Asymmetric Synthesis of (+)-Hirsutene

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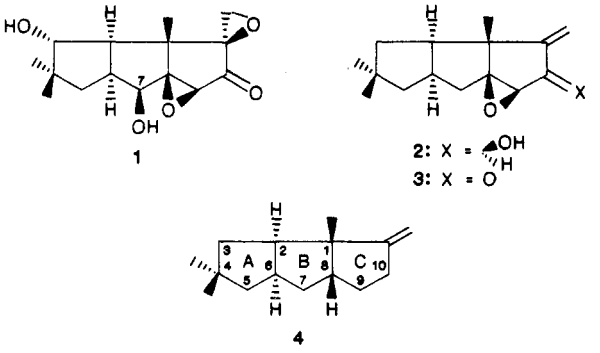
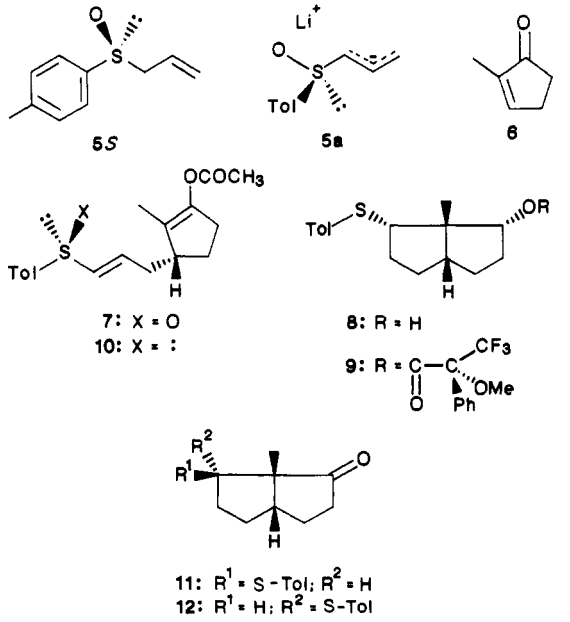
The asymmetric total synthesis of (+)-hirsutene from the regio- and enantioselective 1,4-γ-addition reaction of (−)-(*S*)-allyl *p*-tolyl sulfoxide and 2-methyl-2-cyclopentenone is presented. In this total synthesis, a facile ring closure reaction involving enol thioether and enol acetate moieties and the deoxygenation reaction of a highly hindered secondary alcohol via its 2-propanesulfonate were found. An unexpected displacement reaction at the sulfur atom of alkenyl sulfoxides and the addition reactions of the cis sulfinylallyl anions with cyclic enones were also observed during the studies.

The syntheses of the biologically active linear polyquinanes[1] coriolin (**1**),[2] hirsutic acid C (**2**),[3] and complicatic acid (**3**)[4] and their biogenetic precursor hirsutene (**4**)[5] have been a popular area of study in recent years. As part of our studies on the enantioselective 1,4-addition reactions of chiral sulfinylallyl anions to cyclic enones, we have communicated the synthesis of (+)-hirsutene (**4**).[5y] An unexpected displacement reaction at the sulfur atom of alkenyl sulfoxides and the addition reactions of the cis sulfinylallyl anions with cyclic enones were observed during the studies. Herein, we report the full account of the synthesis of (+)-**4**.



Results and Discussion

I. Asymmetric Synthesis of Hexahydropentalenones 11 and 12. Since the B,C ring of (+)-**4** is readily available from our recent studies,[5y] it is logical to construct the A ring last. This route also provides a general method for the synthesis of **1**, **2**, and **3**. Treatment of the sulfinylallyl anion **5a** [(−)-*S*-allyl *p*-tolyl sulfoxide (**5*S***) and 1 equiv of lithium diisopropylamide (LDA) in THF at −78 °C] with 2-methyl-2-cyclopentenone (**6**)[6] at −78 °C followed by acetyl chloride (AcCl) provided 86% yield of the 1,4-adduct **7**. The absolute configuration at the newly formed stereogenic center of **7** was assigned from our previous studies.[5y,7] The optical purity was determined by ^{19}F NMR spectra of the Mosher's derivative[8] (i.e., **9**) of **8** (vide infra), which indicated 94% ee at this newly formed stereogenic center of **7**.



(1) For reviews, see: (a) Paquette, L. A. *Top. Curr. Chem.* **1979**, *79*, 41. (b) Paquette, L. A. *Ibid.* **1984**, *119*, 1. (c) Paquette, L. A. *Tetrahedron* **1981**, *37*, 4357. (d) Trost, B. M. *Chem. Soc. Rev.* **1982**, *11*, 141. (e) Demuth, M.; Schaffner, K. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 820.

(2) (a) Mehta, G.; Murthy, A. N.; Reddy, D. S.; Reddy, A. V. *J. Am. Chem. Soc.* **1986**, *108*, 3443. (b) Demuth, M.; Ritterskamp, P.; Weight, E.; Schaffner, K. *J. Am. Chem. Soc.* **1986**, *108*, 4149 and references cited therein.

(3) Schuda, P. F.; Phillips, J. L.; Morgan, T. M. *J. Org. Chem.* **1986**, *51*, 2742 and references cited therein.

(4) Isolation and synthesis: Hashimoto, H.; Tsuzuki, K.; Sakan, F.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1974**, 3745.

(5) Isolation: (a) Feline, T. C.; Mellows, G.; Jones, R. B.; Phillips, L. *J. Chem. Soc., Chem. Commun.* **1974**, 63. (b) Nozoe, S.; Furukawa, J.; Sankawa, U.; Shibata, S. *Tetrahedron Lett.* **1976**, 195. Synthesis: (c) Nozoe, S.; Furukawa, J.; Sankawa, U.; Shibata, S. *Tetrahedron Lett.* **1976**, 195. (d) Tatsuta, K.; Akimoto, K.; Kinoshita, M. *J. Am. Chem. Soc.* **1979**, *101*, 6116. (e) Ohfune, Y.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1976**, 2795. (f) Hayano, K.; Ohfune, Y.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1978**, 1991. (g) Hayano, K.; Ohfune, Y.; Shirahama, H.; Matsumoto, T. *Helv. Chim. Acta* **1981**, *64*, 1347. (h) Shirahama, H.; Osawa, E.; Matsumoto, T. *J. Am. Chem. Soc.* **1980**, *102*, 3208. (i) Misumi, S.; Matsushima, H.; Shirahama, H.; Matsumoto, T. *Chem. Lett.* **1982**, *855*. (j) Greene, A. E. *Tetrahedron Lett.* **1980**, *21*, 3059. (k) Hudlicky, T.; Koszyk, F. J.; Kutchan, T. M.; Sheth, J. P. *J. Org. Chem.* **1980**, *45*, 5020. (l) Hudlicky, T.; Kutchan, T. M.; Wilson, S. R.; Mao, D. T. *J. Am. Chem. Soc.* **1980**, *102*, 6351. (m) Mehta, G.; Reddy, A. V. *J. Chem. Soc., Chem. Commun.* **1981**, 756. (n) Mehta, G.; Murphy, A. N.; Reddy, D. S.; Reddy, A. V. *J. Am. Chem. Soc.* **1986**, *108*, 3443. (o) Little, R. D.; Muller, G. W. *J. Am. Chem. Soc.* **1981**, *103*, 2744. (p) Little, R. D.; Muller, G. W.; Venegas, M. G.; Carroll, G. L.; Bukhari, A.; Patton, L.; Stone, K. *Tetrahedron* **1981**, *37*, 4371. (q) Little, R. D.; Higby, R. G.; Moeller, K. D. *J. Org. Chem.* **1983**, *48*, 3139. (r) Wender, P. A.; Howbert, J. J. *Tetrahedron Lett.* **1982**, *23*, 3983. (s) Ley, S. V.; Murray, P. J. *J. Chem. Soc., Chem. Commun.* **1982**, 1252. (t) Magnus, P.; Quagliato, D. *J. Org. Chem.* **1985**, *50*, 1621. (u) Magnus, P.; Quagliato, D. *Organometallics* **1982**, *1*, 1243. (v) Dawson, B. A.; Ghosh, A. K.; Jurlina, J. L.; Stothers, J. B. *J. Chem. Soc., Chem. Commun.* **1983**, 204. (w) Funk, R.; Bolton, G. L. *J. Org. Chem.* **1984**, *49*, 5021. (x) Curran, D. P.; Rakiewicz, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 1448. (y) Hua, D. H.; Sinai-Zingde, G.; Venkataraman, S. *J. Am. Chem. Soc.* **1985**, *107*, 4088. (z) Iyoda, M.; Kushida, T.; Kitami, S.; Oda, M. *J. Chem. Soc., Chem. Commun.* **1986**, 1049.

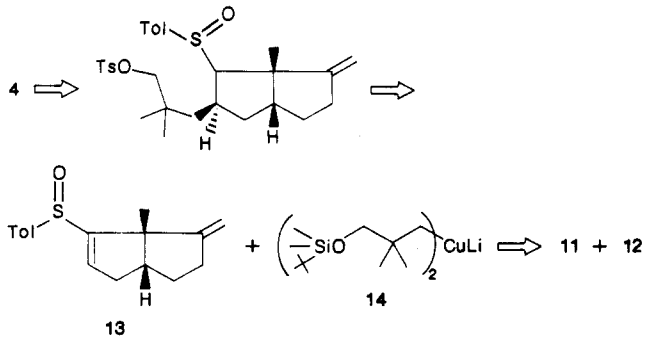
(6) The photooxygenation reaction reported by Mihelich and Eickhoff was adapted to prepare **6**: Mihelich, E. D.; Eickhoff, D. J. *J. Org. Chem.* **1983**, *48*, 4135. For other preparations: Funk, R. L.; Vollhardt, K. P. C. *Synthesis* **1980**, *118* and references cited therein.

(7) (a) Hua, D. H.; Venkataraman, S.; Coulter, M. J.; Sinai, Z. G. *J. Org. Chem.* **1987**, *52*, 719. (b) Hua, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 3835. (c) Hua, D. H.; Takusagawa, F.; Badejo, I.; McCann, P. J. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1987**, *C43*, 1112.

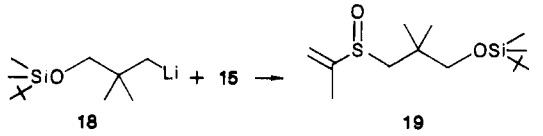
(8) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

0022-3263/88/1953-0507$01.50/0

Scheme I. Retrosynthesis



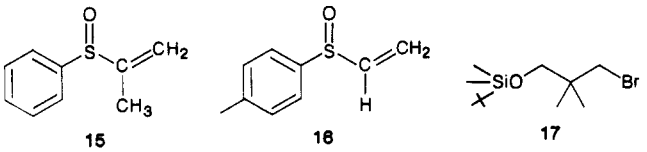
Scheme II



Reduction of **7** with Zn–AcOH at room temperature (produced **10**; 95% yield) followed by intramolecular cyclization of the resulting vinylic sulfide with the enol acetate moiety **10** in the presence of 1 equiv of $TiCl_4$ in AcOH and H_2O at room temperature gave 86% yield of sulfides **11** and **12** (1:4).[7a,9] Sulfides **11** and **12** were separated by column chromatography, and the stereochemistry of the sulfide groups was established by proton–proton NOE-difference spectroscopy.[10]

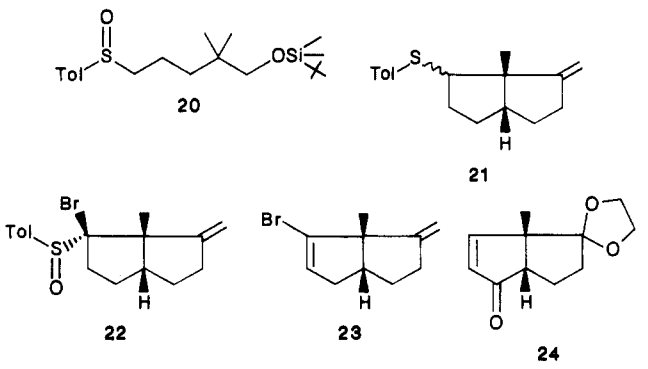
Reduction of sulfide **11** with sodium borohydride in MeOH at −10 °C gave 95% yield of alcohol **8**. Ester **9** was prepared from alcohol **8** and (−)-(*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride,[8] and the ^{19}F NMR method was applied to **9** to determine its optical purity.

