A New Resolution Procedure for the Preparation of Both (*R*)-(+)- and (*S*)-(−)-4-*tert*-Butoxycyclopent-2-enone from Racemic 4-*tert*-Butoxycyclopent-2-enone and Conversion of (*R*)-(+)-4-*tert*-Butoxycyclopent-2-enone into (*R*)-(+)-4-Acetoxycyclopent-2-enone. A New Method for the Determination of the Enantiomeric Purities of the Resolved Enones

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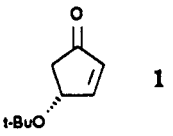
Received November 15, 1990

(1*S*)-(−)-10-Mercaptoisoborneol undergoes conjugate addition to (±)-4-*tert*-butoxycyclopent-2-enone in methanol containing *N,N,N′,N′*-tetramethylethylenediamine to give a 1:1 mixture of diastereomers of 3-*tert*-butoxy-4-[[(*exo*-2′-hydroxy-7′,7′-dimethylbicyclo[2.2.1]heptanyl)methyl]thio]cyclopentanone in 93–95% yield. The mixture is converted by *m*-chloroperbenzoic acid into the corresponding sulfoxide mixture. The (3*R*,4*R*,R_S)-sulfoxide isomer, whose absolute configuration has been determined by X-ray crystallography, crystallizes cleanly from this mixture in an enantiomeric yield of 76% from the corresponding sulfide. It is decomposed on silica gel to generate (*R*)-(+)-4-*tert*-butoxycyclopent-2-enone, with an enantiomeric purity of ≥99.9% in 92% yield from the sulfoxide, and 10-thiodiisobornyl 10′-sulfoxide. Similarly, the (*S*)-(−)-enone is prepared from (1*R*)-(+)-10-mercaptoisoborneol. The (±)- and the (*R*)-(+)-enone, respectively, are converted by a catalytic amount of $FeCl_3$ in acetic anhydride into (±)- and (*R*)-(+)-4-acetoxycyclopent-2-enone (with an enantiomeric purity of ≥99.9%) in 80% yield. The enantiomeric purity of the products was assessed through their treatment with (−)-10-mercaptoisoborneol and analysis of the adducts by HPLC and 400-MHz ^{1}H NMR spectroscopy.

Introduction

The "three-component coupling" method wherein a nucleophile is added to a protected 4-hydroxycyclopent-2-enone and the derived enolate is treated with an electrophile is the most direct in providing prostaglandins.[1,2] The increasing usage both of this and related methods[3] has raised the demand for enantiomerically pure 4-hydroxycyclopent-2-enone and cyclopent-2-enol derivatives. Of the variety of chemical[4,5] and enzyme methods[6-9] that have been developed for their preparation, the latter in providing gram quantities of product are the most useful. However, the starting materials for the enzyme methods, as noted by Mori,[7] are not easily prepared, and several steps are needed to convert the product of the enzyme-catalyzed step into the requisite enone.

As we need to modify our own three-component approach to provide enantiomerically pure prostaglandin derivatives, we required the *R* enantiomer 1 of 4-*tert*-butoxycyclopent-2-enone upon which the preparation is based.[2] As none of the methods for preparation of optically active cyclopentenones can be adapted for preparation of 1, resolution of the racemic enone[10] is required. This in principle can be carried out by conjugate addition of an *enantiomerically pure* thiol to the racemic enone. As in other conjugate additions involving this enone,[12] the addition will proceed trans to the *tert*-butoxy group so that two diastereomers only are produced (Scheme I). The diastereomers may then be separated and degraded at any one of the sulfide (step a), sulfoxide (step b), or sulfone (step c) levels. The chiral group R* in the starting thiol also must exert stereochemical control over oxidation of the sulfide to the sulfoxide so that proliferation in the



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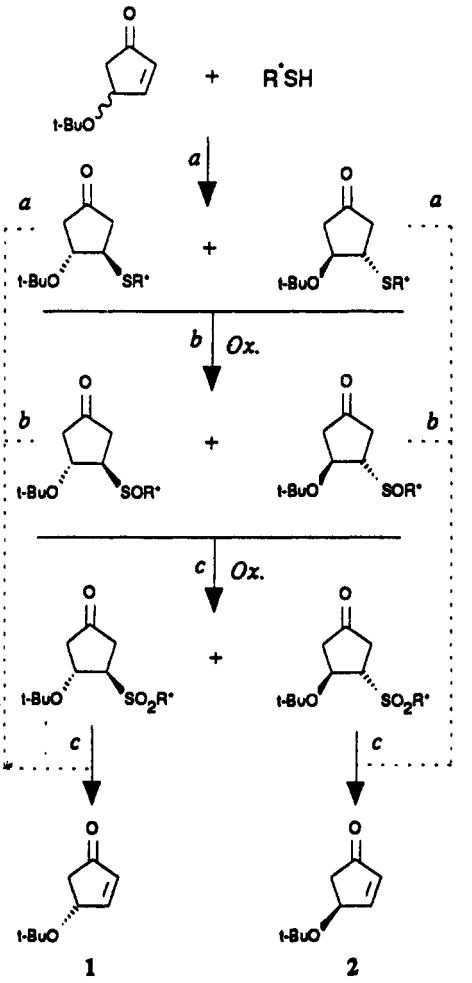
Scheme I



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number of diastereoisomers does not occur. Elimination of the sulfur-bearing group must occur under conditions that leave the *tert*-butoxy group unaffected. Both the conjugate addition of thiols to conjugated enones[13-16] and the reconversion of the adducts at the sulfide[14] or the derived sulfoxide[16,18] and sulfone[17] levels into the parent enone are facile operations. Further, optically active adducts may be prepared by addition of achiral thiols to prochiral enones catalyzed by enantiomerically pure amines and amino alcohols.[15] This reaction appears not to have been applied to racemic enones and certainly has not been used as a means of resolving such enones. There are also no reports describing the addition of thiols, chiral or otherwise, to enones bearing groups which, as in the present case, can undergo elimination in competition with the sulfur-bearing group.

It turns out that we cannot fully implement the strategy encapsulated in Scheme I, as we have not been able to use the one chiral thiol to generate both the (*R*)- and (*S*)-enones 1 and 2. We have nevertheless developed an extremely straightforward means of resolving this enone through use of enantiomeric thiols. We now present a full description of this work, part of which has been published in preliminary form.[19]

Discussion

As both enantiomers of camphor derivatives are generally available, the thiol to be used in the present work logically contains a chiral group R* derived from camphor. As a hydroxyl group proximate to sulfide precisely controls the stereochemical outcome of the oxidation of the sulfide to sulfoxide,[20,21] the group R* (Scheme I) should contain a pendant hydroxyl capable of so influencing the oxidation of the sulfide adducts. The readily available (1*S*)-(−)- and (1*R*)-(+)-10-mercaptoisoborneols (3 and 6)[22] were thus used in this work.

