Asymmetric Syntheses Based on 1,3-Oxathianes. 2. Synthesis of Chiral Tertiary α-Hydroxy Aldehydes, α-Hydroxy Acids, Glycols ($RR'C(OH)CH_2OH$), and Carbinols ($RR'C(OH)CH_3$) in High Enantiomeric Purity[1]

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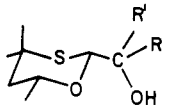
Abstract: A chiral 1,3-oxathiane (**5**) prepared from (+)-pulegone in three steps is converted to diastereomerically pure equatorial 2-acyl derivatives by lithiation, condensation with aldehydes, and Me_2SO oxidation. Reaction of the resulting ketones with Grignard reagents at −78 °C again proceeds highly stereoselectively (diastereomer excess generally above 90%) according to Cram's rule (cyclic model). The resulting tertiary carbinols when cleaved with $NCS/AgNO_3$ give chiral tertiary α-hydroxy aldehydes, $RR'C(OH)CHO$, plus a mixture of epimeric sultines which may be readily reconverted to the starting oxathiane. The hydroxy aldehydes have been oxidized to chiral tertiary α-hydroxy acids, $RR'C(OH)CO_2H$, and reduced to primary–tertiary glycols, $RR'C(OH)CH_2OH$, and further to tertiary carbinols, $RR'C(OH)CH_3$, all with over 90% ee. The opposite enantiomers of these compounds (again >90% ee) may be obtained by starting with a diastereomeric 1,3-oxathiane (**6**), also available from (+)-pulegone. The configurations of the chiral products may be deduced from the manner of preparation and the assumption that Cram's rule is valid and agree with prior assignments in the literature.

In the first paper of this series[1] we have described a highly stereoselective synthesis of oxathiane carbinols (**1**) in two steps,



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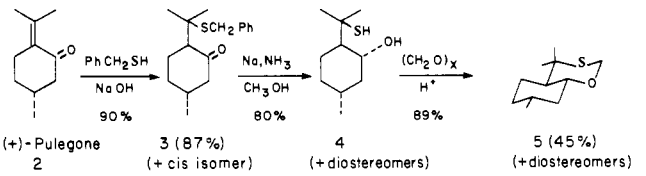
the first one involving a highly stereoselective electrophilic substitution in a conformationally locked 1,3-oxathiane leading to an equatorially substituted ketone, the second involving a highly stereoselective Grignard addition to the ketone to give essentially a single diastereomeric tertiary carbinol (**1**), the diastereomer excess being generally above 90%. In a preliminary communication[3] we have shown that, by making the precursor oxathiane to carbinol **1** optically active and by cleaving **1**, after O-methylation, to an α-methoxy aldehyde, $RR'C(OCH_3)CHO$, which is then oxidized to the corresponding acid, it is possible to obtain atrolactic acid methyl ether, $C_6H_5(CH_3)C(OCH_3)CO_2H$ (above case for R = C_6H_5, R′ = CH_3), in nearly 100% optical yield.

In order to parlay the above observations into a viable[4] asymmetric synthesis, the following problems had to be addressed: (1) convenient synthesis of an enantiomerically pure oxathiane of type **1**, preferably from a readily available natural product; (2) facile cleavage of compounds of type **1** to α-hydroxy aldehydes, $RR'C(OH)CHO$, plus a derivative of the oxathiane moiety which is convertible back to the oxathiane in good yield—both parts of the molecule must be recoverable without racemization; (3) conversion of the chiral α-hydroxy aldehydes (which are only moderately stable chemically) into desirable synthetic targets, such as α-hydroxy acids, $RR'C(OH)CO_2H$, glycols, $RR'C(OH)CH_2OH$, etc., in reasonable chemical yields and without loss of enantiomeric purity. We now report on the outcome of these studies.

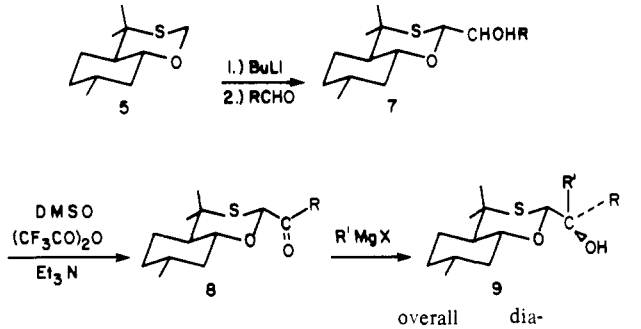
Results

Because of some difficulties in our first attempt to synthesize chiral modifications of **1** from camphorsulfonic acid,[5] we have prepared a close analogue of **1** from (+)-pulegone, readily available in enantiomerically pure form from oil of pennyroyal.[6] The synthesis, previously reported[7] in detail, proceeds as shown in Scheme I. The overall chemical yield of the key chiral adjuvant **5** was about 30% after purification by crystallization which serves to free **5** from other diastereomers formed along with it. In the earlier report,[7] we had described the isolation and identification

Scheme I



Scheme II



R	R′	series	overall yield of 9, %	diastereomer excess
C_6H_5	CH_3	a	76	99
C_6H_5	C_2H_5	b	66	99
C_2H_5	n-C_3H_7	c	70	?
C_2H_5	$HC\equiv C$	d	74	93

(1) Eliel, E. L.; Morris-Natschke, S. *J. Am. Chem. Soc.* **1984**, *106*, preceding paper in this issue.
(2) Lynch, J. E. Ph.D. Dissertation, University of North Carolina, 1982.
(3) Eliel, E. L.; Koskimies, J. K.; Lohri, B. *J. Am. Chem. Soc.* **1978**, *100*, 1614.
(4) Eliel, E. L. *Tetrahedron* **1974**, *30*, 1503.
(5) Eliel, E. L.; Frazee, W. J. *J. Org. Chem.* **1979**, *44*, 3598. The oxathiane is inconvenient to purify, forms a lithio derivative less readily than **1** and has given inconsistent results in the reported cleavage with methyl iodide.
(6) Corey, E. J.; Ensley, H. E.; Suggs, J. W. *J. Org. Chem.* **1976**, *41*, 380. Evidence for the enantiomeric purity of the (+)-pulegone purchased from Givaudan is given in the supplemental part.
(7) Eliel, E. L.; Lynch, J. E. *Tetrahedron Lett.* **1981**, *2855*. A slight improvement in the first step is reported in the experimental part.

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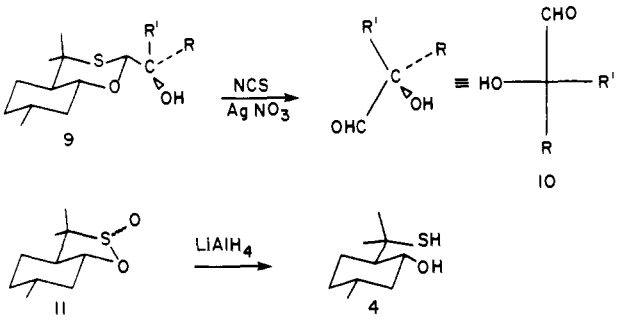
Table I. Chiral α-Hydroxy Acids 14 Synthesized

acid	oxathiane	R	R′	sign[a]	config	ee, %[b]	yield, %[c]	recovery, %/ee, %[d]
14a	5	C_6H_5	CH_3	(+)	*S*	96	34	83/94[e]
14b	5	C_6H_5	C_2H_5	(+)	*S*	91–94	42	84/97
14c	5	C_2H_5	*n*-C_3H_7	(−)	*R*	⩾85	23	56/98
enantio-14b	6	C_6H_5	C_2H_5	(−)	*R*	96	22	
enantio-14c	6	C_2H_5	*n*-C_3H_7	(+)	*S*	90	18	

[a] Sign of rotation of acid. (See Experimental Section for conditions.) [b] Enantiomeric excess of methyl ester 13 obtained in oxidation. [c] Overall yield of acid 14 from oxathiane. [d] For acid obtained by saponification of ester followed by recrystallization. [e] % ee determined by rotation, $[\alpha]^{23}_D$ +35.54° (*c* 3.464, EtOH).

