Enantioselective Synthesis of 2-Methyl-2-hydroxy-γ-butyrolactone and Its Application in the Asymmetric Synthesis of Frontalin and Mevalonolactone

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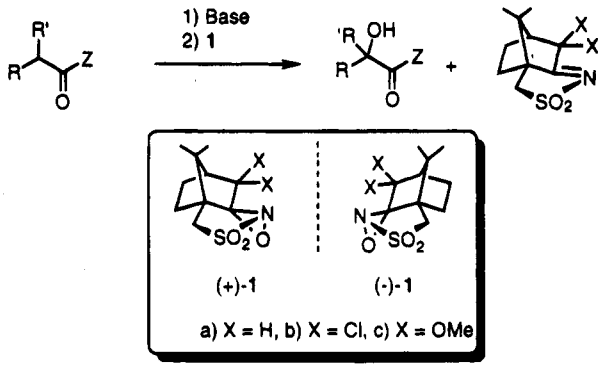
Received May 15, 1995®

The asymmetric hydroxylation of the enolates of fully substituted acyclic ester **8** and lactone **10** with (camphorylsulfonyl)oxaziridines **1a–c** was studied. The stereoselectivities of the tertiary α-hydroxy carbonyl products were highly dependent on the enolate structure, the oxidizing reagents, and the reaction conditions. While high diastereoselectivity (up to 94%) was obtained for enolates of fully substituted menthol ester **8** with substoichiometric amounts of oxaziridine **1a**, the yields were unsatisfactory. On the other hand, the enantioselective α-hydroxylation of the sodium enolate of 2-methyl-γ-butyrolactone (**10**) with [(8,8-dimethoxycamphoryl)sulfonyl]oxaziridine (**1c**) afforded α-hydroxy lactone **11a** in 70% yield and 84% ee. The enantiomeric excess was improved to >93% ee by crystallization of the corresponding benzoyl ester **11c**. The utility of both enantiomers of **11c** were demonstrated in the formal asymmetric syntheses of the pheromone, (1*S*,5*R*)-(−)-frontalin (**13**) and in the asymmetric synthesis of (*R*)-(−)-mevalonolactone (**20**).

Chiral nonracemic α-hydroxy carbonyl compounds are versatile chiral building blocks for asymmetric synthesis and are key structural subunits of natural products.[1] Studies in our laboratory have demonstrated the efficacy of the asymmetric enolate oxidation protocol using the (camphorylsulfonyl)oxaziridine derivatives **1** for the synthesis of this key structural unit (Scheme 1).[1a,b,d] With these reagents high enantioselectivities (>95%) are realized for the hydroxylation of acyclic[2,3] and cyclic ketone enolates.[2–9] However, this protocol is less efficient for the synthesis of acyclic tertiary α-hydroxy acids and esters[2,3,10,11] which are themselves useful intermediates for asymmetric synthesis.[12,13] These materials are only available through fairly elaborate synthetic schemes[14] or by enzymatic kinetic resoluton.[15] In this paper we

Scheme 1



describe studies of the application of the enolate oxidation protocol to the enantioselective synthesis of acyclic tertiary α-hydroxy acids which resulted in the preparation of 2-methyl-2-hydroxy-γ-butyrolactone (**11a**), a useful chiral synthon for this structural unit. In addition its utility is demonstrated in the formal synthesis of (1*S*,5*R*)-(−)-frontalin (**13**) and in the asymmetric synthesis (*R*)-(−)-mevalonolactone (**20**).

The difficulty in achieving high enantioselectivities for the asymmetric hydroxylation of prochiral acyclic enolates is the problem of generating a specific enolate geometric isomer and the degree of enantiofacial discrimination between the re and si faces of the enolate.[1a] For fully substituted enolates (R′ ≠ H, Scheme 1) these

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® Abstract published in *Advance ACS Abstracts,* September 1, 1995.

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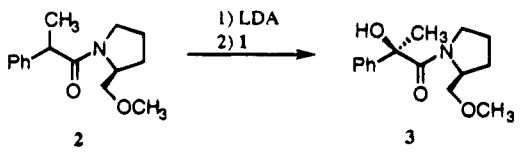
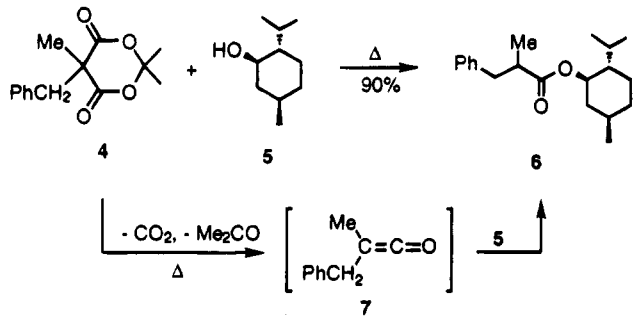
problems are expected to be much worse compared to the monosubstituted enolates (R' = H, Scheme 1) where some success has been reported.[2,3] The necessity for generating a specific enolate geometric isomer as a precondition for high ee's has recently been demonstrated.[3]

It was envisioned that this problem might be resolved by using the double stereodifferentiation strategy,[16] i.e. oxidation of a chiral ester enolate with a chiral oxaziridine oxidizing reagent. For example, the asymmetric hydroxylation of the chiral amide enolates of **2** with oxaziridines (+)-**1a** and (−)-**1a** gave acyclic tertiary α-hydroxy amide **3** in high diastereomeric excess.[11] This reaction was found to be highly substrate dependent because changing phenyl in **2** to a benzyl group resulted in complex reaction mixtures.[17] Furthermore, the lack of varied chiral amine auxiliaries limited the opportunity to screen more general examples of these auxiliaries for amide enolate hydroxylations.