The thiol 3 underwent conjugate addition to the racemic enone (typically 30 mmol) in degassed methanol containing TMEDA (0.04 equiv) under nitrogen during 12 h to give a 1:1 mixture of the sulfide adducts 7 and 8 in yields of 93–95%. Use of sodium methoxide in methanol, cesium fluoride in acetone, or TMEDA in CH_2Cl_2 gave the adducts in lower yields, the disulfide 5, and in the case of the methoxide–methanol system the enone 9. No kinetic

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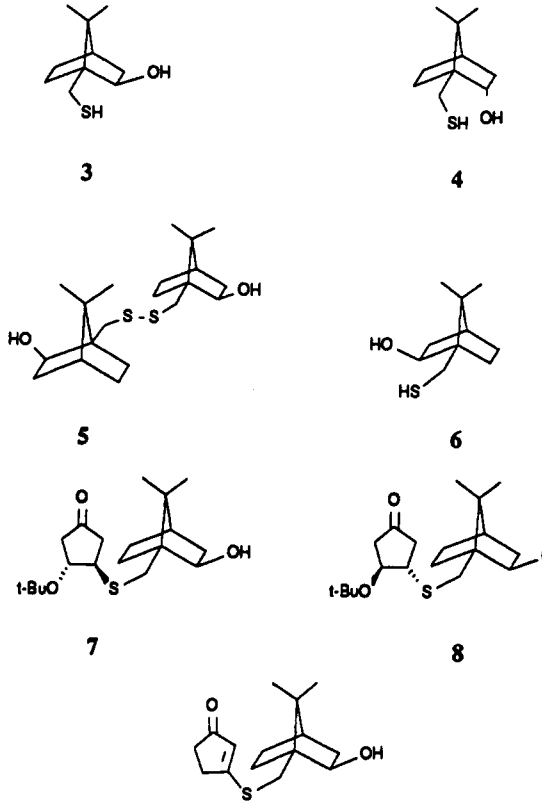
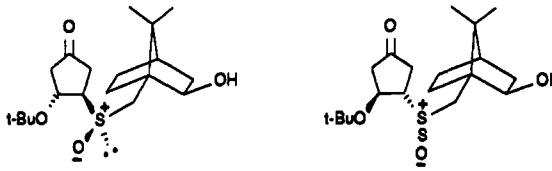


3 4 5 6 7 8 9

stereoselection was observed in conjugate addition of thiol 3 to the racemic 4-*tert*-butoxycyclopent-2-enone. Thus, use of 2 equiv of the enone with one of the thiol in methanol or CH_2Cl_2 containing TMEDA at −12 °C returned at 1:1 mixture of the sulfide adducts 7 and 8 and unreacted but strictly racemic enone.

The mixture of adducts 7 and 8, although resolvable by analytical HPLC, could not be separated on a preparative scale and accordingly was treated with *m*-CPBA in CH_2Cl_2 at −70 °C. The ^1H NMR spectrum of the crude mixture indicated a 64:36 mixture of sulfoxides 10 and 11, a small



10 11

amount (ca. 10%) of possibly a third sulfoxide or sulfone, variable amounts of 4-*tert*-butoxycyclopent-2-enone, and other unidentified compounds. The diagnostically most useful signals, due to the 8- and 9-methyls of the bornane skeleton of each major sulfoxide, appeared at δ 1.080 and 0.829 and at δ 1.136 and 0.860, respectively. HPLC analysis carried out under conditions of rapid elution required to minimize decomposition also indicated the presence of two major sulfoxides. Details are given in the Experimental Section.[17] Two peaks of similar retention times in roughly the same ratio as that observed by NMR spectroscopy were obtained. The origin of the enone is uncertain; it may arise by decomposition of the sulfoxide 11 or other sulfoxide or of a sulfone produced by overoxidation. Because of decomposition, attempts to separate the sulfoxides by column chromatography were unsuccessful. However, a solution of the mixture in ether–hexanes at −12 °C slowly deposited needles of the sulfoxide 10, $[\alpha]^{20}_D$ −210° (*c* 1.72, CH_3OH). The total amount of 10

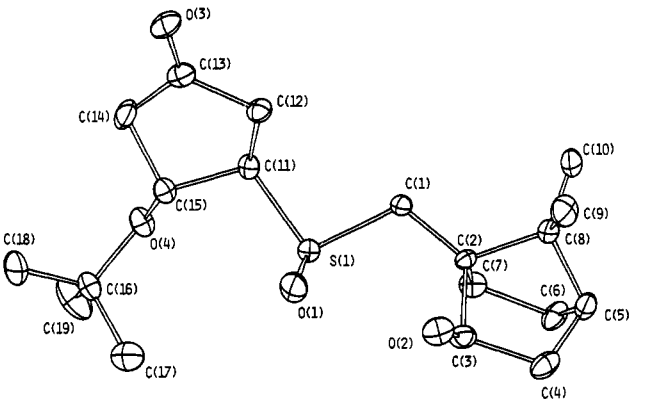
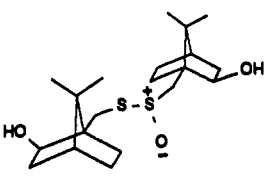


Figure 1. ORTEP plot of (3*R*,4*R*,*R*$_S$)-(−)-3-*tert*-butoxy-4-[[(*exo*-2′-hydroxy-7′,7′-dimethylbicyclo[2.2.1]heptanyl)methyl]-sulfinyl]cyclopentanone (10) showing crystallographic numbering.

recovered in this fashion was 38%, or 76% based on (*R*)-enone. Contamination from the other diastereomer 11 after direct crystallization varied between 0.5 and a probable maximum of 3% as estimated by 400-MHz ^1H NMR analysis of the signals due to the 8- and 9-methyls of the bornane skeleton. Trace amounts of the unwanted sulfoxide were removed through recrystallization from ethyl acetate. Signals from this sulfoxide were then not generally observed, which implies that a diastereomeric purity of 99.9% or greater had been attained. Copies of the spectra including the amplified signals due to the 8- and 9-methyls used for determination of the diastereomeric purities are included in the supplementary material. The absolute configuration was secured through X-ray crystallographic analysis. The ORTEP plot (Figure 1) reveals that the absolute configuration both at sulfur and at C(4) in the cyclopentanone nucleus is *R*. The configuration at the latter center corresponds to that in the 4-*tert*-butoxycyclopent-2-enone required for synthesis of prostaglandins. The plot also reveals an unusually short distance between the isobornyl and sulfoxide oxygens. As the interaction is relievable by rotation about the C(1)–C(2) bond (crystallographic numbering), the hydroxyl group is hydrogen bonded to the sulfoxide, although the hydrogen atom bonded to O(2) was not locatable in the final difference map. The hydrogen bond acts to restrict flexibility of the molecule and possibly enhances its crystallinity. The diastereomeric sulfoxide 11 was not crystalline and could not be recovered from the mixture. Intramolecular hydrogen bonding may not be possible in this diastereomer. In general, β-sulfinyl ketones are not very stable compounds and are usually formed in situ from the sulfide for the purpose of generating the unsaturated ketone.[16-18] However, compound 10 has been stored at 5 °C without decomposition over a six-month period.

