Asymmetric Induction during Organometallic Conjugate Addition to Enantiomerically Pure 2-(Arylsulfinyl)-2-cyclopentenones

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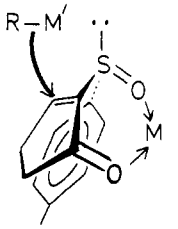
Abstract: Virtually complete asymmetric induction is achieved during methyl-, vinyl-, and naphthylmetallic conjugate addition to enantiomerically pure (*S*)-(+)-2-(*p*-tolylsulfinyl)-2-cyclopentenone ((*S*)-(+)-**1**). (*R*)-3-Methylcyclopentanone is obtained when the enone sulfoxide (*S*)-(+)-**1** is first complexed with divalent zinc and then methylmagnesium iodide is added, whereas (*S*)-3-methylcyclopentanone is obtained when methylmagnesium iodide is added to the *same, uncomplexed* enone sulfoxide. (*R*)-3-Methylcyclopentanone is obtained also when the enone sulfoxide is treated separately with lithium tetramethylaluminate, methyltitanium triisopropoxide, and methylmagnesium *chloride*. (*S*)-(+)-2-(1-Naphthylsulfinyl)-2-cyclopentenone ((*S*)-(+)-**1'**) gives mainly the unexpected (*S*)-3-methylcyclopentanone on reaction with dimethylcopperlithium. Enantiomerically pure steroid intermediates (*S,S*)-(+)-**4** and (*S,S*)-(+)-**7** are prepared in short, convergent, and high-yield sequences starting with enone sulfoxide (*S*)-(+)-**1**.

The past 10 years have witnessed a rapid and impressive maturation of the organic chemist's ability to form carbon–carbon bonds with control of absolute stereochemistry.[1] We focus attention here on chiral 3-substituted carbonyl compounds. In the early 1970s Stirling[2] and Tsuchihashi[3] independently showed that amine and enolate ion β addition to some enantiomerically pure *acyclic* α,β-ethylenic sulfoxides proceeded with 60–74% asymmetric induction. Very recently we reported 59–65% asymmetric induction during organometallic β addition to some enantiomerically pure *acyclic* α-carboxy α,β-ethylenic sulfoxides leading to 3-alkylcarboxylic acids.[4a] Enders also has reported up to 67% enantioselectivity in synthesis of some 3-substituted aldehydes.[5] From a practical synthetic viewpoint, however, much higher [e.g., >95% enantiomeric excess (ee)] and therefore more useful asymmetric syntheses of 3-substituted carboxylic acids have been achieved independently by Meyers,[1d,6] Mukaiyama,[7] and Koga.[8] Despite this rapid development of new synthetic methods for enantioselective synthesis of some *acyclic* systems, virtually no general method has been reported for enantio-controlled preparation of *cyclic* compounds.[9] Because many enantiomerically pure carbocycles are found in nature and are important synthetic intermediates, the need for effective and highly asymmetric syntheses of these compounds is obvious. More specifically, although many naturally occurring 3-alkylcarbocycles with small 3-alkyl groups are known in an enantiomerically pure state, synthesis of these compounds via attachment of the small alkyl group with control of absolute stereochemistry is an extremely difficult process. Despite attempts at asymmetric induction during organometallic conjugate addition to 2-cycloalkenones with optically active solvents[10] or optically active ligands,[11] only poor enantioselectivity has been achieved. We now, therefore, describe our experimental results that have led to enantiospecific synthesis of some 3-substituted cyclopentanones via complete asymmetric induction during organometallic conjugate addition to enantiomerically pure (*S*)-(+)-2-(*p*-tolylsulfinyl)-2-cyclopentenone ((*S*)-(+)-**1**). Specifically we report the following: (1) asymmetric synthesis of *either* (*R*)- or (*S*)-3-methylcyclopentanone from the same sulfoxide, varying only the reaction conditions; (2) use of divalent metal ions to increase enantioselectivity; (3) evidence supporting a chelate model that allows prediction of the absolute stereochemistry of the reaction product; (4) effect of the halide in methylmagnesium halides in determining the sense and the amount of asymmetric induction; (5) effect of the size of the aryl group in 2-(arylsulfinyl)-2-cyclopentenones on the course of asymmetric conjugate additions; (6) enantiospecific synthesis of an (*S*)-3-vinylcyclopentanone, which is an intermediate for total synthesis of natural estrone; and (7) improvement of the yield by a factor of 2 in our stereocontrolled synthesis of 9,11-seco steroid (*S,S*)-(+)-**7**.

Results and Discussion

On the basis of our previously proposed chelate model (*S*)-**1a**,[4a]



chelate model
(*S*)-**1a**

formed by complexation of a metal (M) ion with cyclopentenone sulfoxide (*S*)-(+)-**1**, we expected that the nature and complexing

(1) (a) Morrison, J. D.; Mosher, H. S. "Asymmetric Organic Reactions"; Prentice-Hall: Englewood Cliffs, NJ, 1971. (b) Scott, J. W.; Valentine, D., Jr. *Science (Washington, D.C.)* **1974**, *184*, 943. (c) Valentine, D., Jr.; Scott, J. W. *Synthesis* **1978**, 329. (d) Meyers, A. I. *Acc. Chem. Res.* **1978**, *11*, 375.

(2) Abbott, D. J.; Colonna, S.; Stirling, C. J. M. *J. Chem. Soc., Chem. Commun.* **1971**, 471.

(3) Tsuchihashi, G.; Mitamura, S.; Inoue, S.; Ogura, K. *Tetrahedron Lett.* **1973**, 323.

(4) (a) Posner, G. H.; Mallamo, J. P.; Miura, K. *J. Am. Chem. Soc.* **1981**, *103*, 2886. (b) For a recent use of zinc to complex with an α-sulfinyl ester, see: Cass, Q. B.; Jaxa-Chamiec, A. A.; Sammes, P. G. *J. Chem. Soc., Chem. Commun.* **1981**, 1248.

(5) Ahlbrecht, H.; Bonnet, G.; Enders, D.; Zimmerman, G. *Tetrahedron Lett.* **1980**, *21*, 3175.

(6) Meyers, A. I.; Smith, R. K.; Whitten, C. E. *J. Org. Chem.* **1979**, *44*, 2250.

(7) Mukaiyama, T.; Takeda, T.; Osaki, T. *Chem. Lett.* **1977**, 1165.

(8) (a) Hashimoto, S. I.; Yamada, S. I.; Koga, K. *J. Am. Chem. Soc.* **1978**, *98*, 7450. (b) Hashimoto, S.; Kameshima, N.; Yamada, S.; Koga, K. *Chem. Pharm. Bull.* **1979**, *27*, 2437. (c) Cf. asymmetric synthesis of 3-substituted sulfones: Isobe, M.; Ichikawa, Y.; Kitamura, M.; Goto, T. *Chem. Lett.* **1981**, 457.

(9) (a) For a recently reported synthesis of optically active 3-alkylcycloalkanones, see: Taber, D. F.; Saleh, S. A.; Korsmeyer, R. W. *J. Org. Chem.* **1980**, *45*, 4699. (b) For use of (*R*)-3-methylcyclopentanone as a chiral synthon, see: Takano, S.; Masuda, K.; Ogaswara, K. *Heterocycles* **1981**, *16*, 1509.

(10) Langer, W.; Seebach, D. *Helv. Chim. Acta* **1979**, *62*, 1710.