In contrast to amine auxiliaries, alcohol-based chiral auxiliaries are abundant. The chiral ester substrate chosen for study was **6** readily prepared from 5-methyl-5-benzyl Meldrum's acid (**4**)[18] and commercially available (−)-menthol (**5**). Thus heating equivalent amounts of **4** and **5** at 180 °C without solvent for 0.5 h under argon furnished **6** in 90% yield after flash chromatography. Ketene **7** is considered to be the key intermediate in this transformation.[19]

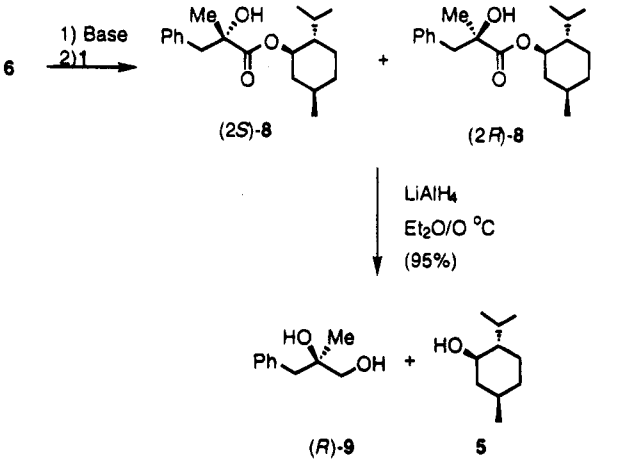


In a typical hydroxylation experiment, the enolate of (1*R*,2*S*,5*R*)-menthyl 2-methyl-3-phenylpropionate (**6**) was formed by addition of 1 equiv of the appropriate base at −78 °C, warming to 0 °C to ensure complete enolate formation, and treatment at −78 °C with (camphorylsulfonyl)oxaziridine (**1a**). After quenching with 10% HCl the α-hydroxy ester **8** was purified by preparative TLC (Table 1). In the ^{1}H-NMR spectrum of **8** the α-methyl protons appears as a singlet at δ 1.45 ppm and α-hydroxy proton at δ 3.30 ppm (D_2O exchangeable). Integration of the diastereomeric benzyl protons at δ 2.95 and 3.00 was used to determine the de's. Reduction of **8** with $LiAlH_4$ to the known (*S*)-2-methyl-3-phenyl-1,2-propanediol (**9**)[20] not only confirmed these assignments, but established the absolute configuration of the major diastereoisomer. These results are summarized in Table 1.

Table 1. Diastereoselective Hydroxylation of the Enolate of 6 with (Camphorylsulfonyl)oxaziridine (1a) to 8

entry	oxaziridine (equiv)	base[a]	% yield[b]	% de[c]	config[d]
1	(+)-**1a** (1.50)	NaHMDS	32	42	(R)
2	(−)-**1a** (1.50)	NaHMDS	33	28	(R)
3	(+)-**1a** (1.50)	LDA	71	66	(S)
4	(−)-**1a** (1.50)	LDA	47	50	(R)
5	(+)-**1a** (1.25)	LDA	54	81	(S)
6	(+)-**1a** (1.00)	LDA	42	84	(S)
7	(+)-**1a** (0.75)	LDA	37	89	(S)
8	(+)-**1a** (0.50)	LDA	33	94	(S)
9	(+)-**1a** (0.25)	LDA	10	94	(S)
10	(−)-**1a** (0.50)	LDA	19	37	(S)

[a] Two equivalents of base used. [b] Isolated yield. [c] Determined by ^{1}H-NMR. [d] Determined by the sign of the optical rotation of diol **9**.



Inspection of Table 1 reveals that (+)-(camphorylsulfonyl)oxaziridine (**1a**) gave better stereoselectivity than (−)-**1a** (Table 1, compare entry 1 with 2 and entry 3 with 4). For the oxidation of the sodium enolate, it seemed that the configuration of the α-hydroxy ester **8** was controlled by the chiral menthyl auxiliary since use of both oxaziridine enantiomers (+)-**1a** or (−)-**1b** gave the same (*R*)-**9**. On the other hand, the configuration of the oxaziridine controlled the stereochemistry of the α-hydroxy product in the oxidation of the lithium enolate of **6**. For example use of oxaziridine (+)-**1a** gave (*S*)-**8** while use of (−)-**1a** afforded (*R*)-**8** (Table 1, entry 3, and 4). Significantly, the diastereoselectivity of the reaction was improved when less than stoichiometric amounts of (+)-**1a** were used, with the best de (94%) obtained for the oxidation of the lithium enolate of **6** with 0.5 equiv of oxaziridine (+)-**1a** (Table 1, entry 8). Further reduction in the amount of the oxidant to 0.25 equiv failed to increase the diastereoselectivity de, but did resulted in a much lower chemical yield (Table 1, entry 9). The improved stereoselectivity observed in the hydroxylation of the enolate of **6** with substoichiometric amounts (+)-**1a** is likely the result of a fortuitous choice of the matched enolate geometry (in a mixture of *E* and *Z* enolates) by the oxidant whereas with (−)-**1a** mismatching occurs (Table 1, entry 10).

