allowed to warm up to room temperature, and excess methanol was added to destroy any residual sodium. Following removal of the solvent, the residue was treated with water and acidified with dilute hydrochloric acid. The mixture was then basified with ammonium hydroxide and extracted with chloroform. The organic phase was dried over sodium sulfate, the solvent evaporated, and the residue subjected to preparative TLC. Average yield: 70% of each component.

(+)-*O*-Methylarmepavine (3): $[\alpha]^{25}_D$ +87° (*c* 0.15, MeOH); CD $\Delta\epsilon_{nm}$ (MeOH) $+1.2_{287}$, $+5.0_{234}$.

Phenolic Tetrahydrobenzylisoquinoline 4: MS, *m/z* (relative intensity) 373 (M^+, $C_{21}H_{27}O_5N$, 0.4), 356 (0.7), 206 (100), 191 (6), 190 (15), 177 (3); λ_{max} (MeOH) 210, 231 sh, 288 nm (log ϵ 4.45, 4.15, 3.89); CD $\Delta\epsilon_{nm}$ (MeOH) -2.9_{295}, $+2.0_{279}$, -4.3_{243}, $+3.9_{232}$; $[\alpha]^{25}_D$ −132° (*c* 0.22, MeOH).

(+)-Vanuatine (5): MS, *m/z* (relative intensity) 670 (M^+, 0.2), 669 (1), 655 (0.4), 535 (0.1), 478 (0.8), 477 (1), 341 (0.1), 192 (a, 100); λ_{max} (MeOH) 210, 230 sh, 286 nm (log ϵ 4.83, 4.48, 4.11); CD $\Delta\epsilon_{nm}$ (MeOH) $+6.2_{289}$, $+23.2_{232}$; $[\alpha]^{25}_D$ +138° (*c* 0.12, MeOH).

(+)-Vateamine (6): MS, *m/z* (relative intensity) 656 (M^+, 0.1), 655 (0.2), 519 (0.1), 464 (0.3), 327 (0.2), 192 (100); λ_{max} (MeOH) 212, 230 sh, 283 nm (log ϵ 4.72, 4.48, 4.07); CD $\Delta\epsilon_{nm}$ (MeOH) $+7.5_{286}$, $+14.6_{233}$; $[\alpha]^{25}_D$ +204° (*c* 0.14, MeOH).

(+)-Malekulatine (7): MS, *m/z* (relative intensity) 670 (M^+, 0.1), 669 (0.2), 533 (8.4), 478 (0.1), 192 (100); λ_{max} (MeOH) 211, 230 sh, 284 nm (log ϵ 4.79, 4.50, 4.18); CD $\Delta\epsilon_{nm}$ (MeOH) $+5.8_{282}$, $+26.5_{232}$; $[\alpha]^{25}_D$ +156° (*c* 0.14, MeOH).

(+)-*O,O*-Dimethylvanuatine (8): MS, *m/z* (relative intensity) 698 (M^+, 0.2), 492 (0.5), 206 (100); CD $\Delta\epsilon_{nm}$ $+5.2_{287}$, $+28.4_{235}$; $[\alpha]^{25}_D$ +78° (*c* 0.12, MeOH).

(+)-*O,O,O*-Trimethylvateamine (9): MS, *m/z* (relative intensity) 698 (M^+, 0.1), 492 (0.4), 206 (100); CD $\Delta\epsilon_{nm}$ $+3.2_{284}$, $+11.3_{235}$; $[\alpha]^{25}_D$ +118° (*c* 0.2, MeOH).

(+)-*O,O*-Dimethylmalekulatine (10): MS, *m/z* (relative intensity) 698 (M^+, 0.4), 547 (38), 492 (0.2), 206 (100); CD $\Delta\epsilon_{nm}$ $+3.05_{283}$, $+14.9_{236}$.

(+)-Laudanidine (11): CD $\Delta\epsilon_{nm}$ (MeOH) $+4.5_{288}$, $+9.3_{238}$; $[\alpha]^{25}_D$ +72° (*c* 0.3, MeOH).

(+)-Laudanosine (12): CD $\Delta\epsilon_{nm}$ (MeOH) $+1.2_{286}$, $+3.5_{237}$; $[\alpha]^{25}_D$ +80° (*c* 0.1, MeOH).

Trimethoxytetrahydrobenzylisoquinoline 13: MS, *m/z* (relative intensity) 327 (M^+, $C_{20}H_{25}O_3N$, 0.2), 310 (0.4), 190 (2), 176 (100); CD $\Delta\epsilon_{nm}$ (MeOH) $+0.8_{280}$ $+4.4_{230}$; $[\alpha]^{25}_D$ +70° (*c* 0.1, MeOH).