II. Displacement Reaction vs Conjugation Addition Reaction of Vinylic Sulfoxides. An approach to construct the linear cis,anti,cis tricyclic (+)-**4** is outlined in Scheme I. α,β-Unsaturated sulfoxide **13** was presumed to be available from sulfides **11** and **12**. Kaji et al.[11] reported that *p*-chlorophenyl vinyl sulfoxide underwent conjugate addition with lithium dialkylcuprates and polymerized with alkyllithium. Phenyl 2-propenyl sulfoxide (**15**) and *p*-tolyl vinyl sulfoxide (**16**) were chosen as models for the conjugate addition study.[12] Cuprate **14** was prepared[13] from the corresponding bromide **17**, which obtained from the silylation of 3-bromo-2,2-dimethyl-1-propanol[14] with *t*-$BuMe_2SiCl_2$–Et_3N–4-(dimethylamino)-pyridine (DMAP) in CH_2Cl_2.



Reaction of sulfoxide **15** and cuprate **14** in THF provides a mixture of byproducts, and the expected conjugate addition product is not detected. Interestingly, the lithiated γ-(silyloxy)propane **18** undergoes exclusive displacement reaction with sulfoxide **15** in THF at −35 °C to give sulfoxide **19** (83% yield; Scheme II). Displacement of an aryl group from aryl alkenyl sulfoxides by an alkyllithium reagent has not been reported; however, displacements from diaryl[15] or aryl alkyl sulfoxides[16] have been described. Reaction of **15** with either methyllithium or *n*-butyllithium under the same conditions gave only polymer. The difference in reactivity between **18** and the simpler alkyllithiums cannot be explained at this time. Treatment of sulfoxide **16** with cuprate **14**, on the other hand, produced a 75% yield of the conjugate addition product **20**. Clearly Michael-type addition of dialkylcuprates and substituted α,β-unsaturated sulfoxides is questionable.[12]

Olefination of **11** and **12** with methylenetriphenylphosphorane in DMSO[17] provided 80% yield of sulfide **21**. Oxidation of **21** with 1 equiv of 30% H_2O_2 in AcOH at 10 °C (95% yield) followed by α-bromination with LDA–THF–CBr_4[18] (95% yield) gave sulfoxide **22**.[19] Attempted



preparation of **13** by treating **22** with 1,5-diazabicyclo-[4.3.0]non-5-ene (DBN) in refluxing toluene provided vinyl bromide **23** as the major product and only 2% of **13**. Use of potassium *tert*-butoxide as base gave similar results. Dehydrosulfenylation is faster than dehydrobromination in this system. This result and the above conjugate addition studies prompted us to choose enone **24** as the alternative intermediate. Furthermore, **24**, possessing a C-4 carbonyl group, could serve as an intermediate for the synthesis of coriolin (**1**).

III. Synthesis of (+)-Hirsutene [(+)-4]. Ketalization of ketones **11** and **12** with 1,2-ethanediol and *p*-toluenesulfonic acid in refluxing benzene[20] followed by oxidation of the resulting sulfides with 1 equiv of *m*-chloroperbenzoic acid (MCPBA) in CH_2Cl_2 at 0 °C gave sulfoxides **25** (90%

(9) Ring closures involving a vinylic sulfide moiety and aromatic ring[a] or β-keto ester:[b] (a) De Waard, E. R.; Reus, H. R.; Huisman, H. O. *Tetrahedron Lett.* **1973**, 4315. (b) Kende, A. S.; Schneider, J. A. *Synth. Commun.* **1979**, *9*, 419.

(10) The percentages of NOE for **11**, 2% for C-1 methyl and C-8 hydrogen and for **12**, 12% for C-1 methyl and C-8 hydrogen.

(11) Sugihara, H.; Tanikaga, R.; Tanaka, K.; Kaji, A. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 655. Conjugation addition of dialkylcuprate and dienyl sulfoxides: Goldmann, S.; Hoffmann, R. W.; Maak, N.; Geueke, K.-J. *Chem. Ber.* **1980**, *113*, 831.

(12) Posner et al. have reported that 1-alkenyl aryl sulfoxides are poor substrates for conjugate additions: Posner, G. H.; Mallamo, J. P.; Miura, K.; Hulce, M. *Asymmetric Reactions and Processes in Chemistry*; Eliel, E. L., Otsuka, S., Eds.; American Chemical Society: Washington, DC, 1982; p 139.

(13) House, H. O.; Chu, C. Y.; Wilkins, J. M.; Umen, M. J. *J. Org. Chem.* **1975**, *40*, 1460.

(14) Searles, S., Jr.; Nickerson, R. G.; Witsiepe, W. K. *J. Org. Chem.* **1960**, *24*, 1839.

(15) Gilman, H.; Eidt, S. H. *J. Am. Chem. Soc.* **1956**, *78*, 3848.

(16) Lockard, J. P.; Schroeck, C. W.; Johnson, C. R. *Synthesis* **1973**, 485 and ref 6 therein.

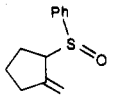
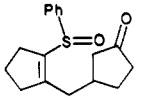
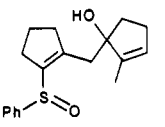
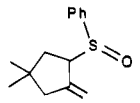
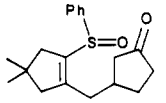
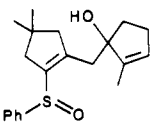
(17) Greenwald, R.; Chaykovsky, M.; Corey, E. J. *J. Org. Chem.* **1963**, *28*, 1128.

(18) α-Halogenation of α-sulfonyl carbanions with polyhaloalkanes: (a) Meyers, C. Y.; Malte, A. M.; Mathews, S. *J. Am. Chem. Soc.* **1969**, *91*, 7510. (b) Meyers, C. Y.; Ho, L. L. *Tetrahedron Lett.* **1972**, 4319. (c) Meyers, C. Y.; Kolb, V. M. *J. Org. Chem.* **1978**, *43*, 1985. (d) Kattenberg, J.; Dewaard, E. R.; Huisman, H. O. *Tetrahedron* **1973**, *29*, 4149.

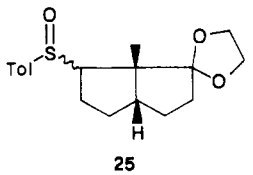
(19) Although the stereochemistry at C-8 is not proven, reactions take place at the exo face of bicyclo[3.3.0]octanes is well known: ref 6c.

(20) Daignault, R. A.; Eliel, E. L. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 303.

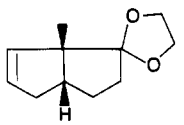
Table I. Reactions of Cis Sulfinylallyl Anions and Cyclic Enones

entry	sulfoxide	enone	1,4-γ-adduct	% yield	1,2-γ-adduct	% yield
1	 36		 39	70		
2	36	 6			 40	83
3	 37		 41	85		
4	37	6			 42	63

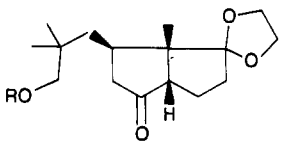
overall yield). Dehydrosulfenylation[21] of **25** with DBN in refluxing toluene provided bicyclooctene **26**. Allylic oxidation of **26** with chromium trioxide–pyridine complex in methylene chloride produced enone **24** (85% yield).



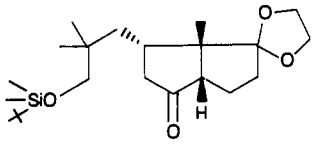
25



26



27: R = *t*-BuMe$_2$Si
29: R = H
30: R = Tol-SO$_2$



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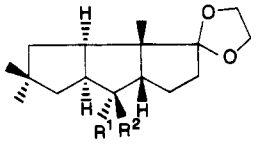
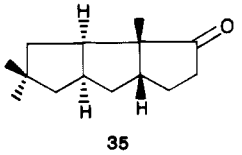


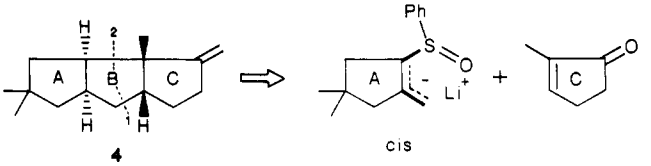
31: R^1; R^2 = O
32: R^1 = H; R^2 = OH
33: R^1 = H; R^2 = OSO$_2$-*i*-Pr
34: R^1 = R^2 = H



35

The C ring was then constructed from the 1,4-addition reaction of enone **24** with cuprate **14** in ether. Extractive isolation and chromatography on silica gel provided 88% yield of exo adduct **27** and 5% yield of endo adduct **28**. Conversion of **27** to tricyclic ketone **31**[22] was effected in 85% overall yield by the following sequence: (i) desilylation with *n*-Bu$_4$NF in THF,[23] (ii) tosylation with *p*-toluenesulfonyl chloride in pyridine, and (iii) cyclization with NaH in refluxing DME.

Scheme III



4 cis

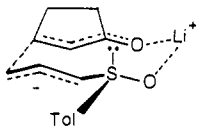
Deoxygenation of **31** to the corresponding tricycloundecane **34** succeeded by the following sequence: (i) reduction with NaBH$_4$ in MeOH at −20 °C (95% yield), (ii) sulfonylation of the resulting alcohol (**32**) with 2-propanesulfonyl chloride and Et$_3$N in ether (93% yield; **33**), and (iii) displacement with LiEt$_3$BH[24] in toluene at 90 °C (72% yield). Only with the 2-propanesulfonate were we able to achieve selective replacement of the sulfonate substituent (i.e., C–O cleavage) by hydride. The corresponding mesylate[24a] and tosylate[24b] when treated with LiEt$_3$BH in THF gave only alcohol **32** (i.e., S–O cleavage).

Deprotection of **34** with *p*-toluenesulfonic acid (TsOH) in THF–MeOH–H$_2$O at room temperature gave 90% yield of ketone **35**. Wittig reaction of **35** with methylenetriphenylphosphorane[25] in refluxing toluene afforded (+)-hirsutene [(+)-**4**] in 80% yield.

IV. Addition Reactions of Cis Sulfinylallyl Anions with Cyclic Enones. Connection of Cyclic Rings A and C. A convergent route to the linear triquinanes would be the connection of rings A and C as outlined in Scheme III.[5w] In this strategy, we expect bond 1 in structure **4** could be formed via the conjugate addition of a cis sulfinylallyl anion to an enone. Bond 2 would subsequently be constructed via the acid-catalyzed ring closure of enol thioethers as described for compound **8**. A potential problem with this approach resides in controlling the relative stereochemistry between the two ring junctures. Since 1,4-addition reactions of cyclic enones have only been reported with trans sulfinylallyl anions,[7,26] the "trans-fused

(21) Goldberg, S. I.; Sahli, M. S. *J. Org. Chem.* **1967**, *32*, 2059.
(22) The cis,anti,cis pattern of ring fusion of **31** was proven by proton–proton NOE difference spectroscopy and COSY two-dimensional NMR spectroscopy.
(23) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(24) (a) Holder, R. W.; Matturro, M. G. *J. Org. Chem.* **1977**, *42*, 2166. (b) Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1976**, *41*, 3064.
(25) Short, R. P.; Ravol, J. M.; Ranu, B. C.; Hudlicky, T. *J. Org. Chem.* **1983**, *48*, 4453.

