

## ASYMMETRIC SYNTHESIS USING ORGANOMETALLIC REAGENTS AND OPTICALLY PURE VINYLIC SULFOXIDES

Gary H. Posner,\* John P. Mallamo, Kyo Miura, and Martin Hulce

Department of Chemistry, The Johns Hopkins University,  
Baltimore, Maryland 21218, USA

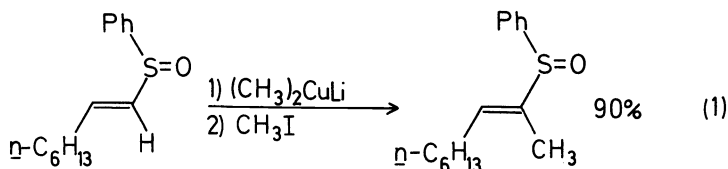
**Abstract** - A new, general method is developed for preparation of various 3-substituted carbonyl compounds of very high optical purity. Application of this method is made to asymmetric synthesis of either enantiomer of 3-methylalkanoic acids, of optically pure 3-methylcyclopentanone, 3-methylcyclohexanone, 3-naphthylcyclopentanone **12** and 3-vinylcyclopentanone **14**. 9,11-Seco steroid **12** and steroid intermediate **14** are precursors of optically pure steroidal equilenin and estrone of natural absolute configuration. The basis for this asymmetric synthetic method rests on the transfer of chirality from the sulfoxide sulfur atom to the  $\beta$ -carbon carbon atom during organometallic  $\beta$ -addition to optically pure  $\alpha,\beta$ -ethylenic sulfoxides.

### INTRODUCTION

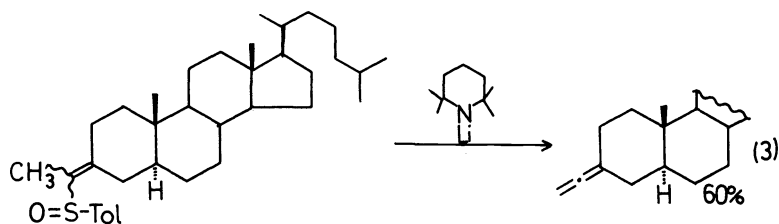
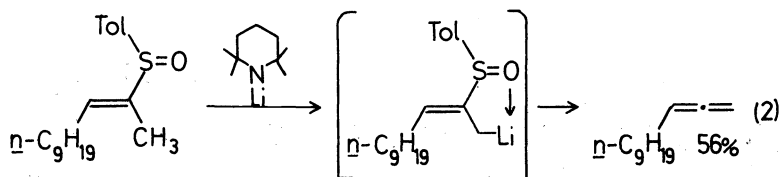
Several years ago we discovered that some  $\alpha,\beta$ -ethylenic sulfoxes, like most  $\alpha,\beta$ -ethylenic ketones, undergo conjugate addition reactions with organocopper reagents (Ref. 1). We reasoned that similar organometallic  $\beta$ -additions to optically active  $\alpha,\beta$ -ethylenic sulfoxides might proceed with high asymmetric induction during formation of the new carbon-carbon bond. Such transfer of chirality from the sulfoxide sulfur atom to the  $\beta$ -carbon atom would be very useful in asymmetric construction of structurally diverse, optically active synthetic intermediates. We report here (1) our initial observations on the behavior of vinylic sulfoxides toward organometallic reagents, (2) our discovery of high asymmetric induction during organometallic  $\beta$ -addition to some optically pure  $\alpha$ -carbonyl  $\alpha,\beta$ -ethylenic sulfoxides, and (3) application of these results to asymmetric synthesis of optically pure steroid intermediates of natural absolute configuration (Ref. 2).