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Enantioselective Hydrolysis of 3-Hydroxy-3-methylalkanoic Acid Esters with Pig Liver Esterase[1]

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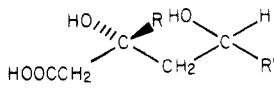
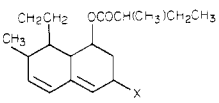
Pig liver esterase has been shown to stereoselectively hydrolyze the *R* enantiomer of several chiral 3-hydroxy-3-methylalkanoic acid esters of the form $RC(Me)(OH)CH_2COOR'$, where R = Et, $CH_2{=}CHCH_2$, $Me(CH_2)_5$, $(MeO)_2CHCH_2$, and $PhCH_2OCH_2CH_2$ and R′ = Me or Et. The unhydrolyzed ester and the reesterified carboxylic acid were analyzed for enantiomeric purity by NMR using the chiral shift reagent $Eu(hfc)_3$. For the compounds studied, the *S* enantiomers consistently showed greater induced shifts. Products of the resolution are potential intermediates in the preparation of compactin analogues having defined stereochemistry at carbon-3. These analogues will be useful in testing the hypothesis that the hypocholesterolemic activity of compactin and its analogues resides in their ability to mimic the binding of mevaldic acid coenzyme A hemithioacetal to HMG-CoA reductase but not be reduced to mevalonate.

During the past several years, a number of 3,5-dihydroxyalkanoic acids have been reported to strongly inhibit the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the key regulated enzyme in sterol biosynthesis. Most notable among these are compactin **1a**)[3,4] and mevinolin (**1b**).[5,6] However, analogues, **2**, of these that have substituted aromatic rings in place of the hexahydronaphthalene of compactin and mevinolin have also proven to be potent HMG-CoA reductase inhibitors.[7] We feel that the ability of 3,5-dihydroxyalkanoic acids to inhibit HMG-CoA reductase resides in their ability to mimic the binding characteristics of either mevaldic acid coenzyme A hemithioacetal, (**3**, (the proposed[8] intermediate in the two-step reduction of HMG-CoA to mevalonic





1, R = H; R′ =
a, X = H;
b, X = CH_3
2a, R = H; R′ = CH_2CH_2Ar;
b, R = CH_3; R′ = CH_2CH_2Ar
3, R = CH_3; R′ = S-CoA

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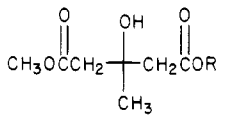
acid) or the transition state leading to it but not be further reduced because they lack the labile hemithioacetal C–S bond that is present in **3**.

To test this hypothesis, we have initiated a synthetic program designed to prepare 3,5-dihydroxyalkanoic acids that mimic the binding characteristics of **3** even more closely than do **1** and **2** but that, like these inhibitors, are unable to undergo a second reduction step because they are secondary alcohols rather than hemithioacetals at carbon five. In view of the observed importance of the carbon three and carbon five stereochemistry on the inhibitory activity for the analogues of **1a** and **1b** that have been prepared,[7] synthesis of specific stereoisomers of our own irreducible analogues of **3** became an important consideration. An attractive method for preparing both enantiomers relative to carbon three involved resolution of a 3-hydroxyalkanoic acid having the appropriate substitution at carbon five for elaboration to the desired inhibitors.

One intriguing approach to such a resolution was suggested by recent reports describing stereoselective hydrolysis of diesters having a prochiral center with pig liver esterase (PLE) to give chiral monoesters.[9] For example, Sih et al. have reported hydrolysis of dimethyl 3-hydroxy-3-methylglutarate (**4**) with PLE to give optically



4, R = CH_3
5, R = H

pure methyl hydrogen (*S*)-3-hydroxy-3-methylglutarate (**5**).[7a] We found that an increase in the buffering capacity of the reaction mixture to maintain the pH between 6.5 and 9 coupled with periodic additions of base and substrate allows this reaction to be scaled up at least 20-fold. Our success in preparing 10–15 g of monoester **5** by a simple, inexpensive procedure using a commercial preparation of PLE encouraged us to study this enzyme's stereoselectivity during the hydrolysis of esters having a chiral center.

We have now shown that PLE will stereoselectively hydrolyze chiral 3-hydroxy-3-methylalkanoic acid esters as well. Some of these resolved substrates may be converted to the desired 3,5-dihydroxyalkanoic acid inhibitors of HMG-CoA reductase much more readily than can monoester **5**. The results of our studies are summarized in Table I.

Alkene ester **6i** (entries 10–13) was chosen as the most promising intermediate for synthesis of mevaldic acid coenzyme A hemithioacetal analogues because of reasonably good stereoselectivity in the hydrolysis, rapid rate of hydrolysis, ease of isolating both the hydrolyzed acid **7i** and the unhydrolyzed **6i**, and relative ease of elaboration to the desired products. Further experiments with **6i** showed that, at an initial concentration of 110 mM, an enantiomeric ratio, *E*,[11] of 4.0 in favor of hydrolyzing the *R* enantiomer is observed (Table I, entry 10). Thus, by allowing the starting ester to undergo extensive hydrolysis, the *S* enantiomer in the racemate can be recovered in good optical purity. (Alternatively, a preparation highly enriched in the *R* enantiomer could reasonably be obtained by successive hydrolyses quenched at 50% completion[12] followed by isolation and reesterification of the *R*-enriched **7i**.)