(11) (a) Colonna, S.; Re, A.; Wynberg, H. *J. Chem. Soc., Perkin Trans. 1* **1981**, 547 and references therein. (b) Gustafsson, B.; Hallnemo, G.; Ullenius, C. *Acta Chem. Scand., Ser. B* **1980**, *B34*, 443. (c) Hermann, K.; Wynberg, H. *J. Org. Chem.* **1979**, *44*, 2238. (d) Ghozland, F.; Luche, J. L.; Crabbé, P. P. *Bull. Soc. Chim. Belg.* **1978**, *87*, 369. (e) Leyendecker, F.; Jesser, F.; Ruhland, B. *Tetrahedron Lett.* **1981**, *22*, 3601. (f) Cf. Mukaiyama, T.; Iwawa, N. *Chem. Lett.* **1981**, 913.

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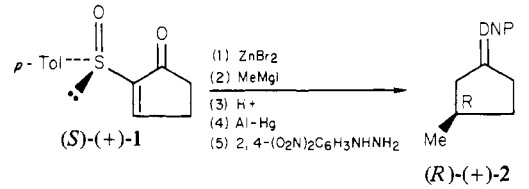
ability of the metal would affect the amount of asymmetric induction during organometallic (R–M′) nucleophilic conjugate addition. Cyclopentenone sulfoxide (*S*)-(+)-**1** therefore was treated first with 1 equiv of different metal dibromides (M = Ni, Co, Pd, Mg) and then with 1 equiv of methylmagnesium bromide or iodide. Aluminum–amalgam reductive cleavage of the carbon–sulfur bond of the resultant conjugate adduct followed by derivatization produced the dinitrophenylhydrazone (DNP) of the expected (*R*)-(+)-3-methylcyclopentanone in overall chemical yields ranging between 53 and 81% and in optical yields of 70–73%. The best result (89% yield, 87% ee) was obtained with zinc dibromide and methylmagnesium iodide (eq 1).

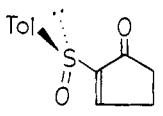


(*S*)-(+)-**1** (*R*)-(+)-**2** (1)

In the absence of divalent metals, mixing a solution of methylmagnesium iodide in THF at −78 °C with a solution of the enone sulfoxide (*S*)-(+)-**1** in THF at −78 °C gave ultimately the (*S*)-(−)-3-methyl adduct in 76% chemical yield and 72% enantiomeric excess (eq 2).

$$(S)\text{-}(+)\text{-}\mathbf{1} \xrightarrow[\text{(4) 2,4-}(O_2N)_2C_6H_3NHNH_2]{\text{(1) MeMgI, −78 °C, THF; (2) H}^+;\ \text{(3) Al-Hg}} (S)\text{-}(-)\text{-}\mathbf{2} \qquad (2)$$

A reasonable rationalization of this result involves the Grignard reagent encountering the cold enone sulfoxide primarily in conformation (*S*)-**1b** having the sulfoxide and carbonyl dipoles oriented in opposite directions;[12] conjugate addition to conformer (*S*)-**1b** apparently occurs on the more exposed side of the enone carbon–carbon double bond, which is that one not blocked by the tolyl group, leading to an (*S*)-3-methylcyclopentanone. Note that when this reaction is done by *first* adding zinc dibromide to the cold enone sulfoxide *before* adding the Grignard reagent, the original sense of asymmetric induction [(*R*)-3-methyl, 87% ee, i.e., eq 1] is obtained probably because a zinc chelate was formed *before* addition of the Grignard reagent.



(*S*)-**1b**

It should be noted that only methylmagnesium *iodide*, and not the bromide or the chloride, affords (*S*)-3-methylcyclopentanone via eq 2. Of the alkylmagnesium halides, the iodides are known to form the weakest complexes.[13] Generalization of this phenomenon to other (i.e., non-methyl) Grignard reagents would constitute a highly useful synthetic method illustrating simple and effective conversion of enone sulfoxide (*S*)-(+)-**1** into either (*R*)- or (*S*)-3-substituted cyclopentanones.

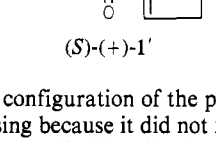
From a synthetic viewpoint, eq 1 and 2 represent the important discovery that the same, readily available, crystalline, stable, enantiomerically pure cyclopentenone sulfoxide (*S*)-(+)-**1** can be converted into either (*R*)- or (*S*)-3-methylcyclopentanone in 72–87% enantiomeric purity simply by selecting appropriate reaction conditions.

The amount of asymmetric induction during methylmetallic conjugate addition to enone sulfoxide (*S*)-(+)-**1** was increased even further by using lithium tetramethylaluminate (90% ee),[14] methyltitanium triisopropoxide (91% ee),[15] and methylmagnesium *chloride* (98–100% ee, 93% chemical yield). In each case (*R*)-3-methylcyclopentanone was formed in good to excellent chemical yield. Of all the alkylmagnesium *halides*, chlorides are known to form the strongest complexes and the largest aggregates.[13,16] This virtually complete asymmetric induction in methylmagnesium *chloride* conjugate addition to enone sulfoxide (*S*)-(+)-**1** (eq 3) is especially noteworthy because it represents

$$(S)\text{-}(+)\text{-}\mathbf{1} \xrightarrow[\text{(4) 2,4-}(O_2N)_2C_6H_3NHNH_2]{\text{(1) MeMgCl (0.4 M, THF); (2) H}^+;\ \text{(3) Al-Hg}} (R)\text{-}(+)\text{-}\mathbf{2} \qquad (3)$$

essentially enantiospecific attachment of the *smallest alkyl group*; attachment of larger alkyl groups, therefore, was expected also to be enantiospecific.

On the basis of chelate model (*S*)-**1a**, we expected that aromatic groups larger than *p*-tolyl attached to sulfur would direct nucleophilic addition to the opposite side of the planar system even more effectively and thus would lead to very high asymmetric inductions. (*S*)-(+)-2-(Naphthylsulfinyl)-2-cyclopentenone ((*S*)-(+)-**1′**), therefore, was prepared; reaction with dimethylcopperlithium gave 3-methylcyclopentanone derivative (*S*)-(−)-**2** reproducibly in 42% yield and 57% enantiomeric purity (eq 4).[17]



(*S*)-(+)-**1′** (*S*)-(−)-**2** (4)

The *S* configuration of the product 3-methylcyclopentanone was surprising because it did not fit chelate model (*S*)-**1a**. Even when naphthyl sulfoxide (*S*)-**1′** was treated first with zinc dibromide and then with a Grignard reagent, asymmetric induction occurred to give the opposite *R* enantiomer, *but the enantiomeric purity was only about 20%*. We conclude, therefore, that the naphthyl group in cyclopentenone sulfoxide (*S*)-**1′** apparently strongly prefers a conformation in which it is spatially distant from the enone unit (i.e., a conformer comparable to (*S*)-**1b**); even in the presence of 1 equiv of divalent zinc, the naphthyl cyclopentenone sulfoxide apparently only partially forms a metal chelate like (*S*)-**1a**. This unexpected result underscores the subtle balance of conformation and chelation factors in these systems and, therefore, the need for study of other aryl 2-cyclopentenone sulfoxides like (*S*)-**1** and (*S*)-**1′**.

Attachment of a *vinyl* group to the 3-position of a cyclopentanone with control of absolute stereochemistry is important because 3-vinylcyclopentanones have been used recently in some highly convergent and efficient syntheses of estrone and estrone derivatives.[18] Specifically, resolved 3-vinylcyclopentanone **4**, R

(12) (a) For a similar line of reasoning, see: Bouffard, F. A.; Christensen, B. G. *J. Org. Chem.* **1981**, *46*, 2208. (b) A single-crystal X-ray analysis of a similar 2-sulfinylcyclopentanone is consistent with this notion of sulfoxide and carbonyl oxygens being oriented away from each other (cf. ref 19).

(13) Ashby, E. C.; Laemmle, J.; Newmann, H. M. *Acc. Chem. Res.* **1974**, *7*, 272 and references therein.

(14) Hiyama, T.; Morizawa, Y.; Yamamoto, H.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2151.

