of the propensity to form the norbornyl cation by σ-bond-assisted solvolysis.[21] It is surmised that the tendency of radical oxidation by metal ions may be related to the extent of the s character of the orbital containing the unpaired electron. The cyclohexenyl radical, containing the unpaired electron in a purely p orbital, is much more readily oxidized than acyclic secondary radicals from 1-hexene and 3,3-dimethyl-1-butene by Cu^{2+} ions. The 2-norbornyl radical is skeletally strained, forcing the singly occupied orbital to have a large percent of s character. We suspect this is one of the factors that retards oxidation.

Experimental Section

General Conditions. The apparatus and analytical procedures were the same as those used in the previous papers.[3,4]

Photolysis of Benzophenone and Cu(acac)$_2$ in the Presence of Olefins. A solution of Cu(acac)$_2$ (0.5 g, 1.92 mmol), benzophenone (1.0 g, 5.55 mmol), and an olefin (5-6 mmol) in glacial acetic acid (100-200 mL) was irradiated under nitrogen for several hours to give a yellow solution and/or until metallic copper began to form. The photolysate was diluted with water (400 mL) and extracted with ether (3 × 100 mL). The ether extracts were washed with Na_2CO_3 solution and water and dried over $MgSO_4$. GC analysis showed the peaks of the acetylacetone addition products eluting before benzophenone in addition to the minor peaks of oxetanes[13] and the addition products[12] of benzophenone to acetylacetone at higher retention times than benzophenone. The crude products were first chromatographed on alumina. The fractions collected were rechromatographed by column chromatography or preparative HPLC to give the addition products. The GC yields were calculated by taking the sum of acetylacetone and its derivatives as 100%. The photoreduction in acetonitrile was generally slower and gave more byproducts arising from benzophenone addition.

In general, if the photoreduction was stopped before metallic copper formation and the fading of the blue color, the byproduct formations were minimal. The addition product of triplet-state benzophenone to olefins (oxetanes) and acetylacetone rapidly increased after the disappearance of Cu(acac)$_2$. GC was carried out with a 10% SE-30 capillary column (isothermal or temperature programming, 100-240 °C at 10 °C/min).

(1) Norbornene. The GC retention times were 0.8 min (acetylacetone), 9.4 min (**6**), 5.2 min (**7**), 3.8 min (**8**), and 7.9 min; the last peak was tentatively assigned to 2-*endo*-norbonylacetone (2.5%). The GC peak of **8** matched with one of the peaks of a mixture of *exo*- and *endo*-2-acetylnorboranes which were prepared by the hydrogenation of 2-acetyl-5-norbornene (Aldrich, an exo and endo mixture). An authentic sample of **6** was prepared by Mn(OAc)$_2$ oxidation of acetylacetone and norbornene[22] in acetic acid. Diketone **6** was treated with hot NaOH solution in aqueous MeOH to afford ketone **7**. The semicarbazone of **7** was obtained as colorless needles, mp 192-195 °C (reported 194-195 °C).[23]

(2) 3,3-Dimethyl-1-butene. The GC retention times were 4.1 min (**9**), 6.4 min (**10**), 4.5 min (**11**), and 4.9 min (**12**). The products **11** and **12** were isolated as a mixture, showing two GC peaks (100 °C isothermal) at 4.9 min for **11** and 5.1 min for **12**.

(3) 1-Hexene. The GC retention times were 1.5 min (acetylacetone), 3.03 min (**14**), 3.13 min (**13**), and 4.16 min (**15**). Products **13** and **14** were isolated as a mixture by preparative GC (25% SE-30, 150-240 °C at 15 °C/min).

(4) Cyclohexene. The GC retention times were 5.9 min (**16**) and 8.5 min (**17**). An authentic sample of **15** was prepared by the oxidation of cyclohexene with Hg(OAc)$_2$ in acetic acid.[24]

ESR Experiments. The details of the apparatus and recordings were the same as those described in the previous publication.[4] The light source was an Osram HBO 200-W high-pressure mercury lamp housed in a Wild Leitz illuminator and was filtered through Wild BG-38 and Corning filter No. 7-60 (glass no. 5840, 4.5 mm thickness) to pass the emission centered around 365 nm. Benzene, toluene, and methylene chloride were Fischer Spectrograde, and NMP (Aldrich) was used as supplied. The solution for ESR spectroscopy contained Cu(acac)$_2$ (0.01-0.001 M), benzophenone (0.005 M), and NMP (0.002 M) in the desired solvent. Each experiment was supported by control experiments to ascertain the origin of the spectra. For example, irradiation of a solution containing benzophenone and NMP in CH_2Cl_2 developed only a weak signal (g value 2.0078, a_N = 8.13 G) after 15 min. Irradiation of a similar solution in toluene developed a triplet of triplet (a_N = 15.25, a_H = 7.63 G, g value 2.0058) which is similar to that observed previously.[8,11]

A solution containing Cu(acac)$_2$ (0.001 M) and benzophenone (0.005 M) in benzene was purged with either purified nitrogen or hydrogen. The solution was irradiated in the ESR cavity as described, and the four-line signal of Cu(acac)$_2$ was scanned every 2 min. The intensity of the former remained constant, but that of the latter decreased regularly with concurrent formation of a copper mirror on the tube surface.

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(21) Berson, J. A. In "Molecular Rearrangements"; de Mayo, P., Ed.; Interscience: New York, 1963; Part 1, p 111.

(22) Vinogradov, M. G.; Fedorova, T. M.; Nikishin, G. I. *Russ. J. Org. Chem.* **1976**, *12*, 1183.

(23) Reusch, W. *J. Org. Chem.* **1962**, *27*, 1982.

(24) Fieser, L. F.; Fieser, M. "Reagents for Organic Synthesis"; John Wiley: New York, 1967; p 646.

Total Synthesis of Natural Estrone and Estradiol Methyl Ethers in Extremely High Enantiomeric Purity via an Asymmetric Michael Addition to an Unsaturated Sulfoxide

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Abstract: Methoxytetralone enolate ion **1b** underwent an asymmetric Michael addition to enantiomerically pure cyclopentenone sulfoxide (*S*)-(+)-**2** with a diastereoselectivity of 91-94%. A series of eight additional steps led to (+)-estrone methyl ether (**11**) in overall 6.3% yield. Chiral HPLC analysis of (+)-estradiol **12** indicated an enantiomeric purity of at least 97.3%.

Steroidal sex hormones such as estrone and estradiol have attracted the attention of organic chemists because these tetracycles possess important physiological activity and because they represent a clear and severe challenge for total synthesis.[1,2] In

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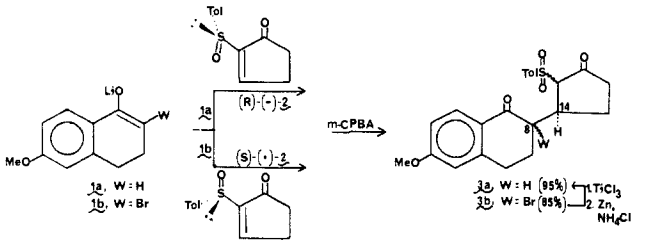
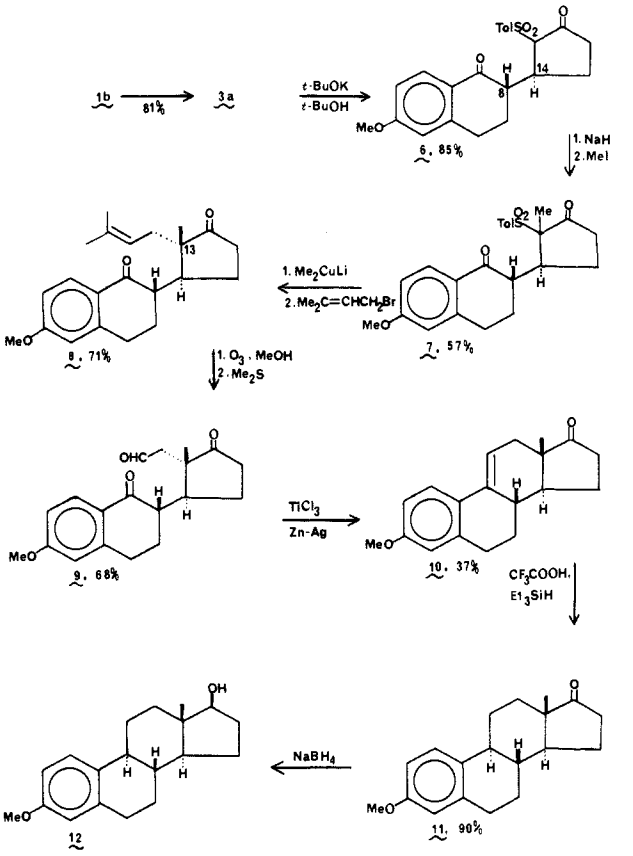
Scheme I