Scheme III



(2 diastereomers)

of two of the diastereomers of the 7-mercaptomenthol, **4**. The oxathiane **6** derived from one of these has now been isolated from

the mother liquor of the crystallization of **5** by preparative high-performance liquid chromatography in quite pure form; its use will be discussed later.

Compound **5** is very similar in structure to the 4,4,6-trimethyl-1,3-oxathiane precursor to **1** and behaved in much the same way.[1] Thus its 2-lithio derivative reacted highly stereoselectively with aldehydes to give essentially purely equatorial carbinols (**7**) which were oxidized by dimethyl sulfoxide/trifluoroacetic anhydride/triethylamine[8] to the corresponding ketones (**8**) in good yield (Scheme II). (Other oxidants are less suitable, because they also promote oxidation of the ring sulfur atom. Direct benzoylation of the oxathianes gave ketones **7**, R = phenyl, in low yields only.) Reaction of the ketones with Grignard reagents at −78 °C in ether THF (conditions which were found optimal in preliminary studies[1]) led to the corresponding tertiary carbinols **9** whose diastereomeric purity exceeded 90% as it had in the model study (Scheme II). The best way to cleave these carbinols was found to be by means of *N*-chlorosuccinimide (NCS) and silver nitrate.[9] As shown in Scheme III, this cleavage led to α-hydroxy aldehydes **10** and the oxathiane-derived sultine **11** (diastereomer mixture). The latter, after separation by chromatography, was reduced with lithium aluminum hydride to the hydroxy thiol **4** from which oxathiane **5** was regenerated as shown in Scheme I; both steps proceeded in excellent (>95%) yield.

The α-hydroxy aldehydes[10] were characterized only spectroscopically; they tend to be unstable both toward dimerization (which is apparently reversible) and toward air oxidation (which in the case of $C_6H_5(C_2H_5)C(OH)CHO$ led to propiophenone as an important byproduct). They were therefore immediately subjected to the next step—either reduction to the glycol—best

Scheme IV

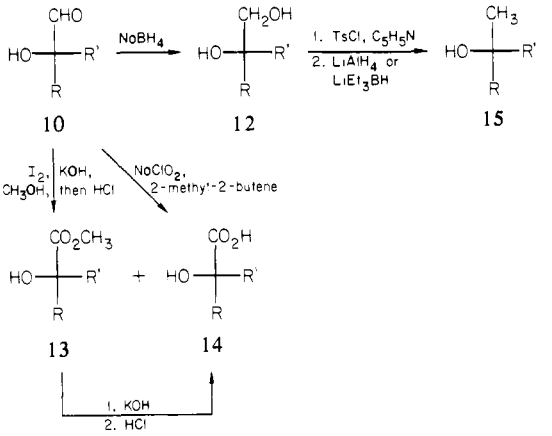


Table II. Chiral Glycols (12) and Carbinols (15) Synthesized

compd	R	R′	sign	config	ee, %	overall yield, %[a]
12a	C_6H_5	CH_3	(+)	*S*	100	26
12b	C_6H_5	C_2H_5	(−)	*S*	95–99[b]	56
12c	C_2H_5	*n*-C_3H_7	(−)	*R*	94[b]	60
enantio-12b	C_2H_5	C_6H_5	(+)	*R*	97[b]	33[c]
12d	C_2H_5	HC≡C	(−)	*R*	(93[d])	44
15b	C_6H_5	C_2H_5	(−)	*S*	100[e]	54[f]
15c	C_2H_5	*n*-C_3H_7	(+)	*S*	93[e]	59[f]

[a] From oxathiane **5** or **6**. [b] Determined through 2-hydroxy-2-phenyl-3,3,3-trifluoropropanoate (Mosher's ester[16]). [c] From **6**. [d] This is the diastereomeric purity of the oxathianecarbinol (**9d**) precursor. [e] Determined by chiral shift reagent Eu(HFC)$_3$. [f] Overall, from glycol **12**.

effected with sodium borohydride[11]—or selective oxidation to the α-hydroxy acid (Scheme IV). Any oxidation scheme must be highly chemoselective since α-hydroxy acids are subjected to ready oxidative cleavage.[12] We found either iodine/KOH/methanol[13] or sodium chlorite/2-methyl-2-butene (chlorine scavenger)[14] satisfactory. The former method yielded a mixture of acid and methyl ester from which the pure acid could be obtained—generally in good yield—by saponification. The latter method, used in a case not included here, yielded the acid directly. The hydroxy acids synthesized in this fashion are listed in Table I. In two of the cases (**14b**, **14c**), both enantiomers were synthesized. While, in principle, this could have been achieved by interchanging the R group derived from the ketone and the R′ group derived from the acid,[1] such a procedure has shortcomings, both because the two ketones (**8**) may not be equally readily available (e.g., it is difficult to synthesize **8**, R = HC≡C—) and because in some

(8) Omura, K.; Sharma, A. K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 957.
(9) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553.
(10) Cf.: Freon, P. *Ann. Chim. (Paris)* **1939**, *11*, 480.

(11) Use of $LiAlH_4$ requires isolation of the aldehyde/sultine mixture from the aqueous CH_3CN solution. $NaBH_4$ can be added after simply filtering the crude reaction mixture. The diols appear to be much easier to isolate than are the comparatively unstable parent aldehydes.
(12) Blumbergs, P.; laMontagne, M. P.; Stevens, J. L. *J. Org. Chem.* **1972**, *37*, 1248.
(13) Inch, T. D.; Ley, R. V.; Rich, P. *J. Chem. Soc. C* **1968**, 1693.
(14) Kraus, G. A.; Roth, B. *J. Org. Chem.* **1980**, *45*, 4825.

instances interchange of the R and R′ groups led to a drop in stereoselectivity. (Thus, we observed[1] that addition of alkyl Grignard reagents to aryl ketones tends to be more stereoselective than the reverse.) We therefore found it expedient to use oxathiane **6** to synthesize the enantiomers of compounds **14b** and **14c**. (It might be noted that the oxathiane moiety in **6** is enantiomeric to that in **5** even though the molecule as a whole is not.[15] Therefore **6** will invariably lead to products enantiomeric with those obtained from **5**.)

The four chiral glycols (**12**, Scheme IV) which were synthesized are listed in Table II (top). By conversion to the primary tosylates followed by hydride reduction, two of these were elaborated into tertiary methyl carbinols **15** (Scheme IV), also indicated in Table II (bottom).

Discussion

As seen in the enantiomeric excess (ee) columns in Tables I and II, the asymmetric synthesis[17] reported here is highly stereoselective. The reasons for this have been discussed in the first paper in this series for the two salient steps. The electrophilic substitution reaction in the 1,3-oxathiane occurs virtually exclusively by equatorial attack,[18] for both steric and stereoelectronic reasons, the latter being explained in terms of the preferred equatorial position of the lithium moiety followed by an electrophilic substitution with retention of configuration.[19] The Grignard addition to the 2-acyl-1,3-oxathiane also proceeds with high stereoselectivity, following Cram's rule in a cyclic (chelated) system,[20,21] with the magnesium presumably acting as the chelating agent which locks the acyl group into a fixed position relative to the oxathiane moiety, so that addition occurs from the less encumbered side of the oxathiane, which is the side of the hydrogen substituent at C(2). In this particular case, Cram's open-chain model[22] leads to the same prediction of stereochemistry; the coincidence of preferred reaction course in the chelated and unchelated substrates may be in part responsible for the high stereoselectivity. The strongly beneficial effect of lowering the temperature[1] suggests, however, that the chelate model (which, for entropic reasons, should be preferred at lower temperature) leads to much higher stereoselectivity than the open-chain one; this is in accord with other observations.[21]

The oxathianecarbinols **9** synthesized in the course of this work are generally crystalline; thus their diastereomeric purity, already high by the manner of synthesis, can be further enhanced by recrystallization. In some cases, we have also found that the diastereomers can be separated by HPLC. Thus, in principle, completely pure tertiary α-hydroxy compounds (acids, glycols, methyl carbinols) can be synthesized, since no racemization is expected in the cleavage and subsequent steps.[23] The oxathiane moiety is recovered in the cleavage as sultine **11**, which is readily reconverted to oxathiane **5** as shown in Schemes II and I.