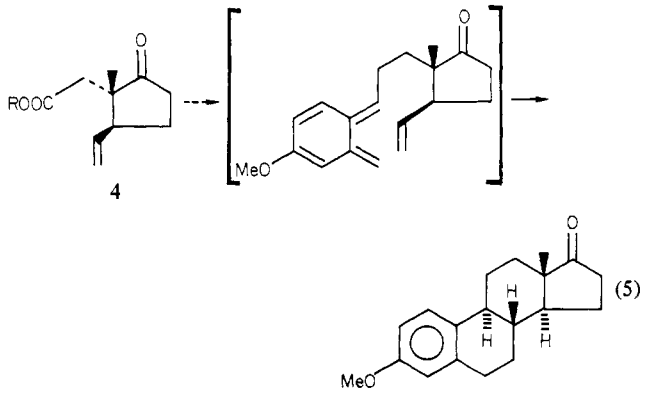
(15) (a) Weidmann, B.; Wilder, L.; Olivero, A. G.; Maycock, L. D.; Seebach, D. *Helv. Chim. Acta* **1981**, *64*, 357. (b) Reetz, M. T.; Steinbach, R.; Westermann, J.; Peta, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 1011.

(16) Alder, R. W.; Baker, R.; Brown, J. M. "Mechanism in Organic Chemistry"; Wiley: New York, 1971; p 144.

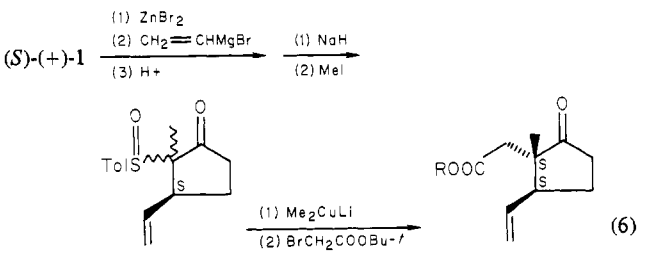
(17) Dimethylcopperlithium reacted with 2-(*tolyl*sulfinyl)cyclopentenone (*S*)-(+)-**1** ultimately to give (*R*)-3-methylcyclopentanone derivative **2**, as predicted by chelate model (*S*)-**1a**, in 91% chemical yield and with 82% ee.

(18) (a) Oppolzer, W.; Petrzilka, M.; Bättig, K. *Helv. Chim. Acta* **1977**, *60*, 2965. (b) Kamentani, T.; Nemoto, H.; Fukumoto, K. *J. Am. Chem. Soc.* **1977**, *99*, 3461. (c) Funk, R. L.; Vollhardt, K. P. C. *Ibid.* **1977**, *99*, 5483; **1979**, *101*, 215. (d) Oppolzer, W.; Bättig, K.; Petrzilka, M. *Helv. Chim. Acta* **1978**, *61*, 1945. (e) Nicolaou, K. C.; Barnette, W. E.; Ma, P. *J. Org. Chem.* **1980**, *45*, 1463. (f) Djuric, S.; Sarkan, T.; Magnus, P. *J. Am. Chem. Soc.* **1980**, *102*, 6885. (g) Quinkert, G.; Weber, W.-D.; Schwartz, U.; Durner, G. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 1027. (h) Quinkert, G.; Schwartz, U.; Stark, H.; Weber, W.-D.; Baier, H.; Adam, F.; Durner, G. *Ibid.* **1980**, *19*, 1029. (i) Oppolzer, W.; Roberts, D. A. *Helv. Chim. Acta* **1980**, *63*, 1703. (j) Ito, Y.; Nakatsuka, M.; Saegusa, T. *J. Am. Chem. Soc.* **1981**, *103*, 476.

= Me, has been used by Oppolzer to prepare optically pure estrone,[18i] and racemic 3-vinylcyclopentanone **4**, R = *t*-Bu, has recently been used by Saegusa to prepare racemic estrone via intramolecular Diels–Alder reaction of an *o*-quinodimethane, as shown schematically in eq 5.[18j]



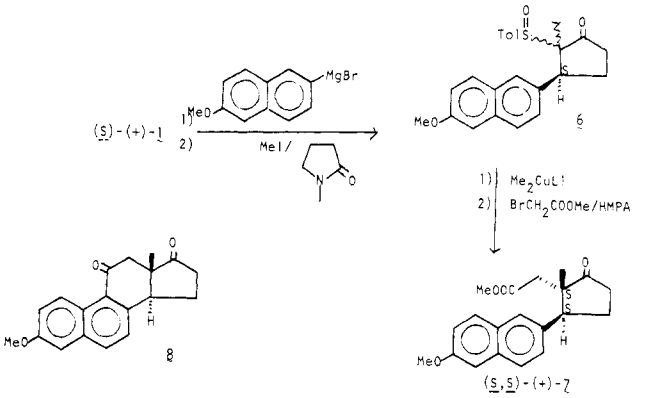
Copper-catalyzed vinylmagnesium bromide conjugate addition to cyclopentenone sulfoxide (*S*)-(+)-**1** proceeded with 80% asymmetric induction to give an (*S*)-3-vinyl adduct.[19] Treating enone sulfoxide (*S*)-(+)-**1** with 1 equiv of zinc dibromide to form a chelate and then with vinylmagnesium bromide, either at −78 °C *or at 0 °C* (a temperature that is much more convenient and economical for industrial-scale reactions), followed by conversion to the more reactive sodio enolate and reaction with methyl iodide, gave a mixture of *cis*- and *trans*-3-vinylcyclopentanone stereoisomers **5**, which we have shown unequivocally by X-ray and by stereochemical correlation to have *only* the (*S*)-3-vinyl stereochemistry;[19] the zinc dibromide mediated vinyl conjugate addition, therefore, proceeded with virtually complete absolute stereocontrol in the sense predicted by chelate model (*S*)-**1a**. Without purification, *cis*- and *trans*-3-vinylcyclopentanones **5** together were reductively cleaved by dimethylcopperlithium[20] into a single enolate ion that was then regiospecifically C-alkylated to give (*S*,*S*)-3-vinylcyclopentanone **4**, R = *t*-Bu, in 30% yield over the 3-pot, seven-step sequence shown in eq 6.[21] The efficiency of this



sequence was maintained even when it was carried out on a gram scale![19] *tert*-Butyl ester **4**, R = *t*-Bu, was converted by methanolic hydrogen chloride into the corresponding methyl ester **4**, R = Me.[18i] Equation 6, therefore, represents an *efficient and enantiospecific formal total synthesis of natural estrone.*

It is worth noting that the transformations shown in eq 6 can be used equally well for introduction of a *trideuterio*methyl group (CD_3I instead of CH_3I in preparation of 2-methylcyclopentanone **5**), which ultimately would afford C-18 perdeuterated estrones.[22]

Scheme I



We recently have reported enantiospecific attachment of a *naphthyl* group to the 3-position of cyclopentenone sulfoxide (*S*)-(+)-**1**, leading to asymmetric synthesis of enantiomerically pure steroid intermediate (*S*,*S*)-(+)-**7**, a precursor of 11-oxoequilenin (**8**, Scheme I).[4] In our original report, the major flaw in the enantiospecific synthesis was the low *chemical* yield associated with introduction of the 2-methyl group to form 2,2,3-trisubstituted cyclopentanone **6**. We have now overcome this difficulty by using *N*-methylpyrrolidinone rather than hexamethylphosphoramide as a polar solvent that allows doubling of the yield (to 80%) in the methylation step. Without separation, stereoisomers *cis*- and *trans*-**6** together were reductively cleaved at 0 °C and regiospecifically and stereospecifically C-alkylated to produce optically pure steroid intermediate (*S*,*S*)-(+)-**7** in 72% yield over the four steps from cyclopentenone sulfoxide (*S*)-(+)-**1** (Scheme I). Synthetic 9,11-seco steroid **7** was identical by HPLC, NMR, IR, mass spectrometry, melting point (116.5–118 °C), mixture melting point, and optical rotation [$[\alpha]^{22}_{365}$ + 168° (*c* 0.36, $CHCl_3$)] to a sample of **7** prepared by degradation of natural estradiol.[23] On the basis of our steroid synthesis using racemic 9,11-seco steroid **7**, Scheme I represents *a short, convergent, enantiospecific, and high-yield (overall ~50%) formal total synthesis of enantiomerically pure steroidal 11-oxoequilenin methyl ether of natural absolute configuration.*

Enantiospecific formation of 2,2,3-trisubstituted cyclopentanones (*S*,*S*)-(+)-**4** and (*S*,*S*)-(+)-**7** represents not only useful syntheses of important steroid synthons but also novel syntheses of compounds containing vicinal tertiary and quaternary[24] carbon centers with complete control of absolute stereochemistry. This methodology undoubtedly, therefore, will find application in asymmetric syntheses of other important compounds as well.