recent years, two general approaches to such commercially important, ring-A aromatic steroids have been used very successfully: (1) formation of rings C and D in high enantiomeric purity by asymmetric intramolecular aldol cyclizations catalyzed by amino acids[3] and (2) formation of rings B and C by intramolecular Diels–Alder cycloadditions.[4] In 1981, we reported a one-pot AB + D + C total synthesis of racemic 9,11-dehydroestrone in 8% yield via sequential 2 + 2 + 2 *Mi*chael–*Mi*chael–*r*ing *c*losure (MIMIRC) reactions.[5] We are now pleased to report a very highly diastereoselective Michael addition of a ketone enolate ion to an enantiomerically pure 2-(arylsulfinyl)-2-cyclopentenone as the key step in an effective *asymmetric* total synthesis (AB + D + C) of estrone and estradiol methyl ethers in at least 97.3% enantiomeric purity and with natural absolute stereochemistry.

This key step represents induction of asymmetry at the prochiral β-carbon atom of an enantiomerically pure α,β-ethylenic sulfoxide, a widely recognized goal of considerable synthetic potential.[6] Although recent and impressive progress has been made in highly stereocontrolled conjugate addition of *hydrocarbon* groups to 2-(arylsulfinyl)cycloalkenones,[7] asymmetric Michael additions of *enolate ions* still present a significant challenge of substantial international interest.[8]

Scheme II



Results and Discussion

During our recent asymmetric synthesis of natural (−)-methyl jasmonate of high enantiomeric purity,[8j] we found that asymmetric Michael addition of an α-*mono*substituted lithioacetate ester to an enantiomerically pure β-keto sulfoxide proceeded via a nonchelated form of the keto sulfoxide, whereas a *di*substituted lithioacetate ester proceeded via a chelated form of the β-keto sulfoxide. Likewise, as shown in Scheme I we have found that α-monosubstituted ketone lithium enolate **1a** reacts with cyclopentenone sulfoxide (*R*)-(−)-**2** in a nonchelated form, whereas α,α-disubstituted ketone lithium enolate **1b**[9] reacts selectively with the chelated form of the β-keto sulfoxide. By combining monosubstituted enolate **1a** with sulfoxide (*R*)-(−)-**2** and separately by combining disubstituted enolate **1b** with the antipodal sulfoxide (*S*)-(+)-**2**, we have prepared Michael adducts **3a** and **3b**, respectively, each having the desired natural absolute stereochemistry at carbon 14 (steroid numbering). A reasonable but speculative interpretation of these results is that the chelated and nonchelated forms of the β-keto sulfoxides are both present in the reaction medium, with the nonchelated form predominating but being less electrophilic (i.e., less reactive) than the chelated form. A relatively unencumbered α-*mono*substituted enolate would then react with the more abundant nonchelated form of the β-keto sulfoxide, whereas an α,α-*di*substituted enolate having a sterically congested nucleophilic center would react selectively with the more reactive chelated form of the β-keto sulfoxide.

(1) (a) Blickenstaff, R. T.; Ghosh, A. C.; Wolf, G. C. "Total Synthesis of Steroids"; Academic Press: New York, 1974. (b) Marples, B. A. *Terpenoids Steroids* **1982**, *11*, 187. (c) Grieco, P. A.; Takigawa, T.; Schillinger, W. J. *J. Org. Chem.* **1980**, *45*, 2247. (d) Mikhail, G.; Demuth, M. *Helv. Chim. Acta* **1983**, *66*, 2362. (e) Bull, J. R.; Bischofberger, K. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2723. (f) Daniewski, A. R.; Kowalcyzk-Przewloka, T. *J. Org. Chem.* **1985**, *50*, 2976.

(2) For a biomimetic polyolefin cyclization leading to estrone, see: Bartlett, P. A.; Johnson W. S. *J. Am. Chem. Soc.* **1973**, *95*, 7501.

(3) (a) Cohen, N. *Acc. Chem. Res.* **1976**, *9*, 412. (b) Eden, U.; Gibian, H.; Neet, G.; Sauer, G.; Wiechert, R. *Chem. Ber.* **1976**, *109*, 2948. (c) Danishefsy, S.; Cain, P. *J. Am. Chem. Soc.* **1976**, *98*, 4975. (d) Agami, C.; Levisalles, J.; Puchot, C. *J. Chem. Soc., Chem. Commun.* **1985**, 441.

(4) (a) Kametani, T.; Nemoto, H. *Tetrahedron* **1981**, *37*, 3. (b) Oppolzer, W. *Pure Appl. Chem.* **1981**, *53*, 1181. (c) Oppolzer, W. *Synthesis* **1978**, 793. (d) Quinkert, G.; Stark, H. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 637. (e) Funk, R. L.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1979**, *101*, 215. (f) Nicolaou, K. C.; Barnette, W. E.; Ma, P. *Ibid.* **1980**, *102*, 6885. (g) Ito, Y.; Nakatsuka, M.; Saegusa, T. *Ibid.* **1981**, *103*, 476. (h) Posner, G. H.; Hulce, M.; Mallamo, J. P.; Drexler, S. A.; Clardy, J. *J. Org. Chem.* **1981**, *46*, 5246. (i) Van Royen, L. A.; Mijngheer, R.; De Clercq, P. J. *Tetrahedron Lett.* **1983**, *24*, 3145. (j) Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 183. (k) Cf.: Bleasdale, D. A.; Jones, D. W. *J. Chem. Soc., Chem. Commun.* **1983**, 1027.

(5) Posner, G. H.; Mallamo, J. P.; Black, A. Y. *Tetrahedron* **1981**, *37*, 3921. For a review, see: Posner, G. H. *Chem. Rev.*, in press.

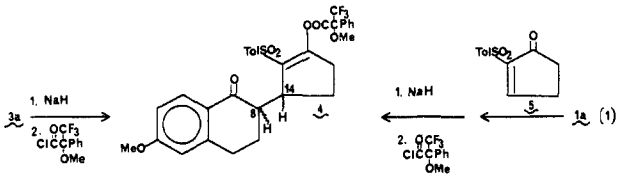
(6) (a) Marino, J. P.; Perez, A. D. *J. Am. Chem. Soc.* **1984**, *106*, 7643 and references therein. (b) Tsuchihashi, G.; Mitamura, S.; Inoue, K. *Tetrahedron Lett.* **1973**, 323. (c) Nudelman, A. "The Chemistry of Optically Active Sulfur Compounds"; Gordon and Breach Science Publishers: New York, 1984. (d) For reviews see: Posner, G. H. In "Asymmetric Synthesis"; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2, Part A, Chapter 8, p 225 and references therein. Colonna, S.; Annunziata, R.; Cinquini, M. *Phosphorus Sulfur* **1981**, *10*, 197. Solladiē, G. *Synthesis* **1981**, 185. (e) cf.: Johnson, C. R. *Acc. Chem. Res.* **1973**, *6*, 341. Johnson, C. R.; Lockard, J. P.; Kennedy, E. R. *J. Org. Chem.* **1980**, *45*, 264.

