concentration of 2 mM in benzene proceeded smoothly to give acetoxyverrucarin A in 52% yield from **12**. Interestingly, cyclization of a mixture of secoacetoxyverrucarin A and its (*E,E*)-muconate isomer led only to cyclization of the (*E,Z*)-secoacetoxyverrucarin A component. This circumstance probably results from the strain of the *E,E* macrocycle and could have significant implications for future synthetic efforts in this area. Deacetylation of the acetoxyverrucarin A thus produced with catalytic sodium methoxide (MeOH, 0 °C, 2 h) gave synthetic verrucarin A (70%) which was shown to be identical by all the usual measurements including ^{13}C NMR and 250-MHz ^1H NMR with an authentic sample of natural material kindly provided by Professor B. B. Jarvis.[18]

Registry No. **1**, 3148-09-2; **2** (R^1 = Ac, R^2 = Si-*t*-BuPh$_2$), 79568-65-3; **3** (R^3 = $CH_2CH_2SiMe_3$), 79568-66-4; **4**, 2198-92-7; **5**, 79568-67-5; **6**, 79568-68-6; **7**, 79568-69-7; **8**, 1122-21-0; **9**, 57314-31-5; **10**, 14032-66-7; **11**, 79568-70-0; **12**, 79568-71-1; propargyl alcohol magnesium salt, 65113-89-5; furfural, 98-01-1; (trimethylsilyl)ethylylidene triphenylphosphine, 79414-15-6.

(18) All new compounds were characterized by ^1H NMR, IR, and MS. Yields reported refer to chromatographically pure isolated material. This work was supported by PHS Grant 2R01 CA23094 awarded by the National Cancer Institute, DHHS.

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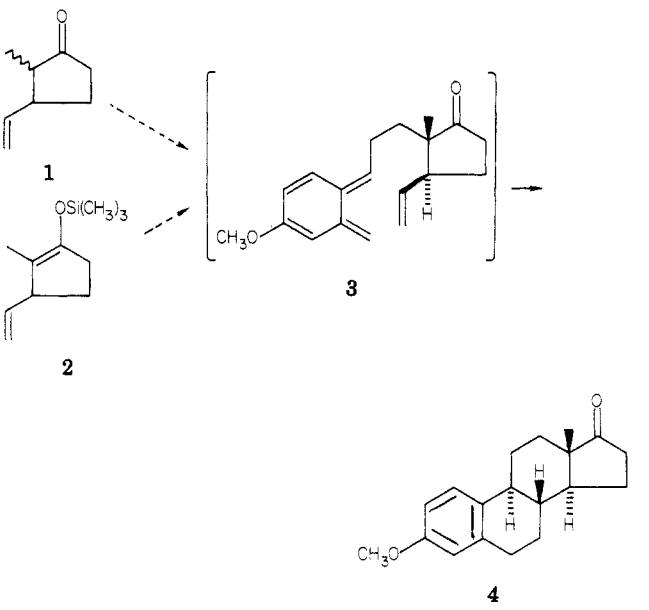
Received September 1, 1981

Complete Asymmetric Induction in Synthesis of Enantiomerically Pure Steroid Intermediates of Natural Configuration

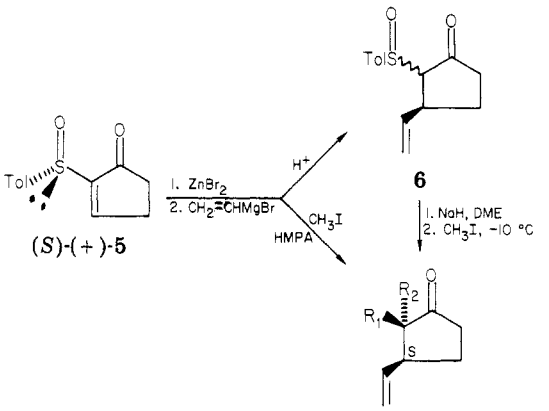
Summary: Enantiomerically pure steroid intermediates (*S*)-**1** and (*S*)-(+)-**2** of natural absolute configuration have been prepared with complete asymmetric induction during zinc dibromide mediated vinylmagnesium bromide conjugate addition to enantiomerically pure, crystalline, stable cyclopentenone sulfoxide (*S*)-(+)-**5**, which has been prepared on a 10-g scale.