(16) For an excellent discussion on double stereodifferentation and leading references see: Roush, W. R.; Hoong, L. K.; Palmer, M. A. J.; Straub, J. A.; Palkowitz, A. D. *J. Org. Chem.* **1990**, *55*, 4117.

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Scheme 2

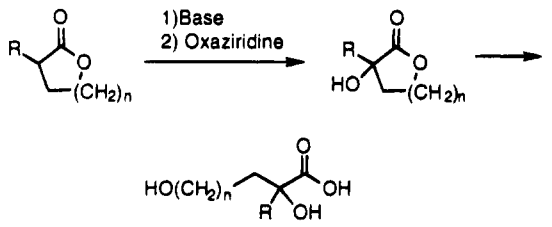


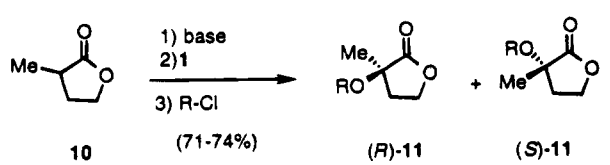
Table 2. Enantioselective Hydroxylation of the Enolate of Lactone 10 to α-Hydroxy Lactone 11 in THF at −78 °C

			α-Hydroxy Lactone **11**	
entry	oxaziridine	base/ZCl	% yield[a]	% ee[b] (config)
1	(+)-**1a** (X = H)	LDA/PDMSCl	70	0
2		NaHMDS/PDMSCl	53	44 (*S*) **11b**
3		NaHMDS/PDMSCl[c]	46	49 (*S*)
4		KHMDS/PDMSCl	*d*	
5	(+)-**1b** (X = Cl)	LDA/PDMSCl	71	2
6		NaHMDS/PDMSCl	66	65 (*S*)
7		NaHMDS/PDMSCl[c]	74	78 (*S*)
8	(+)-**1c** (X = OMe)	LDA/PDMSCl	71	0
9		NaHMDS/PDMSCl	70	80 (*S*)
10		NaHMDS/PDMSCl[c]	69	84 (*S*)
11		NaHMDS/BzCl[c]	70	*d* (*S*) **11c**
12	(−)-**1c** (X = OMe)	NaHMDS/BzCl[c]	70	*d* (*R*) **11c**

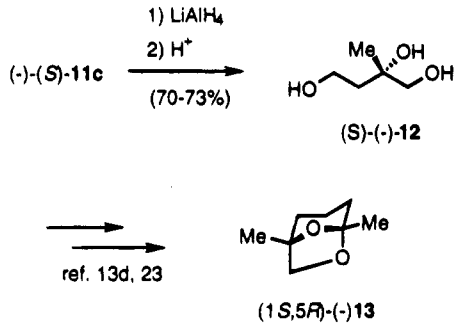
[a] Isolated yields. [b] Determined using Eu(Hfc)$_3$. [c] The oxaziridine is precooled to −78 °C before addition to the enolate. [d] Determined to be 84% ee by conversion of a derivative into the Mosher MTPA ester (see text).

Although this procedure did, in this unique case,[17] give useful levels of stereoinduction it suffers from low yields and the necessity of introducing and eventually removing the chiral auxiliary. It was therefore abandoned in favor of a more direct strategy for the synthesis of chiral nonracemic acyclic tertiary α-hydroxy acids. This approach involves the asymmetric hydroxylation of a lactone enolate, avoiding the problem of generating a specific enolate geometric isomer (Scheme 2). Furthermore, the primary hydroxyl group in the acyclic product should be easily manipulated into a variety of functional groups for further elaboration (see below).

This strategy is demonstrated in the synthesis of 2-methyl-2-hydroxy-γ-butyrolactone (**11a**) from commercially available 2-methyl-γ-butyrolactone (**10**). Typically the enolate of **10** was generated in THF by standard methods at −78 °C and a slight excess of the appropriate oxaziridine **1** added. Since it proved impossible to isolate the **11a** (R = H) from the reaction mixture because of it volatility and lack of a chromophore for TLC detection, the alkoxide was trapped *in situ* with phenyldimethylsilyl chloride (PDMSCl). After standard workup, **11b** was isolated in 71−74% overall yield by flash chromatography. The enantioselectivity was determined using the chiral shift reagent Eu(hfc)$_3$ and the absolute configuration established by chemical correlation (vide infra). These results are summarized in Table 2.



Scheme 3



The results summarized in Table 2 reveal that the highest enantioselectivities achieved for hydroxylation of lactone **10** were with the sodium enolate and (+)-[(8,8-dimethoxycamphoryl)sulfonyl]oxaziridine (**1c**) (Table 2: entry 10). As previously observed for the asymmetric hydroxylation of enolates careful control of the reaction temperature is often critical for high stereoselectivities.[8] In this case addition of a precooled solution of (+)-**1c** to the enolate at −78 °C resulted in the highest ee's (Table 2: compare entries 6 and 9 with entries 7 and 10).