(7) (a) Posner, G. H.; Frye, L. L.; Hulce, M. *Tetrahedron* **1984**, *40*, 1401. (b) Posner, G. H.; Hulce, M. *Tetrahedron Lett.* **1984**, *25*, 379. (c) Posner, G. H.; Kogan, T. P.; Hulce, M. *Ibid.* **1984**, *25*, 383. (d) Posner, G. H.; Kogan, T. P.; Haines, S. R; Frye, L. L. *Ibid.* **1984**, *25*, 2627. (e) Posner, G. H.; Frye, L. L. *Isr. J. Chem.* **1984**, *24*, 88. (f) Frye, L. L.; Kogan, T. P.; Mallamo, J. P.; Posner, G. H. *Org. Synth.* **1985**, *64*, 196. (g) Posner, G. H.; Asirvatham, E.; Ali, S. *J. Chem. Soc., Chem. Commun.* **1985**, 542. (h) Posner, G. H. *Chem. Scr.* **1985**, *25*, 157.

(8) (a) Wynberg, H.; Helder, R. *Tetrahedron Lett.* **1975**, 4057. (b) Hermann, K.; Wynberg, H. *J. Org. Chem.* **1979**, *44*, 2738. (c) Cram, D. J.; Sogah, G. D. Y. *J. Chem. Soc., Chem. Commun.* **1981**, 625. (d) Matsumoto, K.; Uchida, T. *Chem. Lett.* **1981**, 1673. (e) Hodge, P.; Khosdel, E.; Waterhouse, J. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2205. (f) Oppolzer, W.; Pitteloud, R.; Bernardinelli, G.; Baettig, K. *Tetrahedron Lett.* **1983**, *24*, 4975. (g) Brunner, H.; Hammer, B. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 312. (h) Pfau, M.; Revial, G.; Guingant, A.; D'Angelo, J. *J. Am. Chem. Soc.* **1985**, *107*, 273. (i) Nebout, B.; de Jeso, B.; Pommier, J.-C. *J. Chem. Soc., Chem. Commun.* **1985**, 504. (j) Posner, G. H.; Asirvatham, E. *J Org. Chem.* **1985**, *50*, 2589.

(9) For another synthetic use of ketone α-bromo enolate ions, see: Mukaiyama, T.; Haga, T.; Iwasawa, N. *Chem. Lett.* **1982**, 1601.

To determine the level of asymmetric induction at C_{14} during formation of the carbon–carbon bond linking atoms 8 and 14 in 1,5-diketone **3a**,[10] we chose to enolize and *O*-acylate this system (thereby decreasing the number of chiral centers) by using the enantiomerically pure Mosher acid chloride to produce the enol ester derivative **4** in high yield (eq 1); enol ester **4** was prepared



(1)

also from cyclopentenone sulfone **5** (eq 1). The 400-MHz ^1H NMR spectrum of the enol esters **4** derived from *racemic* 1,5-diketone **3a** revealed well-resolved diastereotopic resonances for the four possible diastereomeric products with a very nearly 1:1 ratio for both the syn and anti pairs of diastereomers (i.e., C_{8H_α}–C_{14H_α} and C_{8H_β}–C_{14H_β}, C_{8H_β}–C_{14H_α} and C_{8H_α}–C_{14H_β}; see Experimental Section for details).[11] In this way, the diastereomeric purity of the enol esters **4** derived from enolate **1a** via Michael adduct **3a** was shown to be only 54%. In very pleasing contrast, however, the diastereomeric purity of the enol esters **4** derived from bromo enolate **1b** via Michael adduct **3b** (after reductive cleavage of bromine to give Michael adduct **3a**, and with no intermediate purification, Scheme I) was shown to be 91–94%!

As shown in Scheme II, Michael adduct **3a**, derived from **3b** of high stereochemical purity, was equilibrated in base to provide the C_{8H_β} diastereomer **6** in high yield. At this point, the diastereomeric purity was assayed once again via enol esters **4**, and it was found to be essentially unchanged (95% de). Methylation of β-keto sulfone **6** was followed by a critical step involving Me_2CuLi-induced reductive cleavage of the sulfonyl group followed by C_{13}-dimethallylation. This transformation (**7** → **8**) was particularly risky because any retro-Michael reaction followed then by Michael readdition under these aprotic conditions would have destroyed the crucial chiral center at C_{14} (i.e., achiral 2-methyl-2-cyclopentenone would have been formed); it was especially gratifying therefore to find minimal, if any, loss of enantiomeric purity at this stage, as shown ultimately by the extremely high enantiomeric purity of our synthetic estrone (+)-**11**.

It is noteworthy that the enolate ion formed by Me_2CuLi-induced reductive cleavage of β-keto sulfone **7** could not be alkylated effectively with allyl bromide itself. We have noted recently that some α-cupriocarbonyl compounds possess substantial Lewis acid character and therefore may promote S_N1-type reactions; for example, 3-cuprio-2-pyrone reacts more effectively with piperonyl bromide than with benzyl bromide.[12] The enolate ion derived by Me_2CuLi-promoted reductive cleavage of β-keto sulfone **7** did react successfully with ethyl bromoacetate to form the ethyl ester corresponding to aldehyde **9** in very good yield.[5] Attempts to cause reductive cleavage of β-keto sulfone **7** by using lithium naphthalenide[13] were not encouraging.

Ozonolysis of dimethallylated diketone **8** led to diketo aldehyde **9**, which had been prepared previously by Ziegler and Lim in *racemic* form.[14] The McMurry reductive cyclization procedure was used to convert keto aldehyde **9** into (+)-9,11-dehydroestrone methyl ether (**10**); the yield of this reductive cyclization varied from 30% to 50%, generally being about 50% when 100-mg amounts of reactant were used and being about 30% when 20 mg of reactant was used. Such variability has been noted before in this type of reaction.[15]

The 9,11 double bond in dehydroestrone (+)-**10** allows easy access to 11-oxygenated estrogens of high enantiomeric purity and of pronounced biological activity[16] as well as access to 19-norcorticoids after reduction of the aromatic ring.

Reduction of (+)-9,11-dehydroestrone **10** produced (+)-estrone methyl ether (**11**) in 90% yield,[17] spectroscopically indistinguishable from a sample of (+)-**11** derived from natural sources. Without recrystallization,[18] estrone (+)-**11** was reduced to form estradiol (+)-**12**, which was analyzed by chiral HPLC;[19] its enantiomeric purity was determined to be at least 97.3% (i.e., 98.65:1.35 *d*:*l*)!

In conclusion, Schemes I and II represent a convergent, nine-step, highly asymmetric total synthesis of natural (+)-estrone methyl ether (**11**) with an overall yield of 6.3%. Scheme I shows the first example of a Michael addition of a ketone enolate ion to an enantiomerically pure, α,β-ethylenic sulfoxide which proceeds with *close to complete π-facial diastereoselectivity*. Especially noteworthy also is the absence of any appreciable retro-Michael reaction in the conversion of α-sulfonyl ketone **7** into α-dimethallyl ketone **8**. Finally, Scheme II represents an effective non-aldol[3] and non-*o*-quinodimethane[4] approach to asymmetric total synthesis of biologically active ring-A aromatic steroids of extremely high enantiomeric purity.