Sir: During the past four years, several elegant, creative, and convergent total syntheses of racemic A-ring aromatic steroids have been developed (Scheme I). A common feature in all of these approaches is use of an intramolecular Diels–Alder cyclization of an *o*-quinodimethane such as **3** to produce a 19-nor steroid such as **4** having the natural *relative* configuration at all chiral centers.[2] Many of these approaches start with either racemic 2,3-disubstituted cyclopentanone **1** or with racemic cyclopentanone

Scheme I



Scheme II



(*S*)-(+)-**7a**, R_1 = TolSO; R_2 = CH_3
b, R_1 = CH_3; R_2 = TolSO

enol silyl ether **2**.[3] There is, therefore, a well-recognized need for an efficient and reliable source of *enantiomerically pure* steroid intermediates **1** and **2**. Prompted by Quinkert's recent report on partial asymmetric induction in synthesis of 2,3-disubstituted cyclopentanone **1**,[1i] we now report (1) the effect of divalent zinc on the course of vinyl Grignard conjugate addition to enantiomerically pure cyclopentenone sulfoxide (*S*)-(+)-**5**,[4] and (2) virtually *complete asymmetric induction* in the syntheses of optically pure steroid intermediates (*S*)-**1** and (*S*)-(+)-**2** of natural absolute configuration.

Optically pure, crystalline, stable cyclopentenone sulfoxide (*S*)-(+)-**5**,[5] $[\alpha]^{22}_D$ +141.7° (*c* 0.11, $CHCl_3$), prepared reproducibly on 10-g scale, was treated first with zinc dibromide to preform chelate **5a** and then with vinylmagnesium bromide; conjugate addition[6] led to an enolate ion which was protonated to give 2,3-disubstituted cyclopentanone **6** in quantitative yield and which separately was

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

(2) For reviews see: (a) Oppolzer, W. *Synthesis* **1978**, 793; *Heterocycles* **1980**, *14*, 1615. (b) Kametani, T.; Nemoto, H. *Tetrahedron* **1981**, *37*, 3. (c) Funk, R. L.; Vollhardt, K. P. C. *Chem. Soc. Rev.* **1980**, *9*, 41.

(3) A resolved oxocyclopentaneacetic acid has been used in the synthesis of two optically pure estrone derivatives: Oppolzer, W.; Roberts, D. A. *Helv. Chim. Acta* **1980**, *63*, 1703 and ref 1d.

(4) Posner, G. H.; Mallamo, J. P.; Miura, K. *J. Am. Chem. Soc.* **1981**, *103*, 2886.

(5) Prepared as indicated in ref 4.

(6) Posner, G. H. *Org. React.* **1972**, *19*, 1.

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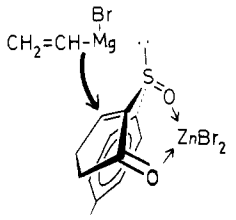


5a

methylated to produce 2,2,3-trisubstituted cyclopentanones **7a** and **7b** in roughly equal amounts (Scheme II). Although ^{1}H NMR analysis of the crude reaction product revealed the presence of both diastereomers **7a** (δ 0.96, s, angular CH_3) and **7b** (δ 1.20, s, angular CH_3), preparative MPLC or TLC allowed isolation only of diastereomer **7a** in 25–30% yield [mp 99.8–100.1 °C; $[\alpha]^{22}_D$ +347.4 4° (*c* 0.92, $CHCl_3$)][7] and of 2-methyl-3-vinyl-2-cyclopentenone [δ 1.6 (t, $J \approx 1$ Hz, allylic CH_3)] derived via syn elimination [8] of *p*-toluenesulfenic acid from diastereomer **7b** in which the sulfoxide group is syn to the vicinal tertiary allylic hydrogen atom. A single-crystal X-ray analysis of 2,2,3-trisubstituted cyclopentanone (+)-**7a** confirmed our expectation based on working model **5a** that (+)-**7a** indeed had the natural 3*S* configuration.

A roughly rectangular crystal with dimensions 0.5 × 0.5 × 0.2 mm was used for the X-ray diffraction experiment. Preliminary photographs revealed monoclinic symmetry, and the diffractometer-measured lattice constants were a = 8.008 (2) Å, b = 10.500 (2) Å, c = 8.494 (2) Å, and β = 104.20 (4)°. Systematic absences, the known chirality, and a rough density measurement indicated space group $P2_1$ with one molecule of $C_{15}H_{18}O_2S$ in the asymmetric unit. All unique diffraction maxima with $2\theta \leq 114°$ were collected on an automated four-circle diffractometer using graphite-monochromated Cu K$\bar{\alpha}$ radiation (1.541 78 Å) and a variable-speed ω scan. Of the 995 reflections surveyed, 904 (91%) were judged observed ($F_0 \geq 3\sigma(F_0)$) after correction for Lorentz, polarization, and background effects. A phasing model was achieved by standard heavy-atom techniques, and the pseudosymmetry of the first electron density synthesis was broken easily.[9] Block-diagonal least-squares refinements with anisotropic heavy atoms and fixed isotropic hydrogens have converged to a current residual of 0.059 for the observed data.