Experimental Section

Melting and boiling points are uncorrected. IR spectra were recorded with a Perkin-Elmer 599B or 457 spectrometer. Proton NMR spectra were recorded with Varian T-60, CFT-20, or JEOL MH-100 spectrometers operating at 60, 80, or 100 MHz, respectively. Mass spectra were recorded with a Hitachi Perkin-Elmer RMU-6 spectrometer. Optical rotations were recorded with a Perkin-Elmer 141 variable-wavelength polarimeter with 1-dm quartz window cells. High-resolution mass spectrometry (HRMS) was performed by the Michigan State University, Department of Biochemistry, Mass Spectrometry Facility, East Lansing, MI. Microanalyses were performed by Galbraith Laboratories, Inc. Gas–liquid phase chromatography (GLPC) data were obtained with a Varian Aerograph Series 1200 gas chromatograph operating at an oven temperature of 170 °C with a carrier gas flow rate of 22 mL/min and

(19) Posner, G. H.; Hulce, M.; Mallamo, J. P.; Drexler, S. A.; Clardy, J. *J. Org. Chem.* **1981**, *46*, 5244.

(20) For use of dimethylcopperlithium in converting various α-heteroatom substituted ketones into the corresponding enolate species, see: (a) Posner, G. H. "An Introduction to Synthesis Using Organocopper Reagents"; Wiley: New York, 1980; pp 22, 42. (b) Posner, G. H.; Sterling, J. J. *J. Am. Chem. Soc.* **1973**, *95*, 3076. (c) Lansbury, P. T.; Erwin, R. W.; Jeffrey, D. A. *Ibid.* **1980**, *102*, 1602. (d) Depreś, J.-P.; Greene, A. E. *J. Org. Chem.* **1980**, *45*, 2037.

(21) We sincerely thank Professors Saegusa and Ito for sending us details of their racemic enolate C-alkylation procedure using *tert*-butyl bromoacetate (ref 18j).

(22) For preparation of some pharmacologically interesting 18-deuterio steroids, see: Green, M. J.; Shire, H.-J.; Bartner, P.; Morton, J. B.; Youngstrom, R. E.; Meinwald, J. *J. Labelled Compd. Radiopharm.* **1980**, *17*, 911.

(23) (a) Dygos, J. H.; Chinn, L. J. *J. Org. Chem.* **1973**, *38*, 4319. (b) Harnik, M.; Szpigielman, R.; Lederman, Y.; Herling, J.; Abramowich, E.; Zaretskii, Z. V. I. *Tetrahedron* **1976**, *32*, 79. We thank Drs. Chinn and Harnik for graciously supplying us with authentic samples of the acid corresponding to ester **7**; we esterified (LiH, MeI) this naturally derived acid to obtain natural ester **7** for comparison with our synthetic ester **7**.

(24) For a review of quaternary carbon synthesis, see: Martin, S. F. *Tetrahedron* **1980**, *36*, 419.

equipped with a 10 ft × $^1/_8$ in. column packed with 5% SE-30 on Chromosorb W and a flame ionization detector.

Tetrahydrofuran (THF), 1,2-dimethoxyethane (DME), and diethyl ether were distilled from sodium–benzophenone ketyl prior to use.

The following reagents were purchased from Aldrich Chemical Co. and were distilled or recrystallized prior to use: methyl iodide, hexamethylphosphoramide, *N*-methylpyrrolidinone, *tert*-butyl and methyl bromoacetate, 1-bromonaphthalene, (−)-menthol, titanium tetrachloride, titanium(IV) isopropoxide, and diisopropylamine. Na_2EDTA, (*R*)-3-methylcyclopentanone, and trimethylaluminum were used as received.

Cuprous bromide and cuprous iodide, purchased from the Eastman Chemical Co., were washed with THF and dried in vacuo.[25] Anhydrous cupric sulfate was purchased from the Fisher Chemical Co. Sodium hydride and zinc dibromide were purchased from Alfa-Ventron.

Alkyllithium reagents were purchased from Aldrich Chemical Co. as solutions in the solvent indicated and were titrated with anhydrous diphenylacetic acid:[26] methyllithium (Et_2O), *n*-butyllithium (hexane). Methylmagnesium chloride (in THF) was purchased from Aldrich. Vinylmagnesium bromide was prepared according to Normant's procedure.[27]

Preparation of Dimethylmagnesium in Tetrahydrofuran. A 3-necked, 100-mL, round-bottomed flask fitted with a reflux condenser, nitrogen inlet, a 50-mL pressure-equalizing dropping funnel, a straight vacuum adapter with serum cap, and a magnetic stirring bar and containing magnesium turnings (1.6 g, 66 mmol) was flame-dried under a stream of nitrogen with stirring of the dry magnesium. After cooling to room temperature under nitrogen the magnesium turnings were washed 3 times in the apparatus via syringe with 15-mL portions of anhydrous THF. The last remaining 5 mL of THF was left in the flask. Freshly distilled methyl iodide (3.8 mL, 60 mmol) in 35 mL of anhydrous THF was added dropwise (slowly) via the addition funnel. The reaction was initiated immediately by heating and was maintained at a moderate rate via continuous addition of the methyl iodide–THF solution. Reflux should be avoided during addition of the methyl iodide solution. After the addition was complete, the reaction mixture was diluted with 20 mL of anhydrous THF, was gently reluxed for 60 min, and then cooled to room temperature without stirring. After sedimentation of a precipitate had occurred, the supernatant was transferred to a dry "hypo-vial" via a gas-tight syringe to give about 45 mL of 0.8 M dimethylmagnesium in THF.

Alternatively, the following procedure may be used: A 100-mL round-bottomed flask equipped with magnetic stirring bar, Claisen adapter, reflux condenser, and a 50-mL pressure-equalizing dropping funnel with serum cap and nitrogen inlet was charged with 2.0 g (82 mmol) of magnesium turnings. The apparatus was flame-dried under a stream of nitrogen and then was allowed to cool to room temperature. Anhydrous diethyl ether (5 mL) was added to the flask, and stirring was begun as 3 mL of a solution of 3.8 mL of methyl iodide (60 mmol) in 30 mL of anhydrous diethyl ether was added all at once. Initiation of the reaction was immediate, and the addition of the ether–methyl iodide solution was continued at such a rate so as to maintain a gentle reflux. After the addition was complete, the reaction was refluxed for an additional 30 min by using an external heat source. Cooling to room temperature was followed by the removal of the diethyl ether by rotary evaporation; traces of ether were removed by exposing the residues to a 0.01 mmHg vacuum at 30 °C for about 1 h. The remaining material was cooled to 0 °C and 35 mL of anhydrous THF was added with swirling. The flask was then left to warm to room temperature as a precipitate sedimented. The supernatant was transferred to a dry "hypo-vial" via a gas-tight syringe to give about 30 mL of 1.4 M dimethylmagnesium in THF.