Because the stereochemistry of the reaction sequence (Scheme II) is so well understood, the absolute configurations of the products are defined by their method of synthesis, which is of definite advantage. Indeed, in all cases where the configurations of the products (Tables I, II) were known, the sign of rotation agreed with prediction. An additional advantage of the synthesis is that both enantiomers of the target compound can be obtained, either by reversing the order of introducing groups R and R′ (Scheme II) or by using the diastereomeric oxathiane **6** as the chiral template in lieu of **5**.

Experimental Section

Proton and carbon-13 NMR spectra were recorded on Varian XL-100 (100 MHz or 25.2 MHz), Bruker WM-250 (250 MHz or 62.89 MHz), or Perkin-Elmer R24B (60-MHz protons only) spectrometers. Chemical shifts are expressed as parts per million downfield from internal tetramethylsilane (Me_4Si); coupling patterns are designated s (singlet), d (doublet), t (triplet), q (quartet), or m (multiplet).

IR spectra were obtained as dilute (1–5%) solutions in 0.5-mm sodium chloride cavity cells or as neat liquid films between sodium chloride plates on a Beckman 4250 spectrophotometer and were calibrated with the 1601-cm^{-1} band of polystyrene. Intensities are reported as s (strong), m (medium), w (weak), and br (broad).

Optical rotations were measured on a Perkin-Elmer 141 polarimeter equipped with sodium and mercury light sources by using a 1-dm thermostated cell; reported temperatures are uncorrected.

Melting points were observed on an Electrothermal melting point apparatus and are uncorrected.

High-pressure liquid chromatography was performed on a Waters Prep-500A instrument equipped with one or two Preppac silica gel cartridges.

5-Methyl-2-[1-methyl-1-(benzylthio)ethyl]cyclohexanone (3).[7] A solution of (+)-pulegone (**2**) (200.00 g, 1.31 mol), benzyl mercaptan (180.00 g, 1.45 mol), and 10 mL of 10% aqueous NaOH in 500 mL of THF was refluxed under N_2 for 2 h. After being cooled the solution was washed with 2 × 500 mL of brine. The water layer was extracted with 3 × 250 mL of ether. The combined organic layers were dried ($MgSO_4$), concentrated, and distilled, giving (after a small forerun) **3**, 326.65 g (90.0%), bp 136–143 °C/0.1 mm, identical in NMR spectrum with that previously reported.[7]

Hexahydro-4,7,7-trimethyl-4*H*-benzoxathiane (6). The mother liquor from the crystallization of oxathiane **5**[7] was concentrated, ultimately at 0.5-mm. HPLC (25% CH_2Cl_2/hexanes) provided the oxathiane **6** as the second substance eluted ($K' = 2$).

^1H NMR ($CDCl_3$): δ 4.98 (d, J = 11 Hz, 1 H), 4.72 (d, J = 11 Hz, 1 H), 3.90 (m, 1 H), 1.55 (s, CH_3), 0.83 (d, J = 6 Hz, CH_3), and others.

^{13}C NMR ($CDCl_3$): δ 73.1, 67.9, 45.1, 42.8, 41.5, 34.6, 29.1, 28.4, 25.8, 22.4, 22.3.

Oxathianecarbinol 7c. To 10 g of oxathiane **5** (50 mmol) in 60 mL of dry THF cooled to −78 °C under N_2 was added, dropwise, 40 mL of 1.3 M n-BuLi in hexane (52 mmol). After being stirred 3 min the solution was allowed to warm to 0 °C and was then immediately recooled to −78 °C. Propanal (8.0 g, 140 mmol) in dry THF was then added, dropwise, over 2.5 h. After being stirred at −78 °C 2 h longer, the solution was allowed to stand overnight at −25 °C. Water (10 mL) and saturated NH_4Cl (10 mL) were then added, the layers were separated, and the organic layer was dried ($MgSO_4$) and concentrated. HPLC (10% EtOAc/hexanes) gave **7c**, 10.28 g (80%) as a diastereomer mixture.

^1H NMR ($CDCl_3$): δ 4.95 (d, J = 5 Hz), 4.78 (d, J = 7 Hz), 1.42 (s, CH_3), 1.28 (s, CH_3), and others.

Oxathianecarbinol 7a. The diastereomeric mixture of carbinols **7a** was prepared in 100% crude yield by the analogous reaction of **5** with benzaldehyde.

^1H NMR ($CDCl_3$): δ 7.25 (s, 5 H), 5.07 (d, J = 5 Hz), 4.90 (d, J = 7 Hz), 4.85 (d, J = 5 Hz), 4.56 (d, J = 7 Hz, total 2 H, 3.42 (dt, J = 4 Hz, 10 Hz, 1 H), 1.31 (s, CH_3), 1.18 (s, CH_3), 0.92 (d, J = 6 Hz, CH_3), and others.

Oxathianecarbinol 16a (R = Et, R′ = H or R = H, R′ = Et). The mixture of carbinols **16a** was prepared by the same procedure from oxathiane **6** and propanal in 63% yield, after HPLC purification (5% EtOAc/hexanes).

^1H NMR ($CDCl_3$): δ 4.87 (d, J = 4 Hz), 4.68 (d, J = 6 Hz), 3.94 (m), 1.51 (s, CH_3), 1.18 (s, CH_3), and others.

Oxathianecarbinol 16b (R = Ph, R′ = H or R = H, R′ = Ph). The carbinol mixture was obtained by the same method from **6** and benzaldehyde in 100% crude yield.

(15) Enantio-pulegone has been synthesized[6] but is not readily available.

(16) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

(17) Morrison, J. D.; Mosher, H. S. "Asymmetric Organic Reactions"; Prentice-Hall: Englewood Cliffs, NJ, 1971, reprinted by American Chemical Society: Washington, DC, 1976. Scott, J. W.; Valentine, D. *Science (Washington, DC)* **1974**, *184*, 943. Valentine, D.; Scott, J. W. *Synthesis* **1978**, 329. Kagan, H. B.; Fiaud, J. C. In "Topics in Stereochemistry"; Eliel, E. L., Allinger, N. L., Eds.; Wiley: New York, 1978; p 175. ApSimon, J. W.; Sequin, R. P. *Tetrahedron* **1979**, *35*, 2797. "Asymmetric Reactions and Processes in Chemistry"; Eliel, E. L., Otsuka, S., Eds.; American Chemical Society: Washington, DC, 1982; ACS Symp. Ser. No. 185.

(18) Amstutz, R.; Seebach, D.; Seiler, P.; Schweizer, B.; Dunitz, J. D. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 53. Amstutz, R.; Dunitz, J. D.; Seebach, D. *Ibid.* **1981**, *20*, 465.