Elimination of the bornylsulfinyl group in compound 10 was easily carried by stirring a solution of the sulfoxide in hexanes with silica gel at room temperature during 12 h to give (*R*)-(+)-4-*tert*-butoxycyclopent-2-enone (1), $[\alpha]^{20}_D$ +52° (*c* 2.30, CH_3OH), in 92% yield and a single stereoisomer of the thiolsulfinate 12 (54%). Competing elim-



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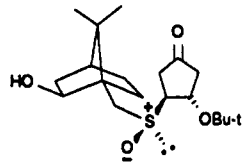
ination of the *tert*-butoxy group was never observed. The

operation is entirely reproducible and can be used to generate gram quantities of the enone. In general, it is convenient to store the sulfoxide **10** and decompose it whenever the optically active enone is required. The sequence was repeated with the (1*R*)-(+)-10-mercaptoisoborneol **6** to provide the sulfoxide **13** (32%), $[\alpha]^{20}_D$ +208° (*c* 2.07, CH_3OH) and thence (*S*)-(−)-4-*tert*-butoxycyclopent-2-enone (**2**; 89%), $[\alpha]^{20}_D$ −51.7° (*c* 1.97, CH_3OH).



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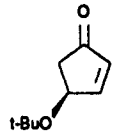

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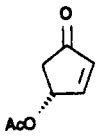
Assessment of the enantiomeric purities of the enones either through conversion of the carbonyl into an acetal group containing homochiral ligands or through use of direct NMR methods based on chiral LIS reagents were thwarted by difficulties encountered in converting the enone into an acetal and lack of signal splitting in the NMR method with various shift reagents. Hence, the following new method was devised. The enones **1** and **2** were each treated with the thiol **3** under the optimum conjugate addition conditions, and the adduct sulfides **7** and **8** were respectively isolated in high yields. Analysis of the crude product mixture from the enone **1** by HPLC failed to detect the presence of adduct **8**. However, the 400-MHz ^1H NMR spectrum revealed the presence of ≤0.1% of this latter adduct through analysis of the signal due to the 9-methyl group. For compound **7**, the signal appears at δ 0.852 and for compound **8** at δ 0.839. A copy of the upfield portion of the spectrum is given in the supplementary material. Both HPLC and NMR analysis of the product from the enone **2** failed to reveal the presence of adduct **7**.[23]

Next, the enone **1** was converted into (*R*)-(+)-4-acetoxycyclopent-2-enone (**14**). We have used the $FeCl_3$–acetic anhydride reagent of Ganem and Small[24] to replace in completely stereoselective fashion the *tert*-butoxy group at C(11) by acetoxy in a prostaglandin intermediate.[2,25] (±)-4-*tert*-Butoxycyclopentenone itself can be smoothly transformed by catalytic $FeCl_3$ in acetic anhydride at 0 °C into (±)-4-acetoxycyclopent-2-enone. The reaction involves an acylated oxonium ion intermediate that decomposes via loss of the *tert*-butyl cation or its equivalent to generate the acetoxy enone. Alternative pathways to the product are of S_N2 displacement at C(4) of *tert*-butyl acetate by acetate and the less likely S_N1 process involving loss of *tert*-butyl acetate to generate an intermediate allylic cation that is strongly destabilized by the carbonyl group. The intercession of the latter pathways will cause some inversion of configuration. It is noted by Ganem that cleavage of an optically active benzyl secondary alkyl ether results in substantial racemization.[24] Hence, the S_N1 reaction proceeding via the benzyl cation is not especially favored over the competing S_N1 and S_N2 processes occurring at the alkyl carbon. The stereochemical outcome of the cleavage reaction when applied to the optically active enone **1** was thus unclear.

In the event, the (+)-enone **1** with $FeCl_3$ in acetic anhydride under the previous conditions underwent a rapid and virtually completely stereoselective conversion into (*R*)-(+)-4-acetoxycyclopent-2-enone (**14**; 80%), $[\alpha]^{20}_D$ +100.6° (*c* 2.98, CH_3OH). The product thus possessed



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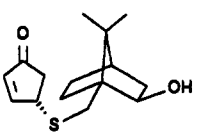
an enantiomeric purity greater than that of samples prepared hitherto,[5,8] with the exception of that of a sample prepared by enzymic means whose rotation of +101° is reported to represent an ee of 100%.[9] In assessing the enantiomeric purity of the enone **14** through reaction with (1*S*)-(−)-10-mercaptoisoborneol (**3**), displacement of the acetoxy group rather than conjugate addition now took place to give the enone **15** (79%), $[\alpha]^{20}_D$ +14° (*c* 1.33, CH_3OH).[26] By comparison of the HPLC trace and the



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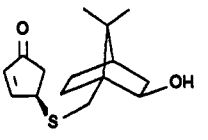

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^1H NMR spectrum with those of the 1:1 mixture of the diastereomeric enones **15** and **16** obtained by treatment of the racemic acetoxy enone with thiol **3**, the enantiomeric purity of the enone **15**, and hence of enone **14**, is established to be greater than 99.9%. In the ^1H NMR spectrum, the shifts of the 9-methyl groups were again used for determination of purity. In the enone **15**, the signal appears at δ 1.050. In the racemic mixture, the signal for the diastereomer **16** appears at δ 1.054. As a concluding comment to this section, we point out that the routes described here to either the (±)- or 4(*R*)-, and potentially, the 4-(*S*)-acetoxycyclopent-2-enone from the (±)- or resolved 4-*tert*-butoxycyclopent-2-enones are considerably more efficient and economical than those described hitherto when the availability of the starting materials used in all preparations is taken into account.[5,8-11,28] The stereoselective cleavage of enantiomerically pure *tert*-butyl ethers in this fashion is of obvious synthetic value.

Because each enantiomer of 10-mercaptoisoborneol was required for preparation of each of the enones **1** and **2**, we sought now to recover both enantiomers from the racemic enone with just the one thiol enantiomer. The method would also rely on the complexing ability of the isobornyl hydroxyl in the sulfide adducts. A metal hydride reagent,

(23) As well as providing a simple means of establishing enantiomeric purity, the method may also be used to enhance the enantiomeric purities of the resolved enones through reoxidation of the sulfide adducts, and recrystallization and decomposition of the sulfoxides.