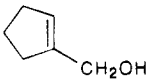
chair–chair"-like transition state was proposed by Haynes et al.;[26f] the reactions of cyclic enones and cis sulfinylallyl



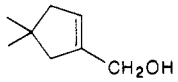
trans

anions are mechanistically and synthetically important.

Sulfoxides **36** and **37** (Table I) were chosen for our study. Alcohol **38**, prepared by reduction of cyclopent-1-enecarbaldehyde[27] with diisobutylaluminum hydride (DIBAL) in THF at −50 °C (98% yield), was treated with PhSCl–Et_3N in benzene at room temperature to give racemic sulfoxide **36**.[28,29] Sulfoxide **37** was prepared by the same method as for **36**, from alcohol **43**, which was obtained from



38



43

allylic oxidation of 1,4,4-trimethylcyclopentene with SeO_2–*t*-BuOOH[31] followed by reduction with DIBAL. Table I summarizes the results of the addition of cis sulfinylallyl anions to cyclic enones. Treatment of **36** with LDA in THF at −78 °C followed by 2-cyclopentenone provided the 1,4-γ-adduct **39** (70% yield; Table I).[30] Enone **6** provided exclusively the 1,2-γ-adducts (**40** and **42**). Apparently, the C-2 methyl group of **6** plays a key role in the regioselection to form 1,2-adduct. Because the desired 1,4-adduct was not formed from the reaction of sulfoxide **37** and enone **6**, the synthesis of hirsutene via this convergent route was not further investigated. The enantioselective connection of two rings with our recently developed chiral phosphonylallyl anions[29] and the subsequent cyclization to the tricyclic systems are now being studied.

Conclusions

1. Functionalized optically active bicyclo[3.3.0]octanones were constructed via the regio- and enantioselective 1,4-addition reactions of chiral sulfinylallyl anions and substituted cyclopentenones followed by intramolecular cyclization. 2. The tricyclo[6.3.0.$0^{2,6}$]undecanones were conveniently prepared, and the versatility of the method was demonstrated in the total synthesis of (+)-hirsutene. The method is general and should be applicable to the syntheses of optically active coriolin, hirsutic acid C, complicatic acid, capnellenols,[32] and pleurotellol.[33] 3. The 1,4- and 1,2-addition reactions of the cyclic cis sulfinylallyl anions and cyclopentenones were examined. The C-2 methyl group of 2-methyl-2-cyclopentenone (**6**) is found to influence the course of the addition reactions (i.e., 1,2-γ-addition). On the other hand, 2-cyclopentenone provides exclusively the 1,4-adducts. The mechanism of this 1,4-addition reaction remains to be determined and is being studied.

Experimental Section

General Methods. Proton magnetic resonance spectra were obtained in deuteriochloroform on Bruker WM-400 (400 MHz for ^1H, 100 MHz for ^{13}C, and 376 MHz for ^{19}F) spectrometer and are reported in ppm (δ units) downfield of the internal standard tetramethylsilane (Me_4Si). Infrared spectra were recorded on a Perkin-Elmer 1330 spectrophotometer and are reported in wavenumbers (cm^{-1} units). Mass spectra were determined on a Finnigan 4000 automated gas chromatograph/EI-CI mass spectrometer. Microanalyses were carried out by the MicAnal Organic Microanalysis, Tuscon, AZ. Samples for microanalysis were purified by recrystallization, by distillation, or, for oils, by rechromatography with extensive drying of the sample under vacuum (<0.01 mm). Optical rotations were measured on a Perkin-Elmer 241 polarimeter. The solvents used in most of the experiments were dried and distilled under argon. Flash chromatography was performed by using Davisil silica gel, grade 643 (200–425 mesh) and ether–hexane as eluent. E. Merck precoated TLC plates, silica gel 60 F-254, were used in preparative thin-layer chromatography. (−)-(*S*)-Allyl *p*-tolyl sulfoxide (**5*S***) was prepared,[28a] purified at 0 °C, and used immediately.

2-Methyl-2-cyclopentenone (6). A standard immersion-well configuration[6] was used in conjunction with a General Electric LU-400 sodium vapor lamp. To the immersion-well reactor equipped with reflux condenser were added 15 g (0.182 mol) of 1-methyl-1-cyclopentene, 18.8 mL (0.188 mol) of acetic anhydride, 7.3 mL (0.091 mol) of pyridine, 0.014 g (0.0227 mmol) of tetraphenylporphine, 0.46 g of DMAP, and 175 mL of CH_2Cl_2. Cold water was circulated through the lamp jacket and condenser. A gentle stream of oxygen was bubbled through the reaction mixture while it was irradiated with the sodium lamp placed in the well. After 24 h, the solution was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The organic layer was then washed with 1 N HCl, aqueous $CuSO_4$ solution, and brine, dried ($MgSO_4$), and concentrated on rotary evaporator. The residue was distilled with a small amount of anhydrous K_2CO_3 through a 5-cm Vigreux column to yield 4.2 g (24% yield) of **6**: bp 82 °C (50 mm) (lit.[34] bp 155 °C); ^1H NMR ($CDCl_3$) δ 7.28 (m, 1 H, =CH), 2.6–2.3 (m, 4 H), 1.78 (s, 3 H, CH_3).

[3(*R*),*S*(*S*)]-2-Methyl-3-[(*E*)-3-(*p*-tolylsulfinyl)-2-propen-1-yl]-1-cyclopentenyl Acetate (7). To a solution of 4.40 g (0.0244 mol) of (−)-(*S*)-allyl *p*-tolyl sulfoxide (**5*S***) in 58 mL of THF at −78 °C under argon was added a cold (−78 °C) solution of LDA prepared at −30 °C from 3.41 mL (0.0244 mol) of diiso-

(26) (a) Kraus, G. A.; Frazier, K. *Synth. Commun.* **1978**, *8*, 483. (b) Binns, M. R.; Haynes, R. K.; Houston, T. L.; Jackson, W. R. *Tetrahedron Lett.* **1980**, *21*, 573. (c) Binns, M. R.; Haynes, R. K. *J. Org. Chem.* **1981**, *45*, 3790. (d) Binns, M. R.; Haynes, R. K.; Houston, T. L.; Jackson, W. R. *Aust. J. Chem.* **1981**, *34*, 2465. (e) Binns, M. R.; Haynes, R. K.; Katsifis, A. A.; Schober, P. A.; Vonwiller, S. C. *Tetrahedron Lett.* **1985**, *26*, 1565. (f) Binns, M. R.; Chai, O. L.; Haynes, R. K.; Katsifis, A. A.; Schober, P. A.; Vonmiller, S. C. *Tetrahedron Lett.* **1985**, *26*, 1569. (g) Nokami, J.; Ono, T.; Iwao, A.; Wakabayashi, S. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3043. (h) Nokami, J.; Ono, T.; Wakabayashi, S.; Hazato, A.; Kurozumi, S. *Tetrahedron Lett.* **1985**, *26*, 1985. (i) Vasil'eva, L. L.; Mel'nikova, V. I.; Gainullina, E. T.; Pivnitskii, K. K. *J. Org. Chem. USSR (Engl. Transl.)* **1983**, *19*, 835. (j) Vasil'eva, L. L.; Mel'nikova, V. I.; Pivnitskii, K. K. *Zh. Org. Khim.* **1984**, *20*, 690. (k) Binns, M. R.; Goodridge, R. J.; Haynes, R. K.; Ridley, D. D. *Tetrahedron Lett.* **1985**, *26*, 6381.

(27) Brown, J. B.; Henbest, H. B.; Jones, E. R. H. *J. Chem. Soc.* **1950**, 3634.

(28) Allyl sulfenate/allyl sulfoxide rearrangement: (a) Bickart, P.; Carson, F. W.; Jacobus, J.; Miller, E. G.; Mislow, K. *J. Am. Chem. Soc.* **1968**, *90*, 4869. (b) Hoffman, R. W. *Organic Sulfur Chemistry*; Freidlina, R. K., Skorova, A. E., Ed.; Pergamon: New York, 1981; p 69. (c) Evans, D. A.; Andrews, G. A. *Acc. Chem. Res.* **1974**, *7*, 147.

(29) Synthesis of the optically active sulfoxides such as **36** and **37** is not known. Furthermore, due to the rapid racemization at sulfur via a reversible [2,3] sigmatropic process,[28] the optically active sulfoxides **36** and **37** were not investigated. Instead, the optically active phosphorus analogues are being studied: Hua, D. H.; Chan, R.-Y.-K.; McKie, J. A.; Myer, L. *J. Am. Chem. Soc.* **1987**, *109*, 5026.

(30) The relative stereochemistry at sulfur and the newly formed stereogenic center is not proven; however, ^1H and ^{13}C NMR spectra of **39** and **41** indicated both diastereomers formed (4:1).

(31) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526. The oxidation provides 4,4-dimethyl-1-cyclopentene-1-carbaldehyde, 2,5,5-trimethyl-2-cyclopentenone, and 3,5,5-trimethyl-2-cyclopentenone. The desired aldehyde was separated by column chromatography (20% yield).

(32) (a) Sheikh, Y. M.; Singy, G.; Kaisin, M.; Eggert, H.; Djerassi, C.; Tursch, B.; Daloze, D.; Braekman, J. C. *Tetrahedron* **1976**, *32*, 1171. (b) Karlsson, R. *Acta. Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1976**, *B32*, 2609. (c) Sheikh, Y. M.; Djerassi, C.; Braekman, J. C.; Daloze, D.; Kaisin, M.; Tursch, B.; Karlsson, R. *Tetrahedron* **1977**, *33*, 2115. (d) Karlsson, R. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1977**, *B33*, 1143. (e) Ayanoglu, E.; Gebreyesus, T.; Beechan, C. M.; Djerassi, C.; Kaisin, M. *Tetrahedron Lett.* **1978**, 1671.

(33) (a) Kupka, J.; Anke, T.; Giannetti, B. M.; Steglich, W. *Arch. Microbiol.* **1981**, *130*, 223. (b) Steglich, W. *Pure Appl. Chem.* **1981**, *53*, 1233.

(34) Singh, G. *J. Am. Chem. Soc.* **1956**, *78*, 6109.

propylamine and 15.3 mL (0.0244 M) of *n*-butyllithium in 40 mL of THF. The yellow solution[35] obtained was stirred at −78 °C for 1 h, and then 4.24 mL (0.0244 mol) of hexamethylphosphoramide (HMPA) and 1.95 g (0.0203 mol) of 2-methyl-2-cyclopentenone were added. After the solution was stirred at −78 °C for 30 min, 5.8 mL (0.0812 mol) of acetyl chloride was added and stirred for 15 min. The reaction mixture was poured into aqueous NH_4Cl solution and extracted three times with ether. The combined extract was washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel to give 5.573 g (86% yield) of **7**: $[\alpha]^{22}_D$ −75° (*c* 0.5, CH_2Cl_2); IR (neat) 1750 (C=O), 1630 (C=C), 1050 (S=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.51 (d, *J* = 8 Hz, 2 H, ortho H), 7.3 (d, *J* = 8 Hz, 2 H, meta H), 6.5 (dt, *J* = 15, 7.1 Hz, 1 H, =CHC), 6.25 (d, *J* = 15 Hz, 1 H, =CHS), 2.40 (s, 3 H, *p*-CH_3), 2.15 (s, 3 H, $OCCH_3$), 2.2–1.2 (m, 7 H); ^{13}C NMR ($CDCl_3$) δ 168.53, 145.16, 141.42, 137.97, 136.78, 134.99, 130.0, 124.65, 114.09, 43.83, 36.14, 29.79, 26.01, 21.39, 20.74, 10.34; HRMS calcd for $C_{18}H_{22}O_3S$ 318.12837, found 318.12804. Anal. Calcd for $C_{18}H_{22}O_3S$: C, 67.89; H, 6.96; S, 10.07. Found: C, 67.95; H, 6.90; S, 9.91.