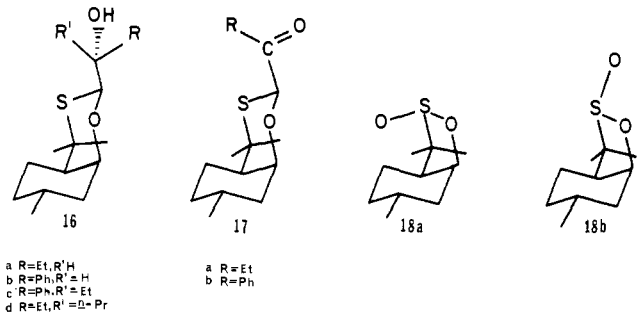
(19) Cram, D. J. "Fundamentals of Carbanion Chemistry"; Academic Press: New York, 1965; p 154.

(20) Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 2748 and references therein.

(21) Eliel, E. L. In "Asymmetric Synthesis", Morrison, J. D., Ed.; Academic Press: New York; Vol. 2, 1984.

(22) Cram, D. J.; Abd Elhafez, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828.

(23) The glycols (Table II) in fact seem to have the same enantiomeric purity as the diastereomeric purity of their precursors (Scheme II) within the limits of experimental uncertainty. The enantiomeric purity of the acids (Table I) in which one substituent is phenyl suggests the possibility of a very small degree of racemization (of unknown origin) in the oxidation and ester hydrolysis steps.



^{1}H NMR ($CDCl_3$): δ 7.25 (brs, 5 H), 5.2–4.5 (m, 2 H), 3.95 (m, 1 H), 1.4 (s, CH_3), 1.1 (s, CH_3), and others.

Acyloxathiane 8c. To a cold (−78 °C) solution of dry Me_2SO (3.0 g, 40 mmol) in dry CH_2Cl_2 (30 mL) under N_2 was added, dropwise, TFAA (8.29 g, 39.5 mmol) in dry CH_2Cl_2 (30 mL). After stirring for 0.5 h the carbinol mixture **7b** (9.28 g, 35.9 mmol) in dry CH_2Cl_2 (60 mL) was added dropwise. After stirring 1 h, triethylamine (12 mL, 86 mmol) was similarly added and the solution was allowed to warm to 0 °C. It was then poured into 300 mL of 5% aqueous HCl and the mixture was shaken thoroughly. The organic layer was washed with saturated $NaHCO_3$ (50 mL), dried ($MgSO_4$), and concentrated to an oil that crystallized on standing, yield 9.06 g (98%). Recrystallization from pentane provided an analytical sample: mp 48–49 °C.

^{1}H NMR ($CDCl_3$): δ 5.54 (s, 1 H), 3.45 (dt, J = 5, 9 Hz, 1 H), 2.67 (q, J = 7 Hz, 2 H), 1.45 (s, CH_3), 1.28 (s, CH_3), and others.

^{13}C NMR ($CDCl_3$): δ 206.2, 82.6, 77.0, 50.4, 43.9, 41.6, 34.5, 31.4, 31.3, 29.3, 22.5, 22.1, 7.3.

IR (CCl_4) cm^{-1}: 2970–2840 (s), 1730 (s), 1460 (m), 1150 (m), 1090 (m), 1070 (m).

Acyloxathiane 8a. The ketone **8a** was prepared by the same procedure from **7a** in 91% crude yield. Recrystallization from pentane provided an analytical sample: mp 94.5–95.5 °C.

^{1}H NMR ($CDCl_3$): δ 8.09 (d, J = 7 Hz, 2 H), 7.57 (t, J = 7.5 Hz, 1 H), 7.45 (t, J = 7.5 Hz, 2 H), 6.25 (s, 1 H), (dt, J = 5, 11 Hz, 1 H), 1.60 (s, CH_3), 1.32 (s, CH_3), 0.95 (d, J = 7 Hz, CH_3).

^{13}C NMR ($CDCl_3$): δ 192.6, 134.1, 133.5, 129.4, 128.3, 81.0, 77.5, 50.5, 44.4, 41.5, 34.5, 31.3, 29.3, 24.3, 22.5, 22.0.

IR (CCl_4) cm^{-1}: 2960–2860 (vs), 1703 (vs), 1683 (vs).

Acyloxathiane 17a (R = Et) was obtained from the carbinol **16a** by the procedure described for ketone **8c** as an oil in 100% crude yield. An analytical sample was provided by flash chromatography (8% EtOAc/hexane).

^{1}H NMR ($CDCl_3$): δ 5.31 (s, 1 H), 4.95 (m, 1 H), 2.70 (q, 2 H), 1.55 (s, CH_3), 1.17 (s, CH_3), and others.

IR (CCl_4) cm^{-1}: 2980–2940 (s), 1725 (s), 1450 (s), 1380 (s), 1140 (s), 1075 (s).

Acyloxathiane 17b (R = Ph) was obtained from **16b** in 63% yield (after crystallization from pentane): mp 75–78 °C (recrystallized).

^{1}H NMR ($CDCl_3$): δ 8.13 (d, J = 7 Hz, 2 H), 7.55 (t, J = 7 Hz, 1 H), 7.45 (t, J = 7 Hz, 2 H), 6.10 (s, 1 H), 4.14 (m, 1 H), 1.68 (s, CH_3), 0.86 (d, J = 7 Hz, CH_3), and others.

^{13}C NMR ($CDCl_3$): δ 193.3, 134.3, 133.5, 129.6, 128.3, 82.5, 74.1, 45.7, 44.0, 41.0, 34.4, 28.8, 25.8, 22.6, 22.2.

IR (CCl_4) cm^{-1}: 3100–3040 (w), 2950 (s), 2875 (s), 2840 (m), 1710 (s), 1685 (s), 1450 (s), 1150 (s).

Carbinol 9c. To a cold (−78 °C) solution of ketone **8c** (2.00 g, 7.8 mmol) in dry THF (50 mL) under N_2 was added, dropwise, 28 mL of 0.57 M *n*-PrMgBr in 80:20 THF:ether (16 mmol). The mixture was stirred 3 h and then warmed to 0 °C. Water (15 mL) and saturated NH_4Cl (15 mL) were added, dropwise, and the mixture was stirred until two clear layers formed. The organic layer was washed with brine (25 mL) and the combined aqueous solution and brine wash were extracted with ether (25 mL). The combined organic solution was dried ($MgSO_4$) and concentrated, giving **9c** as an oil, 2.22 g (97%). Flash chromatography (15% EtOAc/hexane) followed by high-vacuum distillation (bp ca. 70 °C/10^{-4} mm) provided an analytical sample (89% recovery).

^{1}H NMR ($CDCl_3$): δ 4.86 (s, 1 H), 3.40 (dt, J = 4, 10 Hz, 1 H), 1.42 (s, CH_3), 1.27 (s, CH_3), and others; ^{13}C NMR ($CDCl_3$): δ 84.51, 77.9, 75.6, 51.1, 42.9, 41.8, 37.8, 34.8, 31.5, 29.8, 28.4, 24.5, 22.7, 22.1, 16.4, 14.8, 7.62.

IR (CCl_4) cm^{-1}: 3570 (m), 2950–2860 (s), 1455 (m), 1380 (m), 1145 (m).

Carbinol 9b. Addition of EtMgBr (2 equiv) to ketone **8a** by the above procedure gave the crude adduct **9b** as a solid. HPLC (5% EtOAc/hexanes) gave purified **9b** in 73% yield. Recrystallization from pentane provided an analytical sample: mp 118–119 °C.

^{1}H NMR ($CDCl_3$): δ 7.45–7.24 (m, 5 H), 5.15 (s, 1 H), 3.51 (dt, J = 5, 11 Hz, 1 H), 1.34 (s, CH_3), 1.18 (s, CH_3), 0.71 (t, J = 7 Hz, 3 H), and others.

^{13}C NMR ($CDCl_3$): δ 141.5, 127.7, 126.8, 125.7, 85.9, 77.9, 77.5, 50.5, 42.9, 41.6, 35.6, 32.0, 31.3, 29.4, 24.2, 22.6, 22.0, 7.5.

IR (CCl_4) cm^{-1}: 3580 (m), 2960–2860 (s), 1148 (s), 1060 (s).