It is also reasonable that adjustment of certain experimental parameters will provide improved enantioselectivity, a possibility that is being actively expolored. Varying the incubation temperature over the range 20 to 35 °C seemed to have little effect on the preference for hydrolysis of one enantiomer over the other. Changing the incubation pH from 6.0 to 7.0 (Table I, entries 12 and 13) improves the selectivity for hydrolysis of (*R*)-**6i** slightly as *E* increases from 3.9 to 4.4. On the other hand, changing from a methyl to an ethyl ester leads to different observations with different esters. Thus, when the R group is 2,2-dimethoxyethyl (Table I, entries 3 and 4), the *E* value using a methyl ester is 9.0 while an ethyl ester drops *E* to 5.9. However, when the R group on the ester is 2-(benzyloxy)ethyl (entries 6 and 7), using an ethyl ester instead of a methyl ester caused *E* to rise from 2.4 to 6.2. Finally, from the data presently available, it appears that, if R is allyl, the effect of changing from a methyl to an ethyl ester is determined by the conditions under which the enzymatic hydrolysis is performed. (Compare entries 10 and 14 and entries 11 and 15). A number of other parameters including ionic strength, protein concentration, substrate concentration, and use of cosolvents are presently being examined.

The nonpolar substrates **6b**, **6e**, and **6f** (Table I, entries 2, 6, and 7) were hydrolyzed much more slowly than the more polar substrates. The slow rates may be due to a low V_{max}, a high K_m,[13] or poor solubility. Preliminary attempts to improve the rate of reaction by addition of cosolvents[14] to the reaction mixture met with little success. Stereoselective hydrolysis of the readily accessible benzyl ether esters of mevalonic acid **6e** and **6f** can be performed successfully by using a high enzyme/substrate ratio, but use of this method as a practical source of multigram quantities of (*R*)- and (*S*)-mevalonolactones requires further development.

Substrate **6g**, ethyl mevalonate (Table I, entry 8), appeared to offer the optimal precursor to optically active mevalonolactone. However, the mevalonolactone recovered from an enzymatic hydrolysis allowed to proceed to 53% completion was found to be essentially racemic. The low selectivity appears to stem from a rapid, nonenzymatic hydrolysis that competes with the PLE-catalyzed reaction. This nonenzymatic hydrolysis was readily observed as a rapid pH drop when the reaction conditions were duplicated but the PLE was omitted. A further problem arises upon attempted extraction of unhydrolyzed (*S*)-**6g** from the PLE reaction mixture, for the substrate ester is sufficiently water soluble that continuous extraction methods must be used. During this lengthy procedure much of the ethyl (*S*)-mevalonate present is lost to the nonenzymatic hydrolysis, which, of course, significantly reduces the op-

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Table I. Hydrolysis of $RC(CH_3)(OH)CH_2COOR'$ by Pig Liver Esterase

entry	R	R′	method (pH)[a]	fraction of racemate hydrolyzed[b]	time of reaction	recovered ester[c]	recovery[d]	ee(*S*)[e]	recovered acid[c]	recovery[d]	ee(P)[e]	*E*[f]
1	CH_3CH_2	Me	A	0.88	3 days	**(S)-6a**	12%	>98%	**(R)-7a**	51%	13%	≥4.1
2	$CH_3(CH_2)_5$	Me	A	0.36	3 days	**(S)-6b**	41%	26%	**(R)-7b**	22%	47%	3.5
3	$(CH_3O)_2CHCH_2$	Me	A	0.67	1 day	**(S)-6c**	26%	94%	**(R)-7c**	45%	47%	9.0
4	$(CH_3O)_2CHCH_2$	Et	A	0.75	3 days	**(S)-6d**	22%	94%	**(R)-7d**	*g*	32%	5.9
5	$(CH_3O)_2CHCH_2$	Et	B (6.9)	0.50	3 h	**(S)-6d**	48%	44%	*h*	*i*	*i*	3.9
6	$PhCH_2OCH_2CH_2$	Me	A	0.40	3 days	**(S)-6e**	31%	22%	**(R)-7e**	32%	33%	2.4
7	$PhCH_2OCH_2CH_2$	Et	A	0.52	3 days	**(S)-6f**	40%	60%	**(R)-7f**	44%	55%	6.2
8	$HOCH_2CH_2$	Et	A	0.53[j]	3.4 h	**6g**	*i*	*i*	*k*	*i*	*k*	
9	$EtOC(O)OCH_2CH_2$	Et	A	0.44[m]	1.33 h	**6h**	56%	*i*	*n*	15%	~0%[p]	
10	$CH_2=CHCH_2$	Me	A	0.84	4.75 h	**(S)-6i**	11%	94%	**7i**	75%	*i*	4.0
11	$CH_2=CHCH_2$	Me	B (7.0)	0.51	0.75 h	**(S)-6i**	44%	49%	**(R)-7i**	43%	48%	4.5
12[q]	$CH_2=CHCH_2$	Me	B (7.0)	0.51	0.67-0.83 h	**(S)-6i**	40%	48%	**(R)-7i**	45%	47%	4.4
13[r]	$CH_2=CHCH_2$	Me	B (6.0)	0.50	1 h	**(S)-6i**	46%	44%	**7i**	47%	44%	3.9
14	$CH_2=CHCH_2$	Et	A	0.50	2.25 h	**(S)-6j**	51%	50%	*i*	*i*	*i*	4.8
15	$CH_2=CHCH_2$	Et	B (7.0)	0.49	1 h	**(S)-6j**	44%	37%	**(R)-7j**	45%	38%	3.1