Frequently it is possible to improve the enantiomeric purity of a sample that is <95% by crystallization.[21] Unfortunately, the phenyldimethylsilyl derivative **11b** was an oil and therefore could not be upgraded in this manner. However, trapping of the enolate hydroxylation product of **6** with benzoyl chloride (BzCl) gave a crystalline adduct, **11c**, in 70% yield (Table 2: entries 11 and 12). Although chiral shift reagent experiments failed to determine the enantiomeric purity of **11c**, it is reasonable to assume, based on earlier result, that it falls with in 80−84% ee range (Table 2). This enantiomeric purity of this material was later determined to be 84−86% ee by conversion into 2-methyl-4-(benzyloxy)butane-1,2-diol (**16**) and making the Mosher MPTA ester (Scheme 4). A single crystallization of **11c** from ethyl acetate−dichloromethane (95:5) gave a material of constant rotation; e.g. the rotation did not change on further crystallization. Of additional significance is the fact that there was only a 15−20% loss of material resulted. The enantiomeric purity of this upgraded material was 93−95% ee.

To demonstrate the utility of **11c** as a synthon for acyclic tertiary α-hydroxy acids we next explored its conversion into frontalin (**13**) (Scheme 3) and into (*R*)-(−)-mevalonolactone (**20**) (Scheme 4).

Frontalin (**13**) is one of the aggregation pheromones of the southern pine beetles of the family *Denroctonus* and has been the subject of numerous asymmetric syntheses.[22] The female pine beetle produces only the (1*S*,5*R*)-(−)-frontalin (**13**) while the male makes an 85:15 mixture of the (1*S*,5*R*)- and (1*R*,5*S*)- enantiomers. A key intermediate in the enantioselective of both enantiomers is 2-methylbutane-1,2,4-triol (**12**)[13b] which has also been used by Partridge et al. in the synthesis of vitamin D$_3$ metabolite, 25(*S*),26-dihydroxycholecalciferol.[13d] Triol **12** has been prepared in nonracemic form by reduction of lactonic acid, but a classical resolution of the acid was required.[13c] Another synthesis involved a five-step sequence from the metabolite (−)-2-hydroxyparaconic acid.[23] Our synthesis, outlined in Scheme 3, is much simpler

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(22) For a review see: Braun, M. In *Organic Synthesis Highlights*; Mulzer, J., Ed.; VCH Publishers, Inc.: New York, 1991; p 335.
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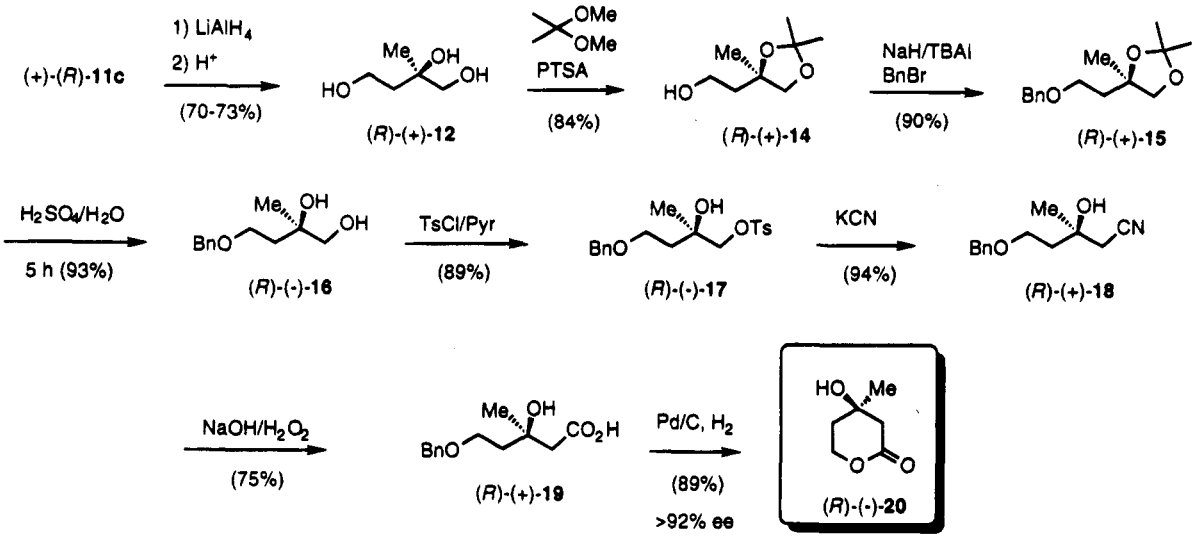
Scheme 4



involving the lithium aluminum hydride ($LiAlH_4$) reduction of the lactone **11c** to give triol **12** in 70–73% isolated yield and 94% ee by comparison of its rotation with literature values.[13b] Both enantiomers are readily available because the configuration of the oxaziridine controls the absolute configuration of the product (Table 2: entries 10 and 11). The enantioselective synthesis of (−)-**12** therefore represents a formal synthesis of (1*S*,5*R*)-(−)-frontalin (**13**).