Carbinol 9a. Addition of MeMgBr (4 equiv) to **8a** as above provided the tertiary carbinol **9a** in 83% yield after recrystallization from MeOH: mp 73–74 °C.

^{1}H NMR ($CDCl_3$): δ 7.43–7.07 (m, 5 H), 5.07 (s, 1 H), 3.60–3.30 (m, 1 H), 2.98 (s, 1 H), 1.64 (s, CH_3), 1.32 (s, CH_3), 0.92 (d, J = 7 Hz, CH_3).

^{13}C NMR ($CDCl_3$): δ 144.2, 127.7, 126.9, 125.3, 86.3, 77.6, 75.4, 50.5, 42.9, 41.7, 34.7, 31.4, 29.6, 27.2, 24.3, 22.7, 22.0.

IR (CCl_4) cm^{-1}: 3580 (m), 3080–3020 (w), 2920 (s), 1450 (m), 1145 (s), 1055 (s).

Carbinol 9d. Ketone **8c** was added to a stirred solution of ethynylmagnesium bromide in THF at 0 °C. After the usual workup, preparative HPLC (10% EtOAc-hexane) gave **9d** (95%) as a pale yellow viscous oil, 93% de.

^{1}H NMR ($COCl_3$): δ 5.03 (s, 1 H), 3.54 (dt, J_1 = 5, 10 Hz 1 H), 2.90 (brs, 1 H), 2.54 (s, 1 H), 2.11–1.99 (m, 1 H), 1.96–1.72 (m, 4 H), 1.50 (s, 3 H), 1.36 (s, 3 H), 1.14 (t, 7 Hz, 3 H), 0.99 (d, J = 5 Hz, 3 H) and others.

^{13}C NMR: δ 84.28, 83.92, 77.70, 72.97, 50.58, 43.00, 41.36, 34.42, 31.17, 30.23, 29.42, 24.14, 22.53, 21.80, 7.91.

IR ($CHCl_3$) cm^{-1}: 3560 (m), 3305 (s), 2920 (s), 2865 (s), 1453 (s), 1365 (s), 1298 (m), 1143 (s), 1084 (s), 1060 (s), 973 (s).

Carbinol 16c (R = Ph, R′ = Et) was obtained similarly as **9c** by addition of EtMgBr to **17a**, 54% yield after recrystallization from petroleum ether: mp 96–98 °C.

^{1}H NMR ($CDCl_3$): δ 7.44–7.21 (m, 5 H), 5.12 (s, 1 H), 4.08 (br s, 1 H), 2.23 (sextet, J = 7 Hz, 1 H), 1.47 (s, CH_3), 1.09 (s, CH_3), 0.89 (d, J = 7 Hz, CH_3), 0.71 (t, J = 7 Hz, 3 H), and others.

^{13}C NMR ($CDCl_3$): δ 141.5, 127.7, 126.9, 125.9, 86.6, 78.2, 73.7, 44.0, 43.9, 41.1, 34.4, 32.0, 29.3, 29.0, 25.9, 22.3, 7.6.

IR (CCl_4) cm^{-1}: 3575 (m), 3090 (m), 3060 (m), 3025 (m), 2950–2840 (s), 1445 (m), 1150 (s), 1060 (s).

Carbinol 16d (R = Et, R′ *n*-Pr). Addition of *n*-PrMgBr (2 equiv) to ketone **17b** gave **16d** in 63% yield after HPLC purification (6% EtOAc/hexane).

^{1}H NMR ($CDCl_3$): δ 4.78 (s, 1 H), 3.93 (m, 1 H), 1.50 (s, CH_3), 1.17 (s, CH_3), and others.

IR (CCl_4) cm^{-1}: 3580 (m), 2950–2840 (s), 1450 (m), 1380 (m), 1145 (s), 1045 (s).

***(R)*-(−)-2-Ethyl-2-hydroxypentanal (10c).** The oxathianecarbinol **9c** (1.570 g, 5.22 mmol) in CH_3CN (10 mL) was added to NCS (1.400 g, 10.5 mmol) and $AgNO_3$ (1.812 g, 10.7 mmol) in 4:1 CH_3CN:H_2O (125 mL). The resulting mixture was stirred 1 h before the successive addition of saturated solutions of Na_2SO_3, Na_2CO_3, and NaCl (5 mL each) at 1-min intervals. Hexanes:CH_2Cl_2, 1:1 (100 mL), was added, the mixture was filtered, and the filter cake was washed thoroughly with hexanes:CH_2Cl_2. The two layers of the filtrate were separated; the hexane layer was washed with saturated Na_2CO_3 (25 mL), dried ($MgSO_4$), concentrated, and partially distilled (Kugelrohr), giving (*R*)-2-ethyl-2-hydroxypentanal (**10c**), 80–126 °C/35 mm, 0.42 g (62%).

^{1}H NMR ($CDCl_3$): δ 9.48 (s, 1 H), 3.2 (s, 1 H), 2.0–0.7 (m, 12 H).

IR (CCl_4) cm^{-1}: 3520 (m), 2960–2870 (m), 1728 (s).

The residue from the above distillation crystallized on cooling, giving sultine **11**, 1.11 g (105%). Proton NMR showed two sets of signals corresponding to the two diastereomers of **11**. Repeated recrystallization from benzene ultimately gave one isomer: mp 119–121 °C; $[\alpha]^{21}_D$ +185.3° (*c* 5.375, benzene).

^{1}H NMR ($CDCl_3$): δ 4.45 (dt, J = 4, 10 Hz, 1 H), 1.42 (s, CH_3), 1.10 (s, CH_3), 1.01 (d, J = 7 Hz, CH_3), and others.

^{13}C NMR ($CDCl_3$): δ 86.7, 69.7, 55.1, 39.5, 33.7, 31.0, 23.8, 23.2, 21.7, 15.4.

IR (CCl_4) cm^{-1}: 2970 (s), 1450 (s), 1150 (vs), 980 (vs), 970 (s).

The second diastereomer was characterized only as a mixture with the above.

^{1}H NMR ($CDCl_3$): δ 4.36 (dt, J = 4, 11 Hz, 1 H), 1.29 (s, CH_3), 1.14 (s, CH_3), 1.01 (d, J = 7 Hz, CH_3), and others.

^{13}C NMR ($CDCl_3$): δ 90.2, 68.4, 48.8, 41.6, 34.0, 31.7, 22.8, 21.5, 19.1, 14.6.

***(R)*-2-Ethyl-2-hydroxypentanoic Acid (14c).** The aldehyde **10c** (210 mg, 1.60 mmol) thus obtained was immediately dissolved in methanol (2 mL) containing I_2 (2.54 mmol), and the resulting solution was heated in a 43 °C water bath. KOH (20 mL, 4% w/v) in methanol was added, dropwise (2 mL/min), and the solution was stirred until it became colorless. It was poured into water (50 mL) and extracted with ether (2 ×

50 mL). The combined ether extracts were washed with water (50 mL), dried ($MgSO_4$), and concentrated, giving 212 mg (78%) of methyl ester **13c**.

Analysis of the ^1H NMR spectrum containing $Eu(HFC)_3$ showed the ester to be at least 85% enantiomerically pure.

^1H NMR ($CDCl_3$): δ 3.79 (s, 3 H), 1.8–1.5 (m, 6 H), 1.0–0.7 (m, 6 H).

IR (CCl_4) cm^{-1}: 3550 (s), 2960–2860 (s), 1735 (vs), 1225 (vs), 1160 (vs).