### RESULTS AND DISCUSSION

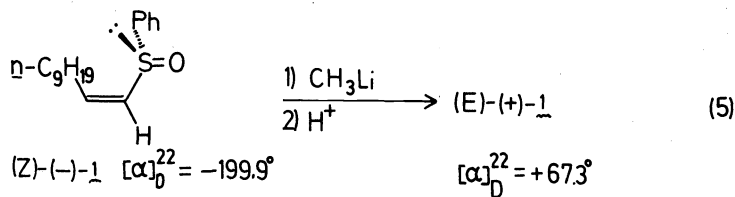
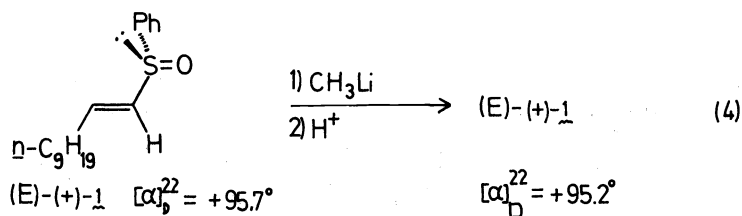
In 1977 we observed that several(E)-1-alkenyl aryl sulfoxides did not undergo the desired conjugate addition with organocopper reagents. Instead of organocopper addition to the carbon-carbon double bond, metalation occurred regio-specifically at the 1-position generating a vinylmetallic species. Likewise, methyllithium and several lithium amides generated such vinylmetallic species which reacted successfully with a variety of electrophiles to give various 1-substituted 1-alkenyl sulfoxides (e.g. eq. 1) (Ref. 3).



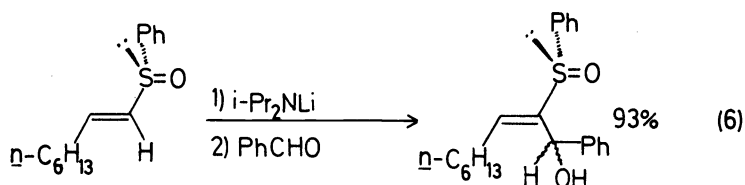
1-Methyl 1-alkenyl sulfoxides, for example, were found to undergo further regioselective deprotonation at the methyl group presumably to afford a transient, sulfoxide-chelated allylic lithium intermediate which underwent spontaneous fragmentation to produce terminal allenes in good yields (e.g. eqs. 2,3). This fragmentation bears close analogy to the widely used thermal *syn*  $\beta$ -elimination of arenesulfenic acids from alkyl aryl sulfoxides, and this method for preparation of terminal allenes is particularly noteworthy when compared with the poor yields of allenes obtained from non-aromatic ketones by other methods (Ref. 3).



Using optically pure 1-alkenyl aryl sulfoxides (E)-(+)- $\underline{1}$  and (Z)-(-)- $\underline{1}$ , we found that 1-deprotonation and then reprotonation of the (E)-(+)- $\underline{1}$  geometric isomer produced no double bond isomerization and no racemization, whereas similar treatment of the (Z)-(-)- $\underline{1}$  geometric isomer produced double bond isomerization and some racemization (eqs. 4,5) (Ref. 2).

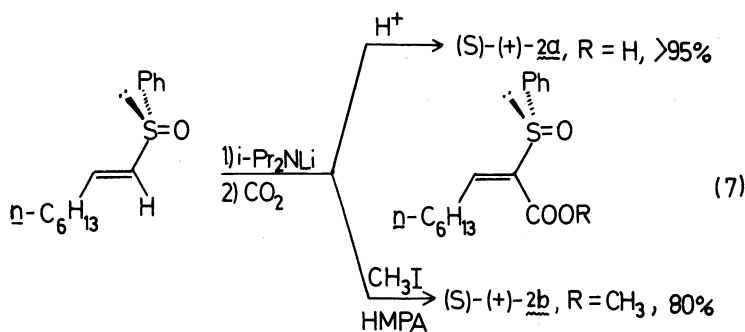


Having established that 1-lithio derivatives of optically pure (E)-1-alkenyl aryl sulfoxides are optically and geometrically stable and are able to act as strong nucleophiles toward  $sp^3$ -hybridized electrophiles, we next added these chiral alkenyllithium reagents to various aldehydes expecting some diastereoselection during formation of the new chiral center (e.g. eq. 6). A thorough study of the effects of solvent, reaction temperature, base used for deprotonation, structure of aldehyde, and various metal additives [e.g.  $MgBr_2$ ,  $Al(CH_3)_3$ ,  $ZnCl_2$ ,  $CuI$ ] revealed that no more than about 20-25% asymmetric induction could be obtained in this aldehyde addition reaction.