(24) Ganem, B.; Small, V. R. *J. Org. Chem.* **1974**, *39*, 3728.

(25) The completely stereoselective cleavage of the *tert*-butyl ether arises as a consequence of the overwhelming steric restraints to attack at C(11) by acetate in an S_N1 or S_N2 process imposed by the adjacent β-configured side chain attached to C(12) of the PG intermediate.[2]

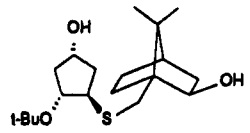
(26) Winterfeldt and co-workers have demonstrated that displacement of acetate from 4-acetoxycyclopent-2-enone with stabilized carbanions under protic conditions takes place via a conjugate addition–enolate isomerization–elimination sequence to generate the 4-alkylcyclopent-2-enone product.[27] As the initial addition proceeds trans to the acetoxy group, the reaction proceeds with overall retention of configuration. We have not established the absolute configuration of the (noncrystalline) enone **15**, but believe this to correspond to the product arising via direct (S_N2) displacement of acetate by the thiolate; cf. displacement of halide from 4-halocyclopent-2-enones by heteroatom nucleophiles.[28,29]

(27) Osterthun, V.; Winterfeldt, E. *Chem. Ber.* **1977**, *115*, 146. Marx, K. H.; Raddatz, P.; Winterfeldt, E. *Liebigs Ann. Chem.* **1984**, 474. Bertram, H.-J.; Janssen, M.; Peters, K.; Meier, A.; Winterfeldt, E. *Liebigs Ann. Chem.* **1986**, 456.

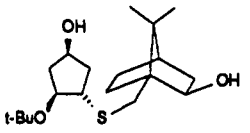
(28) De Puy, C. H.; Isaks, M.; Eilers, K. L.; Morris, G. F. *J. Org. Chem.* **1964**, *29*, 3503.

(29) Baraldi, P. G.; Pollini, G. P.; Simoni, D.; Zanirato, V. *Synthesis* **1986**, 781.

through complexation to the hydroxyl group in each of adducts 7 and 8, will be constrained to deliver hydride to the carbonyl from the *Re* face of sulfide 7 and from the *Si* face of sulfide 8. Thus, reduction of the mixture of sulfides would give two diastereomeric diols, ideally 17 and 18, which upon separation, oxidation, and elimination



17



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would then provide the individual enantiomers 1 and 2. In practice, however, completely selective reduction could not be obtained with a large number of hydride and alane reagents used with or without additives.[30] For example, whereas $NaBH_3CN$ in CH_3CN–CH_3COOH gave all four possible diastereomers in equal amounts, a DIBALH–2,6-di-*tert*-butyl-*p*-cresol reagent[31] in toluene gave a 9:8:36:47 mixture of these alcohols. Although the last result is satisfactory, the mixture could neither be resolved into its individual components on a preparative scale nor be converted into oxidation products in acceptable yields.[30] Further development of the method was not pursued.

Conclusion

The concept of using an enantiomerically pure thiol to convert a racemic enone into a mixture of diastereomeric sulfide adducts through conjugate addition and then to separate the adducts at a higher oxidation level, although not fully realized, has been adapted to provide an efficient method for resolving the readily available 4-*tert*-butoxycyclopent-2-enone. The use of a chiral thiol incorporating a hydrogen bond donor group ensures that the sulfoxides derived from the diastereomeric sulfide adducts of the enones possess different polarities because of differing opportunities for intramolecular hydrogen bonding. Although the enantiomers of 10-mercaptoisoborneol were eminently suited for resolving 4-*tert*-butoxycyclopent-2-enone, other hydroxy thiols may be more suitable for resolution of other enones.

As intimated in the Introduction, a variation of the method wherein an achiral thiol (e.g., 2-mercaptoethanol) can be caused to undergo diastereoselective conjugate addition to a racemic enone in the presence of a catalytic amount of an enantiomerically pure amine or amino alcohol can in principle also be used for resolution. We are currently evaluating the original method and its variant for the resolution of other racemic enones.

Experimental Section

General Aspects. Melting points were recorded on a melting point stage and are uncorrected. ^1H NMR spectra were recorded at 400 MHz for samples in $CDCl_3$. Chromatographic separations were carried out by flash column chromatography with Merck silica gel 60 (230–400 mesh, ASTM). Solvents were purified according to standard methods. Although (±)-4-*tert*-butoxycyclopent-2-enone[11,12] as purified by distillation[12] was successfully used in this work, slightly better yields were obtained if the compound was purified according to the following procedure. The liquid enone was dissolved in an equal volume of low-boiling light petroleum ether (bp 30–40 °C), and the solution was placed in a freezer at −12 °C. A white crystalline mass deposited from the solution. The mother liquor was removed by syringe. Further crops of crystals were obtained from the mother liquor by concentration and refreezing. The residual crystalline mass, which melted at rt, was distilled to give the pure enone.

(1*S*)-(−)- and (1*R*)-(+)-10-Mercaptoisoborneol (3 and 6). Reduction of freshly prepared (1*S*)-(+)-10-camphorsulfonyl chloride with $LiAlH_4$ in ether at −78 °C and then at reflux according to the literature procedure[22] gave (−)-**3** (75%), needles, mp 72–73 °C (lit.[22] 76–78 or 70 °C), $[\alpha]^{20}_D$ −58.3° (*c* 5.15, $CHCl_3$) (lit.[22] −55.4° or −57.44°) from hexanes and (−)-**4** (7%), needles, mp 86–87.5 °C (lit.[22] 66 °C), $[\alpha]^{20}_D$ −11.9° (*c* 9.5, $CHCl_3$) (lit.[22] −11.76°). In addition, an occasional byproduct of the reduction, diisobornyl 10-disulfide **5** (3–6%) was isolated as a powder, mp 159–160 °C, $[\alpha]^{20}_D$ +28° (*c* 5.0, $CHCl_3$) from hexanes. ^1H NMR: δ 3.95 (2 H, s, H2), 3.19 (2 H, d, J_{gem} = 13.0 Hz, H10), 2.79 (2 H, d, J_{gem} = 13.0 Hz, H10), 2.68 (2 H, s, OH), 1.84–1.65 (8 H, m, ring H), 1.51 (2 H, ddd, J_{gem} = 12.8, $J_{3endo,2}$ = 12.0, $J_{3endo,4}$ = 4.0 Hz, $H3_{endo}$), 1.29 (2 H, ddd, J_{gem} = 12.8, $J_{3exo,2}$ = 9.5, $J_{3exo,4}$ = 4.0 Hz, $H3_{exo}$), 1.07 (6 H, s, H8), 1.09–1.031 (2 H, m), 0.84 (6 H, s, H9). Anal. Calcd for $C_{20}H_{34}O_2S_2$: C, 64.8; H, 9.3. Found: C, 64.5; H, 9.2.