Mevalonic acid or mevalonolactone (**20**) is the biosynthetic precursor of most terpenoid, sterols, cytokines, and other isoprenoids[24] and has been the subject of a number of asymmetric synthesis.[20,25] Our synthesis begins with triol (*R*)-(+)-**12**, readily prepared in 75% yield from (+)-(*R*)-**11c** (94% ee). The conversion of (*R*)-(+)-**12** into (*R*)-(−)-mevalonolactone (**20**) was accomplished in seven steps, in 40% overall yield and in 92% ee, as outlined in Scheme 4. The small decrease in optical purity may have resulted in formation of the acetonide **14** which was obtained in 92% optical purity.[23] Our synthesis is comparable with most other asymmetric preparations of mevalonolactone (**20**)[25] and illustrates the easy manipulation and elaboration of the primary hydroxyl groups in triol **12**. A number of these intermediates are expected to be useful in enantioselective synthesis of other oxygenated natural products.

In summary the asymmetric enolate hydroxylation protocol has been extended to the synthesis of enantiomerically enriched acyclic tertiary α-hydroxy acids, useful chiral building blocks for asymmetric synthesis.

Experimental Section

General Procedure. NMR spectra were recorded on a 250 MHz spectrometer. Optical rotations were measured at 20 °C. THF was freshly distilled under nitrogen from sodium and benzophenone. Lithium diisopropylamide (1 M) solution in THF was prepared from *n*-butyllithium [2.5 M solution in hexane's (4.0 mL, 10.0 mmol)] by addition of a cooled solution of diisopropylamine (1.47 mL, 10.5 mmol) in THF (5.0 mL) at 0 °C and stirred for 20 min prior to the reaction. Reagents were purchased from Aldrich Inc. and used without further purfication unless otherwise noted.

Preparation of (*R*)-Menthyl 2-Methyl-3-phenylpropionate (6). In a 25 mL round-bottom flask equipped with condenser and nitrogen inlet was placed 2.60 g (10.5 mmol) of 5-methyl-5-benzyl-2,2-dimethyl-4,6-dioxo-1,3-dioxane (**4**)[18] and 1.56 g of (*R*)-(+)-menthol (**5**). The mixture was stirred at 260 ± 5 °C for 1 h and the residue was purified by flash chromatography (ether/*n*-pentane 3:7) to give 2.70 g (90%) of **6**: mp 35–37 °C; IR (neat) 1725 (C=O), 1602 (Ph) cm^{-1}; ^1H-NMR ($CDCl_3$) δ 7.20 (m, 5H), 4.62 (m, 1H), 3.00 (m, 1H), 2.70 (m, 2H), 0.6–2.0 (m, 18H). Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.74; H, 10.01. Found: C, 79.58; H, 10.38.

(*R*)-Menthyl 2-Hydroxy-2-methyl-3-phenylpropionate (8). In a 25 mL oven dried two-necked round bottomed flask fitted with an argon bubbler, a rubber septum, and a magnetic stirring bar was placed 0.30 g (1 mmol) of (*R*)-**6** in 5 mL of freshly distilled THF. The reaction mixture was cooled to −78 °C, 2 mL (2 mmol, 2.0 equiv based on the ester) of a 1.0 M solution of LDA was added, and the solution was stirred at −78 °C for 10 min and then at 0 °C for 1 h. A solution of the appropriate (camphorylsulfonyl)oxaziridine (**1a**) in 3 mL of THF was added dropwise and the mixture stirred for 30 min. After the reaction was complete, as monitored by TLC, it was quenched at −78 °C by addition of 3 mL of a saturated NH_4I solution, diluted with 10 mL of ethyl acetate, and warmed to rt. The aqueous layer was washed with ethyl acetate (2 × 5 mL), and the combined organic extracts washed successively with saturated aqueous $Na_2S_2O_3$ (2 × 15 mL) and brine (2 × 10 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by preparative TLC (ether/*n*-hexane 3:7) to gave α-hydroxy ester **8** as an oil. The diastereomeric ratio was determined by integration of the benzyl quartet at δ 3.0 or the menthyl methyl protons at δ 0.78 ppm (Table 1). Compound **8** had the following properties: oil; IR (neat) 3505 (OH), 1725 (C=O), 1600 (Ph) cm^{-1}; ^1H-NMR ($CDCl_3$) δ 7.05–7.38 (m, 5H), 4.75 (m, 1H), 3.30 (s, 1H), 0.78 (d, J = 8.2 Hz, 3H), 3.00 (q, J = 12.5 Hz, 2H), 0.50–1.93 (m, 9H), 1.45 (s, 3H, CH_3), 0.82 (d, J = 8.4 Hz, 3H), 0.79 (d, J = 8.2 Hz, 3H); HRMS *m/e* calcd for $C_{20}H_{31}O_3$ (M^+ + H) 319.2273, found 319.2273.