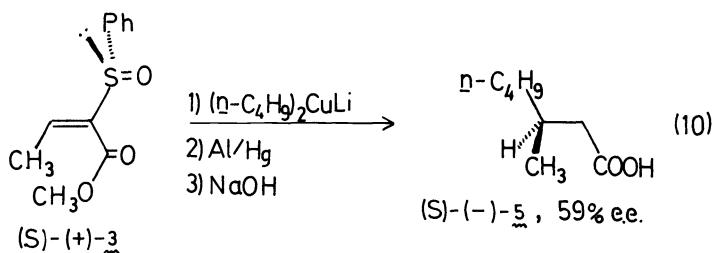
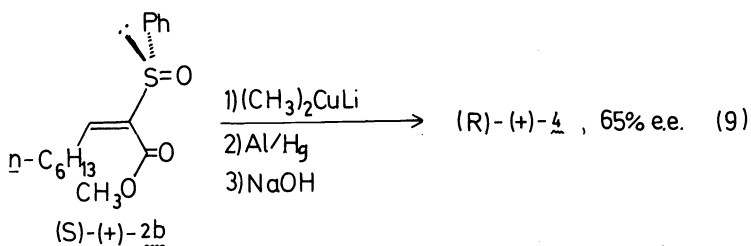
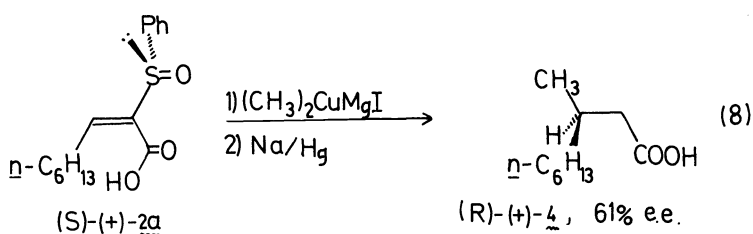


Diastereomeric  
Ratio 1.5:1.0

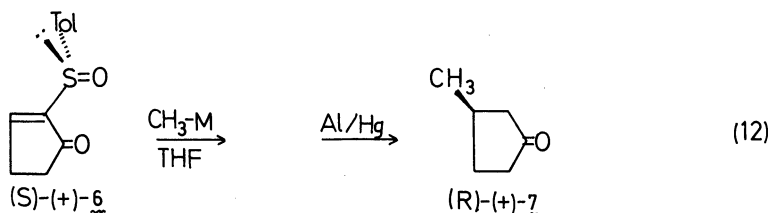
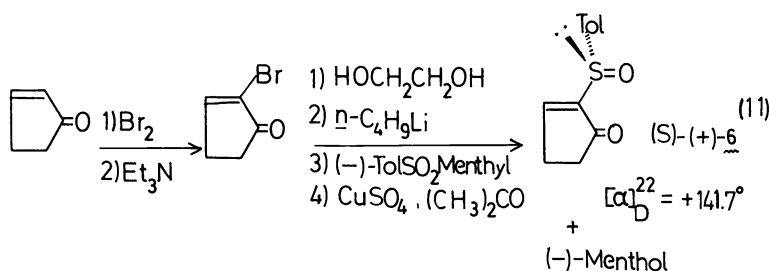
Carboxylation of 1-lithio 1-alkenyl sulfoxides led, for example, to geometrically and optically pure 1-carboxy 1-alkenyl sulfoxide (S)-(+)-2a after protonation of the intermediate lithium carboxylate and to the corresponding methyl ester (S)-(+)-2b after methylation with methyl iodide-hexamethylphosphoramide (HMPA, eq. 7) (Ref. 2).