[a] Method A: The hydrolysis was carried out using 1.0 M phosphate as described in the Experimental Section. Method B: The hydrolysis was carried out at the indicated pH using a pH stat/autotitrator instead of a buffer. [b] Calculated from the ee values of hydrolyzed and unhydrolyzed material according to the formula:[10] fraction of racemate hydrolyzed = ee(ester)/[ee(ester) + ee(acid)] = ee(*S*)/[ee(*S*) + ee(P)]. These values are consistent with values estimated from pH drop (method A) or amount of base added by the autotitrator (method B). The latter estimates were used in cases where both enantiomers were not isolated. [c] With the exception of **6a, 6c, 6d, 6i,** and **7f,** the stereochemical assignments for the products are based on the assumption that the *R* enantiomer is preferentially hydrolyzed by PLE in each case. The stereochemical assignment for **6a** is based on its known behavior in the presence of $Eu(hfc)_3$ as described in a personal communication from Prof. W. Kirmse. The stereochemistry of **6c, 6d, 6i,** and **7f** were determined by conversion to mevalonolactone as described elsewhere in this report. [d] Based on the total amount of racemic ester added. Maximum recovery of a pure enantiomer is 50%. [e] The enantiomeric excess, ee(*S*), for unhydrolyzed substrate ester was determined by proton NMR in the presence of the chiral lanthanide shift reagent $Eu(hfc)_3$. The enantiomeric excess, ee(P), for the carboxylic acid hydrolysis product was determined by NMR analysis of the corresponding methyl ester in the presence of $Eu(hfc)_3$. The required methyl esters were prepared by treating the corresponding acid withdiazomethane except that **7c** and **7d** were re-esterified as the carboxylate salt using dimethyl sulfate. [f] This enantiomeric ratio is calculated from the equation $E = \ln [(1 - c)(1 - ee(S)]/\ln [(1 - c)(1 + ee(S)]$ and provides a measure of the enzyme's ability to discriminate between the two enantiomers of the substrate.[11] The value of *c* for each entry is taken directly from the fifth column of the table; the fraction of racemate hydrolyzed. The value of ee(*S*), the enantiomeric excess of unhydrolyzed substrate ester, is taken from the ninth column of the table. (We thank one of the reviewers for suggesting this valuable method for comparing the selectivity of the enzyme under various conditions.) [g] Methyl ester recovered in low yield by methylation of **7e** anion with dimethyl sulfate in aqueous solution. [h] Not recovered. [i] Not determined. [j] Determined by titration to the starting pH with 0.074 N NaOH. [k] Isolated as mevalonolactone by continuous extraction from aqueous acid solution. Racemic by both polarimetry and NMR analysis. [m] Based on recovered diester. [n] Only hydrolysis product isolated was 15% yield of racemic mevalonolactone. Small amounts of ethyl mevalonate were also detected but no 5-((ethoxycarbonyl)oxy)-3-hydroxy-3-methylpentanoic acid. [p] Determined by polarimetry. [q] Average from five experiments. [r] Average from two experiments.

tical purity of the (*R*)-mevalonate (**7g**) as well as severely limiting the recovery of unhydrolyzed (*S*)-**6g**.

Since the nonenzymatic hydrolysis was only a problem when a 5-hydroxyl group was present and the potential mevalonolctone precursors **6e** and **6f** were not readily hydrolyzed by the enzyme, an alternate substrate was examined. Treatment of the ethyl mevalonate with ethyl chloroformate in pyridine solution converted it to **6h**, ethyl 5-((ethoxycarbonyl)oxy)-3-hydroxy-3-methylpentanoate (Table I, entry 9). It was hoped that the PLE would hydrolyze only one ester in each molecule of this substrate, as has been reported[9] when achiral diesters are used. If this expectation were realized, the *R* enantiomer of **6h** should be hydrolyzed to (*R*)-5-((ethoxycarbonyl)oxy)-3-hydroxy-3-methylpentanoic acid ((*R*)-**7h**) while the *S* enantiomer should provide ethyl (*S*)-mevalonate, **6g**, or (*S*)-mevalonolactone. Unfortunately, all PLE-catalyzed hydrolyses of **6h** attempted to date have led only to recovery of low yields of racemic mevalonolactone and unhydrolized **6h**.

To determine which enantiomer of esters **6** was preferentially hydrolyzed by PLE, the unhydrolyzed ester fraction of three of the substrates, **6c**, **6d**, and **6i**, was converted to the known (*S*)-mevalonolactone.[15] In the case of **6c** or **6d**, the acetal was hydrolyzed with dilute aqueous acid and the resulting aldehyde reduced with borane methyl sulfide.[16] Cyclization to (*S*)-mevalonolactone was effected with dilute acid. The alkene in **6i** was cleaved by ozonization followed by workup with sodium borohydride.[17] Treatment with acid gave a low yield of (*S*)-mevalonolactone. The acid **7f** was readily converted to (*R*)-mevalonolactone by hydrogenolysis of the benzyl ether. The configuration of the mevalonolactone prepared in each case could be determined unambiguously by a chiral lanthanide shift reagent technique.[18]

Analysis of all compounds (except the monoester **5**) for enantiomeric purity was performed by FT-NMR using the chiral lanthanide shift reagent method,[19] which we have found to be reliable, reproducible, and simple to carry out. The sensitivity and resolution obtained usually permitted detection of as little as 2% of the minor enantiomer in a 10-mg sample after only 35 pulses. Generally, the absorption assigned to the protons of the 3-methyl group in each ester gave the largest induced shifts and the greatest enantiomeric shift differences, although for acetal esters **6c** and **6d**, the methoxy peaks provided multiple baseline-resolved peaks for estimating the enantiomeric excess. The results of these experiments are summarized in Table II.