(3*R*)-2-Methyl-3-[(*E*)-3-(*p*-tolylthio)-2-propen-1-yl]-1-cyclopentenyl Acetate (10). A mixture of 5.33 g (0.0167 mol) of **7** and 26 g of activated zinc[36] in 330 mL (5.775 mol) of acetic acid was stirred at room temperature for 10 h, and the reaction was monitored by TLC. The reaction mixture was diluted with ether, filtered through Celite, and neutralized with 5 N NaOH. The organic layer was separated, and the aqueous layer was extracted twice with ether. The combined ether layers were washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel to give 4.79 g (95% yield) of **10**: IR (neat) 1750 (C=O), 1635 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.21 (d, *J* = 8 Hz, 2 H, ortho H), 7.0 (d, *J* = 8 Hz, 2 H, meta H), 6.13 (d, *J* = 14.9 Hz, 1 H, SCH=), 5.86 (dt, *J* = 14.9 Hz, 7.2 Hz, 1 H, =CH), 2.32 (s, 3 H, *p*-CH_3), 2.15 (s, 3 H, CH_3CO), 2.2–1.2 (m, 10 H); MS, *m/e* (relative intensity), 302 (M^+, 5). Anal. Calcd for $C_{18}H_{22}O_2S$: C, 71.49; H, 7.33; S, 10.60. Found: C, 71.17; H, 7.38; S, 10.42.

(3a*R*,6*R*,6a*S*)-(3aα,6aα)-Hexahydro-6a-methyl-6-(*p*-tolylthio)pentalen-1(2*H*)-one (11) and (3a*R*,6*S*,6a*S*)-(3aα,6aα)-Hexahydro-6a-methyl-6-(*p*-tolylthio)pentalen-1-(2*H*)-one (12). To a solution of 5.0 g (16.55 mmol) of sulfide **10** in 275 mL of acetic acid was added a solution of 5 mL (0.0455 mol) of titanium(IV) chloride in 50 mL of acetic acid. The grayish yellow emulsion obtained was stirred for 20 min, diluted with 1.5 mL of water, stirred for additional 10 min, diluted with ether, filtered through Celite, and neutralized with aqueous $NaHCO_3$. The ether layer was separated, and the aqueous layer was extracted twice with ether. The combined ether was washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed to give 0.74 g (17% yield) of **11** and 2.96 g (69% yield) of **12**.

For **11**: $[\alpha]^{22}_D$ +10.0° (*c* 1, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 7.32 (d, *J* = 8 Hz, 2 H, ortho H), 7.08 (d, *J* = 8 Hz, 2 H, meta H), 3.71 (t, *J* = 5.8 Hz, 1 H, CHS), 2.3 (s, 3 H, para CH_3), 1.18 (s, 3 H, CH_3), 2.5–1.3 (m, 9 H); ^{13}C NMR ($CDCl_3$) δ 220.5, 136.7, 132.9, 131.85, 129.5, 58.5, 58.2, 48.7, 39.05, 35.19, 31.18, 25.8, 22.5, 21.03. Anal. Calcd for $C_{16}H_{20}OS$: C, 73.80; H, 7.74; S, 12.31. Found: C, 73.49; H, 7.70; S, 12.55.

For **12**: $[\alpha]^{22}_D$ +11.4° (*c* 0.5, $CHCl_3$); IR (neat) 1735 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.32 (d, *J* = 8 Hz, 2 H, ortho H), 7.08 (d, *J* = 8 Hz, 2 H, meta H), 3.19 (dd, *J* = 7.1 Hz, 6.8 Hz, 1 H, CHS), 2.3 (s, 3 H, *p*-CH_3), 2.5–1.6 (m, 9 H), 1.22 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 222.6, 136.4, 132.5, 131.2, 129.6, 60.1, 55.1, 47.1, 35.8, 33.8, 30.4, 24.9, 20.9, 18.3. Anal. Calcd for $C_{16}H_{20}OS$: C, 73.80; H, 7.74; S, 12.31. Found: C, 73.54; H, 7.62; S, 12.63.

(1*R*,3a*R*,6*S*,6a*S*)-(3aα,6aα)-Octahydro-6a-methyl-6-(*p*-tolylthio)-1-pentalenol (8): To a solution of 0.1 g (0.384 mmol) of ketone **12** in 3 mL of MeOH at −20 °C was added 30 mg (0.768 mmol) of $NaBH_4$. After the mixture was stirred at −20 °C for 30 min, 1 mL of 1 N HCl was added. The mixture was diluted with H_2O and extracted three times with ether. The combined extract was washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel to give 96 mg (95% yield) of alcohol **8**: ^1H NMR ($CDCl_3$) δ 7.39 (d, *J* = 8 Hz, 2 H, ortho H), 7.11 (d, *J* = 8 Hz, 2 H, meta H), 4.08 (m, 1 H, CHO), 3.0 (dd, *J* = 12 Hz, 6 Hz, 1 H, CHS), 2.3 (s, 3 H, *p*-CH_3), 2.1–1.4 (m, 9 H), 1.06 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 137.4 (s), 132.6 (d), 132.0 (s), 129.7 (d), 81.9 (d, CO), 59.6 (d, CS), 57.2 (s), 51.0 (d), 34.5 (t, 2 C), 32.7 (t), 30.2 (t), 29.7 (q), 21.0 (q). Anal. Calcd for $C_{16}H_{22}OS$: C, 73.23; H, 8.45; S, 12.22. Found: C, 73.01; H, 8.57; S, 12.30.

(1*R*,3a*R*,6*S*,6a*S*,1′*R*)-(3aα,6aα)-Octahydro-6a-methyl-6-(*p*-tolylthio)-1-pentalenyl α-Methoxy-α-(trifluoromethyl)-phenylacetate (9). A mixture of 50 mg (0.191 mmol) of alcohol **8**, 71 mg (0.28 mmol) of (+)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride (MTPAC) and 0.6 mL of pyridine in 0.6 mL of toluene was stirred at 70 °C for 24 h. The reaction mixture was poured into water and extracted twice with ether. The combined extract was washed with 1 N HCl, water, and brine, dried ($MgSO_4$), concentrated, and column chromatographed to give 90 mg (99% yield) of ester **9**: ^1H NMR ($CDCl_3$) δ 7.6–7.06 (m, 9 H, Ar H), 5.12 (br s, 1 H, CHO, for the minor diastereomer, 3%), 5.10 (br s, 1 H, CHO, for the major diastereomer, 97%), 3.64 (s, 3 H, OCH_3), 2.93 (t, *J* = 9 Hz, 1 H, CHS), 2.3 (s, H, *p*-CH_3), 2.1–1.1 (m, 9 H), 1.0 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 166.3, 136.3, 134.9, 132.6, 131.2, 129.5, 129.2, 128.2, 127.4, 122.1 (q, CF_3), 59.3, 57.1, 56.3, 49.5, 33.7, 32.9, 31.9, 30.4, 26.6, 20.9; ^{19}F NMR ($CDCl_3$, $CFCl_3$ as internal standard) δ −70.47 (s, CF_3, minor diastereomer, 3%), −70.53 (s, CF_3, major diastereomer, 97%). The corresponding esters were also prepared from racemic alcohol **8**, and ^1H and ^{19}F NMR spectra agree with the above assignments of the diastereomers. The sequence of reactions for the preparation of ketones **11** and **12** has been reported many times. The enantiomeric excess ranges from 86% to 95% depending on the purity of the starting (−)-sulfoxide **5*S***. The preparation of **5*S*** in larger scale provides poorer optical purity due to isomerization at sulfur center[28] during isolation process.

3-Bromo-2,2-dimethyl-1-propanol.[14] A mixture of 10.4 g (0.1 mol) of 2,2-dimethyl-1,3-propanediol, 20 mL of acetic acid, and 0.5 mL of 48% HBr was heated under reflux for 1 h. To the refluxing solution was added 8.91 g (0.11 mol) of dry HBr in 50 mL of acetic acid dropwise over a period of 3 h. After the yellowish-brown mixture was refluxed for an additional 8 h, acetic acid was removed by distillation under reduced pressure. To the residue was added 35 mL of EtOH and 0.3 mL of 48% HBr, and the solvents were removed by distillation through a fractionating column. The residue left behind was fractionally distilled to give 15.2 g of the product: bp 84 °C (13 mm); ^1H NMR and IR spectra indicate it to be a mixture of the desired alcohol and 3-bromo-2,2-dimethylpropyl acetate. To this mixture was added a solution of 2.4 g (0.10 mol) of LiOH in 45 mL of water and 135 mL of 1,2-dimethoxyethane (DME). The solution was stirred for 3 h, poured into water, and extracted three times with ether. The combined extract was washed with 1 N HCl and then with brine, dried ($MgSO_4$), concentrated, and distilled to give 9.8 g (59% yield) of the bromide: bp 80 °C (13 mm) [lit.[14] bp 76–80 °C (13 mm)]; IR (neat) 3400 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.45 (s, 2 H, CH_2), 3.40 (s, 2 H, CH_2), 1.09 (s, 6 H, 2 CH_3).

3-Bromo-2,2-dimethylpropyl *tert*-Butyldimethylsilyl Ether (17). A mixture of 9.5 g (0.058 mol) of 3-bromo-2,2-dimethylpropanol, 2.83 g (0.023 mol) of DMAP, 7 g (0.07 mol) of Et_3N, and 12.25 g (0.081 mol) of *tert*-butyldimethylsilyl chloride in 200 mL of CH_2Cl_2 was stirred for 12 h at room temperature. It was poured into 100 mL of water and extracted three times with ether. The combined extract was washed with 1 N HCl, saturated $NaHCO_3$, and brine, dried ($MgSO_4$), concentrated, and column chromatographed to give 15.8 g (97% yield) of **17**: ^1H NMR ($CDCl_3$) δ 3.48 (s, 2 H, CH_2), 3.41 (s, 2 H, CH_2), 1.1 (s, 6 H, 2 CH_3), 0.9 (s, 9 H, *t*-Bu), 0.06 (s, 6 H, 2 CH_3); MS, *m/e* 283 (M + 2), 282 (M + 1), 281 (M^+), 280.

3-[(*tert*-Butyldimethylsilyl)oxy]-2,2-dimethylpropyl Isopropenyl Sulfoxide (19). To 0.22 g (0.03 mol) of lithium wire in 10 mL of ether was added 1.7 g (0.0063 mol) of bromide **17** in 20 mL of ether. The reaction was exothermic and was stirred for 40 min at room temperature. This mixture was cooled to −10 °C, and only the solution part was transferred to a cold solution (−35

(35) When racemic *p*-tolyl allyl sulfoxide was treated with LDA in THF at −78 °C, a suspension of yellow solids (the lithiated allyl anion) resulted. Hence, the aggregates of the optically active and racemic sulfinylallyl anions have different physical properties. This may suggest that the anions are not a monomeric species.

(36) Tsuda, J.; Ohki, E.; Nozoe, S. *J. Org. Chem.* **1963**, *28*, 783.