In 1980, with optically and geometrically pure 1-carbonyl 1-alkenyl sulfoxides such as **2a** and **2b** in hand, we finally observed the originally sought organometallic conjugate addition to these systems. 1-Carboxyl 1-alkenyl sulfoxide **2a** reacted with dimethylcoppermagnesium iodide in a conjugate manner; sodium amalgam reductive cleavage of the intermediate sulfinyl carboxylic acid produced (R)-(+)-3-methylnonanoic acid in 61% enantiomeric excess (eq. 8). Likewise, 1-methoxycarbonyl 1-alkenyl sulfoxide **2b** reacted with dimethylcopperlithium followed by reductive sulfur-carbon bond cleavage and saponification to produce (R)-(+)-3-methylnonanoic acid in 65% optical purity (eq. 9 53% overall chemical yield). Reversing the order of introducing the larger and the smaller alkyl groups at the prochiral 2-carbon atom afforded mainly that enantiomer having opposite absolute stereochemistry. Thus (E)-1-propenyl sulfoxide (S)-(+)-**3** reacted with di-n-butylcopperlithium and then underwent reductive carbon-sulfur bond cleavage and saponification to form (S)-(-)-3-methylheptanoic acid (**5**) in 59% optical purity (eq. 10) (Ref. 2).

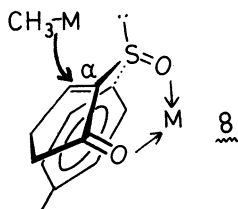


Optically active 3-alkylcyclopentanones and 3-arylcyclopentanones also can be prepared using this methodology. Thus crystalline cyclopentenone sulfoxide (S)-(+)-**6**, prepared in good yield via eq. 11 on multi-gram scale and stable at least for several months, reacted with methylmagnesium iodide [in the absence of copper (I)] in a conjugate addition fashion; aluminum amalgam carbon-sulfur bond reductive cleavage produced (R)-(+)-3-methylcyclopentanone (**7**) in 71% chemical yield and in 80% optical purity (eq. 12) (Ref. 2). We examined a variety of methylmetallic species with the aim of optimizing the amount of asymmetric induction. The best results were obtained using methylmagnesium chloride which gave (R)-(+)-3-methylcyclopentanone (**7**) in 91% yield and in 95-100% optical purity! The only other methylmetallic species which produced at least 88% asymmetric induction were methyl triisopropoxytitanium (Ref. 4) and lithium tetramethylaluminate.



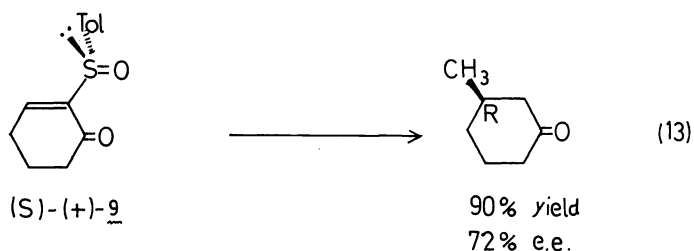
CH <sub>3</sub> -M	% yield	% e.e.
CH <sub>3</sub> MgI	71	80
CH <sub>3</sub> MgBr	86	84
CH <sub>3</sub> MgCl	91	95-100
(CH <sub>3</sub> ) <sub>2</sub> CuLi	100	80
(CH <sub>3</sub> ) <sub>2</sub> CuMgBr	96	60
(CH <sub>3</sub> ) <sub>2</sub> Zn	100	78-84
1. ZnBr <sub>2</sub> / 2. CH <sub>3</sub> MgI	100	87
1. NiBr <sub>2</sub> / 2. CH <sub>3</sub> MgBr	53	70
1. CoBr <sub>2</sub> / 2. CH <sub>3</sub> MgBr	73	70
1. PdBr <sub>2</sub> / 2. CH <sub>3</sub> MgBr	58	71
CH <sub>3</sub> Ti(i-PrO) <sub>3</sub>	44	90
LiAl(CH <sub>3</sub> ) <sub>4</sub>	68	88

To account for the different effects of various metals on the stereochemistry of this conjugate addition reaction and also to rationalize the selective formation of the (R)-enantiomer, we propose working model **8** in which the metal locks the sulfoxide group into one conformation. Now unable to rotate about the α-carbon — sulfur bond, the (S)-sulfoxide group provides an asymmetric environment for a methylmetallic reagent which apparently prefers to enter this environment away from the region of the aromatic group of the aryl sulfoxide and thus to approach the chelate from the pro-R direction.