(1*R*)-(−)-10-Camphorsulfonyl chloride was converted into (1*R*)-(+)-10-mercaptoisoborneol **6**, $[\alpha]_D$ +57.6° (*c* 3.7, $CHCl_3$) (lit.[22] +56.7°), as described for the enantiomeric substance.

Conjugate Addition of (1*S*)-(−)-10-Mercaptoisoborneol (3) to (±)-4-*tert*-Butoxycyclopent-2-enone. To a stirred solution of **3** (6.1 g, 32 mmol) and (±)-enone (5.0 g, 32 mmol) in anhydrous, degassed CH_3OH (100 mL) under N_2 was added TMEDA 0.2 mL, 0.04 equiv). The solution was stirred at rt until TLC monitoring indicated complete consumption of the thiol. Usually, 12 h was required for this scale. The solvent was removed under reduced pressure to leave a yellow-brown oil, which after chromatography with 1:9 EtOAc–hexanes gave a single fraction consisting of a 1:1 mixture of the diastereomeric sulfides **7** and **8** (10.55 g, 95%) as a pale yellow oil. HPLC analysis with 12:88 EtOAc–hexanes on a Waters analytical column at a flow rate of 1.5 mL min^{-1} at 600 psi indicated the presence of the two isomers with t_{R1} 13 min and t_{R2} 14 min. The ^1H NMR spectra for the individual diastereomers are given in the following text. Anal. Calcd for $C_{19}H_{32}O_3S$: C, 67.0; H. 9.5. Found: C, 66.9; H, 9.4.

3-[[(*exo*-2′-Hydroxy-7′,7′-dimethylbicyclo[2.2.1]heptanyl)methyl]thio]cyclopent-2-enone (9). Sodium (6.2 mg, 0.1 equiv) was added to a stirred solution of thiol **3** (500 mg, 2.7 mmol) and the enone (420 mg, 2.7 mmol) in anhydrous CH_3OH under N_2. After 2 h, the solvent was removed under reduced pressure to leave a residue, which was treated with water (15 mL) and extracted with ether (3 × 50 mL). The extracts were washed with water (20 mL), dried (Na_2SO_4), and evaporated to leave the enone **9** as a microcrystalline solid (540 mg, 75%), mp 90–91 °C, $[\alpha]^{20}_D$ −30° (*c* 1.3, CH_3OH) from hexanes. ^1H NMR: δ 6.02 (1 H, dd, $J_{2,5}$ = 1.4, $J_{2,5}$ = 1.4 Hz, H2), 3.91–3.87 (1 H, m, $H2'_{endo}$), 3.25 (1 H, d, J_{gem} = 10.8 Hz, H10′), 2.87 (1 H, d, J_{gem} = 10.8 Hz, H10′), 2.81–2.76 (2 H, m, H5), 2.50–2.48 (2 H, m, H4), 2.195–2.14 (1 H, m, OH), 1.85–1.71 (4 H, m), 1.63–1.56 (1 H, m), 1.26–1.19 (1 H, m), 1.12–1.05 (1 H, m), 1.10 (3 H, s, H8′), 0.91 (3 H, s, H9′). Anal. Calcd for $C_{15}H_{22}O_2S$: C, 67.6; H, 8.3. Found: C, 67.6; H, 8.3.

Oxidation of Sulfide Adducts 7 and 8. A solution of the 1:1 mixture of diastereomers **7** and **8** (10.0 g, 30 mmol) in CH_2Cl_2 (250 mL) under N_2 was cooled to −70 °C. A solution of *m*-CPBA (5.75 g, 33.3 mmol) in CH_2Cl_2 (100 mL) was added dropwise at a rate such that the reaction temperature remained below −60 °C. The resultant mixture was stirred a further 30 min at −70 °C and then was added with stirring to a two-phase system of ether (250 mL) and aqueous $NaHSO_3$ (10%, 250 mL). The organic layer was separated and the aqueous fraction extracted with ether (3 × 150 mL). The extracts were combined and washed with saturated $NaHCO_3$ (3 × 100 mL) and water (150 mL) and then dried (Na_2SO_4). Removal of solvent under vacuum afforded a semicrystalline mass (9.63 g, 90%). Analysis of the crude product mixture by ^1H NMR spectroscopy indicated the presence of a 64:36 mixture of the sulfoxides **10** and **11**, a trace of possibly a third sulfoxide or sulfone, some 4-*tert*-butoxycyclopent-2-enone, and other compounds. Analysis of the mixture by HPLC with 30:70 EtOAc–hexanes on a Brownlee SI 100 column at a flow rate of 1.5 mL min^{-1} at 400 psi indicated the presence of two sulfoxides in approximately the previous ratio with t_{R1} 2.95 min and t_{R2} 3.25 min. A solution of the semicrystalline mass in 1:9 ether–hexanes

(30) Eschler, B. M. M.Sc. Thesis, University of Sydney, 1989.
(31) Iguchi, S.; Nakai, H.; Hayashi, M.; Yamamoto, H.; Maruoka, K. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3033.

at −12 °C slowly deposited the sulfoxide **10**, which was recrystallized from EtOAc to give white needles, mp 109–110 °C (4.11 g, 38.5%), $[\alpha]^{20}_D$ −210° (*c* 1.72, methanol). ^{1}H NMR: δ 4.43 (1 H, ddd, $J_{3\alpha,2\beta}$ = 9.0, $J_{3\alpha,4\beta}$ = 8.0, $J_{3\alpha,2\alpha}$ = 8.0 Hz, H3α), 4.08 (1 H, ddd, $J_{2'endo,3'endo}$ = 8.4, $J_{2'endo,3'exo}$ = 4.0, $J_{2'endo,OH}$ = 3.4 Hz, H2′), 3.80 (1 H, d, $J_{OH,2'endo}$ = 3.4 Hz, OH), 3.12 (1 H, ddd, $J_{4\beta,5\alpha}$ = 8.2, $J_{4\beta,3\alpha}$ = 8.0, $J_{4\beta,5\beta}$ = 8.0 Hz, H4β), 3.12 (1 H, d, J_{gem} = 13.0, H10′), 2.95 (1 H, ddd, J_{gem} = 18.2, $J_{2\beta,3\alpha}$ = 9.0, $J_{2\beta,5\beta}$ = 1.4 Hz, H2β), 2.78 (1 H, ddd, J_{gem} = 18.4, $J_{5\alpha,4\beta}$ = 8.2, $J_{5\alpha,2\alpha}$ = 1.6 Hz, H5α), 2.57 (1 H, ddd, J_{gem} = 18.2, $J_{2\alpha,3\alpha}$ = 8.0, $J_{2\alpha,5\alpha}$ = 1.6 Hz, H2α), 2.36 (1 H, ddd, J_{gem} = 18.4, $J_{5\beta,4\beta}$ = 8.0, $J_{5\beta,2\beta}$ = 1.4 Hz, H5β), 2.29 (1 H, d, J_{gem} = 13.0 Hz, H10′), 1.86–1.61 (4 H, m), 1.61–1.51 (2 H, m), 1.255 (9 H, s, *t*-Bu), 1.22–1.09 (1 H, m), 1.08 (3 H, s, H8), 0.83 (3 H, s, H9). Anal. Calcd for $C_{19}H_{32}O_4S$: C, 64.0; H, 9.1. Found: C, 64.1; H, 9.4.

