Acknowledgment. Support of this research by the National Institutes of Health (GM 25923) and the National Science Foundation (CHE-77-21849) is gratefully acknowledged. The National Science Foundation provided funds for the purchase of a GC-mass spectrometer.

High Asymmetric Induction during Organometallic β Addition to α,β-Ethylenic Sulfoxides. Synthesis of Optically Active β-Alkylcarboxylic Acids, β-Substituted Cyclopentanones, and Steroidal 11-Oxoequilenin Methyl Ether

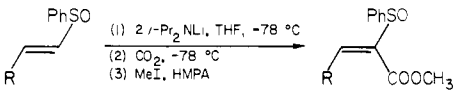
Gary H. Posner,* John P. Mallamo, and Kyo Miura

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

Received December 15, 1980

Pursuing our interest in the chemistry of α,β-unsaturated sulfur compounds,[1] we have discovered that several types of optically pure α-carbonyl α,β-ethylenic sulfoxides undergo facile conjugate addition of organometallic reagents with good to excellent amounts of asymmetric induction.[2-4] This transfer of chirality from the sulfoxide sulfur atom to the β-carbon atom during organometallic β addition, followed by reductive removal of sulfur, produces β-alkylcarboxylic esters in 59–65% optical purity and β-substituted cyclopentanones in 79–>98% optical purity. Virtually complete control of absolute stereochemistry is achieved in preparation of 2,2,3-trisubstituted cyclopentanone **11**, the racemate of which we have recently converted into steroidal (±)-11-oxoequilenin methyl ether.[5]

α-Lithiation[1b] and then protonation of optically pure (*E*)-1-undecenyl phenylsulfoxide (**1**) [R = n-C_9H_{19}, $[\alpha]^{22}_D$ = +95.66° (*c* 0.76, $CHCl_3$)][6,7] caused virtually no loss of optical activity ($[\alpha]^{22}_D$ +95.22°) and no *E* → *Z* isomerization. One-pot α-lithiation followed by carboxylation and esterification produced optically pure α-(methoxycarbonyl)alkenyl sulfoxides (*S*)-**2a** and (*S*)-**2b** in 80 and 40% overall yields, respectively (eq 1).[6]



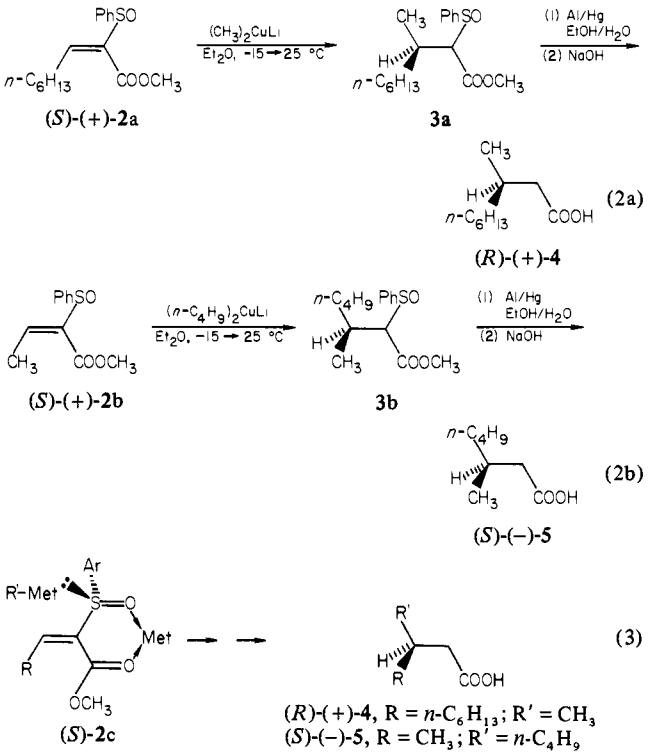
(+)-**1** (*S*)-(+)-**2** (1)