In this context, it is especially noteworthy that when the amount of complex formation between a metal ion and enone sulfoxide (S)-(+)-6 was maximized before addition of the nucleophilic methylmetallic species (e.g., 1. ZnBr<sub>2</sub>, 2. CH<sub>3</sub>MgI), the amount of asymmetric induction was increased from 80 to 87% (eq. 12).

(R)-(+)-3-Methylcyclohexanone also has been prepared via methylmetallic conjugate addition to optically pure cyclohexenone sulfoxide (S)-(+)-9 (eq. 13).

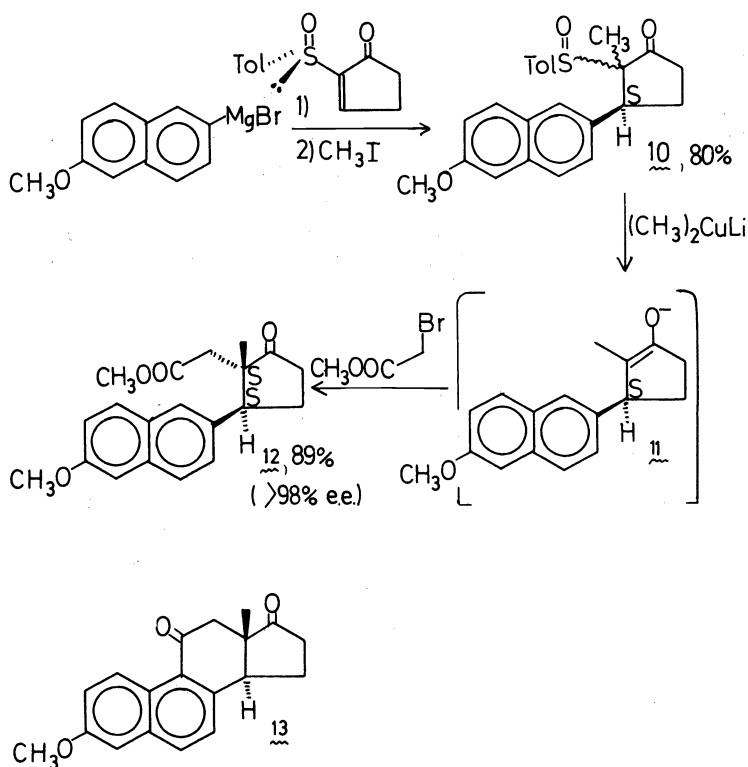


Besides conjugate addition of the small methyl group, cyclopentenone sulfoxide (S)-(+)-6 also underwent conjugate addition of a large naphthyl group. As shown in scheme I, we have applied this complete asymmetric induction reaction to efficient construction of 3-naphthylcyclopentanone 10 having the natural absolute steroid configuration at carbon 14 (steroid numbering). Reductive cleavage of the sulfinyl group using dimethylcopperlithium allowed regiospecific formation of enolate ion 11 which underwent carbon alkylation to give only 9,11-seco steroid 12 having the desired 13S, 14S absolute stereochemistry! Synthetic seco steroid 12 was identical by HPLC, NMR, IR, mass spectrometry, melting point (116.5-118°C), mixed melting point and optical rotation  $[\alpha]_{D}^{25} = +168^\circ$  (c 0.36, CHCl<sub>3</sub>) to a sample of 12 prepared by degradation of natural estradiol (Ref. 2). Because we have previously converted racemic 12 into racemic steroidal equilenin 13, (Ref. 5) preparation of optically pure 12 amounts to an efficient formal total asymmetric synthesis of optically pure equilenin 13.