We are actively pursuing applications of this methodology toward asymmetric syntheses of other physiologically valuable compounds in very high enantiomeric purity.[20]

Experimental Section[21]

Preparation of Michael Adduct 3a (from 1a). Into a 250-mL round-bottom flask was placed 3.39 g (33.5 mmol; 4.70 mL) of diisopropylamine and 25 mL of THF. The solution was cooled to −78 °C and treated dropwise with 2.15 g (33.6 mmol; 25 mL) of *n*-butyllithium (1.36 M in hexanes). Stirring was continued at −78 °C for 30 min, and then 5.36 g (30.4 mmol) of 6-methoxy-1-tetralone in 25 mL of THF was added dropwise over 20 min. After being stirred for 90 min at −78 °C, the reaction mixture was treated with the supernatant from a centrifuged mixture of 9.93 g (91.4 mmol; 13.0 mL) of chlorotrimethylsilane and 9.44 g (93.3 mmol; 13.0 mL) of triethylamine at −78 °C, warmed to 0 °C, stirred for 2 h, and then allowed to stir at room temperature for 18 h. The mixture was poured into a separatory funnel containing 100 mL of

(10) In all cases, Michael adduct **3a** was obtained as a mixture of epimers at C_8 (C_{8H_α} and C_{8H_β}); the stereochemistry assigned to these structures results from their separate conversion to the known diketo aldehydes **9** and C_8-epi **9**,[14a] Scheme II.

(11) The assignment of the absolute stereochemistry at C_{14} for the enol esters **4** derived from Michael adduct **3a** (C_{8H_α}) and Michael adduct **3a** (C_{8H_β}) follows from (1) the interconversion of these enol esters by epimerization at C_8 [this is accomplished for enol esters **4** derived from Michael adduct **3a** (C_{8H_α}) by simply allowing the reaction mixture to stir for 1.5 h after the addition of the Mosher acid chloride in the derivatization reaction before the addition of saturated aqueous sodium dihydrogen phosphate; see Experimental Section for details], allowing a correlation of the diastereotopic resonances between the syn and anti pairs of diastereomeric enol esters **4**, and (2) the conversion of Michael adduct **3a** (C_{8H_β}) (β-keto sulfone **6**) to estrone methyl ether (**11**), thereby allowing a correlation of the chemical shift of the diastereotopic resonances for enol esters **4** (C_{8H_β}–C_{14H_α} and C_{8H_α}–C_{14H_β}) with absolute stereochemistry at C_{14} (see Experimental Section for details).

(12) Posner, G. H.; Harrison, W.; Wettlaufer, D. *J. Org. Chem.* **1985**, *50*, 5041.

(13) Cohen, T.; Wiesenfeld, R. B. *J. Org. Chem.* **1979**, *44*, 3601.

(14) (a) Ziegler, F. E.; Lim, H. *J. Org. Chem.* **1982**, *47*, 5229. (b) We thank Professor Ziegler for sending us experimental details.

(15) McMurry, J. E.; Miller, D. D. *J. Am. Chem. Soc.* **1983**, *105*, 1660 and references therein. We thank Professor McMurry for some helpful comments. Cf.: Denis, J. M.; Girard, C.; Conia, J. M. *Synthesis* **1972**, 549.

(16) (a) Azadian-Boulanger; Bertin D. *Chim. Ther.* **1973**, 451. (b) Gabbard, R. B.; Hamer, L. F.; Segaloff, A. *Steroids* **1981**, *37*, 243. cf.: Schoenamon, K.; Van Vliet, N.; Zeelen, F. J. *Eur. J. Med. Chem.–Chim. Ther.* **1980**, *15*, 333.

(17) These conditions (CF_3COOH/Et_3SiH) were first used in these labs in 1981 by J. P. Mallamo (ref 5); Cf.: Chekhlov, A. N.; Ionov, S. P.; Dodonov, M. V.; Ananchenko, S. N. *Bioorg. Khim.* **1983**, *9*, 978: *Chem. Abstr.* **1983**, *99*, 176136g.

(18) All intermediates were carried on as the chromatograpically purified material; only analytical samples of the intermediates were recrystallized.

(19) Our synthetic estradiol (+)-**11** was derivatized by using 3,5-dinitrophenyl isocyanate and was compared on chiral HPLC (Pirkle, W. H.; Finn, J. M.; Schreiner, J. L.; Hamper, B. C. *J. Am. Chem. Soc.* **1981**, *103*, 3964) to the corresponding ester derivatives of racemic estradiol and natural (+)-estradiol 3-methyl ethers. We warmly thank Professor W. H. Pirkle and G. S. Mahler (University of Illinois) for performing this assay.

(20) Posner, G. H.; Weitzberg, M.; Asirvatham, E.; Cun-Leng, H.; Clardy, J. *Tetrahedron*, in press.

(21) Methyllithium was titrated by using diphenylacetic acid/tetrahydrofuran [Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.]. *n*-Butyllithium was titrated by using 2,5-dimethoxybenzyl alcohol/tetrahydrofuran [Winkle, M. R.; Lansinger, J. M.; Ronald, R. C. *J. Chem. Soc., Chem. Commun.* **1980**, 87.].

CH_2Cl_2, 50 g of ice, and 50 mL of saturated aqueous sodium bicarbonate and shaken quickly, and the organic layer was separated. The aqueous layer was extracted with an additional 50 mL of CH_2Cl_2. The combined organic layers were dried over K_2CO_3. Kugelrohr distillation (90 °C, 0.05 mmHg) gave 6.79 g (95%) of the methoxytetralone enol silyl ether: ^{1}H NMR δ 7.30–6.45 (m, 3 H), 4.80 (t, J = 4.6 Hz, 1 H), 3.53 (s, 3 H), 2.65–2.30 (m, 2 H), 2.20–1.90 (m, 2 H), 0.00 (s, 9 H); IR cm^{-1} (CCl_4) 1640, 1602. HRMS calcd for $C_{14}H_{20}O_2Si$: m/z 248.1233. Found: 248.1229.

A solution of 714 mg (2.87 mmol) of the methoxytetralone enol silyl ether in 28 mL of THF was cooled to 0 °C and treated dropwise with 69.4 mg (3.16 mmol; 2.15 mL) of methyllithium (1.47 M in ether). The ice bath was then removed and the reaction mixture was stirred at room temperature for 1 h. To the solution at −78 °C was added 550 mg (2.50 mmol) of (*R*)-(−)-2-(*p*-tolysulfinyl)-2-cyclopentenone (**2**)[7f] in 2.75 mL of the THF over a 0.5-h period. The reaction mixture was stirred at −78 °C for 2 h, and then it was poured into 25 mL of 0 °C saturated aqueous ammonium chloride. The organic solvents were evaporated at 0 °C, and the residue was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were dried over $MgSO_4$, and then the solvents were removed.

The crude Michael adduct in 13 mL of CH_2Cl_2 was added to a slurry of 647 mg (3.0 mmol) of *m*-chloroperbenzoic acid (80% pure) in 10 mL of CH_2Cl_2 at −78 °C over a 5-min period. The reaction mixture was then warmed to 0 °C and stirred for 0.5 h. After being stirred for an additional 0.5 h at room temperature, the reaction mixture was diluted with 200 mL of CH_2Cl_2 and extracted with saturated aqueous sodium bicarbonate (2 × 100 mL). The organic extract was dried over potassium carbonate and concentrated to provide 1.21 g of crude **3a**. Short-path chromatography (4:1:1; hexanes/ether/CH_2Cl_2) on 70 g of silica gel afforded 825.2 mg (80%) of Michael adduct **3a** (C_{8H_α}) and 156.7 mg (15%) of Michael adduct **3a** (C_{8H_β}) as white crystalline solids. Michael adduct **3a** (C_{8H_α}): ^{1}H NMR δ 7.92 (d, J = 8.5 Hz, 1 H), 7.74 (d, J = 8.6 Hz, 2 H), 7.36 (d, J = 8.6 Hz, 2 H), 6.83–6.70 (m, 2 H), 4.51 (d, J = 7.3 Hz, 1 H), 3.86 (s, 3 H), 3.28–1.74 (m, 10 H), 2.46 (s, 3 H); IR cm^{-1} ($CHCl_3$) 1744, 1663. HRMS calcd for $C_{23}H_{24}O_5S$: m/z 412.1345. Found: 412.1354. An analytical sample was recrystallized from toluene/ether; mp 170–171 °C. Anal. Calcd for $C_{23}H_{24}O_5S$: C, 66.97; H, 5.86; S., 7.77. Found: C, 67.25; H, 5.86; S, 7.96. Michael adduct **3a** (C_{8H_β}): ^{1}H NMR δ 7.96 (d, J = 8.6 Hz, 1 H), 7.72 (d, J = 7.6 Hz, 2 H), 7.35 (d, J = 7.9 Hz, 2 H), 6.84–6.69 (m, 2 H), 3.86 (s, 3 H), 3.64 (d, J = 7.0 Hz, 1 H), 3.6–1.64 (m, 10 H), 2.44 (s, 3 H); IR cm^{-1} ($CHCl_3$) 1747, 1669 An analytical sample was recrystallized from toluene/ether; mp 127–128.5 °C. Anal. Calcd for $C_{23}H_{24}O_5S$ (same as for **3a** (C_{8H_α})). Found: C, 66.79; H, 5.87; S, 8.00.