2a, R = n-C_6H_{13}	$[\alpha]^{22}_D$ +200°	(*c* 2.98, acetone)
b, R = CH_3	$[\alpha]^{22}_D$ +216°	(*c* 1.82, acetone)

(*E*)-1-Octenyl sulfoxide (*S*)-**2a**[7] reacted with dimethylcopperlithium to afford β-adduct **3a** in 86% chemical yield (Scheme I). Reduction of α-sulfinylcarboxylic ester **3a** with aluminum amalgam in ethanol[1a] and saponification gave (*R*)-(+)-3-methylnonanoic acid (**4**), $[\alpha]^{22}_D$ +4.68° (*c* 1.1, acetone), in 53% chemical yield and 65% optical purity.[8] Reversing the order of introducing the larger and the smaller alkyl groups at the prochiral β-carbon atom afforded mainly that enantiomer having opposite absolute stereochemistry. (*E*)-1-Propenyl sulfoxide (*S*)-**2b**[6] reacted with di-n-butylcopperlithium to produce conjugate adduct **3b**; reductive removal of the sulfinyl group and saponification gave (*S*)-(−)-3-methylheptanoic acid (**5**), $[\alpha]^{22}_D$ −2.46° (*c* 0.65, acetone), in 59% enantiomeric excess (eq 2b).[8] Comparable levels of asymmetric induction were also obtained by using >2 equiv of various methylcopper species and the carboxylic *acid* corresponding to *ester* (*S*)-**2a**. We tentatively rationalize these results in terms of an approximately planar metal chelate such as (*S*)-**2c** which suffers nucleophilic addition from that side of the plane containing sulfur's nonbonding electron pair and opposite to that side containing the aryl group.

Activation of α,β-ethylenic sulfoxides toward organometallic β addition is not limited to α-carboxyl groups; α-keto groups also are highly effective. For example, optically pure, crystalline (mp 121–122 °C), stable cyclopentenone *p*-tolyl sulfoxide (*S*)-**6**, $[\alpha]^{22}_D$ +141.7° (*c* 0.11, $CHCl_3$),[6,9] underwent methyl Grignard (1.5 equiv) *conjugate* addition (*even in the absence of copper salts*).

Scheme I



(1) (a) Posner, G. H.; Brunelle, D. J. *J. Org. Chem.* **1973**, *38*, 2747. (b) Posner, G. H.; Tang, P. W.; Mallamo, J. P. *Tetrahedron Lett.* **1978**, 3995. (c) Posner, G. H.; Tang, P. W. *J. Org. Chem.* **1978**, *43*, 4131.

(2) For β addition of alkyllithium reagents to α,β-ethylenic sulfoxides, see: Isobe, M.; Kitamura, M.; Goto, T. *Chem. Lett.* **1980**, 331. Sugihara, H.; Tanikaga, R.; Tanaka, K.; Kaji, A. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 655.

(3) For β addition of enolate ions and heteroatomic nucleophiles to α,β-ethylenic sulfoxides, see: (a) Tsuchihashi, G.; Mitamura, S.; Ione, S.; Ogura, K. *Tetrahedron Lett.* **1973**, 323. (b) Tsuchihashi, G.; Mitamura, S.; Ogura, K. *Ibid.* **1973**, *2469*. (c) Tsuchihashi, G.; Mitamura, S.; Ogura, K. *Ibid.* **1976**, 855. (d) Abott, D. J.; Colonna, S.; Stirling, J. M. *Chem. Commun.* **1971**, 471. (e) Guitet, E.; Julia, S. *Tetrahedron Lett.* **1978**, 1155.

(4) For asymmetric inductions during β additions to closely related sulfoxide derivatives, see: (a) Cinquini, M.; Cozzi, F. *J. Chem. Soc., Chem. Commun.* **1977**, 723. (b) Annunziata, R.; Cinquini, M. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1684.