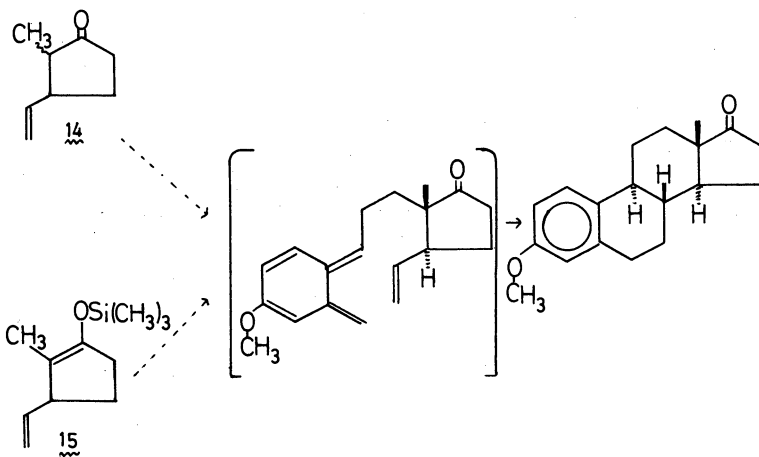
Racemic 3-vinylcyclopentanone 14 and the corresponding racemic enol silyl ether 15 have been used recently in some elegant, creative, and efficient syntheses of estrones via intramolecular Diels-Alder cycloaddition reactions of intermediate O-quinodimethanes (Scheme II) (Refs. 6-8). Only one report has appeared involving asymmetric synthesis of optically active steroid intermediate 14 used in preparation of optically active estrones via generalized scheme II (Ref. 6i).

We found that optically pure cyclopentenone sulfoxide (S)-(+)-6 reacted with vinylmagnesium bromide in the presence of a catalytic amount of cuprous bromide and then with methyl iodide to give 2,2,3-trisubstituted cyclopentanone 16 (Scheme III). Trisubstituted cyclopentanone 16, however, could be formed in better yield (~75%) via the corresponding sodio enolate. Aluminum amalgam reductive cleavage produced 3-vinylcyclopentanone (S)-(+)-14 in 80% optical purity. The amount of asymmetric induction was improved dramatically by first complexing cyclopentenone sulfoxide (S)-(+)-6 with zinc dibromide and then adding vinylmagnesium bromide. In this way, following scheme III, 3-vinylcyclopentanone (S)-(+)-14 was formed in >98% optical purity and in 50-60% overall yield! Reductive cleavage of 2-sulfinylcyclo-