Preparation of Michael Adduct 3a (from 1b). A solution of 2.66 g (16.5 mmol; 3.48 mL) of hexamethyldisilazane in 13.0 mL of THF was cooled to −78 °C and treated dropwise with 1.06 g (16.5 mmol; 12.6 mL) of *n*-butyllithium (1.31 M in hexanes). After the mixture was stirred for 1 h at −78 °C, 2.71 g (15.4 mmol) of 6-methoxy-1-tetralone in 13.0 mL of the THF was added over a 20-min period. The reaction mixture was stirred for 2 h at −78 °C, and then it was treated with 2.46 g (15.4 mmol; 789 μL) of bromine[22] over a 5-min period. The reaction mixture was quenched by the addition of 100 mL of saturated aqueous ammonium chloride 5 min after the addition was complete. The mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated to give 3.763 g of crude 2-bromo-6-methoxy-1-tetralone. Short-path chromatography (10:1:1:1; petroleum ether/ether/toluene/CH_2Cl_2) on 60 g of silica gel afforded 3.230 g (82%) of 2-bromo-6-methoxy-1-tetralone **1b** as a white solid. Recrystallization from $CHCl_3$/ether provided 2.404 g (61%): mp 79–81 °C; ^{1}H NMR δ 8.06 (d, J = 8.9 Hz, 1 H), 6.88–6.86 (m, 1 H), 6.72 (d, J = 2.4 Hz, 1 H), 4.69 (t, J = 4 Hz, 1 H), 3.87 (s, 3 H), 3.35–3.23 (m, 1 H), 2.91–2.81 (m, 1 H), 2.56–2.38 (m, 2 H); IR cm^{-1} ($CHCl_3$) 1671, 1598. HRMS calcd for $C_{11}H_{11}BrO_2$: m/z 253.9942. Found: 253.9945.

A solution of 492 mg (3.05 mmol; 643 μL) of hexamethyldisilazane in 7.5 mL of THF was cooled to −78 °C and treated dropwise with 179 mg (2.79 mmol; 1.86 mL) of *n*-butyllithium (1.50 M in hexanes). After the mixture was stirred for 1 h at −78 °C, 778 mg (3.05 mmol) of 2-bromo-6-methoxy-1-tetralone in 3.0 mL of THF was added over a 15-min period. The reaction mixture was stirred for 50 min at −78 °C, and then 560 mg (2.54 mmol) of the (*S*)-(+)-2-(*p*-tolylsulfinyl)-2-cyclopentenone (**2**)[7f] in 5.2 mL of THF was added to the reaction mixture over a 25-min period. Stirring was continued for 75 min at −78 °C, and then the reaction mixture was quenched by the addition of saturated aqueous ammonium chloride (150 mL). The mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were dried over $MgSO_4$ and the solvents removed at 0 °C.

(22) Stotter, P. L.; Hill, K. A. *J. Org. Chem.* **1973**, *38*, 2577.

The crude Michael adduct in 37.3 mL of CH_2Cl_2 was added to a slurry of 889 mg (3.81 mmol) of *m*-chloroperbenzoic acid (74% pure) in 9.3 mL of CH_2Cl_2 at 0 °C over a 15-min period. The reaction mixture was stirred at 0 °C for 20 min, and then it was stirred at room temperature for 1 h. The reaction mixture was diluted with 200 mL of CH_2Cl_2 and extracted with saturated aqueous sodium bicarbonate (2 × 100 mL). The combined aqueous layers were extracted with 100 mL of CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated to provide 1.491 g of crude **3b**. Short-path chromatography (3:1:1; petroleum ether/ether/CH_2Cl_2) on 30 g of silica gel afforded 557 mg of Michael adduct **3b** (diastereomer 1) as a foam followed by 130 mg of crystalline Michael adduct **3b′**. Continued elution with (1:1:1) petroleum ether/ether/CH_2Cl_2 afforded 352 mg of crystalline Michael adduct **3b** (diastereomer 2). The analytical data obtained for **3b′** are consistent with the loss of the elements hydrogen and bromine from the parent structure **3b**. It was not possible to obtain the above products completely free of trace impurities; therefore, a combined yield of 85% for the above products should be taken as a close approximation. Michael adduct **3b** (diastereomer 1): ^{1}H NMR δ 8.02 (d, J = 9.0 Hz, 1 H), 7.76 (d, J = 8.5 Hz, 2 H), 7.37 (d, J = 8.0 Hz, 2 H), 6.88–6.86 (m, 1 H), 6.69 (d, J = 2.4 Hz, 1 H), 3.91 (br s, 1 H), 3.87 (s, 3 H), 3.33–3.24 (m, 1 H), 2.98–2.91 (m, 1 H), 2.72–2.18 (m, 7 H), 2.45 (s, 3 H); IR cm^{-1} ($CHCl_3$) 1740, 1670, 1595. HRMS calcd for $C_{23}H_{23}O_5SBr$: m/z (M^+ − HBr) 410.1189. Found: 410.1157. Michael adduct **3b** (diastereomer 2): ^{1}H NMR δ 7.94 (d, J = 8 Hz, 1 H), 7.58 (d, J = 8.5 Hz, 2 H), 6.88 (d, J = 8 Hz, 2 H), 6.80 (m, 1 H), 6.36 (d, J = 2 Hz, 1 H), 4.10 (d, J = 8 Hz, 1 H), 3.84 (s, 3 H), 2.80–1.45 (m, 9 H), 2.20 (s, 3 H); IR cm^{-1} ($CHCl_3$) 1730, 1674, 1598. HRMS calcd for $C_{23}H_{23}O_5SBr$: m/z (M^+ − HBr) 410.1189. Found: 410.1206. An analytical sample was recrystallized from $CHCl_3$/ether; mp 216–219 °C. Michael adduct **3b′**: ^{1}H NMR δ 8.00 (d, J = 8 Hz, 2 H), 7.90 (d, J = 8 Hz, 1 H), 7.31 (d, J = 9 Hz, 2 H), 6.82–6.78 (m, 1 H), 6.70 (d, J = 2 Hz, 1 H), 3.85 (s, 3 H), 3.27 (d, J = 8 Hz, 1 H), 3.29–3.10 (m, 1 H), 2.98–2.90 (m, 1 H), 2.65–2.68 (m, 1 H), 2.65–1.60 (m, 5 H), 2.41 (s, 3 H); IR cm^{-1} ($CHCl_3$) 1732, 1663 (w), 1597. HRMS calcd for $C_{23}H_{22}O_5S$: m/z 410.1186 Found: 410.1179. An analytical sample was recrystallized from $CHCl_3$/ether; mp 194–196 °C. Anal. Calcd for $C_{23}H_{22}O_5S$: C, 67.30; H, 5.40. Found: C, 67.52; H, 5.51.