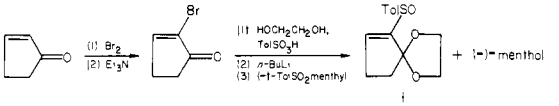
(5) Posner, G. H.; Chapdelaine, M. J.; Lentz, C. M. *J. Org. Chem.* **1979**, *44*, 3661.

(6) All new compounds were fully characterized spectroscopically and by combustion and/or high resolution mass spectral analysis.

(7) Prepared according to ref 1c.

(8) (a) Optically pure (*R*)-(+)-**4** is reported to have $[\alpha]^{24}_D$ +7.6° and optically pure (*S*)-(−)-**5** to have $[\alpha]^{27}_D$ −4.2°: Meyers, A. I.; Kamata, K. *J. Am. Chem. Soc.* **1976**, *98*, 2290. (b) For other examples of high asymmetric induction in preparation of β-alkylcarboxylic acids, see: Meyers, A. I.; Smith, R. K.; Whitten, C. E. *J. Org. Chem.* **1979**, *44*, 2250. Hashimoto, S.; Yamada, S.; Koga, K *J. Am. Chem. Soc.* **1976**, *98*, 7450.

(9) Cyclopentenone sulfoxide (*S*)-**6** was prepared from 2-bromo-2-cyclopentenone (Branca, S. J.; Smith, A. B., III *J. Am. Chem. Soc.* **1978**, *100*, 7767) as follows: Note that preparation of optically pure ketal sulfoxide i



involves liberation of optically pure (−)-menthol which, as the original source of chirality for the entire scheme, can be recycled easily. Ketal sulfoxide i, $[\alpha]^{22}_D$ +49.5° (*c* 1.03, $CHCl_3$), was easily and quantitatively converted into the corresponding ketone (*S*)-**6** by stirring it in acetone at room temperature over copper sulfate (Posner, G. H.; Mallamo, J. P.; Rose, R. K., unpublished results).

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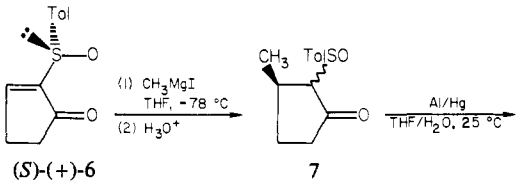
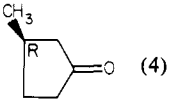


(S)-(+)-6 7

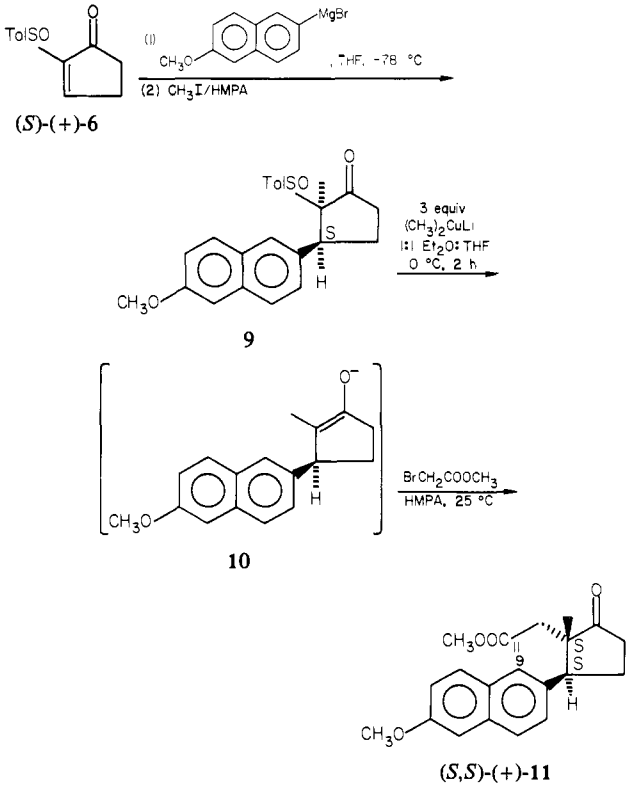


(R)-(+)-8 (4)

Reductive removal of the sulfinyl group gave (*R*)-(+)-3-methylcyclopentanone (**8**), $[\alpha]^{22}_D$ +116° (*c* 0.36, CH_3OH), in 77% overall chemical yield and 79% optical purity.[10] The absolute stereochemistry of this product is predictable from the tentative working model (*S*)-**2c** in which in this instance a metal is presumably complexed between the ketone carbonyl and the sulfinyl oxygen atoms.