Sulfoxide **11** could not be obtained in a state suitable for adequate characterization. Signals in the ^{1}H NMR spectrum of the crude reaction mixture at δ 4.71 (m, H(4)), 1.28 (*t*-Bu), 1.14 (H(8′)), and at 0.86 (H(9′)) remain once the sulfoxide **10** is removed and are attributed to sulfoxide **11**.

(*R*)-(+)-4-*tert*-Butoxycyclopent-2-enone (1). The sulfoxide **10** (1.44 g, 5.5 mmol) in hexanes (30 mL) containing flash silica gel (15 g) was stirred overnight. The mixture was placed on a chromatography column containing silica gel (200 g), which was then eluted with 1:4 EtOAc–hexanes. Two fractions were obtained. The less polar fraction was the disulfide *S*-oxide **12**, needles (597 mg, 54%), mp 140–141 °C, $[\alpha]^{20}_D$ +54° (c 2.87, acetone) from hexanes. ^{1}H NMR: δ 3.98 (1 H, dd, $J_{2endo,3endo}$ = 8.0, $J_{2endo,3exo}$ = 4.0 Hz, $H2_{endo}$), 3.89 (1 H, dd, $J_{2'endo,3'endo}$ = 8.0, $J_{2'endo,3'exo}$ = 4.0 Hz, $H2'_{endo}$), 3.80 (1 H, d, J_{gem} = 12.4 Hz, H10), 3.50 (1 H, d, J_{gem} = 13.6 Hz, H10′), 3.26 (1 H, d, J_{gem} = 13.6 Hz, H10′), 2.865 (1 H, d, J_{gem} = 12.4 Hz, H10), 1.87–1.66 (8 H, m), 1.62–1.55 (1 H, m), 1.49–1.40 (2 H, m), 1.25 (1 H, m), 1.19–1.14 (1 H, m), 1.12 (3 H, s, H8), 1.11 (3 H, s, H8), 1.095–1.03 (1 H, m), 0.88 (3 H, s, H9), 0.86 (3 H, s, H9). Anal. Calcd for $C_{20}H_{34}O_3S_2$: C, 62.2; H, 8.8. Found: C, 62.4; H, 8.9.

The more polar fraction was (+)-**1**, a colorless oil (572 mg, 92%), bp 65–67 °C (0.4 mm), $[\alpha]_D$ +52° (*c* 2.30, CH_3OH). ^{1}H NMR: δ 7.43 (1 H, dd, $J_{3,2}$ = 5.7, $J_{3,4\beta}$ = 2.4 Hz, H3), 6.18 (1 H, dd, $J_{2,3}$ = 5.7, $J_{2,4\beta}$ = 1.6 Hz, H2), 4.83–4.80 (1 H, m, H4β), 2.68 (1 H, dd, J_{gem} = 18.3, $J_{5\beta,4\beta}$ = 6.0 Hz, H5β), 2.26 (1 H, dd, J_{gem} = 18.3, $J_{5\alpha,4\beta}$ = 2.1 Hz, H5α), 1.27 (9 H, s, *t*-Bu).

(*S*)-(−)-4-*tert*-Butoxycyclopent-2-enone (2). Thiol **6** (6.1 g, 32 mmol) was added to (±)-enone (5.0 g, 32 mmol) to afford a 1:1 mixture of the diastereomeric sulfides (10.20 g, 92%). Oxidation of the mixture with *m*-CPBA at −78 °C followed by recrystallization of the product mixture from 1:9 ether–hexanes afforded the sulfoxide **13** (3.50 g, 32%), $[\alpha]^{20}_D$ +208° (*c* 2.07, methanol). Degradation of the sulfoxide (3.5 g) with silica gel as before yielded after purification (−)-**2** (1.83 g, 89%), $[\alpha]_D$ −51.7° (*c* 1.97, CH_3OH).

Verification of Optical Purity of Enones 1 and 2. TMEDA (2 drops) was added to a stirred solution of **3** (50 mg, 0.27 mmol) and enone **1** (42 mg, 0.27 mmol) in anhydrous CH_3OH (6 mL) under N_2. Monitoring of the reaction by TLC indicated that it was complete within 3–4 h. The solvent was removed to furnish a yellow oil (90 mg, 99%), a ^{1}H NMR spectrum of which indicated that it consisted of the sulfide adduct **7** containing less than 0.1% of **8**. The specific rotation of the mixture after purification by chromatography was $[\alpha]^{20}_D$ −8.6° (*c* 2.01, acetone). ^{1}H NMR 1′*S*,3*R*,4*R* diastereomer **7**: δ 4.21 (1 H, ddd, $J_{3\alpha,2\beta}$ = 7.8, $J_{3\alpha,4\beta}$ = 6.0, $J_{3\alpha,2\alpha}$ = 6.0 Hz, H3α), 3.89–3.83 (1 H, m, $H2'_{endo}$), 3.34–3.29 (1 H, m, H4β), 2.98 (1 H, d, J_{gem} = 11.4 Hz, H10′), 2.811 (1 H, ddd, J_{gem} = 18.6, $J_{2\beta,3\alpha}$ = 7.8, $J_{2\beta,5\beta}$ = 1.5 Hz, H2β), 2.72 (1 H, ddd, J_{gem} = 18.6, $J_{2\alpha,3\alpha}$ = 6.0, $J_{2\alpha,5\alpha}$ = 1.5 Hz, H2α), 2.69 (1 H, d, J_{gem} = 11.4 Hz, H10′), 2.44 (1 H, s, OH), 2.21 (1 H, ddd, J_{gem} = 18.6, $J_{5\alpha,4\beta}$ = 4.8, $J_{5\alpha,2\alpha}$ = 1.5 Hz, H5α), 2.14 (1 H, ddd, J_{gem} = 18.6, $J_{5\beta,4\beta}$ = 7.2, $J_{5\beta,2\beta}$ = 1.5 Hz, H5β), 1.83–1.66 (4 H, m), 1.545–1.49 (1 H, m), 1.255–1.215, (1 H, m), 1.24 (9 H, s, *t*-Bu), 1.08–1.02 (1 H, m), 1.06 (3 H, s, H8), 0.85 (3 H, s, H9).