°C) of 0.7 g (0.0042 mol) of phenyl isopropenyl sulfoxide in 10 mL of THF via cannula. The yellowish solution obtained was stirred at −35 °C for 1 h, poured into 200 mL of saturated NH_4Cl solution, and extracted three times with ether. The combined extract was washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel to give 1.0 g (83% yield) of **19**: IR (neat) 1625 (C=C), 1045 (S=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.8 (s, 1 H, =CH), 5.58 (s, 1 H, =CH), 3.57 (d, J = 9.7 Hz, 1 H, CHO), 3.33 (d, J = 9.7 Hz, 1 H, CHO), 2.85 (d, J = 13.5 Hz, 1 H, CHS), 2.40 (d, J = 13.5 Hz, 1 H, CHS), 1.96 (s, 3 H, CH_3C=), 1.15 (s, 3 H, CH_3), 1.08 (s, 3 H, CH_3), 0.87 (s, 9 H, t-Bu), 0.05 (s, 6 H, CH_3Si); ^{13}C NMR ($CDCl_3$) δ 149 (s, =CS), 116.6 (t, $=CH_2$), 70.8 (t, CO), 62.5 (t, CS), 36.2 (s, CMe_2), 25.8 (q, 3 C, CH_3 of t-Bu), 25.0 (q, CH_3), 23.7 (q, CH_3), 18.2 (s, C of t-Bu), 14.6 (q, CH_3), −5.1 (q, CH_3Si), −5.2 (q, CH_3Si); MS, m/e 291 (M + 1), 290 (M^+), 232 (M − t-Bu), 146. Anal. Calcd for $C_{14}H_{30}O_2SSi$: C, 57.88%; H, 10.41; S, 11.04; Si, 9.67. Found: C, 57.67; H, 10.38; S, 10.91; Si, 9.48.

5-[(*tert*-Butyldimethylsilyl)oxy]-4,4-dimethylpentyl *p*-Tolyl Sulfoxide (20). To 0.23 g (0.032 mol) of lithium wire in 10 mL of ether was added 1.8 g (0.0064 mol) of bromide **17** in 10 mL of ether under argon. The reaction was stirred for 1 h at room temperature and then cooled to −10 °C, and only the solution part was transferred to a cold (−35 °C) suspension of 0.9 g (0.00356 mol) of CuI·MeSMe complex in 15 mL of ether and 15 mL of dimethyl sulfide. After 30 min of stirring at −35 °C, a solution of 0.83 g (0.005 mol) of *p*-tolyl vinyl sulfoxide (**16**) in 20 mL of ether was added. The dark yellow solution obtained was stirred at −35 °C for 2 h. It was poured into 200 mL of a mixture of saturated NH_4Cl and NH_4OH (4:1), stirred for 20 min, and extracted three times with ether. The combined extract was washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed to give 1.38 g (75% yield) of sulfoxide **20** and 58 mg (7% recovery) of **16**. For **20**: IR (neat) 1045 (S=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.54 (d, J = 8 Hz, 2 H, ortho H), 7.36 (d, J = 8 Hz, 2 H, meta H), 3.20 (s, 2 H, CH_2O), 2.74 (m, 2 H, CH_2S), 2.41 (s, 3 H, p-CH_3), 1.8–1.2 (m, 4 H, CH_2), 0.89 (s, 9 H, t-Bu), 0.83 (s, 3 H, CH_3), 0.82 (s, 3 H, CH_3), −0.02 (s, 3 H, CH_3Si), −0.04 (s, 3 H, CH_3Si). Anal. Calcd for $C_{20}H_{36}O_2SSi$: C, 65.16; H, 9.84; S, 8.70; Si, 7.62. Found: C, 64.88; H, 9.61; S, 8.39; Si, 7.37.

(3a*R*,6a*S*)-(3aα,6aα)-Octahydro-6a-methyl-1-methylene-6-(*p*-tolylthio)pentalene (21). To a three-necked flask equipped with a reflux condenser and maintained under argon at room temperature was added 0.48 g (0.01 mol) of NaH (50% oil dispersion), and then the mixture was washed twice with ether (2 × 5 mL) to remove the oil. Dimethyl sulfoxide (DMSO) (5 mL) was added, and the mixture was heated to 60 °C for 1 h to obtain a greenish solution. The solution was cooled (0 °C), and a solution of 3.57 g (10 mmol) of methyltriphenylphosphonium bromide in 10 mL of DMSO was added. The resulting mixture was heated to 40 °C for 30 min to obtain a clear solution. To a solution of 1.3 g (5 mmol) of a mixture of ketones **11** and **12** (1:4) in 5 mL of DMSO, the above Wittig reagent was added via cannula, and the reaction was heated to 55 °C for 16 h. It was cooled, diluted with ether, and poured into water. The ether layer was separated, and the aqueous layer was extracted twice with ether. The combined ether layer was washed with water and brine, dried ($MgSO_4$), concentrated, and column chromatographed to give 1.226 g (95% yield) of olefin **21**: IR (neat) 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.32 (d, J = 8 Hz, 2 H, ortho H), 7.05 (d, J = 8 Hz, 2 H, meta H), 5.3 (m, 1 H, =CH), 5.1 (m, 1 H, =CH), 3.6 (t, J = 6 Hz, 1 H, CHS of cis isomer), 3.2 (dd, J = 12 Hz, 6 Hz, 1 H, CHS of trans isomer), 2.4 (s, 3 H, p-CH_3), 2.7–1.3 (m, 10 H), 1.3 (s, 3 H, CH_3); MS, m/e 258 (M^+). Anal. Calcd for $C_{17}H_{22}S$: C, 79.01; H, 8.58; S, 12.41. Found: C, 78.88; H, 8.53; S, 12.28.

(3a*R*,6a*S*)-(3aα,6aα)-Octahydro-6a-methyl-1-methylene-6-(*p*-tolylsulfinyl)pentalene. To a solution of 0.88 g (3.4 mmol) of sulfide **21** in 5 mL of acetic acid at 0 °C was added 0.47 mL (4.1 mmol) of 30% H_2O_2. The mixture was stirred for 30 min, diluted with ether, and neutralized with 1 N NaOH solution. The organic layer was separated, and the aqueous layer was extracted three times with ether. The combined extract was washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed to give 0.92 g (99% yield) of the sulfoxide: IR (neat) 1620, 1045 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45 (d, J = 8 Hz, 2 H, ortho H), 7.3 (d, J = 8 Hz, 2 H, meta H), 5.3 (m, 1 H, =CH), 5.1 (m, 1 H, =CH), 2.8–1.3 (m, 10 H), 2.4 (s, 3 H, p-CH_3), 1.3 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 157.6 (s, =C), 141.6 (s), 140.3 (s), 129.5 (d, 2 C), 124.2 (d, 2 C), 108.7 (t, $=CH_2$), 76.01 (d, CS), 54.9 (s), 53.6 (d), 35.0 (t), 30.0 (t), 29.5 (t), 28.9 (t), 21.4 (q, CH_3), 21.3 (q); MS, m/e 274 (M^+). Anal. Calcd for $C_{17}H_{22}OS$: C, 74.41; H, 8.08; S, 11.68. Found: C, 74.27; H, 8.13; S, 11.40.

(1*R*,3a*R*,6a*S*)-(3aα,6aα)-Octahydro-1-bromo-6a-methyl-6-methylene-1-(*p*-tolylsulfinyl)pentalene (22). To a solution of 0.54 g (1.97 mmol) of the mixture of the above sulfoxides in 5 mL of THF at −78 °C was added a cold (−78 °C) solution of LDA (2.1 mmol) in THF. The yellow solution obtained was stirred at −78 °C for 1 h, and a solution of 0.697 g (2.1 mmol) of CBr_4 in 2 mL of THF was added. After the dark brown solution was stirred at −78 °C for 1 h, it was poured in water and extracted twice with ether. The combined extract was washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed to give 0.60 g (95% yield) of bromide **22**: IR (neat) 1625, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.55 (d, J = 8 Hz, 2 H, ortho H), 7.3 (d, J = 8 Hz, 2 H, meta H), 5.6 (s, 1 H, =CH), 5.45 (s, 1 H, =CH), 2.55–1.25 (m, 9 H), 2.4 (s, 3 H, p-CH_3), 1.6 (s, 3 H, CH_3); MS, m/e 354 (M + 1), 352 (M − 1). Anal. Calcd for $C_{17}H_{21}BrOS$: C, 57.79; H, 5.99; Br, 22.62; S, 9.07. Found: C, 57.62; H, 5.83; Br, 22.41; S, 9.12.

Treatment of Sulfoxide 22 with DBN. Formation of (3a*R*,6a*S*)-(3aα,6aα)-3,3a,4,5,6,6a-Hexahydro-1-bromo-6a-methyl-6-methylenepentalene (23) and (3a*R*,6a*S*)-(3aα,6aα)-3,3a,4,5,6,6a-Hexahydro-6a-methyl-6-methylene-1-(*p*-tolylsulfinyl)pentalene (13). A mixture of 0.6 g (1.7 mmol) of sulfoxide **22** and 1.1 mL (8.5 mmol) of DBN in 20 mL of toluene was heated under reflux for 1 h. It was cooled, poured in water, and extracted three times with ether. The combined extract was washed with 1 N HCl, saturated $NaHCO_3$ solution, and brine, dried ($MgSO_4$), concentrated, and column chromatographed to give 0.20 g (55% yield) of vinyl bromide **23**, 0.01 g (2% yield) of vinyl sulfoxide **13**, and 0.12 g (20% recovery) of sulfoxide **22**.

For vinyl bromide **23**: IR (neat) 1640, 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.71 (t, J = 2.5 Hz, 1 H, =CH), 4.96 (s, 2 H, $=CH_2$), 2.65–1.2 (m, 7 H), 1.2 (s, 3 H, CH_3); MS, m/e 214 (M + 1), 212 (M − 1). Anal. Calcd for $C_{10}H_{13}Br$: C, 56.36; H, 6.15; Br, 37.49. Found: C, 56.21; H, 6.17; Br, 37.36.

For vinyl sulfoxide **13**: IR (neat) 1645, 1625, 1045 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.51 (d, J = 8 Hz, 2 H, ortho H), 7.24 (d, J = 8 Hz, 2 H, meta H), 6.16 (t, J = 2 Hz, 1 H, $=CHCH_2$), 4.92 (s, 1 H, $=CH_2$), 4.80 (s, 1 H, $=CH_2$), 2.8–1.2 (m, 7 H), 2.37 (s, 3 H, p-CH_3), 1.43 (s, 3 H, CH_3); MS, m/e 272 (M^+). Anal. Calcd for $C_{17}H_{20}OS$: C, 74.96; H, 7.40; S, 11.77. Found: C, 74.68; H, 7.38; S, 11.58.

(3a*R*,6a*S*)-(3aα,6aα)-Hexahydro-6a-methyl-6-(*p*-tolylthio)-1(2*H*)-pentalenone Ethylene Ketal. A mixture of 2.0 g (7.7 mmol) of ketones **11** and **12**, 1.67 mL (30 mmol) of 1,2-ethanediol, and 57 mg (3.0 mmol) of *p*-toluenesulfonic acid monohydrate in 90 mL of benzene was refluxed for 6 h with a Dean–Stark apparatus. The reaction solution was diluted with ether, washed with water, saturated $NaHCO_3$, and brine, dried ($MgSO_4$), concentrated, and column chromatographed to give 2.22 g (95% yield) of the ketal: ^1H NMR ($CDCl_3$) δ 7.32 (d, J = 8 Hz, 2 H, ortho H), 7.05 (d, J = 8 Hz, 2 H, meta H), 4.15 (m, 2 H, OCH_2), 3.85 (m, 2 H, OCH_2), 3.61 (dd, J = 10 Hz, 6 Hz, 1 H, CHS, the cis isomer), 2.74 (dd, J = 12.5 Hz, 6.2 Hz, 1 H, CHS, the trans isomer), 2.3 (s, 3 H, p-CH_3), 2.2–1.36 (m, 9 H), 1.28 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 136.6, 135.9, 131.2, 129.4, 119.2, 64.5 (2 C), 60.7, 55.1, 49.7, 35.7, 34.7, 30.4, 29.0, 25.5, 21.0; MS, m/e 304 (M^+).