(*S*)-(−)-2-Methyl-3-phenyl-1,2-propanediol (9). In a 25 mL oven-dried two-necked round bottomed flask fitted with an argon bubbler, a rubber septum, and a magnetic stirring bar was placed 0.04 g (1 mmol) of $LiAlH_4$ in 10 mL of freshly distilled ether. The solution was cooled to 0 °C, 0.16 g of (*R*)-**8** in 5 mL of ether was added, and the reaction mixture stirred at 0 °C for 2 h and quenched by addition of 0.5 mL of 10% NaOH solution. The inorganic salts were filtered, the ethereal solution was concentrated, and the residue was purified by preparative TLC (ether/*n*-hexane 1:4) to give 0.078 g (95%) of (*S*)-**9**: mp 65–66 °C (lit.[20] mp 66.5–67.5 °C); $[\alpha]^{20}_D$ −14.5° (*c*

(24) Goodwin, T. W. *Natural Substances formed Biologically from Mevalonic Acid*; Academic Press: New York, 1970.

(25) (a) Sugai, T.; Kakeya, H.; Ohta, H. *Tetrahedron*, **1990**, *46*, 3463. (b) Bolitt, V.; Mioskowski, C.; Bhatt, R. K.; Falck, J. R., *J. Org. Chem.* **1991**, *56*, 4238. (c) Ray, N. C.; Raveendranath, P. C.; Spencer, T. A. *Tetrahedron* **1992**, *48*, 9427. (d) Ferraboschi, P.; Grisenti, P.; Casati, S.; Santaniello, E. *Synlett* **1994**, 754.

1.2, 95% EtOH) (84% ee); (lit.[20] $[\alpha]^{20}_D$ +17.3° (*c* 1.2, 95% EtOH) for the (*R*)-enantiomer).

(*S*)-(+)-2-[(Dimethylphenylsilyl)oxy]-2-methyl-γ-butyrolactone (11b). In a 50 mL two-necked round-bottomed flask equipped with a magnetic stir bar and argon inlet was placed sodium bis(trimethyl)silylamide (1.2 mL, 1.2 mmol, 1 M in THF) in dry THF (2 mL) and cooled to −78 °C. Added via syringe to this solution was 0.10 g (1.0 mmol) of 2-methyl-γ-butyrolactone (**10**, Aldrich) in 2 mL of dry THF. After stirring for 1 h a precooled −78 °C solution of 0.318 g (1.1 mmol) of (+)-[(8,8-dimethoxycamphoryl)sulfonyl]oxaziridine (**1c**) in 10 mL of THF was added to the enolate via a double ended needle. After stirring for 1 h at this temperature the reaction mixture was warmed to rt and stirred for 2 h and a solution of 0.171 g (1.0 mmol) phenyldimethylsilyl chloride (PDMSCl) in THF (1 mL) was added. The reaction mixture was stirred for 6 h, and the solution was diluted with 15 mL of ether, washed with saturated $NaHCO_3$ (5 mL) and brine (5 mL), dried ($MgSO_4$), filtered, and concentrated to give the crude silyl ether. Purification by silica gel column chromatography (*n*-pentane:ether, 80:20) gave 0.15 g (60%) of **11b** as an oil: $[\alpha]^{20}_D$ +1.43 (*c* 4.4, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.60 (m, 2H), 7.40 (m, 3H), 4.37−4.25 (m, 1H), 4.21−4.10 (m, 1H), 2.41−2.30 (m, 1H), 2.19−2.06 (m, 1H), 1.45 (s, 3H), 0.41 (s, 6H). The enantiomeric excess was determined using the chiral shift reagent Eu(hfc)$_3$ and found to be 84% by monitoring the methyl protons at δ 1.45 ppm.

Attempts to obtain a satisfactory elemental analysis of this highly moisture sensitive material was unsuccessful.

(*S*)-(−)-2-(Benzoyloxy)-2-methyl-γ-butyrolactone (11c). The same procedure was employed as in the preceding example except that 0.141 g (1.0 mmol) of benzoyl chloride was added in the place PDMSCl. Purification by silica gel column chromatography (*n*-hexane:EtOAc, 60:40) gave 0.15 g (70%) of **11c** as a white crystalline solid: mp 140−145 °C; $[\alpha]^{20}_D$ −16.2 (*c* 2.2, $CHCl_3$). After recrystallization (EtOAc:CH_2Cl_2, 95:5) 0.135 g (61%) of **11c** was obtained: mp 143−145 °C; $[\alpha]^{20}_D$ −18.3 (*c* 4.3, $CHCl_3$); IR (KBr) 1786 (C=O), 1720 (C=O), cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.05 (d, *J* = 7.8 Hz, 2H), 7.60 (m, 1H), 7.45 (m, 2H), 4.64 (td, *J* = 9.4, 3.7 Hz, 1H), 4.34 (q, *J* = 8.2, 17.0 Hz, 1H), 2.90 (m, 1H), 2.60 (m, 1H), 1.76 (s, 3H); ^{13}C NMR (CD_2Cl_2) δ 175.4, 165.6, 134.0, 130.1, 129.5, 128.8, 77.5, 65.2, 33.7, 23.4. Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.45; H, 5.44. Found: C, 65.19; H, 5.61.

(*R*)-(+)-2-(Benzoyloxy)-2-methyl-γ-butyrolactone (11c). Prepared as described above using (−)-[(8,8-dimethoxycamphoryl)sulfonyl]oxaziridine (**1c**): $[\alpha]^{20}_D$ +18.9 (*c* 3.8, $CHCl_3$).