Preparation of (*S*)-(+)-2-(*p*-Tolylsulfinyl)-2-cyclopentenone ((*S*)-(+)-1). A flame-dried, 3-necked, 250-mL round-bottomed flask fitted with serum cap, nitrogen inlet, addition funnel, and magnetic stirring bar and containing 70 mL of anhydrous THF at −78 °C was charged with *n*-butyllithium (42 mL, 1.5 M, 63 mmol). Freshly distilled 2-bromo-2-cyclopentenone ethylene ketal[28] [bp 38 °C (0.1 mm), 11.7 g, 57 mmol] in 30 mL of anhydrous THF was added dropwise via the addition funnel. Stirring was continued at −78 °C for 90 min. This solution was then transferred under positive nitrogen pressure via a dry ice/acetone-cooled cannula to a vigorously stirred suspension of (S_S)-(−)-menthyl *p*-toluenesulfinate[29] (25 g, 85 mmol) in 500 mL of anhydrous THF in a dry 1-necked, 1-L, round-bottomed flask. Stirring was continued under nitrogen at −78 °C for 15 min, at which time the cold bath was removed and 100–150 mL of saturated NaH_2PO_4 was poured into the reaction vessel. After the solution was warmed to room temperature, the THF was removed under aspirator vacuum. The crude reaction mixture was diluted with 300 mL of H_2O and extracted with 200 mL of $CHCl_3$ and then with 3 × 100 mL of $CHCl_3$. The combined organic extracts were dried over $MgSO_4$, filtered, and rotary evaporated to give about 45 g of a yellow oil. The desired ketal sulfoxide (11.0 g, 74%) corresponding to ketone sulfoxide (*S*)-(+)-**1** was isolated by medium-pressure liquid chromatography (MPLC, 50 × 600 mm column, 240–400 mesh SiO_2, EtOAc, 6 mL/min, R_f 0.4) as an oil: NMR ($CDCl_3$, 100 MHz) δ 7.5 (dd, 4 H), 6.8 (t, J = 2 Hz, 1 H), 4.1–3.7 (m, 4 H), 2.7–2.4 (m, s, 5 H), 2.2–2.0 (m, 2 H); IR ($CHCl_3$, cm^{-1}) 3050 (w), 2890 (s), 1635 (m), 1605 (s), 1080 (s); MS (70 eV), *m/e* 264 (M^+); $[\alpha]^{22}_D$ + 49° (*c* 0.25, $CHCl_3$).

A 500-mL Erlenmeyer flask containing a 2-in. magnetic stirring bar and about 100 g of *anhydrous* cupric sulfate was oven dried at 130 °C for 3 h and then cooled in a desiccator.[30] The ketal sulfoxide (11.0 g, 42 mmol) in 300 mL of reagent grade acetone was poured into the 500-mL flask. The flask was flushed with nitrogen and then stoppered and stirred vigorously overnight. The next morning the entire contents were vacuum filtered through a fine glass frit filter and rinsed thoroughly with 500–700 mL of acetone. Rotary evaporation gave 8.90 g (97%) of the crystalline enone sulfoxide (*S*)-(+)-**1**, mp 118–120 °C. Recrystallization from 10:1 EtOAc/Et_2O (no heating) gave pure (*S*)-(+)-**1** (7.9 g, 90%), mp 121–122 °C. The analytical sample had mp 121.5–122.5 °C: NMR ($CDCl_3$, 80 MHz) δ 8.12 (t, J = 2 Hz, 1 H), 7.46 (dd, 4 H), 3.0–2.4 (m, 4 H), 2.37 (s, 3 H); IR ($CHCl_3$, cm^{-1}) 1715 (s), 1040 (s); MS (70 eV), *m/e* 220 (M^+), 172 (base); $[\alpha]^{22}_D$ +142° (*c* 0.11, $CHCl_3$), $[\alpha]^{22}_{365}$ + 1213°. Anal. Calcd for $C_{12}H_{12}SO_2$: C, 65.43; H, 5.49; S, 14.56. Found: C, 65.53; H, 5.51; S, 14.72.

Preparation of (*S*)-(+)-2-(1-Naphthylsulfinyl)-2-cyclopentenone ((*S*)-(+)-1'). (S_S)-(−)-Menthyl 1-naphthalenesulfinate was prepared as follows: An oven-dried, 3-necked, 200-mL, round-bottomed flask with serum cap, nitrogen inlet, addition funnel with nitrogen inlet and magnetic stirring bar and containing 50 mL of anhydrous THF at −78 °C was charged with *n*-butyllithium (7.1 mL, 1.5 M, 10.7 mmol). 1-Bromonaphthalene (1.35 mL, 9.7 mmol) in 35 mL of anhydrous THF was added dropwise; after the addition was complete, stirring was continued at −78 °C for 90 min. A dry ice/acetone condenser with N_2/SO_2 inlet was placed on the addition funnel, and approximately 125 mL of sulfur dioxide was condensed into the reaction vessel. Stirring was continued at −78 °C for 2 h, followed by warming to 0 °C. The reaction was stirred at 0 °C until excess sulfur dioxide had evaporated. At 0 °C, freshly distilled thionyl chloride (7.1 mL, 98.0 mmol) was added dropwise, and the reaction was allowed to warm to room temperature overnight. The flask contents then were transferred to a 1-necked, 250-mL, round-bottomed flask and the THF removed in vacuo. Excess thionyl chloride was removed as an azeotrope with anhydrous ether (300 mL). This flask, containing the crude sulfinyl chloride, was equipped with an addition funnel, nitrogen inlet, and magnetic stirring bar; the resultant yellow slurry was dissolved in anhydrous THF (125 mL) and cooled to −78 °C, and (−)-menthol (1.65 g, 10.7 mmol) in 40 mL of anhydrous THF was added dropwise followed by addition of freshly distilled pyridine (1.6 mL, 19.4 mmol) in 40 mL of anhydrous THF. The reaction was allowed to warm to room temperature as it stirred overnight. THF then was removed in vacuo and the crude reaction mixture was poured into 200 mL of ice-cold 5% aqueous $NaHCO_3$ and extracted 3 timed with 200 mL of $CHCl_3$. The combined $CHCl_3$ layers were washed with 100 mL of ice-cold 1 M HCl, 100 mL of ice-cold 5% aqueous $NaHCO_3$, and twice with ice-cold aqueous saturated NaCl. The aqueous layers were combined, saturated with NaCl, and back-extracted with 200 mL of $CHCl_3$. The combined $CHCl_3$ layers were dried with anhydrous $MgSO_4$ and filtered, and the $CHCl_3$ was removed in vacuo. The white crystalline sulfinate ester (2.3 g, 72%) was isolated by MPLC (50 × 600 mm column, 240–400 mesh SiO_2, benzene, flow rate 7 mL/min, R_f 0.38) as a mixture of diastereomers [(S_S)-(−), 26%; (R_S)-(+), 46%]. The diastereomers were separated by reverse-phase preparative HPLC (Whatman M9-ODS-3 column, 70:30 acetonitrile/H_2O, 6 mL/min) to give the desired (S_S)-(−)-menthyl naphthalenesulfinate (0.55 g, 17%): HPLC retention time, 42.0 min; mp, 118.0–118.5 °C; NMR ($CDCl_3$, 100 MHz) δ 8.5–8.2 (m, 2 H), 8.1–7.8 (br t, 2 H), 7.8–7.5 (m, 3 H), 4.5–4.0 (m, 1 H), 2.6–0.65 (m, 18 H); $[\alpha]^{24}_D$ −432.1° (*c* 1.84, acetone) (lit.[31] $[\alpha^{24}_D$ −433.2°, mp 118–119 °C).