(3a*R*,6a*S*)-(3aα,6aα)-Hexahydro-6a-methyl-6-(*p*-tolylsulfinyl)-1(2*H*)-pentalenone Ethylene Ketal (25). To a solution of 0.64 g (2.105 mmol) of the above sulfide in 50 mL of CH_2Cl_2 at −20 °C was added 0.438 g (2.105 mmol) of *m*-chloroperbenzoic acid (MCPBA). The mixture was stirred at 0 °C for 5 h. It was diluted with ether, washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), concentrated, and column chromatographed to give 0.64 g (95% yield) of sulfoxide **25**. For one (major) diastereomer: IR (neat) 1050 (S=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.56 (d, J = 8 Hz, 2 H, ortho H), 7.31 (d, J = 8 Hz, 2 H, meta H), 4.25 (m, 2 H, OCH_2), 3.95 (m, 2 H, OCH_2), 2.82 (dd, J = 12 Hz, 6.5 Hz, 1 H, CHS), 2.4 (s, 3 H, p-CH_3), 2.2–1.2 (m, 9 H), 0.9 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 142.8 (s), 141.0 (s), 129.5 (d, 2 C), 124.9 (d, 2 C), 118.8 (s), 76.5 (d), 63.9 (t, 2 C), 55.0 (s), 51.7

(d), 34.7 (t), 30.0 (t), 28.6 (t), 26.5 (t), 25.3 (q), 21.3 (t); MS, *m/e* 320 (M^+).

(3a*R*,6a*R*)-(3aα,6aα)-3,3a,4,6a-Tetrahydro-6a-methyl-1-(2*H*)-pentalenone Ethylene Ketal (26). A mixture of 1.0 g (3.125 mmol) of sulfoxide **25** and 0.387 g (3.125 mmol) of DBN in 40 mL of toluene was refluxed for 10 h. It was cooled, poured in water, and extracted twice with ether. The combined extract was washed with 1 N HCl, saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and distilled under normal pressure to remove solvent. The crude material was carefully chromatographed to give 0.506 g (90% yield) of olefin **26**: IR (neat) 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.65 (m, 1 H, =CH), 5.5 (m, 1 H, =CH), 3.95 (m, 4 H, OCH_2), 1.07 (s, 3 H, CH_3), 2.8–1.5 (m, 7 H); MS, *m/e* 180 (M^+).

(3a*S*,6a*S*)-(3aα,6aα)-2,3,3a,6a-Tetrahydro-6a-methyl-1,4-pentalenedione Ethylene Ketal (24). To a red solution of 6.4 g (25 mmol) of freshly prepared $CrO_3 \cdot (C_5H_4N)_2$ complex[37] in 15 mL of CH_2Cl_2 under argon was added a solution of 0.3 g (1.66 mmol) of olefin **26** in 34 mL of CH_2Cl_2. After the mixture was stirred for 24 h, it was diluted with ether and filtered through Celite. The filtrate was washed with 1 N HCl, saturated $NaHCO_3$, and brine, dried ($MgSO_4$), concentrated, and column chromatographed to give 0.274 g (85% yield) of enone **24**: $[\alpha]^{22}_D$ +160° (*c* 0.2, $CHCl_3$); IR (neat) 1700, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.58 (d, *J* = 5.6 Hz, 1 H, =CH), 6.15 (d, *J* = 5.6 Hz, 1 H, =CH), 4.0 (m, 4 H, OCH_2), 2.3–1.5 (m, 5 H), 1.2 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 209 (s), 170.1 (d), 133.2 (d), 116.1 (s), 65.4 (t), 64.8 (t), 57.1 (s), 64.7 (d), 33.0 (t), 24.0 (t), 17.8 (q); MS, *m/e* 194 (M^+). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.17; H, 7.38.

(3a*S*,6*R*,6a*S*)-(3aα,6aα)-2,3,3a,5,6,6a-Hexahydro-6α-[3-[(*tert*-butyldimethylsilyl)oxy]-2,2-dimethylpropyl]-1,4-pentalenedione Ethylene Ketal (27) and (3a*S*,6*S*,6a*S*)-(3aα,6aα)-2,3,3a,5,6,6a-Hexahydro-6β-[3-[(*tert*-butyldimethylsilyl)oxy]-2,2-dimethylpropyl]-1,4-pentalenedione Ethylene Ketal (28). To 0.16 g of lithium wire in 5 mL of ether was added 2.17 g (7.73 mmol) of bromide **17** in 4 mL of ether. The reaction was stirred for 1 h. The mixture was cooled to −10 °C, and only the solution part was transferred to a cold (−10 °C) suspension of 0.98 g (3.8 mmol) of $CuI \cdot Me_2S$ complex in 5 mL of ether. The resulting mixture was stirred for 30 min and cooled to −30 °C, and a solution of 0.25 g (1.29 mmol) of enone **24** in 6 mL of ether was added. The solution was stirred at −30 °C for 1 h. It was poured into 20 mL of a mixture of saturated NH_4Cl and NH_4OH (4:1), stirred for 5 min, and extracted three times with ether. The combined ether extract was washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed to give 0.43 g (85% yield) of **27** and 26 mg (5% yield) of **28**.

For **27**: IR (neat) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.9 (m, 4 H, OCH_2), 3.25 (d, *J* = 9 Hz, 1 H, CHO), 3.18 (d, *J* = 9 Hz, 1 H, CHO), 2.6–1.5 (m, 10 H), 1.0 (s, 3 H, CH_3), 0.9 (s, 3 H, CH_3), 0.85 (s, 9 H, *t*-Bu), 0.07 (s, 3 H, CH_3Si), 0.06 (s, 3 H, CH_3Si); ^{13}C NMR ($CDCl_3$) δ 219.9, 119.9, 72.4, 65.39, 64.4, 58.5, 53.9, 46.1, 40.3, 36.1, 35.6, 34.0, 25.9 (3 C, *t*-Bu), 24.9, 24.5, 23.1, 18.2, 14.5, −6.0 (2 C). Anal. Calcd for $C_{22}H_{40}O_4Si$: C, 66.62; H, 10.16; Si, 7.08. Found: C, 66.54; H, 10.07; Si, 6.83.

For **28**: IR (neat) 1743 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.9–3.7 (m, 4 H, OCH_2), 3.24 (d, *J* = 9 Hz, 1 H, CHO), 3.20 (d, *J* = 9 Hz, 1 H, CHO), 2.9 (t, *J* = 6 Hz, 1 H), 2.6–1.2 (m, 9 H), 1.03 (s, 3 H, CH_3), 0.97 (s, 3 H, CH_3), 0.9 (s, 9 H, *t*-Bu), 0.81 (s, 3 H, CH_3), 0.04 (s, 6 H, CH_3Si); MS, *m/e* 396 (M^+). Anal. Calcd for $C_{22}H_{40}O_4Si$: C, 66.62; H, 10.16; Si, 7.08. Found: C, 66.41; H, 9.98; Si, 6.87.

(3a*S*,6*R*,6a*S*)-(3aα,6aα)-2,3,3a,5,6,6a-Hexahydro-6α-(2,2-dimethyl-3-hydroxypropyl)-1,4-pentalenedione Ethylene Ketal (29). To a solution of 0.2542 g (0.64 mmol) of silyl ether **27** in 9 mL of THF under argon was added 1.28 mL (1.28 mmol) of *n*-Bu_4NF in THF (1 M solution). The reaction solution was stirred at 25 °C for 15 h, diluted with 20 mL of saturated NH_4Cl, and extracted three times with ether. The combined ether extract was washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed to give 0.1756 g (97% yield) of alcohol **29**: IR (neat) 3450, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.95 (m, 4 H, CH_2O), 3.52 (d, *J* = 12 Hz, 1 H, CHO), 3.14 (d, *J* = 12 Hz, 1 H, CHO), 2.97 (s, 1 H, OH), 2.6–1.6 (m, 10 H), 1.05 (s, 3 H, CH_3), 0.96 (s, 3 H, CH_3), 0.93 (s, 3 H, CH_3); MS, *m/e* 282 (M^+).

(3a*S*,6*R*,6a*S*)-(3aα,6aα)-2,3,3a,5,6,6a-Hexahydro-6α-[2,2-dimethyl-3-(tosyloxy)propyl]-1,4-pentalenedione Ethylene Ketal (30). To a solution of 1.52 g (5.4 mmol) of alcohol **29** in 30 mL of pyridine was added 3.08 g (16 mmol) of *p*-toluenesulfonyl chloride. The mixture was stirred at 25 °C for 20 h, diluted with ether and 3 N HCl, and extracted three times with ether. The combined extract was washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), concentrated, and column chromatographed to give 2.35 g (99% yield) of tosylate **30**: IR (neat) 1740, 1360, 1180 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.78 (d, *J* = 8 Hz, 2 H, ortho H), 7.35 (d, *J* = 8 Hz, 2 H, meta H), 3.9 (m, 4 H, CH_2O), 3.69 (d, *J* = 9 Hz, 1 H, CHO), 3.66 (d, *J* = 9 Hz, 1 H, CHO), 2.46 (s, 3 H, *p*-CH_3), 2.45–1.2 (m, 10 H), 0.98 (s, 3 H, CH_3), 0.90 (s, 3 H, CH_3), 0.86 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 219.8, 144.7, 133.4, 129.8, 127.9, 119.8, 78.6, 65.3, 64.6, 58.5, 53.9, 45.8, 40.3, 35.9, 34.6, 34.1, 24.8, 24.3, 23.0, 21.6, 14.5. Anal. Calcd for $C_{23}H_{32}O_6S$: C, 63.28; H, 7.39; S, 7.34. Found: C, 63.01; H, 7.11; S, 7.19.

(1*S*,2*R*,6*S*,8*S*)-11,11-(Ethylenedioxy)-1,4,4-trimethyl-*cis*-*anti*-*cis*-tricyclo[6.3.0.0^{2,6}]undecan-7-one (31). To a three-necked flask equipped with a reflux condenser and maintained under argon was added 0.192 g (4 mmol) of NaH (50% oil dispersion), and the mixture was washed twice with ether (2 × 5 mL) to remove oil. A solution of 0.872 g (2 mmol) of tosylate **30** in 200 mL of DME was added, and the mixture was allowed to reflux for 5 h. The solution was cooled, diluted with saturated NH_4Cl solution, and extracted three times with ether. The combined ether extract was washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed to give 0.4752 g (90% yield) of ketone **31**: IR (neat) 1740 cm^{-1}; ^1H NMR 3.9 (m, 4 H, CH_2O), 2.93 (dd, *J* = 17.5 Hz, 8.5 Hz, 1 H, CHC=O), 2.69 (m, 1 H), 2.38 (dd, *J* = 10 Hz, 3 Hz, 1 H), 2.02–1.2 (m, 8 H), 1.15 (s, 3 H, CH_3), 1.06 (s, 3 H, CH_3), 0.95 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 216.5, 119.6, 65.2, 64.4, 54.9, 54.1, 51.7, 45.0, 43.8, 43.6, 40.7, 32.8, 29.0, 26.8, 21.3, 19.6; MS, *m/e* 264 (M^+). Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.54; H, 9.01.

(1*S*,2*R*,6*S*,7*S*,8*S*)-11,11-(Ethylenedioxy)-1,4,4-trimethyl-*cis*-*anti*-*cis*-tricyclo[6.3.0.0^{2,6}]undecan-7-ol (32). To a solution of 0.67 g (2.54 mmol) of ketone **31** in 15 mL of MeOH at −10 °C under argon was added 0.2 g (5.08 mmol) of $NaBH_4$. The solution was stirred at −10 °C for 1 h, diluted with saturated NH_4Cl, and extracted three times with ether. The combined ether extract was dried ($MgSO_4$), concentrated, and column chromatographed to give 0.642 g (95% yield) of alcohol **32**: IR (neat) 3400 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.92 (m, 4 H, CH_2O), 3.76 (m, 1 H, CHO), 2.7–1.2 (m, 11 H), 1.05 (s, 3 H, CH_3), 1.01 (s, 3 H, CH_3), 0.91 (s, 3 H, CH_3); MS, *m/e* 266 (M^+). Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.08; H, 9.77.