(*S*)-(−)-2-Methylbutane-1,2,4-triol (12). In a 500 mL two-necked round-bottomed flask equipped with an argon inlet and a magnetic stir bar was placed 2.8 g (74.0 mmol) of $LiAlH_4$ in 200 mL of freshly distilled THF. The slurry was cooled to 0 °C and a solution of 4.0 g (18.2 mmol) of lactone **11c** in 40 mL of dry THF was added via syringe. The reaction mixture was warmed to rt, stirred for 5 h, cooled to 0 °C, and quenched by the addition of a saturated Na_2SO_4 solution (12 mL). After stirring for 1 h the solution was filtered through Celite, the filter cake was washed with THF (7 × 50 mL), and the combined filtrates were concentrated to give the crude triol **12**. Purification by flash chromatography ($CHCl_3$:THF, 3:2) afforded 1.53 g (70%) of (*S*)-**12** as a viscous oil which was used directly in the next step; $[\alpha]^{20}_D$ −1.41 (*c* 3.52, EtOH); [lit.[26] $[\alpha]_{20D}$ −1.50° (*c* 3.07. EtOH).

(*R*)-(+)-2-Methylbutane-1,2,4-triol (12). Prepared as described above from (*R*)-(+)-**11c**; $[\alpha]^{20}_D$ +1.39 (*c* 2.02, EtOH).

(*R*)-(+)-2,2,4-Trimethyl-1,3-dioxolane-4-ethanol (14). In a 25 mL two-necked round-bottomed flask equipped with an argon inlet and a magnetic stirring bar was placed 1.50 g (12.5 mmol) of triol (*R*)-(+)-**12** to which was added 2,2-dimethoxypropane (7 mL) and 0.24 g (1.25 mmol) of *p*-toluenesulfonic acid. The reaction mixture was stirred at rt for 2 h, the solvent removed, and the residue dissolved in 15 mL of ether which was washed with saturated $NaHCO_3$ (20 mL) and brine (30 mL), dried ($MgSO_4$), and concentrated. The crude acetonide was purified by flash chromatography (*n*-hexane:EtOAc, 60:40) affording 1.68 g (84%) of **14** as an oil: $[\alpha]^{20}_D$ +8.16° (*c* 4.3, $CHCl_3$); [lit.[26] $[\alpha]^{20}_D$ −8.9° (*c* 2.82, $CHCl_3$) for (*S*)-**14**]; ^1H NMR ($CDCl_3$) δ 3.90−3.60 (m, 4H), 2.80 (bs, 1H), 2.00−1.85 (m, 1H), 1.81−1.66 (m, 1H), 1.42 (s, 6H), 1.34 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 109.5, 81.3, 74.6, 59.2, 41.0, 27.0, 24.9.

(*R*)-(+)-2,2,4-Trimethyl-4-[2-(benzyloxy)ethyl]-1,3-dioxolane (15). This material was prepared from (*R*)-(+)-**14** and benzyl bromide according to the procedure of Gill and Smrdel[26] and isolated as an oil in 90% yield: $[\alpha]^{20}_D$ +2.5° (*c* 2.5, $CHCl_3$) [lit.[26] $[\alpha]^{20}_D$ −2.9° (*c* 3.88, $CHCl_3$) for the (*S*)-isomer].

(*R*)-(−)-2-Methyl-4-(benzyloxy)butane-1,2-diol (16). This compound was prepared in 93% yield by treatment of (*R*)-(+)-**15** with dilute sulfuric acid according the procedure reported by Gill and Smrdel:[26] $[\alpha]^{20}_D$ −9.2° (*c* 1.2, $CHCl_3$); [lit.[26] $[\alpha]^{20}_D$ +9.5° (*c* 4.0, $CHCl_3$) for the (*S*)-isomer].

Determination of Enantiomeric Purity. Preparation of the Mosher Ester of (*R*)-(−)-16. In a 25 mL two-necked round-bottomed flask equipped with an argon inlet and magnetic stir bar were placed 0.063 g (0.30 mmol) of diol **16**, 0.2 mL of triethylamine, 0.114 g (0.45 mmol) of (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (Mosher chloride), and a catalytic amount of DMAP in 2.0 mL of $CHCl_3$. The reaction was complete on stirring overnight as determined by TLC at which time 5 mL of saturated $NaHCO_3$ solution was added and the solution extracted with ether (3 × 10 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated and the residue passed through a short silica gel column (*n*-hexane:EtOAc, 70:30). The enantiomeric excess (% ee) was determined to be 93% by monitoring the methylene protons at δ 4.50 (for major) and δ 4.55 (for minor) in ^1H NMR and at δ −72.0 (for major) and δ −63.3 (for minor) in the ^{19}F NMR spectra.