An oven-dried, 2-necked, 25-mL, round-bottomed flask with serum cap, nitrogen inlet, and stirring bar and containing 1.0 mL of anhydrous

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(31) Andersen, K. K.; Garfield, W.; Papanikolaou, N. E.; Foley, J. W.; Perkins, R. I. *J. Am. Chem. Soc.* **1964**, *86*, 5637.

THF at −78 °C was charged with *n*-butyllithium (1.0 mL, 1.5 M, 1.5 mmol). Freshly Kugelrohr-distilled 2-bromo-2-cyclopentenone ethylene ketal[28] (281 mg, 1.37 mmol) in 1.5 mL of anhydrous THF was added dropwise to the −78 °C *n*-butyllithium solution and the resultant solution stirred at −78 °C for 90 min. This solution was transferred dropwise under positive nitrogen pressure via a dry ice cooled cannula to a briskly stirred −78 °C solution of (S_S)-(−)-menthyl 1-naphthalenesulfinate (457.0 mg, 1.38 mmol) in 7 mL of THF. After the solution was stirred at −78 °C for 5 min the mixture was quenched with aqueous saturated NaH_2PO_4 and allowed to warm to room temperature. THF was removed in vacuo and the residues were extracted with $CHCl_3$. The $CHCl_3$ was dried with anhydrous K_2CO_3; filtration and evaporation gave 813.4 mg of yellow (*S*)-(+)-2-(1-naphthylsulfinyl)-2-cyclopentenone (*S*)-(+)-**1′**) ethylene ketal as an oil that was purified by MPLC (25 × 300 mm column, 240–400 mesh SiO_2, flow rate 9 mL/min, ethyl acetate, R_f 0.39), giving 268.8 mg (65%) of a white crystalline solid: mp 96.5–98.0 °C; NMR ($CDCl_3$, 60 MHz) 8.3–7.2 (m, 7 H), 6.47 (t, J = 2 Hz, 1 H), 4.2–3.5 (m, 4 H), 2.6–1.9 (m, 4 H); IR ($CHCl_3$, cm^{-1}) 3000 (m), 1610 (w), 1505 (w), 1435 (w), 1322 (m), 1050 (s); $[\alpha]^{25}_D$ +233.6 (*c* 0.69, $CHCl_3$); HRMS calcd for $C_{17}H_{16}O_3S$, 300.08202; found, 300.07936.

A 25-mL Erlenmeyer flask equipped with magnetic stirring bar and charged with approximately 12.5 g of $CuSO_4$ was dried in an oven (130 °C) for 1 h and cooled in a desiccator.[30] The ethylene ketal (250.0 mg, 1.22 mmol) in 10 mL of reagent grade acetone was added to the dried $CuSO_4$, the flask was stoppered, and the contents were stirred at room temperature overnight. The suspension was filtered and the $CuSO_4$ cake was washed thoroughly with acetone. Evaporation gave spectroscopically pure (*S*)-(+)-**1′** (200.6 mg, 94%) as a crystalline solid that was recrystallized from 1:1 ethyl acetate/pentane: mp 96.5–97.0 °C; NMR ($CDCl_3$, 80 MHz) δ 8.5–7.2 (m, 8 H), 3.0–2.6 (m, 2 H), 2.6–2.2 (m, 2 H); IR ($CHCl_3$, cm^{-1}) 3000 (m), 1712 (s), 1590 (m), 1500 (w), 1435 (m), 1292 (m), 1055 (s); $[\alpha]^{24}_D$ +291.5° (*c* 1.30, acetone). Anal. Calcd for $C_{15}H_{12}O_2S$: C, 70.29; H, 4.72; S, 12.51. Found: C, 70.05; H, 4.80; S, 12.62.

Preparation of (*R*)-(+)-3-Methylcyclopentanone 2,4-Dinitrophenylhydrazone (2). A. Via Zinc Dibromide Mediated Methylmagnesium Iodide Conjugate Addition. A flame-dried, 2-necked, 10-mL, round-bottomed flask fitted with a serum cap, nitrogen inlet, and magnetic stirring bar and containing enone sulfoxide (*S*)-(+)-**1** (54 mg, 0.25 mmol) in 1 mL of anhydrous THF at room temperature was treated with anhydrous zinc dibromide (100 μL, 0.25 mmol, 2.5 M THF solution) and cooled to −78 °C. Methylmagnesium iodide (500 μL, 0.4 mmol, 0.8 M in THF) was added dropwise via syringe. After 30 min at −78 °C, the reaction vessel was warmed to 0 °C, and the contents were quenched with 3 mL of saturated aqueous NaH_2PO_4, rotary evaporated at 0 °C, and then extracted with diethyl ether (3 × 10 mL). The combined ether extracts were filtered through $MgSO_4$, rotary evaporated at 0 °C, and diluted with $CHCl_3$ for chromatography. Preparative TLC (SiO_2, 20 cm × 20 cm × 1000 μm, 10:1 benzene/acetone, R_f 0.38) gave the pure conjugate adduct (62 mg, 100%) after desorption with acetone and rotary evaporation; NMR ($CDCl_3$, 100 MHz) δ 7.7–7.3 (dd, 4 H), 3.4–1.3 (br m, 6 H), 2.44 (s, 3 H), 1.28 and 0.64 (2d, total 3 H) (the 2 methyl doublets represent cis,trans isomers).

The above conjugate adduct was dissolved in 10 mL of 9:1 THF/H_2O, cooled to 0 °C, and treated with 10 equiv of freshly prepared Al–Hg.[32] The resulting mixture was stirred with slow warming to room temperature overnight, filtered through a fine glass frit filter, rinsed with ether, rotary evaporated at 0 °C, and diluted with 2 mL of absolute ethanol. The ethanolic solution was warmed to 50 °C and treated with several drops of dinitrophenylhydrazine reagent prepared according to ref 33 and then with several drops of 20% H_2SO_4. After 30 min at 50 °C, the reaction mixture was cooled to room temperature (crystallization occurs) and rotary evaporated to dryness. The product was extracted into ether, dried over $MgSO_4$, and purified by preparative TLC (SiO_2, 20 cm × 20 cm × 1500 μm, 10% EtOAc/hexane, R_f 0.20) to give (*R*)-(+)-**2** (49 mg, 71%), $[\alpha]^{28}_D$ +18.4° (*c* 0.55, EtOH), with 87% enantiomeric purity compared to an authentic sample of enantiomerically pure (*R*)-(+)-**2**: $[\alpha]^{28}_D$ 21.1° (*c* 0.35, EtOH);[9] NMR ($CDCl_3$, 100 MHz) δ 9.12 (d, J = 3 Hz, 1 H), 8.30 (dd, J = 3, 11 Hz, 1 H), 7.91 (d, J = 11 Hz, 1 H), 2.6–1.6 (m, 6 H), 1.26–1.1 (m, 5 H).

B. Via Lithium Tetramethylaluminate.[14] A flame-dried, 2-necked, 10-mL, round-bottomed flask fitted with a serum cap, nitrogen inlet, and magnetic stirring bar and containing 1.5 mL of anhydrous THF was charged with trimethylaluminum (2.0 M in toluene, 250 μL, 0.50 mmol) and cooled to −78 °C. To this was added methyllithium (1.4 M, 370 μL, 0.52 mmol) via syringe. After the mixture was stirred at −78 °C for 15 min, enone sulfoxide (*S*)-(+)-**1** (77.5 mg, 0.35 mmol) in 1 mL of THF was added dropwise via syringe. The reaction was stirred at −78 °C for 60 min, then warmed to 0 °C, quenched with 10% HCl, and rotary evaporated to remove the THF. The remainder of the procedure was performed as described above to give 67 mg (68%) of (*R*)-(+)-**2**, $[\alpha]^{28}_D$ +18.6° (*c* 0.29, EtOH), with 88% ee.