The ester **13c** so obtained (378 mg, 2.36 mmol) in MeOH (5 mL) and 10% aqueous KOH (5 mL) was stirred at room temperature for 0.5 h, heated to 40–45 °C with stirring for 1 h, and then stirred again at room temperature for 1 h. The solution was poured into water (20 mL) and the aqueous solution extracted with ether. The ether extract was discarded; the aqueous layer was acidified and extracted with ether (2 × 10 mL). The ether extract was dried ($MgSO_4$) and concentrated, giving an oil that crystallized on standing, 292 mg (85%). Recrystallization from pentane gave 165 mg (57% recovery) of acid **14c**, mp 72–74 °C, $[\alpha]^{23}_D$ −6.58° (*c* 1832, MeOH). This sample was treated with diazomethane to regenerate the methyl ester, 98% ee by ^1H NMR analysis using $Eu(HFC)_3$. A second crystallization of the acid from pentane gave a sample: mp 74.5–76 °C; $[\alpha]^{23}_D$ −6.97° (*c* 2.201, MeOH).

^1H NMR ($CDCl_3$): δ 2.0–1.8 (m, 4 H), 1.8–1.1 (m, 2 H), 0.93 (t, 6 H).

^{13}C NMR ($CDCl_3$): δ 180.9, 78.4, 41.2, 32.1, 17.0, 14.2, 7.7.

IR (CCl_4) cm^{-1}: 3550 (m), 3400–2400 (s), 2960–2860 (s), 1700 (s), 1450 (m), 1240 (m), 1170 (s).

(*S*)-(+)-2-Ethyl-2-hydroxypentanoic Acid (*enantio*-14c). Treatment of **16d** with NCS and $AgNO_3$ as above followed by preparative HPLC (4:1 pentane:ether) of the crude product mixture gave the aldehyde enantio-**10c** (57%), the sultine **18a** (60%), and the sultine **18b** (28%).

Compound **18a** was crystallized from pentane: mp 61.5–64.5 °C.

^1H NMR ($CDCl_3$): δ 4.7 (m, 1 H), 1.38 (s, CH_3), 1.27 (s, CH_3), 0.91 (d, J = 7 Hz, CH_3), and others.

IR (CCl_4) cm^{-1}: 2970 (s), 1140 (s), 1128 (s), 947 (w), 915 (m).

Compound **18b** was recrystallized from pentane: mp 71–74 °C.

^1H NMR ($CDCl_3$): δ 5.16 (m, 1 H), 1.38 (s, CH_3), 1.28 (s, CH_3), 0.91 (d, J = 7 Hz, CH_3), and others.

IR: identical with that of **18a**.

Oxidation of *enantio*-**10c** by the method described for **10c** gave the (*S*)-methyl ester, enantio-**13c** (77%), which was identical with the *R* isomer with respect to GC, IR, and ^1H NMR. Analysis of the ^1H NMR in the presence of $Eu(HFC)_3$ showed the ester had 90% ee.

Saponification of the above ester (683 mg, 4.26 mmol) as before gave, after acidification, (*S*)-(+)-**14c** as a white solid, 576 mg (92.4%). The acid was recrystallized from pentane (15 mL), giving 422 mg (73%): mp 70–73 °C; $[\alpha]^{23}_D$ +5.85° (*c* 2.049, MeOH).

(*S*)-(−)-Hydroxy-2-phenylbutanal (10b). The oxathianecarbinol **9b** was treated with NCS and $AgNO_3$ as described for **10c**. Workup as before followed by chromatography on silica gel (40 g, 60–200 mesh, 1% EtOAc/hexane) gave the aldehyde: bp 120–170 °C/23 mm (Kugelrohr), 357 mg (73%); $[\alpha]^{23}_D$ −13.4° (*c* 18.8, EtOH), (lit. bp 65–68 °C/0.7 mm).[24]

^1H NMR ($CDCl_3$): δ 9.62 (s, 1 H), 7.7–7.2 (m, 5 H), 2.10 (q, J = 7 Hz, 2 H), 0.91 (t, J = 7 Hz, 3 H), 3.77 (br s, 1 H).

^{13}C NMR ($CDCl_3$): δ 200.6, 138.5, 128.8, 127.9, 125.9, 82.1, 29.8, 7.0.

IR (CCl_4) cm^{-1}: 3500 (s), 1725 (s).

(*S*)-(+)-2-Hydroxy-2-phenylbutanoic Acid (14b). Oxidation of the aldehyde, obtained above as described for **14c**, gave the methyl ester **13b** in 82.4% yield, $[\alpha]^{25}_D$ +7.35° (*c* 9.6, MeOH), 94% ee by $Eu(HFC)_3$, ^1H NMR analysis.

^1H NMR ($CDCl_3$): δ 7.6 (m, 2 H), 7.4–7.2 (m, 3 H), 3.77 (s, 4 H), 2.24 (sextet, J = 7 Hz, 1 H), 2.03 (sextet, J = 7 Hz, 1 H), 0.92 (t, J = 7 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ 175.9, 142.0, 128.3, 127.7, 125.7, 53.1, 32.8, 8.0; assignment of quaternary carbon not possible due to impurities in sample.

IR (CCl_4) cm^{-1}: 3590 (m), 3520 (s), 1730 (s).

Saponification of the ester **13b** in KOH/50% aqueous MeOH gave **14b** as a white solid, 695 mg (83%), mp 123–125 °C. Recrystallization from pentane:toluene (55:45, 100 mL) returned 588 mg (70%), mp 124–127 °C, $[\alpha]^{23}_D$ 30.74° (*c* 3.829, EtOH). Methylation (CH_2N_2) regenerated the methyl ester, 97% ee by $Eu(HFC)_3$, ^1H NMR analysis. A second crystallization of the acid provided a sample: mp 127.5–128 °C, $[\alpha]^{24}_D$ 31.53°, $[\alpha]^{17}_D$ 32.56° (*c* 3.700, EtOH) (lit. mp 128–129 °C); $[\alpha]^{20}_D$ 32.7° (*c* 3.996, EtOH), for the *S* isomer.[25,26]

^1H NMR (Me_2SO-d_6): δ 7.6–7.2 (m, 5 H), 2.3–1.7 (m, 2 H), 0.80 (t, J = 7 Hz, 3 H).

^{13}C NMR (Me_2SO-d_6): δ 175.8, 143.1, 127.7, 127.0, 125.6, 77.9, 32.3, 8.0.

IR (CCl_4) cm^{-1}: 3540 (m), 3100–2500 (m), 1700 (s).

(*R*)-(−)-Hydroxy-2-phenylbutanoic acid (*enantio*-14b). Treatment of oxathiane **16c** with NCS and $AgNO_3$ in the usual manner gave a mixture of aldehyde *enantio*-**10b** and sultines **18** which could not be easily separated. Therefore the mixture was oxidized in the usual manner using I_2 and 4% KOH in 50% MeOH. The ester, *enantio*-**13b**, still was not readily separated from the sultines **21**, so the mixture was saponified. After acidification the acid (*enantio*-**14b**) was conveniently separated from the recyclized sultine by extraction with $NaHCO_3$ solution followed by acidification and reextraction into ether, ultimately giving acid (*enantio*-**14b**) in 70% overall yield from oxathiane **19c**. Recrystallization from benzene gave a sample (91% recovery) of mp 128–129 °C $[\alpha]^{23}_D$ −30.9° (*c* 3.680, EtOH), 94% ee based on $[\alpha]_D^{max}$ 32.7°.[25]

(*S*)-(+)-Atrolactic Acid (14a). Treatment of oxathiane **16a** as described for homologue **16c** above, followed by NCS/$AgNO_3$ cleavage, oxidation, saponification, and separation by extraction (see above), led to isolation of **14a** in 45% overall yield.