(*R*)-(−)-2-Hydroxy-2-methyl-4-(benzyloxy)butyl-*p*-toluenesulfonate (17). In a 50 mL two-necked round-bottomed flask equipped with an argon inlet and a magnetic stir bar was placed 1.05 g (5.0 mmol) of diol (*R*)-(−)-**16** in 8 mL of dry pyridine and cooled to 0 °C. To the reaction mixture was added 1.14 g (6.0 mmol) of *p*-toluenesulfonyl chloride in 7 mL of pyridine. After standing overnight at 10 °C in the refrigerator, the mixture was poured onto crushed ice and extracted with ether (3 × 100 mL). The ether extracts were washed with water (100 mL), 2 N HCl (3 × 100 mL), water (50 mL), and brine (50 mL) and dried ($MgSO_4$). Concentration of the ether solution gave the crude tosylate, which was purified by silica gel column chromatography (*n*-hexane:ether, 50:50) affording 1.62 g (89%) of **17** as a viscous oil: $[\alpha]^{20}_D$ −4.33° (*c* 1.78, $CHCl_3$); IR (neat) 3474 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.30 (m, 7H), 4.45 (s, 2H), 3.85 (dd, *J* = 9.4, 25.5 Hz, 2H), 3.65 (m, 2H), 2.43 (s, 3H), 1.84 (m, 2H), 1.16 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 144.7, 137.3, 132.4, 129.7, 128.3, 127.8, 127.7, 127.5, 75.1, 73.2, 70.9, 66.5, 36.6, 24.4, 21.4. Anal. Calcd for $C_{19}H_{24}O_5S$: C, 62.62; H, 6.64. Found: C, 62.47; H, 6.60.

(*R*)-(+)-3-Hydroxy-3-Methyl-5-(benzyloxy)valeronitrile (18). In a 50 mL single-necked round-bottomed flask equipped with a magnetic stir bar was placed 1.20 g (3.3 mmol) of tosylate **17** in 6 mL of ethanol and 4 mL of H_2O. The reaction mixture was cooled to 0 °C, 0.66 g (9.9 mmol) of KCN was added, and the solution was warmed to rt. After stirring for 8 h the reaction mixture was concentrated, 10 mL of H_2O was added, and the mixture was extracted with ether (4 × 20 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated and the residue purified by silica gel column chromatography (*n*-hexane:ether, 50:50) to give 0.68 g (94%) of **18** as a viscous oil: $[\alpha]^{20}_D$ +4.19° (*c* 1.6, $CHCl_3$); IR (neat) 3454 (OH), 2248 (CN) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45−7.30, (m, 5H), 4.45 (s, 2H), 3.75 (m, 2H), 2.53 (s, 2H), 2.10−1.85 (m, 2H), 1.38 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 137.1, 128.6, 128.1, 127.8, 117.7, 73.6, 71.1, 66.8, 38.8, 31.0, 27.0. Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71,21; H, 7.81. Found: C, 71.08; H, 7.69.

(*R*)-(+)-3-Hydroxy-3-Methyl-5-(benzyloxy)pentanoic Acid (19). In a 50 mL two-necked round-bottomed flask equipped with a magnetic stir bar and reflux condenser was placed 0.60 g (2.7 mmol) of cyanide **18**, 20 mL of 3 N NaOH,

(26) Gill, M.; Smrdel, A. F. *Tetrahedron: Asymmetry* **1990**, *1*, 453.

and 7 mL of 30% H_2O_2. The reaction mixture was heated at 70 °C for 1 h and 1 h at 90 °C and cooled to rt, and the solution was washed once with ether (10 mL) which was discarded. The aqueous solution was cooled to 0 °C and enough 6 N HCl was added until the pH was brought to 4–5. The aqueous suspension was extracted with ether (5 × 50 mL), and the organic phase was washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated. The crude acid was purified by silica gel column chromatography (EtOAc) to give 0.50 g (75%) of **19** as a viscous oil: $[\alpha]^{20}_D$ +2.08 (*c* 2.0, $CHCl_3$); IR (neat) 3600–2778 (OH), 1706 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.50–7.25 (m, 5H), 4.53 (s, 2H), 3.75 (m, 2H), 2.55 (dd, *J* = 15.5, 24.4 Hz, 2H), 2.10–1.80 (m, 2H), 1.32 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 174.9, 137.2, 128.5, 128.0, 127.8, 73.5, 71,5, 66.8, 45.6, 39.4, 26.7. Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.67; H, 7.55.

(*R*)-(−)-Mevalolactone (20). In a 50 mL two-necked round-bottomed flask equipped with a hydrogen filled balloon, a stopper, and a magnetic stir bar was placed 0.56 g (2.54 mmol) of hydroxy acid **19** in 10 mL of THF. The flask was flushed with hydrogen gas, 0.1 g of 10% Pd/C was added, and the reaction mixture was stirred at 1 atm of hydrogen for 8–10 h. When the reaction was complete, as determined by TLC, the solution was filtered through Celite, the filter cake was washed with THF (2 × 10 mL), and 0.1 mL of concd hydrochloric acid was added to the filtrate. After stirring for 2 h the solvent was removed and crude product was purified by flash chromatography (EtOAc) to give 0.29 g (88%) of (*R*)-(−)-**20** as a colorless oil: $[\alpha]^{20}_D$ −19.9° (*c* 1.9, $CHCl_3$); [lit.[25a] $[\alpha]^{20}_D$ −21.6°]. A chiral shift reagent experiment indicated that **20** was >92% ee.

Acknowledgment. The support of this work by the National Institutes of Health (General Medical Sciences) is gratefully acknowledged.

JO950900B