Conversion of Michael Adduct 3b → 3a. Into a 100-mL round-bottom flask was placed 557 mg (1.13 mmol) of Michael adduct **3b** (diastereomer 1) and 352 mg (0.716 mmol) of Michael adduct **3b** (diastereomer 2) along with 5.90 g (38.3 mmol) of titanium trichloride.[23] To the mixture was added 24 mL of acetonitrile followed by the slow addition of 27 mL of distilled water (15 min). The reaction mixture was heated at 75 °C as it was vigorously stirred for 9 h. Upon cooling to room temperature, the reaction mixture was diluted with 75 mL of water, and then it was extracted with $CHCl_3$ (3 × 100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated to provide 906 mg of crude Michael adduct **3a**. Before purification, the crude Michael adduct **3a** obtained from the reduction of Michael adducts **3b** (diastereomers 1 and 2) was combined with the crude Michael adduct **3a** obtained from the reduction of Michael adduct **3b′**; this was done in order to allow an accurate determination of the diastereoselectivity in the initial Michael reaction (see preparation of enol esters **4** from Michael adduct **3a** obtained from **1b**).

Into a 25-mL round-bottom flask was placed 130 mg (0.317 mmol) of Michael adduct **3b′**, 517 mg (7.91 mmol) of zinc dust, and 285 mg (5.33 mmol) of ammonium chloride. To the mixture was added 7.0 mL of methanol. The reaction mixture was stirred vigorously at room temperature for 1 h, and then it was filtered through 2 g of Celite; the Celite was washed with methanol (75 mL). The solvent was removed, and to the residue was added 50 mL of CH_2Cl_2 along with 20 mL of saturated aqueous ammonium chloride. The organic layer was separated, and the aqueous layer was extracted with two additional 50-mL portions of CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated to provide 144 mg of crude Michael adduct 3a. This crude Michael adduct was combined with the crude Michael adduct **3a** obtained from Michael adducts **3b** (diastereomers 1 and 2, see above); an aliquot of this crude **3a** was assayed by conversion to the diasteriomeric enol esters **4** (see preparation of enol esters **4** from Michael adduct **3a** obtained from **1b**). Short-path chromatography (3:3:1; petroleum ether/CH_2Cl_2/ether) on 20 g of silica gel afforded 843 mg (81% overall from **1b**) of Michael adducts **3a** ($C_{8H_\beta}/C_{8H_\alpha}$; 1.2:1); the spectral properties are the same as those given above.

Additionally, the crude Michael adducts **3b** (diastereomers 1 and 2) and **3b′** were exposed without intermediate purification sequentially to the titanium trichloride reduction the the zinc reduction to provide Michael adducts **3a** in the same overall yield (81% from **1b**). An aliquot

(23) Ho, T.; Wong, C. M. *Synth. Commun.* **1973**, *3*, 237.

of the crude Michael adducts **3a** obtained by using this procedure was also assayed by conversion to the enol esters **4** (see below).

Preparation of Enol Esters 4 from Racemic Michael Adduct 3a via 5. A solution of 81.8 mg (0.33 mmol) of the methoxytetralone enol silyl ether in 3.0 mL of THF was cooled to 0 °C and treated dropwise with 7.25 mg (0.33 mmol; 179 μL) of methyllithium (1.84 M in ether). The ice bath was removed and the reaction mixture was stirred at room temperature for 1 h. To the solution at −78 °C was added 66.1 mg (0.28 mmol) of 2-(*p*-tolylsulfonyl)-2-cyclopentenone (**5**)[24] in 1.5 mL of THF over a 10-min period. The reaction mixture was stirred at −78 °C for 2 h, and then it was poured into 25 mL of 0 °C saturated aqueous ammonium chloride. The organic solvents were evaporated at 0 °C, and the residue was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were dried over $MgSO_4$, and then the solvents were removed to provide 116 mg of crude (±)-**3a**. Preparative TLC (4:1:1; hexanes/CH_2Cl_2/ether; 20 cm × 20 cm × 1500 μm SiO_2) afforded 66.3 mg (57%) of Michael adduct **3a** (C_{8H_α}) and 44.1 mg (38%) of Michael adduct **3a** (C_{8H_β}); the spectral properties are the same as those given above.

Into a 50-mL pear-shaped flask was placed 3.7 mg (8.97 μmol) of (±)-Michael adduct **3a** (C_{8H_α}) and 0.5 mg (12.5 μmol) of sodium hydride (60% dispersion in mineral oil). To the mixture was added 0.5 mL of DME, and the reaction mixture was stirred for 50 min at room temperature. The mixture was then treated with 5 μL of (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride.[25] After being stirred for 10 min, the reaction mixture was quenched by the addition of 2 mL of saturated aqueous sodium dihydrogen phosphate. To the mixture was added 3 mL of CH_2Cl_2, and after vigorous stirring the organic layer was removed via capillary pipette; in this way the aqueous layer was extracted with two additional 3-mL portions of CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, and the solvents removed to afford crude enol esters **4** (C_{8H_α}–C_{14H_α} and C_{8H_β}–C_{14H_β}). The relative ratio of these diastereomeric enol esters was determined from the 400-MHz ^{1}H NMR spectrum of the crude mixture by using the diastereotopic resonances at both δ 3.844 and 3.836 and δ 2.354 and 2.369; there was found to be a 1.016:1 ratio of enol ester **4** (C_{8H_α}–C_{14H_α}) to enol ester **4** (C_{8H_β}–C_{14H_β}) (0.77% de).[11] The diastereomic enol esters were separated from excess of the Mosher acid chloride by preparative TLC (3:3:1; hexanes/CH_2Cl_2/ether; 5 cm × 10 cm × 250 μm SiO_2) for determintion of the full ^{1}H NMR spectrum. Enol ester **4** (C_{8H_α}–C_{14H_α}): ^{1}H NMR δ 7.90 (d, *J* = 9 Hz, 1 H), 7.74–7.43 (m, 7 H), 7.14 (d, *J* = 7.5 Hz, 2 H), 6.83–6.79 (m, 1 H), 6.67 (d, *J* = 2.5 Hz, 1 H), *3.844* (s, 3 H), 3.69 (m, 3 H), 3.35–1.70 (m, 10 H), *2.354* (s, 3 H). Enol ester **4** (C_{8H_β}–C_{14H_β}): ^{1}H NMR δ 7.84 (d, *J* = 9 Hz, 1 H), 7.74–7.43 (m, 7 H), 7.19 (d, *J* = 7.5 Hz, 2 H), 6.81–6.76 (m, 1 H), 6.66 (d, *J* = 2.5 Hz, 1 H), *3.836* (s, 3 H), 3.70 (m, 3 H), 3.35–1.70 (m, 10 H), *2.369* (s, 3 H); IR cm^{-1} ($CHCl_3$) 1768, 1665, 1640, 1600.

The enol esters **4** (C_{8H_β}–C_{14H_α} and C_{8H_α}–C_{14H_β}) were prepared from (±)-Michael adduct **3a** (C_{8H_β}) by the same procedure used to prepare the enol esters **4** of (±)-Michael adduct **3a** (C_{8H_α}) (see above). The relative ratio of these diastereomeric enol esters was determined from the 400-MHz ^{1}H NMR spectrum of the crude product mixture by using the diastereotopic resonances at both δ 3.860 and 3.852 and at δ 2.414 and 2.429; there was found to be a 1.020:1 ratio of enol ester **4** (C_{8H_β}–C_{14H_β}) to enol ester **4** (C_{8H_α}–C_{14H_β}) (1.1% de).[11] The diastereomeric enol esters were separated from excess of the Mosher acid chloride by preparative TLC (3:3:1; hexanes/CH_2Cl_2/ether; 5 cm × 10 cm × 250 μm SiO_2) for determination of the full ^{1}H NMR spectrum. Enol ester **4** (C_{8H_β}–C_{14H_α}): ^{1}H NMR δ 7.99 (d, *J* = 9 Hz, 1 H), 7.72–7.20 (m, 9 H), 6.83–6.80 (m, 1 H), 6.71 (d, *J* = 2 Hz, 1 H), *3.860* (s, 3 H), 3.75 (m, 3 H), 3.38–1.80 (m, 10 H), *2.414* (s, 3 H). Enol ester **4** (C_{8H_α}–C_{14H_β}): ^{1}H NMR δ 7.99 (d, *J* = 9 Hz, 1 H), 7.72–7.20 (m, 9 H), 6.83–6.80 (m, 1 H), 6.69 (d, *J* = 2 Hz, 1 H), *3.852* (s, 3 H), 3.71 (m, 3 H), 3.38–1.80 (m, 10 H), *2.429* (s, 3 H); IR cm^{-1} ($CHCl_3$) 1768, 1664, 1640, 1600. HRMS calcd for $C_{33}H_{31}O_7SF_3$: *m/z* 628.1743. Found: 628.1733.