It is significant that, for those cases where the absolute configuration of the enantiomer which was preferentially hydrolyzed could be determined (vide supra), the 3-methyl resonance for the *S* enantiomer consistently showed a greater induced shift in the presence of the chiral shift reagent than that for the *R* enantiomer. This observation suggests that the absolute configurations of an enantiomeric pair of 3-hydroxy-3-methylalkanoic acid esters having a variety of functional groups at carbon-5-can be distinguished by NMR in the presence of a chiral shift reagent.

Prior to analysis, the 3-hydroxy-3-methylalkanoic acids **7** were reesterified. Diazomethane was used in the case of **7a,b,e,f,i**. However, acidification of the aqueous phase containing the salt of **7c** or **7d** led to formation of a mixture of products, presumably including the corresponding δ-lactol methyl ether. Methylation was, therefore, performed directly on the salt with dimethyl sulfate, using, in the case of **7c**, a two-phase system (water/dichloromethane) with Adogen 464 as a phase transfer catalyst. (Preliminary results suggest this may be a useful general procedure for preparing methyl esters of acid-sensitive carboxylates. Further experiments are under way to confirm these observations.)

Table II. Assignments of Chiral Shift Reagent Spectra

ester	$Eu(hfc)_3$[a]	δ *S*[b]	δ *R*[b]	assignment
6a	0.61	4.36[c]	4.26[c]	OMe
6b	0.66	4.45[d]	4.32[d]	OMe[e]
6c	1.1[f]	4.43	4.34	OMe (ester)[e]
		4.09	4.16	OMe (acetal)
		3.78	3.88	OMe (acetal)
6d	0.15	4.50	4.09	3-Me
6e	0.22	3.49[g]	3.27[g]	3-Me
6f	0.23	2.40	2.27	3-Me
6g	0.90	5.76[h]	5.65[h]	3-Me
6i	0.40	5.19[i]	5.01[i]	3-Me

[a] Approximate molar equivalents of $Eu(hfc)_3$ per equivalent of ester. Since this parameter is rather susceptible to impurities in the ester or shift reagent as well as traces of water and hydroxylic solvents, the chemical shifts δ *S* and δ *R* are approximate. [b] Chemical shift expressed in ppm downfield from Me_4Si. [c] Assignments kindly provided by Dr. W. Kirmse in a personal communication. See also ref 21. [d] Assuming the *R* enantiomer is preferentially hydrolyzed by PLE. [e] The 3-methyl peak of the *S* enantiomer is also downfield of the corresponding (*R*)-enantiomer peak. [f] $Eu(tfc)_3$. [g] T_1(inversion recovery) of 0.5 s and 0.6 s measured for resonances at 3.49 and 3.27, respectively. [h] Determined using racemic **6g**. Assumes that the absorption due to the *S* enantiomer is downfield of that for the *R* enantiomer, which is questionable due to the stronger binding to the shift reagent which should occur when there is a free hydroxyl at carbon-5. [i] T_1(inversion recovery) of 0.4 s measured for resonances at 5.19 and 5.01.

In contrast to reports in the literature that PLE selectivity in the hydrolysis of racemic mixtures of chiral esters is low[20] or nonexistent,[21] we have found that PLE exhibits significant stereoselectivity for most esters studied. The highest selectivity was observed for the acetal methyl ester **6c**. Conversion of four compounds resolved by PLE (**6c**, **6d**, **6i**, and **7f**) to mevalonolactone shows that, for the examples studied, PLE preferentially hydrolyzes the esters of the *R* configuration.

Experimental Section

Proton (^1H) and carbon (^{13}C) nuclear magnetic resonance (NMR) spectra were obtained as $CDCl_3$ solutions on a Varian FT-80A spectrometer. The proton spectra for pure samples were obtained by using the $^{13}C/^1H$ switchable probe with an 8-s acquisition time. Proton spectra recorded in the presence of shift reagent were obtained using the 80-MHz (^1H) receiver coil with an acquisition time of 4 s and a pulse delay of 1 s, parameters we have shown to be adequate to provide a relaxation time of $5T_1$. All proton absorptions are reported as ppm (δ) downfield from internal Me_4Si. The ^{13}C NMR absorptions are reported with respect to Me_4Si as determined from $CDCl_3$ by assuming a chemical shift of 76.9 ppm for deuteriochloroform. The pig liver esterase hydrolyses were monitored by using a Radiometer Titrigraph pH stat fitted with Radiometer pH Meter 28, Radiometer Titrator 11, and Radiometer SBUla syringe buret fitted with a

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5-mL Precision Sampling Pressure Lok syringe. Elemental anaylses were performed by Ruby Ju of the University of New Mexico, Department of Chemistry.