The crude acid shows ^1H NMR and IR spectra nearly identical with those of a commercial sample of racemic atrolactic acid monohydrate. The acid **14a** was treated with diazomethane to regenerate the methyl ester **13a**. Analysis of the ^1H NMR spectrum with $Eu(HFC)_3$ showed the ester and thus the acid was 96% enantiomerically pure. The acid was recrystallized from CCl_4, providing a sample with mp 114–116 °C and $[\alpha]^{23}_D$ 35.5° (*c* 3.464 EtOH) [lit. mp 116–117 °C, $[\alpha]^{15}_D$ 37.7s (*c* 3.500, EtOH) for the *S* isomer[25]].

(*S*)-2-Phenyl-1,2-propanediol (12a). Oxathiane **9a** (321 mg, 1.00 mmol) was treated with NCS (4 mmol) and $AgNO_3$ (4.5 mmol) as described for 2-ethyl-2-hydroxypentanal. The hexane–CH_2Cl_2 solution obtained on workup was dried ($MgSO_4$) and concentrated. The residue was dissolved in ether and added, dropwise, to a suspension of $LiAlH_4$ (0.5 g) in ether (15 mL). The mixture was refluxed 1 h before adding saturated Na_2SO_4 (10 mL). The ether solution was decanted and the salts were rinsed with CH_2Cl_2 (5 × 10 mL). The combined organic solution was washed with water (25 mL), dried ($MgSO_4$), concentrated, and distilled to give **12a**, 116 mg (76%), 80–90 °C/0.5 mm. TLC showed the presence of the sultine **11**. Flash chromatography (40% EtOAc/pet ether) provided purified **12a**, 62 mg (41%); $[\alpha]^{23}_D$ 4.2° (*c* 4.5, EtOH) (lit. $[\alpha]^{8}_D$ +5.4° for the *S* isomer).[27]

^1H NMR ($CDCl_3$): δ 7.6–7.2 (m, 5 H), 3.83–3.52 (AB q, J = 11 Hz, 2 H), 2.39 (br s, 2 H), 1.51 (s, 3 H), identical with an authentic sample obtained by $LiAlH_4$ reduction of commercial atrolactic acid.

IR (neat) cm^{-1}: 3600–3100 (s), 3040 (w), 3020 (w), 2960 (m), 1490 (m), 1445 (m), 1370 (w), 1035 (s).

The MTPA ester[16] was prepared from a sample of MTPA–Cl of 94% ee.

^1H NMR ($CDCl_3$): δ 7.45–7.2 (m, 10 H), 4.19 (d, J = 11 Hz, 1 H), 4.31 (d, J = 11 Hz, 1 H), 3.37 (s, 3 H), 1.54 (s, 3 H). A signal for the diastereomer at 3.40 ppm was 3% of the signal at 3.37 ppm (94% de), but since the MTPA–Cl was only 94% enantiomerically pure it follows that the diol was of 100% ee.

The salts from the LAH reduction were dissolved in 15% HCl (25 mL) and the resulting solution was extracted with CH_2Cl_2 (2 × 15 mL). The extract was dried ($MgSO_4$), concentrated, and distilled, giving the mercapto alcohol 4, 109 mg (58%).

^1H NMR and IR were identical with those of an authentic sample.[7]

(*R*)-(−)-2-Ethyl-1,2-pentanediol (12c). Oxathiane **9c** (1.003 g, 3.34 mmol) in CH_3CN (10 mL) was added to NCS (0.933 g, 6.99 mmol) and $AgNO_3$ (1.187 g, 6.99 mmol) in 89% CH_3CN (50 mL). The mixture was stirred 5 min and quenched as previously described. The mixture was filtered and the filter cake was washed with CH_3CN (4 × 10 mL). Piecemeal addition of $NaBH_4$ (0.5 g, 13 mmol) was accompanied by vigorous foaming and the formation of a black precipitate (Ag). The mixture was stirred 1 h before addition of acetone (5 mL), dropwise. The solution was decanted from a gelatinous precipitate that had formed. The combined CH_3CN solution and acetone washings were filtered and concentrated. The residue was extracted with ether (50 mL) the aqueous layer was saturated with Na_2SO_4 and further extracted with ether (50 mL, then 25 mL). The ether extract was dried ($MgSO_4$) and concentrated to an oil that partially crystallized. This was triturated with hexanes, and the supernatant hexane solution was filtered and concentrated. Flash chromatography (40% EtOAc/hexane) gave, in order of elution the sultine **11**, 608 mg (90%), and the diol **12c**, 374 mg (85%): $[\alpha]^{22}_D$ −3.29° (*c* 5.958, $CHCl_3$).

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^{1}H NMR ($CDCl_3$): δ 3.46 (s, 2 H), 2.6–2.0 (s, 2 H), 1.7–1.1 (m, 6 H), 1.0–0.7 (m, 6 H).

^{13}C NMR ($CDCl_3$): δ 75.1, 67.7, 37.7, 28.3, 16.7, 14.7, 7.8; IR (CCl_4) 3950 (m), 3500–3200 (m), 2970–2870 (s), 1460 (s), 1040 (s).

The MTPA ester was prepared by the reaction of this diol with (*S*)-MTPA–Cl by the method of Dale and Mosher.[16]

^{1}H NMR (C_6D_6): δ 7.67 (m, 2 H), 7.15–7.0 (m, 3 H), 4.00 (AB q, 2 H), 3.42 (s, 3 H), 1.28–0.91 (m, 6 H), 0.75 (t, *J* = 7 Hz, 3 H), 0.66 (t, *J* = 7 Hz, 3 H). A signal for the diastereomer is seen at 3.99 ppm and is 3% of the corresponding signal at 3.98 ppm (94% de). (This resolution was possible only on the 250-MHz instrument.)

(*S*)-(−)-Phenyl-1,2-butanediol (12b). Treatment of oxathiane **9b**, as described under 2-ethyl-1,2-pentanediol above, gave a mixture of diol **12b** and **11**. HPLC purification (50% EtOAc/hexanes) gave **12b** (86.4%) and **11** (86.9%).

12b: $[\alpha]^{22}_D$ −10.92° (*c* 14.0, EtOH) (lit. $[\alpha]^{19}_D$ −11.4° (*c* 7.4, EtOH) for the *S* isomer).[27]

^{1}H NMR ($CDCl_3$): δ 7.5–7.2 (m, 5 H), 3.83 (d, *J* = 11 Hz, 1 H), 3.65 (d, *J* = 11 Hz, 1 H); 1.82 (q, *J* = 7 Hz, 2 H); 0.76 (t, *J* = 7 Hz, 3 H), 2.8–2.1 (s, 2 H).

IR (CCl_4) cm^{-1}: 3570 (s), 3600–3200 (s), 3200–3080 (m), 2960–2870 (s), 1050 (s).

MTPA ester:[16] ^{1}H NMR ($CDCl_3$) δ 7.45–7.21 (m, 10 H), 4.70 (d, *J* = 11 Hz, 1 H), 4.38 (d, *J* = 11 Hz, 1 H), 3.34 (s, 3 H), 1.87 (q, *J* = 7 Hz, 2 H), 0.78 (t, *J* = 7 Hz, 3 H). The signal for the diastereomer at 3.38 ppm was 2.5% of the signal at 3.34 ppm (95% ee).

(*R*)-(+)-2-Phenyl-1,2-butanediol (*enantio*-12b) was obtained from **16c** by the procedure described for **12b** in 97% yield after separation from **18** (86%) by flash chromatography (40% EtOAc in hexane) and distillation, bp 95–100 °C/0.01 mm (Kugelrohr), $[\alpha]^{25}_D$ 10.6° (*c* 6.8, EtOH), identical with respect to ^{1}H NMR and IR with the *S* enantiomer above.

The ^{1}H NMR spectrum of the MTPA ester was identical with that above except that the signal at 3.34 ppm was 1.5% of the signal at 3.38 ppm (97% ee).

2-Ethyl-3-butyne-1,2-diol (12d). Treatment of oxathiane **9d** as described for (*R*)-(−)-2-methyl-1,2-pentanediol (**12c**) gave **12d** (41%): mp 41–42 °C, after HPLC (30% EtOAc/hexane) purification.