Preparation of Enol Esters 4 from Michael Adducts 3a Derived via 1a. The enol esters **4** were prepared from Michael adduct **3a** (C_{8H_α}) (derived from **1a**) by the same procedure used to prepare the enol esters **4** of (±)-Michael adduct **3a** (C_{8H_α}); the diastereomeric excess of the crude enol esters so obtained was determined to be 76.5% with the enol ester **4** (C_{8H_α}–C_{14H_α}) as the major diastereomer. Similarly, the enol esters **4** were prepared from Michael adduct **3a** (C_{8H_β}) (derived from **1a**); the diastereomeric excess of the crude enol esters so obtained was found to be 67.5% with the enol ester **4** (C_{8H_α}–C_{14H_β}) as the major diastereomer. Based on the relative ratio of 5.33:1 of Michael adduct **3a** (C_{8H_α}) to Michael adduct **3a** (C_{8H_β}) isolated from the Michael addition–oxidation sequence used in their formation and the above results, the diastereoselectivity of the Michael addition was determined to be 54%.

Preparation of Enol Esters 4 from Michael Adducts 3a Derived via 1b. The enol esters **4** were prepared from an aliquot of crude Michael adducts **3a** (C_{8H_β} and C_{8H_α}) derived from **1b** *with* intermediate purification of Michael adducts **3b** and **3b′** by the same procedure used to prepare the enol ester **4** of (±)-Michael adduct **3a** (C_{8H_α}); the diastereomeric excess of the crude enol esters so obtained was determined to be 92% with the enol esters **4** (C_{8H_α}–C_{14H_α} and C_{8H_β}–C_{14H_α}) as the major diastereomers.

The enol esters **4** were prepared from an aliquot of crude Michael adducts **3a** (C_{8H_β} and C_{8H_α}) derived from **1b** *without* intermediate purification of Michael adducts **3b** and **3b′** by the same procedure used to prepare the enol ester **4** of (±)-Michael adduct **3a** (C_{8H_α}); the diastereomeric excess of the crude enol esters so obtained was determined to be 91–94% with the enol esters **4** (C_{8H_α}–C_{14H_α} and C_{8H_β}–C_{14H_α}) as the major diastereomers.

Preparation of β-Keto Sulfone 6. Into a flask was placed 715 mg (1.73 mmol) of the Michael adducts **3a** (derived from **1b**) and 233.4 mg (2.08 mmol) of potassium *tert*-butoxide. To the mixture was added 37 mL of anhydrous 2-methyl-2-propanol. The reaction mixture was stirred at room temperature for 2 h, and then it was quenched by the addition of saturated aqueous sodium dihydrogen phosphate (20 mL). After evaporation of the 2-methyl-2-propanol, 100 mL of CH_2Cl_2 was added to the mixture. The organic phase was separated, and the aqueous phase was extracted with two additional 100-mL portions of CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, and then the solvents were removed to provide 706 mg of crude **6**. Analysis of the crude product mixtue by ^{1}H NMR indicated a 93:7 ratio of Michael adduct **3a** (C_{8H_β}) to Michael adduct **3a** (C_{8H_α}). Short-path chromatography (3:1:1; petroleum ether/CH_2Cl_2/ether) on 21 g of silica gel afforded 607 mg (85%) of β-keto sulfone **6** [Michael adduct **3a** (C_{8H_β})]. The spectral properties of **6** [**3a** (C_{8H_β})] are the same as those given above; $[\alpha]^{25}_D$ 102.6° (*c* 0.78, $CHCl_3$). The diastereomeric excess of the enol esters **4** derived from **6** was determined, from ^{1}H NMR analysis, to be 95% with the enol esters **4** (C_{8H_α}–C_{14H_α} and C_{8H_β}–C_{14H_α}) as the major diastereomers.

Preparation of β-Keto Sulfone 7. Into a flask was placed 301 mg (0.73 mmol) of β-keto sulfone **6** along with 29.2 mg (0.73 mmol) of sodium hydride (60% dispersion in mineral oil). To the mixture was added 12 mL of 1,2-dimethoxyethane. The reaction mixture was stirred at room temperature for 1 h, and then a mixture of 2.4 mL of hexamethylphosphoric triamide (HMPT) and 1.49 g (10.5 mmol; 654 μL) of iodomethane was added over a 1-min period. After the mixture was stirred at room temperature for 1.5 h, the DME and excess iodomethane were evaporated. The residue was dissolved in 1:1 carbon tetrachloride/petroleum ether (125 mL) and then washed with water (2 × 50 mL). The organic phase was then dried over $MgSO_4$, and the solvents were removed to provide crude **7**. Preparative TLC (3:3:1; petroleum ether/CH_2Cl_2/ether; 20 cm × 20 cm × 2000 μm SiO_2) afforded 177 mg (57%) of crystalline β-keto sulfone **7**: ^{1}H NMR δ 8.02 (d, *J* = 8.9 Hz, 1 H), 7.56 (d, *J* = 8.2 Hz, 2 H), 7.32 (d, *J* = 8.5 Hz, 2 H), 6.85–6.81 (m, 1 H), 6.73 (m, 1 H), 3.86 (s, 3 H), 3.70–3.65 (m, 1 H), 3.55–3.49 (m, 1 H), 3.30–3.19 (m, 1 H), 3.07–2.98 (m, 2 H), 2.85–2.76 (m, 1 H), 2.63–2.34 (m, 2 H), 2.45 (s, 3 H), 2.09–1.82 (m, 2 H), 1.30 (s, 3 H); IR cm^{-1} ($CHCl_3$) 1739, 1667, 1599; $[\alpha]^{25}_D$ 6.18° (*c* 1.1, $CHCl_3$), $[\alpha]^{25}_{365}$ 723.5° (*c* 1.1, $CHCl_3$). HRMS calcd for $C_{24}H_{26}O_5S$: *m/z* 426.1502. Found: 426.1507. An analytical sample was recrystallized from $CHCl_3$/ether; mp 168.5–170 °C.

Preparation of Diketone 8. A slurry of 78.3 mg (0.41 mmol) of copper(I) iodide in 1.7 mL of ether was cooled to 0 °C and treated dropwise with 17.1 mg (0.78 mmol; 486 μL) of methyllithium (1.60 M in ether). After being stirred for 15 min at 0 °C, to the reaction mixture was added 49.5 mg (0.116 mmol) of β-keto sulfone **7** in 1.3 mL of THF over a 20-min period. The mixture was stirred at 0 °C for 1.25 h. To the reaction mixture at −20 °C was added 125 μL of 1-bromo-3-methyl-2-butene (dimethallyl bromide) over a 5-min period. The mixture was stirred for 1.25 h at −20 °C and then quenched by the addition of saturated aqueous ammonium chloride (15 mL). The mixture was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic extracts were dried over $MgSO_4$. Removal of the solvents gave crude **8** which was purified by preparative TLC (5:1:1; benzene/hexanes/ether; 20 cm × 20 cm × 500 μm SiO_2) to afford 31.1 mg of diketone **8** as an oil, determined by ^{1}H NMR spectroscopy to be 85 mol % pure (contaminated by an inseparable compound derived from reaction of the *p*-toluenesulfinate cleavage product and dimethallyl bromide). From these data, the yield was estimated to be 71%. Diketone **8**: ^{1}H NMR δ 8.00 (d, *J* = 8.9 Hz, 1 H), 6.85–6.81 (m, 1 H), 6.69–6.67 (m, 1 H), 4.89 (t, *J* = 1.4 Hz, 1 H), 3.86 (s, 3 H), 3.10–2.89 (m, 3 H), 2.65–2.58 (m, 1 H), 2.46–1.82 (m, 8 H), 1.61 (br s, 3 H), 1.51 (br s, 3 H), 1.05 (s, 3 H); IR cm^{-1}

(24) 2-(*p*-Tolylsulfonyl)-2-cyclopentenone (**5**) was prepared in three steps from 2-lithio-2-cyclopentenone ethylene ketal:[7f] (1) *p*-tolyl *p*-toluenethiosulfonate, THF, −78 °C; (2) *m*-chloroperbenzoic acid (2 equiv) CH_2Cl_2; and (3) $CuSO_4$, acetone.[7f]

(25) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2545.