Conjugate addition of the larger 6-methoxy-2-naphthylmagnesium bromide[5] to cyclopentenone sulfoxide (*S*)-**6** followed by in situ C-methylation of the intermediate enolate ion gave, after 24 h at 33 °C, crystalline β-naphthyl-α-methylcyclopentanone sulfoxide **9**,[6] mp 132–133 °C, in 42% yield after preparative TLC along with 40–50% of the corresponding unmethylated cyclopentanone sulfoxide (Scheme II); more vigorous methylation conditions led to loss of *p*-toluenesulfenic acid from **9** via thermolytic β elimination.[11] Only one diastereomer of 2,2,3-trisubstituted cyclopentanone **9** was formed [^{1}H NMR δ 1.0 (s, 3 H, angular CH_3)] which probably has the angular methyl group and the naphthyl group in a trans relationship.[12] Use of the optically active lanthanide shift reagent tris[3-[[(trifluoromethyl)-hydroxy]methylene]-*d*-camphorato]europium[13] in varying ratios with optically active cyclopentanone sulfoxide **9**, as well as with independently prepared racemic **9**, indicated that β-naphthyl-α-methyl adduct **9** was formed with at least 98% enantioselectivity! The higher degree of asymmetric induction in this Grignard conjugate addition to cyclopentanone (*S*)-**6** (>98%) compared to that in eq 4 (79%) is probably due to the much larger size of the naphthyl group compared to that of the methyl group. Conversion of α-sulfinylcyclopentanone **9** into enolate **10** was achieved in excellent yield (as indicated by enol silylation) by using dimethylcopperlithium.[14] Regiospecific and stereospecific alkylation of enolate ion **10** with methyl bromoacetate proceeded as we described recently in the racemic case[5] to produce exclusively 2,2,3-trisubstituted cyclopentanone **11** [^{1}H NMR δ 0.7 (s, 3H)] which was isolated by preparative HPLC in 89% yield from α-sulfinylcyclopentanone **9**. Synthetic 9,10-seco steroid **11** was identical by HPLC, NMR, IR, mass spectroscopy, melting point (116.5–118 °C), mixture melting point, and optical rotation [$[\alpha]^{22}_{365}$ +168° (*c* 0.36, $CHCl_3$)] to a sample of **11** prepared by degradation of natural estradiol.[15] Based on our steroid synthesis

Scheme II



using racemic 9,11-seco steroid **11**,[5] *Scheme II represents a short, convergent, stereospecific and high-yield (overall ~25%) formal total synthesis of optically pure steroidal 11-oxoequilenin methyl ether of natural configuration.*

Cyclopentenone sulfoxide (*S*)-**6** also can be used easily and very effectively to prepare some other optically active 2,2,3-trisubstituted cyclopentanones similar to **11** which are key intermediates in the *o*-quinodimethane intramolecular Diels–Alder route to steroids[16] as well as to prepare some optically active 2,3-disubstituted cyclopentanones in the prostaglandin E series.[17] Application to asymmetric synthesis of optically active β-lactam sulfoxides may also be possible.[18]

The results reported here represent several novel and significant breakthroughs, as follows: (1) a new, general asymmetric synthesis of β-substituted cyclopentanones having very high optical purity and of either enantiomer of β-substituted carboxylic acids, (2) a new, high-yield method using dimethylcopperlithium for reductively cleaving α-sulfinyl ketones (i.e., β-keto sulfoxides) into the corresponding synthetically useful and regiospecifically generated enolate ions, and (3) a highly convergent and stereocontrolled approach to asymmetric synthesis of some optically pure steroids of natural configuration. Full details and extension of these results to use of other organometallic reagents and preparation of other optically active compounds (e.g., estrone derivatives) will be reported in due course.