Pig liver esterase (Type I) was purchased (Sigma) as a suspension in 3.2 M $(NH_4)_2SO_4$ solution adjusted to pH 8 and was used as received. 4-(Benzyloxy)-2-butanone (Fluka) was used as received. All other reagents were purchased from Aldrich, Eastman, or Fisher and were the best grade available. Butyllithium was titrated prior to use. Isopropylcyclohexylamine and acetylacetaldehyde dimethyl acetal (both Aldrich) were distilled before using.

Synthesis of Methyl and Ethyl 3-Hydroxy-3-methylalkanoates. The procedure used parallels that of Rathke and Sullivan[22] with some modifications in the workup. To a solution of 14.8 g (0.105 mol) of *N*-isopropylcyclohexylamine in 100 mL of anhydrous THF at −75 °C was added 66.6 mL (0.100 mol) of a 1.5 M solution of butyllithium in hexanes. After several minutes, 0.100 mol of ethyl or methyl acetate in 80 mL THF was added dropwise at a rate that permitted the temperature to remain below −70 °C. After stirring for 15 min following the ester addition, 0.100 mol of an appropriate methyl ketone in 10 mL THF was slowly added to the ethyl or methyl lithioacetate solution at −75 °C. The mixture was then stirred for 0.5 h at −75 °C and poured into 300 mL of saturated NH_4Cl at −10 °C with stirring to hydrolyze the alkoxide. The phases were separated, and the aqueous phase was extracted with 5 to 8 × 30 mL of ether. The combined organic phases were washed with 4 × 50 mL of saturated NH_4Cl to remove the amine, 50 mL of $NaHCO_3$, and 50 mL of saturated brine, then dried over $MgSO_4$, and filtered, and the solvent was removed to provide the oily products. Distillation of each hydroxy ester was performed in vacuo as indicated below.

Methyl 3-hydroxy-3-methylpentanoate (6a):[23] ^{1}H NMR δ 3.75 (s, 3 H, OCH_3), 3.35 (s, 1 H, OH), 2.50 (s, 2 H, $(CCH_2C{=}O)$), 1.55 (crude q, CH_3CH_2C), 1.22 (s, 3 H, CCH_3), 0.93 (t, 3 H, CH_2CH_2); ^{13}C NMR δ_c 172.2 (C=O), 70.3 (C_3COH), 50.5 (OCH_3), 43.9 ($CH_2C{=}O$), 33.9 (CCH_2COH), 25.3 (CH_3COH), 7.3 (CH_3CH_2).

Methyl 3-hydroxy-3-methylnonanoate (6b):[24] bp 67–72 °C (0.01 mm); 47% yield; ^{1}H NMR δ 3.70 (s, 3 H, OCH_3), 3.5 (s, 1 H, OH), 2.47 (s, 2 H, $CCH_2C{=}O$), 1.1–1.8 (m, 10 H, $(CH_2)_5$), 0.88 (crude t, 3 H, CH_3CH_2); ^{13}C NMR δ_c 172.7 (C=O), 70.6 (C_3COH), 50.9 (OCH_3), 44.6 ($CH_2C{=}O$), 41.8 (CH_2CH_2COH), 31.4, 29.4, 26.3, 23.5, 22.2 ($(CH_2)_4$ and CH_3COH), 13.6 (CH_3CH_2).

Methyl 3-hydroxy-5,5-dimethoxy-3-methylpentanoate (6c):[25] bp 81–86 °C (0.005 mm); 49% yield; ^{1}H NMR δ 4.60 (t, J = 5.5 Hz, 1 H, $(MeO)_2CH$), 3.9 (s, 1 H, OH), 3.67 (s, 3 H, $COOCH_3$), 3.30 (s, 6 H, $(CH_3O)_2CH$), 2.52 (s, 2 H, $CCH_2C{=}O$), 1.87 (d, J = 5.5 Hz, 2 H, $CHCH_2$), 1.27 (s, 3 H, CH_3COH); ^{13}C NMR δ_c 171.6 (C=O), 101.6 ($(MeO)_2CH$), 68.7 (C_3COH), 52.0 and 51.9 ($(CH_3O)_2CH$), 50.5 ($COOCH_3$), 44.8 ($CH_2C{=}O$), 42.6 ($CHCH_2COH$), 26.9 (CH_3COH).

Ethyl 3-hydroxy-5,5-dimethoxy-3-methylpentanoate (6d):[26] bp 85 °C (0.05 mm); 58% yield; ^{1}H NMR δ 4.65 (t, J = 5.5 Hz, 1 H $(MeO)_2CH$), 4.2 (q, J = 7 Hz, 2 H, OCH_2CH_3), 4.0 (s, 1 H, OH) 3.36 (s, 6 H, $(CH_3O)_2CH$), 2.53 (s, 2 H, $CCH_2C{=}O$), 1.92 (d, J = 5.5 Hz, 2 H, $CHCH_2$), 1.30 (s, 3 H, CH_3COH), 1.28 (t, J = 7 Hz, 3 H, OCH_2CH_3); ^{13}C NMR δ_c 171.8 (C=O), 101.9 ($(MeO)_2CH$), 69.1 (C_3COH), 60.0 (OCH_2CH_3), 52.5 ($(CH_3O)_2CH$), 45.2 ($CH_2C{=}O$), 42.8 ($CHCH_2COH$), 27.3 (CH_3COH) 13.8 (OCH_2CH_3).