($CHCl_3$) 1726, 1669, 1599. HRMS calcd for $C_{22}H_{28}O_3$: m/z 340.2039. Found: 340.2043.

Preparation of Keto Aldehyde 9. A solution of 31 mg (0.0774 mmol) of diketone **8** (85 mol % pure, see above) in 0.8 mL of CH_2Cl_2 and 3.2 mL of methanol was cooled to −78 °C, and then an excess of ozone was passed through the mixture (the solution becomes deep blue in color when saturated with ozone). After the reaction mixture was purged with argon for 20 min at −78 °C, it was treated with 300 μL of dimethyl sulfide. The cold bath was removed, and the mixture was allowed to stir at room temperature for 30 min. Removal of the solvents provided crude **9** which was purified by preparative TLC (1:1:1; hexanes/CH_2Cl_2/ether; 20 cm × 20 cm × 250 μm SiO_2) to afford 17.5 mg (68%; 48% overall from diketone **8**) of crystalline diketo aldehyde **9**: ^1H NMR δ 9.35 (s, 1 H), 7.92 (d, J = 8.9 Hz, 1 H), 6.82–6.66 (m, 2 H), 3.84 (s, 3 H), 3.3–1.4 (m, 12 H), 1.06 (s, 3 H); IR cm^{-1} ($CHCl_3$) 1734, 1716, 1669. $[\alpha]^{25}_D$ 5.04° (c 1.19, $CHCl_3$). HRMS calcd for $C_{19}H_{22}O_4$: m/z 314.1519. Found: 314.1503. An analytical sample was recrystallized from diethyl ether; mp 108–110 °C [lit.[14a] mp 106–108 °C].

Preparation of 9,11-Dehydroestrone Methyl Ether (10). Into a 25-mL flask was placed 108.5 mg (0.704 mmol) of titanium trichloride and 91.6 mg (1.40 mmol) of Zn–Ag[26] couple under a nitrogen atmosphere in a glove bag. Into the flask was added 11.25 mL of DME, and the mixture was stirred vigorously as it was heated at reflux for 2 h. To the reaction mixture was added 45 mg (0.143 mmol) of diketo aldehyde **9** in 4.5 mL of DME over a 10-min period. The reaction mixture was heated at reflux for 2 h. Upon cooling to room temperature, the mixture was passed through 1 g of florisil; the florisil was washed with ethyl acetate (200 mL). Removal of the solvent provided 38 mg of crude **10**. Preparative TLC (12.5:1; benzene/ethyl acetate; 20 cm × 20 cm × 500 μm SiO_2) afforded 14.9 mg (37%) of crystalline 9,11-dehydroestrone methyl ether (**10**): ^1H NMR δ 7.54 (d, J = 8.8 Hz, 1 H), 6.76–6.72 (m, 1 H), 6.63 (d, J = 2.5 Hz, 1 H), 6.14 (t, J = 2.7 Hz, 1 H), 3.80 (s, 3 H), 3.00–1.2 (m, 12 H), 0.94 (s, 3 H); IR cm^{-1} ($CHCl_3$) 1731. $[\alpha]^{25}_D$ 247.2° (c 0.50, $CHCl_3$) [lit.[28] $[\alpha]_D$ 276° (c 0.5, $CHCl_3$)]. HRMS calcd for $C_{19}H_{22}O_2$: m/z 282.1621. Found 282.1619. An analytical sample was recrystallized from ethyl acetate/ethanol; mp 144–145 °C [lit.[27] mp 145–147 °C].

Preparation of Estrone Methyl Ether (11) and Estradiol 3-Methyl Ether (12). A solution of 15 mg (0.0531 mmol) of 9,11-dehydroestrone in 1.8 mL of anhydrous benzene was treated with 117.5 mg (1.03 mmol; 79.4 μL) of trifluoroacetic acid and 61.7 mg (0.531 mmol; 84.8 μL) of triethylsilane. The reaction mixture was allowed to stir at room temperature for 15 h. The mixture was then added to 0 °C saturated aqueous sodium bicarbonate (10 mL), and the organic phase was removed via a capillary pipet. The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). Removal of the solvents provided crude **11** which was purified by preparative TLC (10:1.2; hexanes/ethyl acetate; 10 cm × 20 cm × 250 μm SiO_2) to afford 15.0 mg of crystalline estrone methyl ether (**11**) containing a trace of an impurity which could be removed only through crystallization. Without crystallization, an aliquot of this material was converted to estradiol 3-methyl ether (**12**) (see below). Crystallization from ethyl acetate/ethanol provided 13.6 mg (90%, after correction for the aliquot removed as indicated above) of crystalline estrone methyl ether (**11**): ^1H NMR δ (80 MHz) 7.26–6.55 (m, 3 H), 3.78 (s, 3 H), 3.00–1.25 (m, 15 H), 0.90 (s, 3 H); IR cm^{-1} ($CHCl_3$) 1731; $[\alpha]^{25}_D$ 156.7° (c 0.1021, dioxane) [lit.[29] $[\alpha]^{25}_D$ 159.3° (c, 1, dioxane)]. HRMS calcd for $C_{19}H_{24}O_2$: m/z 284.1777. Found 284.1783. Mp 165–167.5 °C [lit.[28] mp 164–167.5 °C, lit.[29] mp 172–173 °C].

Into a flask was placed 1.6 mg of an aliquot of unrecrystallized estrone methyl ether (**11**) and 2.7 mg (0.071 mmol) of sodium borohydride. To the mixture was added 840 μL of ethanol and 210 μL of THF. After being stirred for 1 h, the reaction mixture was quenched by the addition of 0.5 mL of water followed by the cautious dropwise addition of 0.25 mL of 2 M HCl. The mixture was then extracted with 3:1 CH_2Cl_2/ethyl acetate (3 × 20 mL): the combined organic extracts were dried over $MgSO_4$. Removal of the solvents followed by preparative TLC (10:1.5; hexanes/ethyl acetate; 5 cm × 10 cm × 250 μm SiO_2) afforded 1 mg of crystalline estradiol 3-methyl ether (**12**) (^1H NMR angular - CH_3, 0.78 ppm).[30] Derivation of **12** with 3,5-dinitrophenyl isocyanate was followed by its comparison on a chiral HPLC column to the corresponding ester derivatives of racemic estradiol and natural (+)-estradiol 3-methyl ethers;[19] based upon these comparisons, the synthetic estradiol 3-methyl ether (**12**) was determined to be at least 97.3% enantiomerically pure.[19]

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(26) Denis, J. M.; Girard, C.; Conia, J. M. *Synthesis* **1972**, 549.
(27) Cambie, R. C.; Carlisle, V. F. *J. Chem. Soc. C* **1970**, 1706.
(28) Cohen, N.; Banner, B. L.; Eichel, W. F.; Parrish, D. R.; Saucy, G. *J. Org. Chem.* **1975**, *40*, 681.
(29) Quinkert, G., et al., *Liebigs Ann. Chem.* **1982**, 1999.
(30) Kametani, T.; Matsumoto, H.; Nemoto, H.; Fukumoto, K. *J. Am. Chem. Soc.* **1978**, *100*, 6218.