(10) Optically pure *R*-(+)-**8** is reported to have $[\alpha]_D$ + 154° (*c* 0.6 CH_3OH): Kokke, W. C. M. C.; Varkevisser, F. A. *J. Org. Chem.* **1974**, *39*, 1535. For a recent asymmetric synthesis of *R*-(+)-**8**, see: Taber, D. F.; Saleh, S. A.; Korsmeyer, R. W. *J. Org. Chem.* **1980**, *45*, 4699.

(11) (a) Trost, B. M. *Acc. Chem. Res.* **1978**, *11*, 453 and references therein. (b) A variety of other methylating agents gave no better yields of α-methylcyclopentanone **9**.

(12) The major reason for this assignment is as follows: the good thermal stability and long shelf life of cyclopentanone sulfoxide **9** suggest that the sulfinyl group is not located cis to the vicinal tertiary hydrogen atom in the cyclopentane ring (i.e., no facile thermal syn elimination to form a 2-cyclopentenone); when elimiation of *p*-toluenesulfenic acid from **9** did occur, it provided initially the corresponding *exo*-methylenecyclopentanone.[11]

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

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(17) See: (a) Monteiro, H. *J. Org. Chem.* **1977**, *42*, 2324. (b) Toru, T.; Kurozumi, S.; Tanaka, T.; Miura, S.; Kobayashi, M.; Ishimoto, S. *Tetrahedron Lett.* **1976**, 4087.

(18) See: Spry, D. O. *Tetrahedron Lett.* **1980**, *21*, 1293.

Acknowledgment. Acknowledgment is made to the National Science Foundation (CHE 79-15161), the donors of the Petroleum Research Fund, administered by the American Chemical Society, the Merck, Sharp and Dolme Co., and the G. D. Searle Co. for support of this research. We further gratefully acknowledge the help of Dr. P. W. Tang on the early parts of this project.

Electronic States of Iron Oxyporphyrin and Verdohemochrome Obtained by Coupled Oxidation of Iron Porphyrin

Seiyo Sano*

Department of Public Health
Faculty of Medicine, Kyoto University
Kyoto 606, Japan

Yukio Sugiura

Faculty of Pharmaceutical Sciences, Kyoto University
Kyoto 606, Japan

Yutaka Maeda

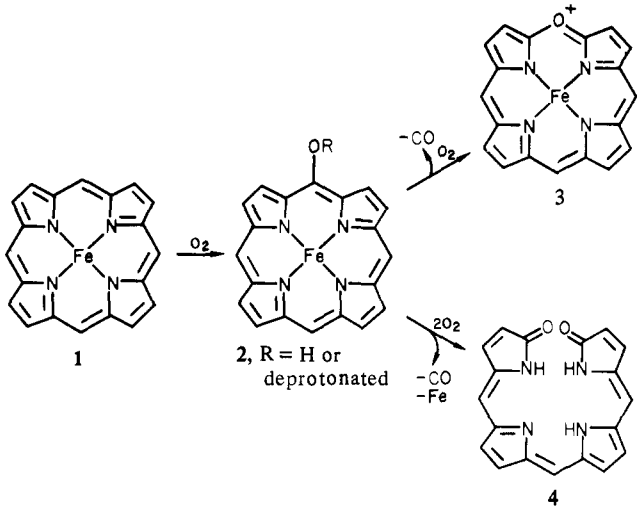
Research Reactor Institute, Kyoto University
Osaka 590-04, Japan

Satoshi Ogawa and Isao Morishima

Department of Hydrocarbon Chemistry
Faculty of Engineering, Kyoto University
Kyoto 606, Japan