Methyl 5-(benzyloxy)-3-hydroxy-3-methylpentanoate (6e): bp 112 °C (0.02 mm); 78% yield; ^{1}H NMR δ 7.24 (s, 5 H, C_6H_5), 4.44 (s, 2 H, $PhCH_2O$), 3.9 (s, 1 H, OH) 3.63 (t, J = 6 Hz, 2 H, OCH_2CH_2C), 3.58 (s, 3 H, OCH_3), 2.51 (s, 2 H, $CCH_2C{=}O$), 1.89 (t, J = 6 Hz, 2 H, OCH_2CH_2C) 1.25 (s, 3 H, CH_3COH); ^{13}C NMR δ_c 172.0 (C=O), 137.9, 128.2 and 127.7 (C_6H_5), 72.9 ($PhCH_2O$), 70.2 (C_3COH), 66.6 (OCH_2CH_2C), 51.0 (OCH_3), 45.2 ($CCH_2C{=}O$), 40.3 (OCH_2CH_2C), 26.9 (CH_3COH).

Anal. Calcd for $C_{14}H_{20}O_4$: 66.64; H, 7.99. Found: C, 66.84; H, 8.08.

Ethyl 5-(benzyloxy)-3-hydroxy-3-methylpentanoate (6f):[27] bp 125–132 °C (0.05 mm); 78% yield; ^{1}H NMR δ 7.43 (br s, 5 H, C_6H_5), 4.60 (s, 2 H, $PhCH_2O$), 4.26 (q, J = 7 Hz, 2 H, OCH_2CH_3), 4.1 (s, 1 H, OH), 3.80 (t, J = 6 Hz, 2 H, OCH_2CH_2C), 2.68 (s, 2 H, $CCH_2C{=}O$), 2.03 (t, J =6 Hz, 2 H, OCH_2CH_2C), 1.26 (s, 3 H, CH_3COH), 1.22 (t, J = 7 Hz, 3 H, OCH_2CH_3); ^{13}C NMR δ_c 171.5 (C=O), 137.7, 127.7, and 126.9 (C_6H_5), 72.5 ($PhCH_2O$), 70.0 (C_3COH), 66.3 (OCH_2CH_2C), 59.6 (OCH_2CH_3), 45.2 ($CCH_2C{=}O$), 40.1 (OCH_2CH_2C), 26.7 (CH_3COH), 13.5 (OCH_2CH_3).

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.83; H, 8.22.

Ethyl 3,5-Dihydroxy-3-methylpentanoate (Ethyl Mevalonate) (6g). To a solution of 1.33 g (5 mmol) of ethyl 5-(benzyloxy)-3-hydroxy-3-methylpentanoate (**6f**) in 50 mL of 95% ethanol was added 0.25 g of 10% Pd on powdered charcoal (Sargent) and the mixture hydrogenated on the Parr apparatus at 3.3 atm H_2 pressure for 20 hr. The catalyst was removed by filtration through a glass frit and the solvent removed on the rotary evaporator to give 0.85 g (96% yield) of a yellow oil. [Using larger amounts (10-fold) of certain lots of the catalyst was found to cause partial or complete conversion of the ethyl mevalonate to mevalonolactone.] ^{1}H NMR δ 4.20 (q, J = 7 Hz, 2 H, OCH_2CH_3), 3.86 (t, J = 6 Hz, 2 H, OCH_2CH_2C) 3.85 (s, 2 H, 2 OH), 2.57 (s, 2 H, $CCH_2C{=}O$), 1.82 (t, J = 6 Hz, 2 H, OCH_2CH_2C), 1.33 (s, 3 H, CH_3COH), 1.28 (t, J = 7 Hz, 3 H, OCH_2CH_3); ^{13}C NMR δ_c 171.3 (C=O), 70.7 (C_3COH) 59.7 (OCH_2CH_3), 58.0 (OCH_2CH_2C), 45.2 ($CCH_2C{=}O$), 41.8 (OCH_2CH_2C), 26.3 (CH_3COH), 13.3 (OCH_2CH_3).

Anal. Calcd for $C_8H_{16}O_4$: C, 54.53; H, 9.15. Found: C, 54.70; H, 8.99.