SCHEME I



SCHEME II

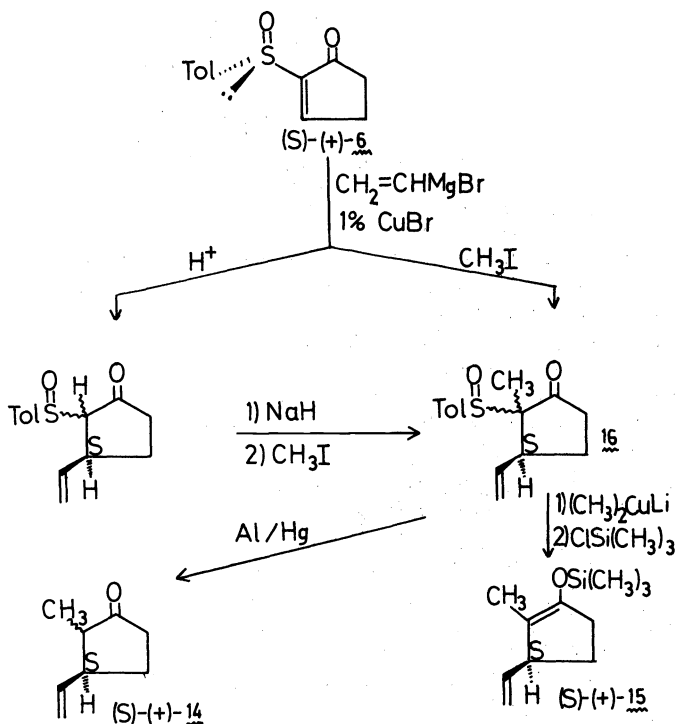


pentanone **14** using dimethylcopperlithium followed by addition of trimethylsilyl chloride gave optically pure enol silyl ether (S)-(+)-**15** in 40% overall yield (Ref. 9). This complete asymmetric induction in synthesis of steroidal intermediates (S)-(+)-**14** and (S)-(+)-**15** amounts to a formal total asymmetric synthesis of optically pure estrone!

It is clear from the results summarized here that some very efficient and highly desirable asymmetric syntheses can be performed using optically pure 1-carbonyl 1-alkenyl sulfoxides and various organometallic reagents. We are actively investigating other applications of this useful methodology.

**Acknowledgement** - We gratefully acknowledge financial support from the National Science Foundation (CHE 79-15161), from the Donors of the Petroleum Research Fund, administered by the

SCHEME III



American Chemical Society, from G. D. Searle and Co., and from Merck, Sharp and Dohme. We warmly acknowledge experimental help from P-W. Tang and A. Y. Black.

## REFERENCES

- G.H. Posner and D.J. Brunelle, *J. Org. Chem.*, **38**, 2747 (1973).
- G.H. Posner, J.P. Mallamo and K. Miura, *J. Amer. Chem. Soc.*, **103**, 000 (1981).
- G.H. Posner, P-W. Tang and J.P. Mallamo, *Tetrahedron Lett.*, 3995 (1978).
- (a) B. Weidmann and D. Seebach, *Helv. Chim. Acta*, **63**, 2451 (1980);  
(b) M.T. Reetz, J. Westerman and R. Steinbach, *Angew. Chem. Int. Ed. Engl.* **19**, 900 (1980).
- G.H. Posner, M.J. Chapdelaine and C.M. Lentz, *J. Org. Chem.*, **44**, 3661 (1979);  
(a) W. Oppolzer, W. Petrzilka and K. Bättig, *Helv. Chim. Acta*, **60**, 2965 (1977);  
(b) T. Kametani, H. Nemoto and K. Fukumoto, *J. Amer. Chem. Soc.*, **99**, 3461 (1977);  
(c) R.L. Funk and K.P.C. Vollhardt, *J. Amer. Chem. Soc.*, **99**, 5483 (1977) and **101**, 215 (1979);  
(d) W. Oppolzer, K. Bättig and M. Petrzilka, *Helv. Chim. Acta*, **61**, 1945 (1978);  
(e) K.C. Nicolaou, W.E. Barnette and P. Ma, *J. Org. Chem.*, **45**, 1463 (1980);  
(f) S. Djuric, T. Sarkan and P. Magnus, *J. Amer. Chem. Soc.*, **102**, 6885 (1980);  
(g) Y. Ito, M. Nakatsuka and T. Saegusa, *J. Amer. Chem. Soc.*, **103**, 476 (1981);  
(h) G. Quinkert, W-D. Weber, U. Schwartz and G. Dürner, *Angew. Chem. Int. Ed. Engl.*, **19**, 1027 (1980);  
(i) G. Quinkert, U. Schwartz, H. Stark, W-D. Weber, H. Baier, F. Adam and G. Dürner, *Angew. Chem. Int. Ed. Engl.*, **19**, 1029 (1980)
- For a review, see W. Oppolzer, *Synthesis*, 793 (1978).
- A resolved cyclopentanoneacetic acid has been used in synthesis of two optically pure estrone derivatives: W. Oppolzer and D.A. Roberts, *Helv. Chim. Acta*, **63**, 1703 (1980).
- G.H. Posner, M. Hulce, J.P. Mallamo, S.A. Dexler and J. Clardy, in preparation.