Received October 9, 1980

Iron porphyrin (**1**) is oxidized by molecular oxygen or hydrogen peroxide to iron oxyporphyrin (**2**), which is further oxidized to verdohemochrome (**3**) by molecular oxygen.[1-5] Iron oxyporphyrin



(**2**) also has been detected as a primary product in the biological degradation of heme to biliverdin (**4**).[6,7]

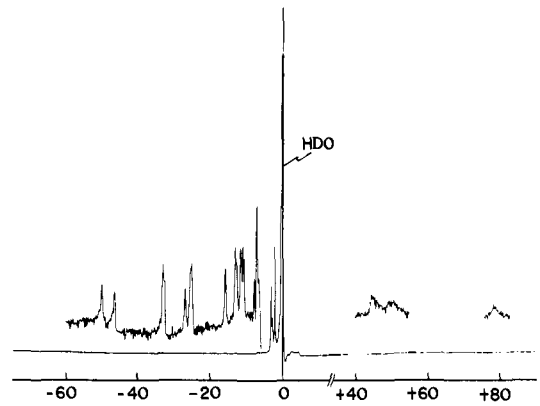
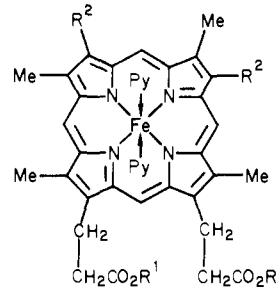
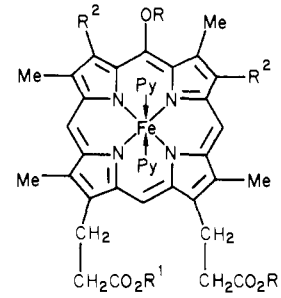


Figure 1. Iron oxymesoporphyrin (**6b**; ~2 mM) in 60% pyridine-*d* solution at room temperature. NMR spectrum was recorded with Varian HR-220/Nicolet TT-100 in a pulsed Fourier transfer mode.

The purpose of the present investigation is to elucidate the electronic and oxidation states of the iron of iron oxyporphyrin (**2**) and verdohemochrome (**3**) by using ESR, NMR, and Mössbauer techniques. We wish to report that the electronic state of iron oxyporphyrin **2** in pyridine is most likely low-spin Fe(I) and that of verdohemochrome low-spin Fe(II). Such assignments have not yet been made despite extensive studies carried out in the past decade.[8-12]

Iron oxymesoporphyrin **6a** or **6b** was prepared, according to





5a, R^1 = H; R^2 = Et
b, R^1 = Me; R^2 = Et

6a, R^1 = H; R^2 = Et; R = H
b, R^1 = H; R^2 = Et; R = deprotonated
c, R^1 = Me; R^2 = Et; R = H
d, R^1 = Me; R^2 = Et; R = Bz

the method of Bonnett et al.[5] with a minor modification, by reducing ferric mesoporphyrin dipyridine **5a** with ascorbate followed by addition of hydrogen peroxide. Compound **6b** in a pyridine solution was stable under argon gas and showed Soret absorption band at 402 nm and a broad but significant band at 630 nm. This compound gave an anomalous ESR signal at $g_\perp$ = 2.30 and $g_\parallel$ = 1.76 at 77 K; the NMR spectrum of **6b** was well resolved having the signal spreading from 10 to 50 ppm downfield from the HDO signal and exhibited signals locating at +45 to +80 ppm (Figure 1). This spectrum was entirely different from that of **5a**. The Mössbauer spectra, however, showed no paramagnetic hyperfine interaction and the quadrupole splitting (ΔE_Q/(mm s^{-1}) = 1.18 at 77 K and 1.15 at 4.2 K) and the isomer shift (δFe/(mm s^{-1}) = 0.37 at 77 K and 0.49 at 4.2 K) resembled the corresponding parameters obtained with ferrous low-spin compounds.[13,14]

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