(1*R*,2*S*,6*S*,7*S*,8*S*)-7-[(Isopropylsulfonyl)oxy]-2,10,10-trimethyl-*cis*-*anti*-*cis*-tricyclo[6.3.0.0^{2,6}]-3-undecanone Ethylene Ketal (33). To a solution of 0.3 g (1.13 mmol) of alcohol **32** and 0.57 g (5.6 mmol) of Et_3N in 20 mL of ether at 0 °C was added 0.24 g (1.7 mmol) of 2-propanesulfonyl chloride. The mixture was then stirred at 25 °C for 3 h, diluted with aqueous NH_4Cl solution, and extracted three times with ether. The combined extract was washed with water and brine, dried ($MgSO_4$), concentrated, and column chromatographed to give 0.39 g (93% yield) of sulfonate **33**: IR (neat) 1350, 1180 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.80 (dd, *J* = 8 Hz, 7 Hz, 1 H, CHO), 3.9 (m, 4 H, CH_2O), 3.23 (h, *J* = 7 Hz, 1 H, CHS), 2.0–1.2 (m, 11 H), 1.40 (d, *J* = 7 Hz, 6 H, CH_3), 1.09 (s, 3 H, CH_3), 0.98 (s, 3 H, CH_3), 0.95 (s, 3 H, CH_3); MS, *m/e* 372 (M^+).

(1*R*,2*S*,6*R*,8*S*)-2,10,10-Trimethyl-*cis*-*anti*-*cis*-tricyclo-[6.3.0.0^{2,6}]-3-undecanone Ethylene Ketal (34). A solution of 4.0 mM of lithium triethylborohydride in THF (4 mL; 1 M solution) was concentrated under vacuum to remove all THF and then maintained under argon. To the above hydride was added a solution of 0.37 g (1.0 mmol) of sulfonate **33** in 3 mL of toluene. After being stirred at 90 °C for 24 h, the mixture was cooled, diluted with 30 mL of ether, 20 mL of 1 N K_2CO_3, and 2 mL of 30% H_2O_2, and extracted three times with ether. The combined extract was washed with water and brine, dried ($MgSO_4$), distilled under normal pressure to remove solvent, and column chromatographed to give 0.18 g (72% yield) of ketal **34**: ^1H NMR ($CDCl_3$) δ 3.9 (m, 4 H, CH_2O), 2.0–1.1 (m, 13 H), 1.05 (s, 3 H, CH_3), 0.95

(37) Dauben, W. G.; Lorber, M.; Fullerton, D. S. *J. Org. Chem.* **1969**, *34*, 3587.

(s, 3 H, CH_3), 0.94 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 120.88 (s, CO), 65.11 (t, CH_2O), 64.46 (t, CH_2O), 51.37 (s), 49.44 (t), 48.21 (d), 44.01 (d), 42.85 (d), 42.44 (s), 40.40 (t), 40.39 (t), 36.64 (t), 26.7 (t), 29.97 (q), 27.81 (q), 18.07 (q); MS, *m/e* 250 (M^+). Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.68; H, 10.59.

(1*R*,2*S*,6*R*,8*S*)-2,10,10-Trimethyl-*cis*-*anti*-*cis*-tricyclo[6.3.0.0^{2,6}]-3-undecanone (35).[38] A solution of 0.26 g (1.04 mmol) of ketal **34** and 0.2 g (1.04 mmol) of *p*-toluenesulfonic acid monohydrate in 36 mL of MeOH, 4 mL of H_2O, and 20 mL of THF was stirred at 25 °C for 1 h. The solution was carefully neutralized with saturated $NaHCO_3$ and extracted three times with pentane. The combined extract was washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed to give 0.193 g (90% yield) of nor ketone **35**: $[\alpha]^{22}_D$ +81° (*c* 0.2, hexane); IR (neat) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.79 (dd, *J* = 19 Hz, 8.6 Hz, 1 H), 2.6–1.0 (m, 12 H), 1.04 (s, 3 H, CH_3), 0.94 (s, 3 H, CH_3), 0.90 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 244.68 (s), 59.32 (s), 48.97 (d), 48.89 (t), 46.80 (d), 43.34 (t), 41.91 (d), 41.15 (s), 37.66 (t), 34.26 (t), 29.26 (q), 26.59 (q), 22.44 (t), 17.34 (q); ORD (*c* 0.004, hexane) 22°, $[\Phi]_{600}$ +278°, $[\Phi]_{500}$ +309°, $[\Phi]_{400}$ +762°, $[\Phi]_{328}$ +4738°, $[\Phi]_{321}$ +3214°, $[\Phi]_{316}$ +3708°, $[\Phi]_{284}$ −2987°, $[\Phi]_{230}$ +309°; CD (*c* 0.004, hexane) 22°, $[\Theta]_{400}$ 0°, $[\Theta]_{330}$ +772°, $[\Theta]_{332}$ +3090°, $[\Theta]_{311}$ +5407°, $[\Theta]_{305}$ +4841°, $[\Theta]_{301}$ +5376°, $[\Theta]_{293}$ +4038°, $[\Theta]_{280}$ +2060°, $[\Theta]_{260}$ +412°, $[\Theta]_{250}$ +206°, $[\Theta]_{230}$ 0°; MS, *m/e* 206 (M^+), 205 (M − 1), 191, 177, 169, 149, 133, 121, 110, 99, 93, 81, 69, 57.

(+)-Hirsutene [(+)-4].[5t,38] A solution of 1.0 g (2.8 mmol) of methyltriphenylphosphonium bromide and 0.339 g (3.08 mmol) of sodium *tert*-amyloxide in 40 mL of toluene was stirred at 25 °C for 1 h. This solution was then added to a solution of 0.19 g (0.922 mmol) of nor ketone **35** in 3 mL of toluene. After refluxing for 3 h, the solution was cooled, diluted with aqueous NH_4Cl solution, and extracted twice with pentane. The combined extract was washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed to give 0.15 g (80% yield) of (+)-**4**: $[\alpha]^{22}_D$ +48° (*c* 0.35, in pentane);[39] IR (neat) 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.81 (br s, 1 H, =CH), 4.78 (br s, 1 H, =CH), 2.7–1.1 (m, 13 H), 1.05 (s, 3 H, CH_3), 0.95 (s, 3 H, CH_3), 0.92 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 162.94 (s), 103.53 (t), 55.99 (s), 53.51 (d), 50.04 (d), 49.03 (t), 44.29 (t), 41.93 (d), 41.13 (s), 36.68 (t), 30.97 (t), 29.78 (q), 27.29 (q), 26.89 (t), 23.23 (q); ORD (*c* 0.0035, pentane) 22°, $[\Theta]_{300}$ +117°, $[\Theta]_{290}$ +146°, $[\Theta]_{280}$ +466°, $[\Theta]_{270}$ +641°, $[\Theta]_{260}$ +991°, $[\Theta]_{250}$ +1632°, $[\Theta]_{240}$ +2390°, $[\Theta]_{230}$ +4197°, $[\Theta]_{220}$ +6295°; MS, *m/e* 204 (M^+, 15), 189 (M − CH_3, 3), 176 (3), 147 (4), 136 (5), 107 (7), 94 (100), 79 (20), 67 (5), 55 (8). Anal. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.01; H, 11.99.

Benzenesulfenyl Chloride.[40] To a mixture of 5.42 g (40.6 mmol) of *N*-chlorosuccinimide in 150 mL of benzene under argon was added slowly 4.47 g (40.6 mmol) of benzenethiol. The mixture was stirred at 25 °C for 1 h and then filtered through Celite under argon to remove succinimide. The filtrate, which contains benzenesulfenyl chloride and benzene (0.26 M solution), was used in the next reaction.

1-(Phenylsulfinyl)-2-methylenecyclopentane (36). To a solution of 0.237 g (2.41 mmol) of 1-(hydroxymethyl)-1-cyclopentene (**38**) in 1.34 mL (9.6 mmol) of Et_3N was added 12 mL (3.13 mM) of a solution of benzenesulfenyl chloride in benzene (0.26 M). The solution was stirred at 25 °C for 15 min, diluted with water, and extracted three times with ether. The combined extract was washed with saturated NH_4Cl and brine, dried ($MgSO_4$), concentrated, and column chromatographed to give 0.43 g (87% yield) of sulfoxide **36**: IR (neat) 1650, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ (two diastereomers) 7.7–7.4 (m, 5 H, Ph), 5.23 (s, 1 H, =CH), 5.18 (s, 1 H, =CH), 4.90 (s, 1 H, =CH), 3.8 (m, 1 H, CHS), 3.57 (m, 1 H, CHS), 2.6–1.4 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 146, 131.2, 130.98, 128.75, 125.56, 125.08, 112.89, 111.94, 69.76, 68.47, 33.57, 33.49, 26.44, 24.56, 24.38, 24.27; MS, *m/e* 206 (M^+). Due to the decomposition[41] of these types of allylic sulfoxides at room temperature, the elemental analyses of sulfoxides **36** and **37** were not performed.

4,4-Dimethyl-2-methylene-1-(*p*-tolylsulfinyl)cyclopentane (37). To a solution of 0.86 g (6.8 mmol) of 4,4-dimethyl-1-(hydroxymethyl)-1-cyclopentene (**43**) in 1.9 mL (13.65 mmol) of Et_3N was added 31 mL (8.16 mM) of a solution of benzenesulfenyl chloride in benzene (0.26 M). Workup was the same as that described for the preparation of **36**: 1.353 g (85% yield) of sulfoxide **37** was produced: IR (neat) 1645, 1055 cm^{-1}; ^1H NMR ($CDCl_3$) δ (two diastereomers) 7.7–7.4 (m, 5 H, Ph), 5.25 (s, 1 H, =CH), 5.22 (s, 1 H, =CH), 5.2 (s, 1 H, =CH), 3.83 (td, *J* = 8 Hz, 2 Hz, 1 H, CHS), 3.6 (td, *J* = 8 Hz, 2 Hz, 1 H, CHS, major diastereomer), 2.2–1.0 (m, 4 H), 1.1 (s, 3 H, CH_3), 0.99 (s, 3 H, CH_3), 0.87 (s, 3 H, CH_3), 0.86 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 147.32, 146.0, 131.23, 130.71, 129.20, 128.83, 125.73, 124.56, 113.72, 111.96, 67.84, 67.58, 55.60, 55.45, 49.05, 48.96, 40.14, 35.86, 28.21, 28.01, 27.52, 27.45; MS, *m/e* 234 (M^+).

2-[(3-Oxo-1-cyclopentyl)methyl]-1-(phenylsulfinyl)-1-cyclopentene (39). To a cold (−78 °C) solution of 0.364 g (1.77 mmol) of sulfoxide **36** in 10 mL of THF was added a cold (−78 °C) solution of LDA (1.9 mmol) in 10 mL of THF via cannula. After the resulting red solution was stirred at −78 °C for 15 min, 0.16 mL (1.9 mmol) of 2-cyclopentenone was added, and the solution was stirred at −78 °C for 15 min. To it was added a solution of 0.23 g (3.8 mmol) of acetic acid in 2 mL of ether, and the mixture was warmed to 25 °C, diluted with aqueous NH_4Cl, and extracted three times with ether. The combined extract was washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed to give 0.356 g (70% yield) of ketone **39**: IR (neat) 1730, 1620, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.5 (m, 5 H, Ph), 2.9–1.6 (m, 15 H); ^{13}C NMR ($CDCl_3$) δ 217.96 (C=O), 152.84, 142.28, 140.35, 130.09, 128.79, 123.88, 44.77, 37.77, 36.73, 35.14, 34.40, 28.94, 27.37, 21.33; MS, *m/e* 288 (M^+). Anal. Calcd for $C_{17}H_{20}O_2S$: C, 70.80; H, 6.99; S, 11.12. Found: C, 70.61; H, 6.67; S, 11.01.