Similarly, enone **2** was treated with thiol **3** to provide the sulfide **8** as a pale yellow oil, $[\alpha]_D$ −23.0° (*c* 1.35, acetone). No trace of **7** was detected by ^{1}H NMR spectroscopy of the crude product. ^{1}H NMR: δ 4.21 (1 H, ddd, $J_{3\alpha,2\beta}$ = 7.8, $J_{3\alpha,2\alpha}$ = 6.0, $J_{3\alpha,4\beta}$ = 6.0 Hz, H3α), 3.95–3.85 (1 H, m, $H2'_{endo}$), 3.25 (1 H, m, H4β), 2.93 (1 H, d, J_{gem} = 11.2 Hz, H10′), 2.83 (1 H, ddd, J_{gem} = 18.6, $J_{2\beta,3\alpha}$ = 7.8, $J_{2\beta,5\beta}$ = 1.5 Hz, H2β), 2.67 (1 H, ddd, J_{gem} = 18.6, $J_{2\alpha,3\alpha}$ = 6.0, $J_{2\alpha,5\alpha}$ = 1.5 Hz, H2α), 2.66 (1 H, d, J_{gem} = 11.2 Hz, H10′), 2.52 (1 H, s, OH), 2.205 (1 H, ddd, J_{gem} = 18.6, $J_{5\alpha,4\beta}$ = 4.8, $J_{5\alpha,2\alpha}$ = 1.5 Hz, H5α), 2.16 (1 H, ddd, J_{gem} = 18.6, $J_{5\beta,4\beta}$ = 7.2, $J_{5\beta,2\beta}$ = 1.5 Hz, H5β), 1.87–1.66 (4 H, m), 1.545–1.49 (1 H, m), 1.255–1.215 (1 H, m), 1.23 (9 H, s, *t*-Bu), 1.08–1.01 (1 H, m), 1.06 (3 H, s, H8), 0.84 (3 H, s, H9).

(±)-4-Acetoxycyclopent-2-enone. (±)-4-*tert*-Butoxycyclopent-2-enone (15.4 g, 0.1 mol) was added slowly dropwise with stirring to anhydrous $FeCl_3$ (1.6 g, 0.01 mol) in acetic anhydride (30 mL) at a temperature not greater than 0 °C. After the addition was complete, the solution was allowed to warm to rt over 20 min and then kept at 40 °C for 30 min. The solution was cooled to 0 °C and treated with ether (150 mL) and ice water (5 mL). The ether layer was separated, and the dark aqueous phase was extracted further with ether (3 × 30 mL). The ether extracts were concentrated under reduced pressure to leave a dark oil, chromatography of which with 3:7 EtOAc–hexanes gave the enone as a colorless oil (10.2 g, 73%), which was distilled at 74–75 °C (1.5 mm; Kugelrohr) [lit.[38] bp 51–52 (2 mm)], fp ∼15 °C. Alternatively, the chromatography was omitted as follows. The dark oil was dissolved in water (120 mL), and the solution was filtered through cotton wool to remove residual tarry material. The solution was extracted with hexanes (2 × 20 mL) to remove nonpolar impurities. The aqueous layer was saturated with NaCl and extracted with ether (5 × 50 mL). The ether extracts were combined, dried ($MgSO_4$), and evaporated to leave a pale yellow liquid that was distilled to give the enone in comparable yield.

(*R*)-(+)-4-Acetoxycyclopent-2-enone (14). The enone **1** (200 mg, 1.30 mmol) in acetic anhydride (1 mL) was added dropwise to anhydrous $FeCl_3$ (10 mg, 0.05 equiv) in acetic anhydride (5 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min and then at 40 °C for 30 min. The solution was cooled to 0 °C and immediately quenched with a 10:1 ether–ice water mixture (11 mL). The aqueous layer was extracted with ether (2 × 5 mL). The combined organic fraction was washed with brine (2 mL), dried, and then concentrated under reduced pressure to leave an oil, which was placed under high vacuum to remove acetic anhydride. Purification by chromatography with 3:7 EtOAc–hexanes followed by distillation at 76–77 °C (0.5 mm; Kugelrohr) gave the enone **14** as a colorless oil (145 mg, 80%), $[\alpha]_D$ +100.6° (*c* 2.98, CH_3OH) (lit.[9] +101°). ^{1}H NMR: δ 7.61 (1 H, dd, $J_{3,2}$ = 5.8, $J_{3,4\beta}$ = 2.3 Hz, H3), 6.34 (1 H, dd, $J_{2,3}$ = 5.8, $J_{2,4\beta}$ = 1.2 Hz, H2), 5.89–5.84 (1 H, m, H4β), 2.83 (1 H, dd, J_{gem} = 18.6, $J_{5\beta,4\beta}$ = 6.2 Hz, H5β), 2.32 (1 H, dd, J_{gem} = 18.6, $J_{5\alpha,4\beta}$ = 2.1 Hz, H5α), 2.08 (3 H, s, $COCH_3$).

Verification of Optical Purity of Enone 14. A solution of (±)-4-acetoxycyclopent-2-enone (151 mg, 1.08 mmol) and thiol **3** (200 mg, 1.08 mmol) in anhydrous CH_3OH (10 mL) containing TMEDA (2 drops) under N_2 was stirred for 3–4 h. The solvent was removed under reduced pressure, and the residual brown oil in 1:4 EtOAc–hexanes was passed through a filter pad of silica gel to remove base-line impurities. Evaporation of the filtrate left a mixture of enones **15** and **16** as a pale yellow oil (245 mg, 85%). HPLC analysis of the mixture with 1:4 EtOAc–hexanes on a Whatman Partisil 5 column at a flow rate of 1.5 mL min^{-1} at 600 psi indicated a 1:1 mixture of isomers with t_{R1} **15** 32 min and t_{R2} **16** 34 min. ^{1}H NMR: δ 7.61 (1 H, 2 × ddd, $J_{3,2}$ = 5.5, $J_{3,4}$ = 5.0, $J_{3,5}$ = 2.5 Hz, H3), 6.26 (1 H, 2 × ddd, $J_{2,3}$ = 5.5, $J_{2,4}$ = 3.0, $J_{2,5}$ = 1.5 Hz, H2), 4.10–4.15 (1 H, m, H4), 3.87–3.82 (1 H, m, $H2'_{endo}$), 2.87 (1 H, dd, $J_{5\alpha/\beta,4\beta/\alpha}$ = 6.8 Hz, J_{gem} = 19.2 Hz, H5α/β), 2.84 (1 H, 2 × d, J_{gem} = 10.5 Hz, H10′), 2.51 (1 H, 2 × d, J_{gem} = 10.5 Hz, H10′), 2.41 (1 H, ddd, J_{gem} = 19.2, $J_{5\beta/\alpha,4\beta/\alpha}$ = 4.2, $J_{5\beta/\alpha,\beta}$ = 2.5 Hz, H5β/α), 1.83–1.66 (5 H, m), 1.63 (1 H, s, OH), 1.56–1.45, 1.28–1.16 (1 H, m), 1.054 (3 H, s, H8′, *S*-(+)), 1.050 (3 H, s, H8′, *R*-(−)), 1.09–1.02 (1 H, m), 0.845 (3 H, s, H9′). HRMS calcd for $C_{15}H_{22}O_2S$ 266.3976, found 266.3997.

