20 mL). The aqueous layer was extracted with EtOAc (2 × 30 mL) and CH_2Cl_2 (3 × 30 mL), dried over Na_2SO_4, and evaporated under vacuum. The crude product was purified by flash chromatography on silica gel using EtOAc/CH_3OH (30/1) as an eluent.

For compounds **2**, **18**, and **19**, the mixture was stirred overnight, quenched with saturated NH_4Cl solution (20 mL), and extracted with EtOAc (2 × 30 mL) and CH_2Cl_2 (3 × 30 mL). The organic layer was dried over Na_2SO_4 and evaporated under vacuum. The crude product was purified by flash chromatograpy on silica gel using EtOAc/CH_3OH (30/1) for compound **2** and (60/1) for compounds **18** and **19**.

(+)-(*S*) and (−)-(*R*)-(methylsulfinyl)methyl 2-pyridyl ketone (1*S* and 1*R*): mp 78−79 °C; IR (KBr, cm^{-1}) 1692, 1051; ^{1}H NMR ($CDCl_3$) δ 2.77 (s, 3H), 4.69 (AB system, J = 13.7Hz, $\Delta\upsilon$ = 46.4Hz, 2H), 7.55 (ddd, J = 7.5, 4.7, 1.5 Hz, 1H), 7.89 (td, J = 7.5, 1.5 Hz, 1H), 8.09 (dt, J = 7.5, 1.0 Hz, 1H), 8.72 (dt, J = 4.7, 1.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 39.6, 61.2, 122.3, 128.1, 137.2, 149.3, 152.1, 193.3. **1*S*:** yield 50%; $[\alpha]^{22}_D$ +33 (*c* 0.8, EtOH). **1*R*:** yield 45%; $[\alpha]^{22}_D$ −32 (*c* 0.5, EtOH).

(+)-(*S*)-(Methylsulfinyl)methyl phenyl ketone (2): yield 90%; IR (KBr, cm^{-1}) 1675, 1049; ^{1}H NMR ($CDCl_3$) δ 2.62 (s, 3H), 4.29 (AB system, J = 14.5Hz, $\Delta\upsilon$ = 29.5 Hz, 2H), 7.32−7.53 (m, 3H), 7.82−7.86 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 39.5, 62.0, 128.7, 128.9, 134.4, 135.8, 192.0; HRMS mass exact calcd for $C_9H_{10}SO_2$ 182.0399, found 182.0400; $[\alpha]^{22}_D$ +63 (*c* 1.4, EtOH).

(+)-(*S*)-(Methylsulfinyl)methyl 5-(trimethylsilyl)-2-furyl ketone (18): yield 85%; IR (KBr, cm^{-1}) 1665, 1043, 844; ^{1}H NMR ($CDCl_3$) δ 0.24 (s, 9H), 2.68 (s, 3H), 4.20 (AB system, J = 13.6 Hz, $\Delta\upsilon$ = 42.7 Hz, 2H), 6.67 (d, J = 3.6 Hz, 1H), 7.24 (d, J = 3.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −2.1, 39.9, 61.9, 119.9, 121.8, 155.5, 169.0, 179.3; $[\alpha]^{22}_D$ +74 (c 1.9, EtOH).

(+)-(*S*)-(Methylsulfinyl)methyl 5-(trimethylsilyl)-2-thienyl ketone (19): yield 67%; IR (KBr, cm^{-1}) 1652, 1058, 843; ^{1}H NMR ($CDCl_3$) δ 0.35 (s, 9H), 2.76 (s, 3H), 4.28 (AB system, J = 13.5 Hz, $\Delta\upsilon$ = 27.4 Hz, 2H), 7.27 (d, J = 3.6 Hz, 1H), 7.82 (d, J = 3.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −0.6, 39.3, 62.4, 134.9, 135.3, 147.4, 154.1, 183.3; HRMS mass exact calcd for $C_{10}H_{16}S_2O_2Si$ 260.0360, found 260.0358; $[\alpha]^{22}_D$ +83 (*c* 8.8, acetone).

Desilylation of Compounds 18 and 19. General Procedure. To a solution of the silyl derivative **18** or **19** (0.8 mmol, 1 equiv) in THF (5 mL) was added 1.45 mL of tetrabutylammonium fluoride (1.1 M in THF, 1.6 mmol, 2 equiv). After the mixture was stirred overnight, a saturated solution of NH_4Cl (10 mL) was added and extracted with EtOAc (2 × 20 mL) and CH_2Cl_2 (3 × 20 mL). The organic layer was dried over Na_2SO_4, evaporated under vacuum, and purified by flash chromatography, using EtOAc/CH_3OH (60/1) as an eluent.

(+)-(*S*)-(Methylsulfinyl)methyl 2-furyl ketone (3): yield 71%; mp 82−84 °C; IR (KBr, cm^{-1}) 1656, 1031; ^{1}H NMR ($CDCl_3$) δ 2.76 (s, 3H), 4.21 (AB system, J = 13.4 Hz, $\Delta\upsilon$ = 25.2 Hz, 2H), 6.62 (dd, J = 3.7, 1.7 Hz, 1H), 7.35 (dd, J = 3.7, 0.7 Hz, 1H), 7.68 (dd, J = 1.7, 0.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 39.1, 61.2, 112.6, 119.6, 147.6, 151.9, 179.2; $[\alpha]^{22}_D$ +75 (*c* 1.8, ethanol).

(+)-(*S*)-(Methylsulfinyl)methyl 2-thienyl ketone (4): yield 70%; mp 81−82°C; IR (KBr, cm^{-1}) 1655, 1030; ^{1}H NMR ($CDCl_3$) δ 2.75 (s, 3H), 4.25 (AB system, J = 13.5 Hz, $\Delta\upsilon$ = 23.5Hz, 2H), 7.18 (dd, J = 3.9, 4.9 Hz, 1H), 7.76 (dd, J = 4.9, 1.1 Hz, 1H), 7.81 (dd, J = 3.9, 1.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 39.2, 62.2, 128.4, 134.5, 135.6, 143.4, 183.7; $[\alpha]^{22}_D$ +59 (*c* 5.3, ethanol).

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for compounds **1**−**4**, **6**−**11**, and **14**−**19** (32 pages). This material is contained in 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.

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