2-[(1-Hydroxy-2-methyl-2-cyclopenten-1-yl)methyl]-1-(phenylsulfinyl)-1-cyclopentene (40). The procedure was the same as that described for the preparation of **39**, except the sulfinylallyl anion was allowed to react with enone **6** for 1 h at −78 °C prior to the addition of acetic acid. Alcohol **40** (83% yield) was isolated after column chromatographic purification: IR (neat) 3390, 1620, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.62 (m, 2 H, Ar H), 7.5 (m, 3 H, Ar H), 5.50 (br s, 1 H, =CH), 3.11 (d, *J* = 14 Hz, 1 H, CHC=C), 2.69 (d, *J* = 14 Hz, 1 H, CHC=C), 2.7–1.7 (m, 10 H), 1.78 (d, *J* = 2 Hz, 3 H, $=CCH_3$); ^{13}C NMR ($CDCl_3$) δ 152.55, 144.05, 142.38, 140.29, 130.25, 128.83, 126.99, 124.46, 84.55 (CO), 38.68, 37.95, 37.46, 28.51, 28.51, 21.74, 11.52; MS, *m/e* 302 (M^+). Anal. Calcd for $C_{18}H_{22}O_2S$: C, 71.49; H, 7.33; S, 10.60. Found: C, 71.26; H, 7.13; S, 10.35.

4,4-Dimethyl-2-[(3-oxo-1-cyclopentyl)methyl]-1-(phenylsulfinyl)-1-cyclopentene (41). The procedure was the same as that described in the preparation of **39**, except sulfoxide **37** was used. Ketone **41** (85% yield) was isolated after column chromatographic purification. IR (neat) 1730, 1620, 1035 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.5 (m, 5 H, Ph), 2.8–1.7 (m, 13 H), 1.09 (s, 3 H, CH_3), 0.90 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 218.11 (C=O), 151.47 (C=), 142.43, 139.37 (C=), 130.17, 128.91, 123.91, 51.41, 44.93, 41.67, 38.23, 37.94, 37.08, 35.29, 34.68, 29.10, 28.76; MS, *m/e* 316 (M^+). Anal. Calcd for $C_{19}H_{24}O_2S$: C, 72.11; H, 7.64; S, 10.13. Found: C, 71.97; H, 7.38; S, 10.03.

4,4-Dimethyl-2-[(1-hydroxy-2-methyl-2-cyclopenten-1-yl)methyl]-1-(phenylsulfinyl)cyclopentene (42). The procedure was the same as that described for the preparation of **39**, except the sulfinylallyl anion, derived from **37**, was allowed to react with enone **6** for 30 min at −78 °C and then 30 min at −50 °C prior to the addition of acetic acid. Alcohol **42** (63% yield) was isolated after column chromatographic purification: IR (neat) 3390, 1610, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.62 (m, 2 H, Ar H), 7.51 (m, 3 H, Ar H), 5.52 (br s, 1 H, =CH), 3.12 (d, *J* = 13 Hz, 1 H, CHC=), 2.61 (d, *J* = 13 Hz, 1 H, CHC=), 2.5–1.1 (m, 8 H), 1.78 (br s, 3 H, CH_3C=), 1.04 (s, 3 H, CH_3), 0.93 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 150.66, 144.20, 142.75, 139.44, 130.39, 128.96, 127.24, 124.66, 84.79 (CO), 53.57, 42.76, 37.88, 37.68, 37.34, 28.88,

(38) The spectral data (IR, ^1H and ^{13}C NMR, and mass spectra) of **35** and **4** are identical with those of the authentic materials, which were kindly provided by Professor Tomas Hudlicky of Virginia Polytechnic Institute and State University and Professor Kuniaki Tatsuta of Keio University.

(39) The exact specific rotation of the natural hirsutene is not kwown;[5b] however, in the ORD measurement, a positive plain curve has been reported.[5b]

(40) Ende, H. *Chem. Abstr.* **1952**, *46*, 529.

(41) Snider, B. B. *J. Org. Chem.* **1981**, *46*, 3155.

28.83, 28.66, 11.57; MS, m/e 330 (M^+, 2), 312 ($M - H_2O$, 30), 295 (100), 264, 216, 203.

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Registry No. (+)-**4**, 59372-72-4; **5S**, 96844-07-4; **6**, 1120-73-6; **7**, 111954-77-9; **8**, 111954-78-0; **9**, 111849-24-2; **10**, 111849-21-9; **11**, 111849-22-0; **11** (ethylene ketal), 111849-18-4; **12**, 111849-23-1; **12** (ethylene ketal), 111954-74-6; **13**, 111849-17-3; (±)-**15**, 111849-26-4; (±)-**16**, 110455-66-8; **17**, 111849-25-3; (±)-**19**, 111849-27-5; (±)-**20**, 111849-28-6; *cis*-**21**, 111849-11-7; *trans*-**21**, 111849-12-8; *cis*-**21** (sulfoxide), 111849-13-9; *trans*-**21** (sulfoxide), 111849-14-0; **22**, 111849-15-1; **23**, 111849-16-2; **24**, 96759-78-3; *cis*-**25**, 111849-19-5; *trans*-**25**, 111954-75-7; **26**, 96759-77-2; **27**, 96759-79-4; **28**, 111954-76-8; **29**, 96759-80-7; **30**, 111849-20-8; **31**, 96759-82-9; **32**, 96759-83-0; **33**, 96759-84-1; **34**, 96759-85-2; **35**, 96844-05-2; (±)-(*R**,*R**)-**36**, 111849-08-2; (±)-(*R**,*S**)-**36**, 111849-07-1; (±)-(*R**,*R**)-**37**, 111849-10-6; (±)-(*R**,*S**)-**37**, 111849-09-3; **38**, 1120-80-5; (±)-(*R**,*R**)-**39**, 111849-01-5; (±)-(*R**,*S**)-**39**, 111849-02-6; **40**, 111849-03-7; (±)-(*R**,*R**)-**41**, 111849-04-8; (±)-(*R**,*S**)-**41**, 111849-05-9; **42**, 111849-06-0; **43**, 64493-28-3; (+)-(*S*)-$CF_3C(OMe)(Ph)COCl$, 20445-33-4; $HOCH_2C(CH_3)_2CH_2OH$, 126-30-7; $BrCH_2C(CH_3)_2CH_2OCOCH_3$, 3492-41-9; $BrCH_2C(CH_3)_2CH_2OH$, 40894-00-6; $Ph_3PMe^+Br^-$, 1779-49-3; *i*-$PrSO_2Cl$, 10147-37-2; 1-methyl-1-cyclopentene, 693-89-0; 2-cyclopentenone, 930-30-3.

Microbial Transformation of Zearalenone. 2. Reduction, Hydroxylation, and Methylation Products

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Microbial transformations have been employed as a means of preparing analogues of the resorcylic acid lactone zearalenone. Microbial transformation products were initially identified by thin-layer chromatography of fermentation extracts and then prepared by large-scale incubations. Each metabolite was subjected to structural elucidation employing carbon-13 and proton NMR, mass spectrometry, and infrared analysis. Metabolites were identified as α- and β-zearalenol, α- and β-zearalanol, zearalanone, 8′(*S*)-hydroxyzearalenone, 2,4-dimethoxyzearalenone, and 2-methoxyzearalenone. Binding affinities to rat uterine estrogen receptors were carried out. Only those metabolites having a free 4-phenolic group were capable of binding to the estrogen receptor. However, 8′-hydroxyzearalenone, even with a 4-phenolic hydroxyl, did not bind to the receptor. It is possible that hydrogen bonding of the aliphatic hydroxyl groups to the C-6′ carbonyl of zearalenone or equilibrium between the hydroxy ketone and its tautomeric hemiketal may lead to distortion of the conformation of the molecule resulting in loss of binding to the receptor.

Introduction

Zearalenone 1, 6-(10-hydroxy-6-oxo-*trans*-1-undecenyl)-β-resorcylic acid lactone, is a fungal metabolite produced by certain *Fusarium* sp. when hosted on corn and other cereal grains. This compound possesses estrogenic- and growth-promoting activity in laboratory and farm animals.[1,2] The economic loss associated with impaired fertility in cows[3] and hyperestrogenism in swine has promoted further investigations on the metabolism of zearalenone by mammalian species[4-8] to determine the structure of the active compound(s).

In view of the fact that zearalenone is a good growth promoter in farm animals, and since diethylstilbestrol was found to be potentially carcinogenic[9] and therefore banned as a growth promoter in animals, several investigators were led to conduct a systematic study on the biological activities of zearalenone and several of its synthetic analogues[10-12] and to establish structure–activity relationships

Table I. Percent Microbial Transformation of Zearalenone to α- and β-Zearalenols

microorganism	α-zearalenol (%)	β-zearalenol (%)
Absidia coerulea MR-27B	*a*	5
Absidia spinosa NRRL 3033	4	*a*
Aspergillus niger ATCC 11394Y	12	4
Fusarium avenaceum 12 F-6	5	6
Fusarium oxysporum 5F-3	5	5
Mucor bainieri NRRL 2988	*a*	60
Penicillium stipitatum MR-336	8	8
Streptomyces griseus ATCC 13273	40	7
Streptomyces rimosus NRRL 2234	12	*a*
Streptomyces rutgersensis NRRL B1256	8	23

[a] No transformation.

(1) Mirocha, C. J.; Christensen, C. M.; Nelson, G. J. In *Microbial Toxins*; Ajl, S. J., Kadis, S., Ciegler, A., Eds.; Academic Press: New York, 1971; Vol. 7, pp 107–138.
(2) Mirocha, C. J.; Christensen, C. M. In *Mycotoxins*; Purchase, J. F. H., Ed.; Elsevier: Amsterdam, 1974; pp 129–149.
(3) Roine, K.; Karpinen, E. L.; Kallela, K. *Nord. Vet. Med.* **1971**, *23*, 628.
(4) Kiessling, K. H.; Petterson, H. *Acta Pharmacol. Toxicol.* **1978**, *43*, 285.
(5) Mirocha, C. J.; Abbas, H. K.; Olson, M. *Poultry Sci.* **1986**, *65*, 1905.
(6) Allen, N. K.; Mirocha, C. J.; Weaver, G.; Aakhus, S.; Bates, F. *Poultry Sci.* **1981**, *60*, 124.
(7) Chi, M. S.; Mirocha, C. J.; Weaver, G. A.; Kurtz, H. J. *Appl. Environm. Microbiol.* **1980**, *39*, 1026.
(8) Dailey, R. E.; Reese, R. E.; Brauwer, F. A. *J. Agric. Food Chem.* **1980**, *22*, 286.
(9) Herbst, A. L.; Scully, R. E. *Cancer* **1970**, *25*, 745.
(10) Kiang, D. T.; Kennedy, B. J.; Pathre, S. V.; Mirocha, C. J. *Cancer Res.* **1978**, *38*, 3611.
(11) Mastri, C.; Mistry, P.; Lucier, G. W. *J. Steroid Biochem.* **1985**, *23*, 279.
(12) Katzenellenbogen, B. S.; Katzenellenbogen, J. A.; Mordecai, D. *Endocrinology* **1979**, *105*, 33.

0022-3263/88/1953-0515$01.50/0