Figure 1 is a computer-generated perspective drawing of the final X-ray model. The choice of enantiomers was made from the known *S* configuration of the tolyl sulfur atom. The methyl group at C(2) and the vinyl group at C(3) are trans. There is a possible interaction of the sulfoxide oxygen, O(18), and the carbonyl carbon, C(1),

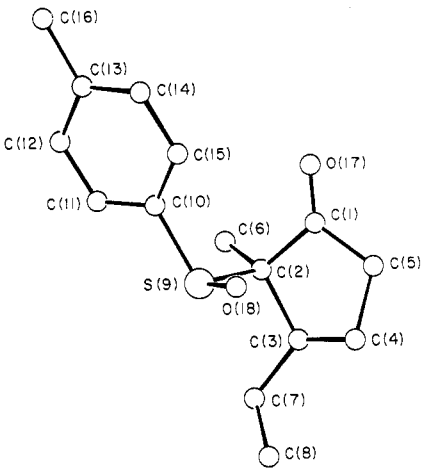
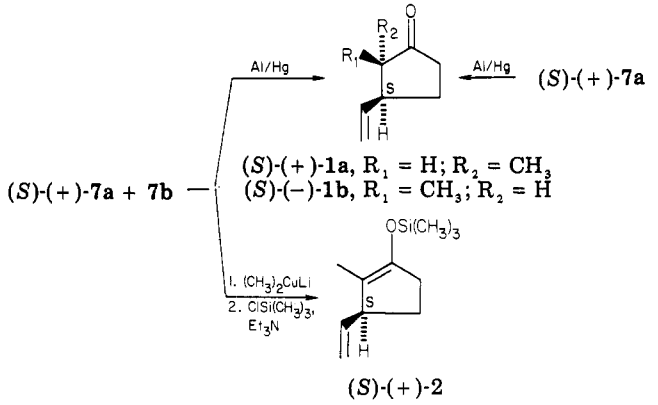


Figure 1. Computer-generated perspective drawing of the X-ray model of cyclopentanone sulfoxide (*S*)-(+)-**7a**. Hydrogens are omitted for clarity, and the configuration shown is based on the known configuration of the sulfoxide.

Scheme III



with a distance of 2.88 Å.[10] The C(1)–C(2)–S(9)–O(18) torsional angle is 36°. Further crystallographic details can be found in the supplementary material.

Aluminum amalgam reductive cleavage of crystalline, enantiomerically pure, trisubstituted cyclopentanone (*S*)-(+)-**7a** gave a mixture of *cis*- and *trans*-2-methyl-3-vinylcyclopentanones which were separated by preparative GLC into enantiomerically pure *trans*-2-methyl-3-vinylcyclopentanone [(*S*)-(+)-**1a**, $[\alpha]^{24}_D$ +148.6° (*c* 0.66, CH_2Cl_2)] and *cis*-2-methyl-3-vinylcyclopentanone [(*S*)-(−)-**1b**, $[\alpha]^{24}_D$ −61.4° (*c* 0.48, CH_2Cl_2)]. Knowing the specific rotations of these optically pure compounds, we examined the entire sequence **5** → **6** → **7a** + **7b** → **1a** + **1b** without purification of any of the compounds intermediate between cyclopentenone sulfoxide (*S*)-(+)-**5** and steroid intermediates **1a** and **1b** (Scheme III).

2,3-Disubstituted cyclopentanone **6** was converted into its sodium enolate and then methylated in 1,2-dimethoxyethane (DME) at −5 °C for 2 h, at which time TLC analysis indicated absence of any unmethylated cyclopentanone **6** and ^{1}H NMR indicated formation of both diastereomers **7a** and **7b**. The DME was then removed

(7) Anal. Calcd for $C_{15}H_{18}O_2S$: C, 68.87; H, 6.92; S, 12.22. Found: C, 68.50; H, 6.96; S, 12.21. IR($CHCl_3$) 3000, 1725, 1225, 1080, 1050, 925 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.96 (s, 3 H, angular CH_3), 2.0–3.0 (m, 5 H), 2.42 (s, 3 H, tolyl CH_3), 5.45 (m, 2 H, vinyl CH_2), 6.55 (m, 1 H, vinyl CH), 7.4 (q, 4 H, aromatic H).

(8) Trost, B. M. *Acc. Chem. Res.* **1978**, *11*, 453 and references therein.