Repetition of the reaction utilizing the (*R*)-(+)-enone **14** afforded the enone **15** as a pale yellow oil (227 mg, 79%), $[\alpha]_D$ +14° (*c* 1.33, CH_3OH). HPLC analysis according to the previous conditions revealed only the enone **15** with t_{R1} 32 min (>99%). The diastereomer **16** could not be detected by ^{1}H NMR analysis. ^{1}H NMR: δ 7.61 (1 H, ddd, $J_{3,2}$ = 5.5, $J_{3,4}$ = 5.0, $J_{3,5}$ = 2.5 Hz, H3), 6.26 (1 H, ddd, $J_{2,3}$ = 5.5, $J_{2,4}$ = 3.0, $J_{2,5}$ = 1.5 Hz, H2), 4.06 (1 H, m, H4), 3.86 (1 H, dd, $J_{2',3'}$ = 7.8, $J_{2',OH}$ = 3.5 Hz, $H2'_{endo}$), 2.87 (1 H, dd, J_{gem} = 18.9, $J_{5\beta,4\beta}$ = 6.8 Hz, H5β), 2.82 (1 H, d, J_{gem} = 10.0 Hz, H10′), 2.54 (1 H, d, J_{gem} = 10.0 Hz, H10′), 2.40 (1 H,

dd, J_{gem} = 18.9, $J_{5\alpha,3}$ = 2.5 Hz, H5α), 1.85–1.68 (5 H, m), 1.56–1.45 (1 H, m), 1.24–1.15 (1 H, m), 1.08–1.00 (1 H, m), 1.054 (3 H, s, H8′), 0.845 (3 H, s, H9′).

Acknowledgment. We thank the Australian Research Council both for financial support of this work and for the award of a National Research Fellowship to M.D.I.

Supplementary Material Available: IR and MS data for compounds 1, 3–5, 7–10, 12, 15, and 16, 400-MHz ^{1}H NMR spectra of crude mixture of compounds 10 and 11 obtained from oxidation of sulfides 7 and 8, of compound 10, including high-field regions of spectra used for determination of diastereomeric purity of 10 before and after crystallization, of compound 7 and of 1:1 mixture of compounds 7 and 8, of compound 15, and of mixture of compounds 15 and 16, and crystallographic data for compound 10, including an ORTEP plot and tables of positional parameters, bond lengths and angles, and hydrogen atom positional and thermal parameters (22 pages). Ordering information is given on any current masthead page.

The *Cinchona* Alkaloids: A Silicon-Directed Synthesis of Some Advanced Intermediates

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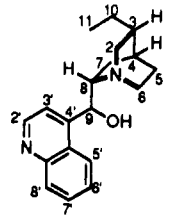
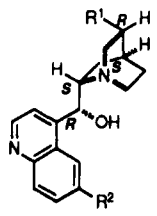
Received February 21, 1991

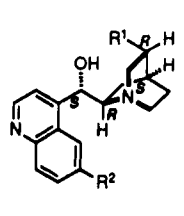
N-Benzylmeroquinene aldehyde (**5b**) was prepared in 10 steps and 21% overall yield from benzylamine. The key transformations involved a stereoselective Lewis acid catalyzed Diels–Alder reaction to produce bicyclic amide **18**, which in turn underwent a regioselective Baeyer–Villager oxidation to produce lactone **20**. Acid-catalyzed ring opening with concomitant Peterson olefination afforded the meroquinene skeleton, which was converted in high yield to meroquinene aldehyde via a reduction/oxidation sequence. Treatment of this aldehyde with anions derived from 4-methylquinoline smoothly generated alcohols **23a,b**, which on acetylation yielded the advanced *Cinchona* alkaloid intermediates **24a,b**.

Introduction

Historically, the *Cinchona* alkaloids have proven to be important therapeutic agents.[1] Today, quinine (**1a**), perhaps the most noted member of this family and best known for its use in the treatment of malaria, is more commonly used for the treatment of leg cramps and quinidine (**2a**) is used to treat cardiac arrhythmias.[2]







Substituents:	1	2
a. R^1 = -C_2H_3; R^2 = -OCH_3	Quinine	Quinidine
b. R^1 = -C_2H_3; R^2 = -H	Cinchonidine	Cinchonine
c. R^1 = -C_2H_5; R^2 = -OCH_3	Dihydroquinine	Dihydroquinidine
d. R^1 = -C_2H_5; R^2 = -H	Dihydrocinchonidine	Dihydrocinchonine

In the early 1900s Rabe pioneered the structure elucidation of these alkaloids by converting degradation products to the naturally occurring material.[3] However, the first total synthesis of quinine did not appear in the literature until Woodward and Doering published their classic synthesis some thirty years later.[4] Despite its elegance, this synthesis was not particularly well-suited for large-scale production of either the natural compounds or new analogues, and researchers at Hoffmann-La Roche therefore reinvestigated the total synthesis of these alkaloids. Their efforts culminated in a series of new syntheses,[5] all of which are based on derivatives of 6-methoxyquinoline and analogues of meroquinene. Since the appearance of these papers, several total syntheses,[6a,b] including a chiral formal synthesis,[6c] and a multitude of meroquinene syntheses have been reported.[6d]

Our initial interest in the key synthetic intermediate meroquinene stemmed from our previous work on the application of ceric ammonium nitrate (CAN) to natural product synthesis.[7a,b] Since it is known that 3-(trimethylsilyl)cyclohexanol (**3**) undergoes oxidation with CAN to give 5-hexenal (eq 1), we anticipated that an appropriately substituted octahydroisoquinoline (**4**) should

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