C. Via Methyltitanium Triisopropoxide. A flame-dried, 2-necked, 25-mL, round-bottomed flask fitted with a serum cap, nitrogen inlet, and magnetic stirring bar and containing 2 mL of anhydrous THF at −78 °C was charged with chlorotriisopropoxytitanium (700 μL, 65 wt % in CH_2Cl_2, 1.75 mmol).[15] This solution was then treated, via syringe, with methyllithium (1.3 M, 1.90 mL, 1.92 mmol, low halide content) and stirred at −78 °C for 30 min. Cyclopentenone sulfoxide (*S*)-(+)-**1** (107 mg, 0.47 mmol) in 2 mL of THF was added dropwise via syringe. The cold bath was not replenished with dry ice, thus allowing slow warming to room temperature over 4 h. The reaction vessel was then cooled to 0 °C, quenched with 10% HCl, and rotary evaporated to remove the THF. The remainder of the procedure was performed as described above to give (*R*)-(+)-**2** (122 mg, 90%), $[\alpha]^{28}_D$ +19.1° (*c* 0.226, EtOH), with 90% ee.

D. Via Methylmagnesium Chloride. A flame-dried, 2-necked, 10-mL, round-bottomed flask fitted with a serum cap, nitrogen inlet, and magnetic stirring bar and containing 1 mL of anhydrous THF was charged with methylmagnesium chloride (3.0 M, 160 μL, 0.5 mmol) in THF and cooled to −78 °C. A solution of enone sulfoxide (*S*)-(+)-**1** (58 mg, 0.26 mmol) in 0.5 mL of THF was added dropwise via syringe with stirring. After 10 min at −78 °C the reaction mixture was warmed to 0 °C, quenched with 10% HCl, and rotary evaporated to remove the THF. Following the procedure above, there was isolated 68.2 mg (93%) of (*R*)-(+)-**2**, $[\alpha]^{28}_D$ 20.6–21.1° (*c* 0.35, EtOH), with 98–100% ee.

Preparation of (*S*)-(−)-3-Methylcyclopentanone 2,4-Dinitrophenylhydrazone (2). A. Via Addition of Enone Sulfoxide (*S*)-(+)-1 to Methylmagnesium Iodide.[34] A flame-dried, 2-necked, 10-mL, round-bottomed flask fitted with a serum cap, nitrogen inlet, and magnetic stirring bar and containing 0.5 mL of anhydrous THF at room temperature was charged with methylmagnesium iodide (0.8 M in THF, 880 μL, 1.1 mmol) and cooled to −78 °C. Enone sulfoxide (*S*)-(+)-**1** (161 mg, 0.73 mmol) in 1 mL of THF was added dropwise via syringe, and the reaction mixture was stirred at −78 °C for 20 min, then warmed to 0 °C, quenched with 10% HCl, and rotary evaporated at 0 °C to remove the THF. The remainder of the procedure was performed as described above to give 155 mg (76%) of (*S*)-(−)-**2**, $[\alpha]^{28}_D$ −15.1° (*c* 1.13, EtOH), with 72% ee.

B. Via Addition of Dimethylcopperlithium to Enone Sulfoxide (*S*)-(+)-1′. An oven-dried, 25-mL, 2-necked, round-bottomed flask with magnetic stirring bar, serum cap, and nitrogen inlet and containing CuI (29 mg, 0.15 mmol) and 1 mL of anhydrous ether was cooled to 0 °C. Methyllithium (0.19 mL, 1.5 M, 0.29 mmol) was added dropwise via syringe. The resultant solution, cooled to −78 °C, was added dropwise via dry ice cooled cannula to enone sulfoxide (*S*)-(+)-**1′** (31.8 mg, 0.12 mmol) in 0.5 mL of anhydrous THF at −78 °C. Stirring was continued at −78 °C for 20 min followed by warming to 0 °C for 15 min. The reaction was quenched at 0 °C with aqueous saturated NH_4Cl. The THF was removed in vacuo at 0 °C, and the residues were extracted 5 times with 10-mL portions of ether. The combined ether layers were filtered through anhydrous $MgSO_4$. The ether was removed in vacuo at 0 °C. As above, product isolation provided 13.2 mg (42%) of (*S*)-(−)-**2**, $[\alpha]^{28}_D$ −12.0° (*c* 0.25, EtOH), with 57% ee.

Preparation of 2,2,3-Trisubstituted Cyclopentanone (*S*,*S*)-(+)-4. A dry, 25-mL, 2-necked, round-bottomed flask equipped with nitrogen inlet, magnetic stirring bar, and rubber septum was charged with enone sulfoxide (*S*)-(+)-**1** (204 mg, 0.93 mmol), 4.0 mL of THF, and 375 μL (0.93 mmol, 1.0 equiv) of a 2.5 M THF solution of zinc dibromide. The resulting solution was cooled to −78 °C and 1.40 mL (1.40 mmol, 1.5 equiv) of 1.01 M vinylmagnesium bromide was added dropwise over a 5-min period. After the solution was stirred for 1.5 h at −78 °C, the flask was warmed to 0 °C and the reaction quenched with 10 mL of aqueous saturated NaH_2PO_4. The THF was removed by rotary evaporation at ca. 20 °C, and the residues were extracted with 25 mL of diethyl ether. The diethyl ether then was drawn off, dried through a sintered glass funnel containing magnesium sulfate, and evaporated at ca. 20 °C, giving

(32) Cf. Corey, E. J.; Weigel, L. O.; Chamberlin, A. R.; Cho, H.; Hua, D. H. *J. Am. Chem. Soc.* **1980**, *102*, 6613.

(33) Fieser, L. F.; Fieser, M. "Reagents for Organic Synthesis"; Wiley: New York, 1968; Vol. I, p 330.

(34) In this procedure, it is best to remove any traces of metals from the glassware and syringes by sonicating them in aqueous acidic ethylenediaminetetraacetic acid (prepared by acidifying 10% aqueous Na_2EDTA with concentrated HCl until acidic by a litmus paper test), rinsing with water, and drying as usual.

(35) Harrison, I. T. U.S. Patent 3658858. Cf. Posner, G. H.; Chapdelaine, M. J.; Lentz, C. M. *J. Org. Chem.* **1979**, *44*, 3661.

243.5 mg (106%) of the 3-vinyl adduct as a clear oil, which was used without further purification: NMR ($CDCl_3$) δ 7.34 (br q, 4 H), 5.47–4.98 (m, 1 H), 4.79–4.42 (m, 2 H), 3.38 (br t, 1 H), 3.13 (d, 1 H), 2.38 (s, 3 H), 2.54–1.54 (m, 4 H); IR ($CHCl_3$, cm^{-1}) 1741 (s), 1600 (w), 1490 (w), 1260 (m), 1145 (w), 1045 (s).