(9) All crystallographic calculations were done on a PRIME 4000 computer operated by the Materials Science Center and the Department of Chemistry, Cornell University. The principal programs used were as follows: REDUCE and UNIQUE, data reduction programs: Leonowicz, M. E., Cornell University, 1978. BLS78A, anisotropic block-diagonal least-squares refinement: Hirotsu, K.; Arnold, E., Cornell University, 1980. XRAY; an X-ray system of crystallographic programs: Stewart, J. M., Ed., University of Maryland Technical Report TR-445, Mar 1976. ORTEP, crystallographic illustration program: Johnson, C. K., Oak Ridge National Laboratory Report ORNL-3794. MULTAN-78 (locally modified): Main, P. (principal author) "A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data"; University of York: York, England. For literature description of MULTAN see: Germain, G.; Main, P.; Woolfson, M. M.; *Acta Crystallogr., Sect. B* **1970**, *B26*, 274–285. Woolfson, M. M. *Acta Crystallogr., Sect. A* **1977**, *A33*, 219–225.

(10) This type of possible intramolecular interaction between nucleophilic and electrophilic portions of a molecule, when these centers are separated by 2.5–3.0 Å, has been interpreted in terms of donor–acceptor or dipole–dipole nonbonded interactions: Bürgi, H. B.; Dunitz, J. D.; Shefter, E. *J. Am. Chem. Soc.* **1973**, *95*, 5065. We thank Professor Craig A. Townsend (Johns Hopkins University) for bringing this reference to our attention. See also: Procter, G.; Britton, D.; Dunitz, J. D. *Helv. Chim. Acta* **1981**, *64*, 471.

under vacuum at −10 °C, and aqueous THF was added. This mixture of cyclopentanone sulfoxide diastereomers (*S*)-(+)-**7a** and **7b** was reductively cleaved by aluminum amalgam; after preparative TLC and 0 °C rotary evaporation of most of the solvent, complete removal of solvent diethyl ether at 0.025 mmHg from the cold (−78 °C), crystalline product mixture reproducibly gave pure *trans*-(*S*)-(+)-**1a** [^{1}H NMR δ 1.08 (3 H, d, J = 9 Hz] and *cis*-(*S*)-(−)-**1b** [^{1}H NMR δ 0.98 (3 H, d, J = 9 Hz] in a 92:8 ratio ($[\alpha]^{24}_D$ +130°) in 55–61% overall yield from cyclopentenone sulfoxide (*S*)-(+)-**5** with *100% asymmetric induction*! If zinc bromide was not used to preform chelate **5a**, 1% copper bromide catalyzed vinylmagnesium bromide conjugate addition to cyclopentenone sulfoxide (*S*)-(+)-**5** proceeded with 80% asymmetric induction. In a separate experiment, the cyclopentanone sulfoxide diastereomers (*S*)-(+)-**7a** and **7b** from the zinc bromide mediated vinyl conjugate addition were treated with dimethylcopperlithium at −78 °C;[4,11] after reductive cleavage of the sulfinyl group had occurred (0 °C, 3 h), the regiospecifically formed enolate ion intermediate was added to a solution of trimethylsilyl chloride and triethylamine to form cyclopentenol silyl ether (*S*)-(+)-**2** in 54% yield by GLC calibration; preparative GLC provided (*S*)-(+)-**2**, $[\alpha]^{25}_D$ +55.4° (*c* 0.79, CCl_4).

Optically pure steroid intermediates (*S*)-**1** and (*S*)-(+)-**2**, available for the first time via a reliable, convenient, and *complete* asymmetric synthesis, will certainly be used for preparation of optically pure estrone and estrone derivatives. Furthermore, optically pure cyclopentenone sulfoxide (*S*)-(+)-**5** and related enone sulfoxides have many possible applications in synthesis of complex, enantiomerically pure compounds of broad interest and utility. We are actively pursuing such applications.

Acknowledgment. G.H.P. acknowledges financial support from the National Science Foundation (Grant No. CHE 79-15161), and J.C. acknowledges financial support from the National Institutes of Health (Grant No. CA-24487).

Registry No. (2*S*,3*S*)-**1a**, 75917-46-3; (2*R*,3*S*)-**1b**, 75917-45-2; (*S*)-**2**, 74036-33-2; (*S*)-**5**, 79681-26-8; **6**, 79681-27-9; **7a**, 79681-28-0; **7b**, 79732-89-1; vinyl bromide, 593-60-2.