^{1}H NMR (250 MHz): δ 3.77 (brs, 1 H), 3.68, 3.54 (HB, *J* = 12.5 Hz, 2 H), 3.46 (brs, 1 H), 2.52 (s, 1 H), 1.69 (q, *J* = 7 Hz, slightly doubled, 2 H), 1.07 (t, *J* = 7 Hz, 3 H).

^{13}C NMR: δ 84.77, 73.70, 72.30, 69.00, 30.69, 8.37.

IR ($CHCl_3$) cm^{-1}: 3590 (m), 3300 (s), 3000 (s), 2960 (s), 2930 (m), 2870 (w), 2380 (m), 1520 (m), 1418 (s), 1220 (s), 1190 (s), 1043 (s), 922 (s), 842 (m).

(*R*)-(−)-3-Methyl-3-hexanol (15c). Diol **12c** (234 mg, 1.77 mmol) in dry pyridine (1 mL) was treated with *p*-toluenesulfonyl chloride (342 mg, 1.80 mmol) at room temperature. After stirring 18 h, the mixture was poured into cold water (25 mL) and was extracted with ether (25 mL). The ether extract was washed with ice-cold 5% H_2SO_4 (10 mL) and saturated $NaHCO_3$ (10 mL), dried ($MgSO_4$), and concentrated (ultimately at 0.1 mm), giving the tosylate as a clear oil, 453 mg (89.4%), pure by TLC, $[\alpha]^{23}_D$ 0.25° (*c* 6.355, $CHCl_3$). Flash chromatography (25% EtOAc/hexane) gave an analytical sample.

^{1}H NMR ($CDCl_3$): δ 7.73 (d, *J* = 8.4 Hz, 2 H), 7.27 (d, *J* = 8.4 Hz, 2 H), 3.83 (s, 2 H), 2.43 (s, 3 H), 1.85 (s, 1 H), 1.6–0.6 (m, 12 H).

IR (CCl_4) cm^{-1}: 3600 (s), 3530 (m), 2960–2980 (s), 1370 (s) 1198 (s), 1170 (s), 1100 (s).

The tosylate (650 mg, 2.27 mmol) in ether (2 mL) was added, dropwise, to a suspension of $LiAlH_4$ (350 mg, in ether (30 mL). The mxiture was stirred 1 h at room temperature and then refluxed for 0.5 h. Water (0.35 mL), 15% NaOH (0.35 mL), and water (1.05 mL) were added successively, and the mixture was stirred 2 h, filtered, dried ($MgSO_4$), concentrated, and distilled, giving **15c**: 155 mg (52%), bp 50–60 °C/25 mm, $[\alpha]^{25}_D$ 0.82° (*c* 2.066, CCl_4) (lit. bp 51 °C/18 mm, $[\alpha]^{20}_D$ 1.2° (neat), for *R* isomer[28]).

(28) Richter, W. J. *Liebigs Ann Chem.* **1975**, 401.

^{1}H NMR ($CDCl_3$): δ 1.6–1.2 (m, 6 H), 1.22 (s, 3 H), 1.05–0.7 (m, 6 H).

IR (CCl_4) cm^{-1}: 3600 (s), 3550–3300 (br, m), 2970–2870 (s), 1460 (s), 1375 (s), and others.

^{1}H NMR in the presence of $Eu(HFC)_3$ indicated 93% ee for the alcohol.

(*S*)-(−)-2-Phenyl-2-butanol, 15b. The diol **12b** was tosylated by the procedure described under 3-methyl-3-hexanol in 98% yield after purification by flash chromatography (20% EtOAc/hexanes), mp 78–81 °C, $[\alpha]^{21}_D$ −7.11° (*c* 4.768, EtOH). Recrystallization (pentane) gave the tosylate, mp 81–82.5 °C, $[\alpha]^{25}_D$ −7.4° (*c* 4.5 EtOH) (lit. mp 80–82 °C, $[\alpha]^{16}_D$ −5.4° (*c* 4.4, EtOH, for the *S* enantiomer[27]).

^{1}H NMR ($CDCl_3$): δ 7.6 (d, *J* = 8.4 Hz, 2 H), 7.3–7.1 (m, 7 H), 4.05 (s, 2 H), 2.35 (s, 3 H), 1.79 (q, *J* = 7 Hz, 2 H), 0.68 (t, *J* = 7 Hz, 3 H), 1.95 (s, 1 H).

IR (CCl_4) cm^{-1} 3590 (s), 3100–3000 (m), 1595 (m), 1380 (s), 1190 (s), 1175 (s), 970 (s).

$LiEt_3BH$, 2 M in THF (2 mL, 2 mmol), was added to the tosylate from above (206 mg, 0.642 mmol) in dry THF under N_2 at 0 °C. After stirring 1 h, 15% NaOH (1 mL) and 30% H_2O_2 (1 mL) were added, and the mixture was stirred overnight. The layers were separated and the organic layer was dried ($MgSO_4$). Evaporation of solvent gave an oil mixed with a waxy material. This was triturated with ether (in which the wax did not dissolve) and filtered through a glass wool plug. Evaporation and distillation gave **15b** as a colorless liquid: 80 mg (83%); bp 110–140 °C/25 mm (Kugelrohr); $[\alpha]^{23}_D$ −16.1° (*c* 3.650, CCl_4) (lit. $[\alpha]^{38}_D$ −18.4° (neat) for the *S* enantiomer[26]).

^{1}H NMR analysis of the spectrum in the presence of $Eu(HFC)_3$ suggested this material was enantiomerically pure.

^{1}H NMR ($CDCl_3$): δ 7.47 (m, 5 H), 1.95–1.77 (m, 2 H), 1.73 (s, 1 H), 1.56 (s, 3 H), 0.80 (t, *J* = 7 Hz, 3 H).

IR (CCl_4) cm^{-1}: 3600 (m), 3100–3000 (m), 2970–2850 (s), 1378 (m).

5-Methyl-2-(1-methyl-1-thioethyl)cyclohexanol (4). Sultine **11** (4.238 g, 20.9 mmol) in dry THF was added, dropwise, to a suspension of $LiAlH_4$ (1.0 g) in dry THF (125 mL) under N_2. The mixture was refluxed 2 h and allowed to cool to room temperature. EtOAc (3 mL) was added, dropwise, followed by 10% H_2SO_4 (30 mL), dropwise, with vigorous stirring. The layers were separated and the THF layer was washed with brine. The combined aqueous solution was extracted with ether and the combined organic solution was dried ($MgSO_4$), concentrated, and distilled, giving **4** as a clear liquid, 3.912 g (97%), pure by TLC.

Hexahydro-4,7,7-trimethyl-4*H*-benzoxathiin (5). The mercapto alcohol **4** obtained (1.011 g, 5.37 mmol), paraformaldehyde (176 mg, 5.87 mmol), and *p*-toluenesulfonic acid (10 mg) were refluxed 1 h in benzene (8 mL), water being collected in a Dean-Stark trap. TLC showed three spots, including the product and starting material. A second portion of paraformaldehyde (90 mg, 3.0 mmol) was added and reflux continued 1 h (no Dean-Stark trap); a third portion of paraformaldehyde (20 mg, 0.6 mmol) was added and reflux continued 1 h more. TLC now showed complete conversion to the desired product. The reaction mixture was diluted with ether (10 mL) and was washed with water (5 mL) and saturated $NaHCO_3$, dried ($MgSO_4$), and concentrated (ultimately at 0.05 mm), giving **5** as an oil that crystallized on standing, 1.063 g (98.8%).

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Supplementary Material Available: Determination of enantiomeric purity of (+)-pulegone and elemental (C, H) analyses of new compounds (3 pages). Ordering information is given on any current masthead page.