A dry, 25-mL, 2-necked, round-bottomed flask equipped with nitrogen inlet, magnetic stirring bar, and rubber septum was charged with 25.4 mg (1.06 mmol, 1.1 equiv) of sodium hydride and 1.5 mL of DME. The resulting suspension was cooled to −7 °C and stirred well as 243.5 mg (0.93 mmol, 1.0 equiv) of the 3-vinyl adduct in 2.0 mL of DME was added dropwise over a 5-min period. After the mixture was stirred for 10 min at −7 °C, 2.0 mL (32.1 mmol, 34.5 equiv) of methyl iodide was added, and stirring was continued at −7 °C for 1 h. The nitrogen inlet then was replaced with a vacuum adaptor, and the methyl iodide and DME were removed at −7 °C by aspirator; traces of remaining DME were removed by subsequent exposure to a 0.025 mmHg vacuum. At −7 °C 2 mL of THF, precooled to 0 °C, was added. This solution was transferred at −7 °C via cannula under positive nitrogen pressure to a −7 °C solution of dimethylcopperlithium [made from 531.3 mg (2.80 mmol, 3.0 equiv) of CuI in 2.0 mL of diethyl ether and 4.0 mL (5.32 mmol, 5.7 equiv) of 1.33 M methyllithium] in a 25-mL, 2-necked, round-bottomed flask. An exothermic reaction took place as the solution slowly turned grey-green. After the solution was stirred for 2.5 h, over which time the temperature rose to −2 °C, the flask was cooled to −78 °C, and 1.20 mL (6.98 mmol, 7.5 equiv) of HMPA and 1.13 mL (6.98 mmol, 7.5 equiv) of *tert*-butyl bromoacetate were added sequentially. The reaction slowly warmed to room temperature overnight as the cold bath warmed up. The next morning, 10 mL of aqueous saturated ammonium chloride was added, and the volatile solvents were removed by rotary evaporation. The residues were taken up in diethyl ether; the ether layer was washed 3 times with 25-mL aliquots of aqueous saturated ammonium chloride, twice with 25-mL aliquots of water, and once with a 25-mL aliquot of brine. The diethyl ether layer was drawn off and was dried over potassium carbonate. Filtration and rotary evaporation gave 1.192 g of a clear, yellow liquid, which was placed on a 0.010 mmHg vacuum pump for 6 h, leaving 638 mg. Preparative TLC (SiO_2, 4:1 pentane/Et_2O, R_f 0.40) gave 2,2,3-trisubstituted cyclopentanone (*S*,*S*)-(+)-**4**, R = *t*-Bu (66.4 mg, 30%), in at least 97% isomeric purity, which was identical by GLPC with an authentic racemic sample of (**4**):[18j] $[\alpha]^{25}_D$ +31.1° (*c* 2.71, $CHCl_3$); GLPC retention time, 17.1 min; NMR ($CDCl_3$) δ 5.90–5.55 (m, 1 H), 5.21–5.00 (m, 2 H), 2.80–1.52 (br m, 7 H), 1.41 (s, 9 H), 0.81 (s, 3 H); IR ($CHCl_3$ cm^{-1}) 2980 (m), 1735 (s), 1370 (m), 1360 (w), 1265 (m), 1160 (s).

Preparation of 2,2,3-Trisubstituted Cyclopentanone (*S*,*S*)-(+)-7. A flame-dried, 25-mL, 2-necked, round-bottomed flask fitted with serum cap, 3-way stopcock, and magnetic stirring bar and containing 5 mL of anhydrous THF was charged with 6-methoxy-2-naphthylmagnesium bromide[35] (300 μL, 0.54 mmol) and cooled to −78 °C. After the Grignard reagent had cooled, enone sulfoxide (*S*)-(+)-**1** (107 mg, 0.49 mmol) in 2 mL of THF was added dropwise via syringe. After 20 min at −78 °C, the cold bath was removed to allow warming to room temperature. The THF was removed under reduced pressure (20 mmHg) at 20 °C. The resultant semisolid was treated sequentially with methyl iodide (5 mL) and dry *N*-methylpyrrolidinone (4 mL). The homogeneous reaction mixture was stirred at room temperature overnight (20 °C, 12 h). The crude product was concentrated under vacuum (20 → 0.1 mmHg) and purified by preparative TLC (SiO_2, 20 cm × 20 cm × 1500 μm, 1:1:1 pentane/ether/methylene chloride, R_f 0.33) to give a 2:1 mixture of *cis*- and *trans*-**6**, 149 mg (78%), as a semisolid: NMR ($CDCl_3$, 100 MHz) δ 8.1–7.0 (m, 10 H), 3.95 (s, 3 H), 3.90–1.8 (br m, 5 H), 2.40 (s, 3 H), 1.2 and 0.99 (2 s, 1:2, 3 H); IR ($CHCl_3$, cm^{-1}) 1730 (s), 1601 (s), 140 (s). Anal. Calcd for $C_{29}H_{29}O_3S$: C, 73.44; H, 6.16; S, 8.17. Found: C, 73.50; H, 6.19, S, 7.91.

A flame-dried, 2-necked, 25-mL round-bottomed flask was fitted with a serum cap, nitrogen inlet, and magnetic stirring bar and containing cuprous iodide (100 mg, 0.52 mmol) in 250 μL of anhydrous diethyl ether at 0 °C was charged with "low halide" methyllithium (750 μL, 1.0 mmol) and stirred at 0 °C for 30 min. This homogeneous solution of lithium dimethylcuprate at 0 °C was then treated dropwise via syringe with the above 3-naphthylcyclopentanone (70 mg, 0.18 mmol) in 1 mL of anhydrous THF. After the solution was stirred at 0 °C for 90 min, methyl bromoacetate (275 mg, 1.8 mmol) in 0.8 mL of dry HMPA was added rapidly via syringe. After the solution was stirred at room temperature overnight, the solvents were removed under vacuum. The crude product was then poured into 20 mL of saturated NH_4Cl and extracted with 25 mL of Et_2O. The aqueous phase was then extracted with 3 × 10 mL of Et_2O. The combined ether extracts were washed with 3 × 20 mL portions of H_2O, dried over Na_2SO_4, filtered, rotary evaporated, and left overnight under high vacuum (0.1 mmHg). The remaining oil (120 mg) was purified by reverse-phase HPLC on a Whatman M9-ODS-3 column with 70:30 acetonitrile/water at a flow rate of 3.5 mL/min (retention time = 17.2 min) to give the desired (*S*,*S*)-(+)-**7** (54 mg, 93%) as a solid, mp 105–115 °C. Crystallization from ether–pentane gave pure (*S*,*S*)-(+)-**7** (52 mg, 90%), mp 116.5–118 °C: NMR ($CDCl_3$, 80 MHz) δ 7.80–7.10 (m, 6 H), 3.92 (s, 3 H), 3.73 (s, 3 H), 2.95–2.10 (m, 7 H), 0.66 (s, 3 H); IR ($CHCl_3$, cm^{-1}) 1735 (vs), 1635 (w), 1605 (m); MS (70 eV) *m/e* 326 (M^+), 272 (base); $[\alpha]^{22}_D$ +1.9° (*c* 0.36, $CHCl_3$), $[\alpha]^{22}_{365}$ +168°.

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Registry No. (*S*)-(+)-**1**, 79681-26-8; (*S*)-(+)-1′, 82136-10-5; (*R*)-(+)-**2**, 82136-11-6; (*S*,*S*)-(+)-**4** (R = *t*-Bu), 82136-12-7; *cis*-**5**, 79681-28-0; *trans*-5, 79732-89-1; *cis*-**6**, 82136-13-8; *trans*-*6*, 82188-51-0; (*S*,*S*)-(+)-**7**, 59531-62-3; *N*-methylpyrrolidinone, 872-50-4; 2-bromo-2-cyclopentenone ethylene ketal, 68241-78-1; (*S*)-(−)-methyl *p*-toluenesulfinate, 1517-82-4; (*S*)-(−)-methyl 1-naphthalenesulfinate, 2642-99-1; 1-bromonaphthalene, 90-11-9; (B)-(−)-methyl 1-naphthalenesulfinate, 82188-52-1; *cis*-2,3-dimethylcyclopentanone DNP, 82136-14-9; *trans*-2,3-dimethylcyclopentanone DNP, 82188-53-2; (−)-menthol, 2216-51-5; vinyl bromide, 593-60-2; 6-methoxy-2-naphthyl bromide, 5111-65-9; (*S*)-(+)-**1** ketal sulfoxide, 82136-15-0; (*S*)-(−)-2, 74965-63-2.

(36) **Note Added in Proof**: Methylmagnesium iodide in THF at low temperature apparently is really dimethylmagnesium (Paris, G. E.; Ashby, E. C. *J. Am. Chem. Soc.* **1971**, *93*, 1206).