Supplementary Material Available: Experimental details for the **5** → **6** → **7a** + **7b** → **1a** + **1b** conversions and Tables I–III consisting of fractional coordinates, bond distances, bond angles, and observed and calculated structure factors for cyclopentane sulfoxide (*S*)-(+)-**7a** (6 pages). Ordering information is given on any current masthead page.

(11) For use of dimethylcopper–lithium in converting various α-heteroatom-substituted ketones into the corresponding enolate species, see: (a) Posner, G. H. "An Introduction to Synthesis Using Organocopper Reagents"; Wiley: New York, 1980; pp 22, 42. (b) Posner, G. H.; Sterling, J. J. *J. Am. Chem. Soc.* **1973**, *95*, 3076. (c) Lansbury, P. T.; Erwin, R. W.; Jeffrey, D. A. *Ibid.* **1980**, *102*, 1602. (d) Deprés, J.-P.; Greene, A. E. *J. Org. Chem.* **1980**, *45*, 2036.

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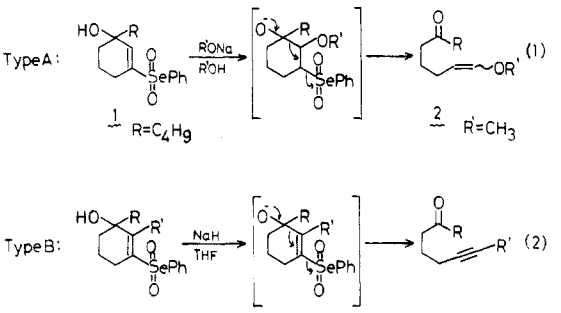
Received June 29, 1981

Highly Efficient Method for Ethylenic or Acetylenic Ketones via Fragmentation of Hydroxy Vinyl Selenones

Summary: Treatment of cyclic 3-hydroxyvinyl selenones with bases at room temperature leads to the formation of ethylenic or acetylenic ketones in good yields via 1,4-fragmentation, where phenylselenonyl group behaves as an excellent nucleofuge.

Sir: During our continuing study on the novel reactivity of aryl vinyl selenoxides[1] and/or selenones,[2] we have already demonstrated that an arylseleninyl or arylselenonyl group worked both as a very effective electronegative activator of olefinic bonds and as a good leaving group; e.g., some efficacy of these groups was shown in the cyclopropanation reaction[1] and the methoxyoxetane formation.[2]

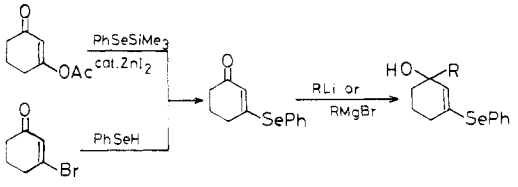
Further investigation has revealed that the phenylselenonyl group behaves quite effectively as a nucleofuge[3] in 1,4-fragmentation reactions[4] as outlined in eq 1 and 2.



When 1-butyl-3-(phenylselenonyl)-2-cyclohexen-1-ol (**1**) was treated with sodium methoxide in methanol at room temperature overnight and then at 45 °C for 3 h, 10-methoxy-9-decen-5-one (**2**) was obtained in 86% yield.[5] This reaction proceeds most probably via the conjugate addition of methoxide[6] to vinyl selenones followed by a 1,4-fragmentation reaction. This type of reaction (type A) was observed in the reaction of **1** with alkoxides (methoxide, ethoxide) and benzenethiolate to give 1,6-dicarbonyl derivatives in good to excellent yields. Results are summarized in Table I.

For the preparation of the starting hydroxy vinyl selenones it should be noted that the oxidation of hydroxy vinyl selenides to the corresponding vinyl selenones was quite difficult because of lability of allylic tertiary alcohols;[7] i.e., they underwent dehydration readily even on standing

(1) Shimizu, M.; Kuwajima, I. *J. Org. Chem.* **1980**, *45*, 2921.
(2) Shimizu, M.; Kuwajima, I. *J. Org. Chem.* **1980**, *45*, 4063.
(3) For the use of this term, see ref 4.
(4) Grob, C. A.; Schiess, P. W. *Angew. Chem.* **1967**, *79*, 1. Grob, C. A. *Ibid.* **1969**, *81*, 543. Recent examples, see: Clark, D. A.; Fuchs, P. L. *J. Am. Chem. Soc.* **1979**, *101*, 3567 and references cited therein.
(5) In contrast to the acyclic system, neither the oxetane nor the oxirane could be detected (see ref 2).
(6) The ability of the phenylselenonyl moiety as a leaving group has already been attested (see ref 2).
(7) Hydroxy vinyl selenides were usually prepared in the following manner:



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