Ethyl 5-((Ethoxycarbonyl)oxy)-3-hydroxy-3-methylpentanoate (6h). To a solution of 1.76 g (10 mmol) of ethyl mevalonate, **6g**, in 10 mL of dry pyridine was added dropwise with stirring 2.90 g (27 mmol) of ethyl chloroformate. The reaction temperature was maintained near 25 °C using a water bath. After addition, the mixture was allowed to stir overnight during which time it separated into two phases. After filtering, the filtrate was poured into 300 mL of saturated NH_4Cl and stirred for 0.25 h. The aqueous solution was extracted with 3 × 50 mL ether and the combined organic phases were washed twice with 25 mL of NH_4Cl solution and twice with 25 mL of saturated brine. After drying over $MgSO_4$, the solvent was removed to give 1.78 g (72%) of an oil having a bp 87–92 °C (0.01 mm); ^{1}H NMR δ 4.2 (2q) and 4.1 (t, J = 7 Hz, 6 H combined, $CH_3CH_2OC(C{=}O)OCH_2$ + $(C{=}O)OCH_2CH_3$), 3.73 (s, 1 H, OH), 2.52 (s, 2 H, $CCH_2C{=}O$), 1.92 (t, J = 7 Hz, 2 H, OCH_2CH_2C), 1.27 (s and t, J = 7 Hz, 9 H total, 2 CH_3CH_2O and CH_3COH); ^{13}C NMR δ_c 171.3 ($CH_2C(O)OCH_2$), 154.3 ($OC(O)O$), 69.0 (C_3COH), 63.4 and 62.9 ($CH_2OC(O)OCH_2$), 59.7 ($CC(O)OCH_2CH_3$), 44.9 ($CCH_2C{=}O$), 39.4 (OCH_2CH_2C), 26.4 (CH_3COH), 13.3 (2 OCH_2CH_3).

Anal. Calcd for $C_{11}H_{20}O_6$: C, 53.20; H, 8.12. Found: C, 53.38; H, 8.29.

3-Hydroxy-3-methyl-5-hexenoic Acid (7i). *tert*-Butyl 3-hydroxy-3-methyl-5-hexenoate was prepared in 82% yield according to Tschesche and Machleidt[28] except that granular zinc was substituted for the turnings specified in that procedure. (Attempts to use mossy zinc gave only low yields of the desired product.) ^{1}H NMR δ 5.5–6.1 (m 1 H, $CH_2{=}CH$), 5.1 and 4.8–5.0 (finely split s and m, 2 H, $CH_2{=}CH$), 3.8 (s, 1 H, OH), 2.36 (s, 2 H, $CCH_2C{=}O$ 2.35 (d, J = 5 Hz, 2 H, $=CHCH_2$) 1.5 (s, 9 H, $C(CH_3)_3$), 1.2 (s, 3 H, CH_3COH); ^{13}C NMR δ_c 171.7 (C=O), 133.7 ($CH_2{=}CH$), 117.6 ($CH_2{=}CH$), 80.6 ($C(CH_3)_3$), 70.4 (C_3COH), 46.2 ($=CHCH_2C$) and 45.3 ($CCH_2C{=}O$), 27.7 ($C(CH_3)_3$), 26.4 (CH_3COH). Alkaline hydrolysis of the *tert*-butyl ester as described

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(23) Kirmse, W.; Rauleder, G. *Liebigs Ann. Chem.* **1976** 1333–1342. (These workers have synthesized the racemic ester using the Reformatsky reaction.)

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by Tschesche and Machleidt[28] provided 3-hydroxy-3-methyl-5-hexenoic acid (**7i**) in 93% yield: ^{1}H NMR δ 6.9 (s, 2 H, OH, COOH), 5.5–6.2 (m, 1 H, CH_2=C*H*), 5.2 and 4.9–5.1 (s and m, 2 H, CH_2=CH), 2.5 (s, 2 H, CCH_2C), 2.35 (d, J = 6.5 Hz, 2 H, =CHCH_2), 1.3 (s, 3 H, CH_3); ^{13}C NMR δ_c 176.9 (C=O), 133.4 (CH_2=CH), 119.3 (CH_2=CH), 71.6 (C_3COH), 46.6 (=CHCH_2C), and 44.6 (CH_2CO_2), 26.9 (CH_3COH).

Methyl 3-Hydroxy-3-methyl-5-hexenoate (6i). 3-Hydroxy-3-methyl-5-hexenoic acid (52 g, 0.36 mmol) was dissolved in 1.3 L of absolute methanol and 35.6 mL of concentrated H_2SO_4 added dropwise with stirring. The reaction mixture was allowed to stand for 48 h and then a solution of 30 g of sodium carbonate in 200 mL of water was added slowly. Additional solid carbonate was added with vigorous stirring until the pH stabilized at 7. (Excess carbonate was found to cause hydrolysis of the ester.) The volume of the neutral solution was reduced to approximately 0.5 L on the rotary evaporator then 0.5 L of saturated brine added. The resulting mixture was extracted with 5 × 100 mL of ether. The combined extracts were washed with brine and dried over $MgSO_4$, and the solvent was evaporated. Distillation in vacuo provided 33 g (58%) of an oil having bp 75–80 °C (0.01 mm): ^{1}H NMR δ 5.55–6.15 (m, 1 H, CH_2=C*H*), 5.15 and 4.95–5.1 (finely split s and finely split m, 2 H, CH_2=CH), 4.0 (br s, 1 H, OH), 3.70 (s, 3 H, OCH_3), 2.5 (finely split s, 2 H, CCH_2C=O), 2.30 (br d, J = 7.2 Hz, 2 H, =CHCH_2), 1.25 (s, 3 H, CH_3COH); ^{13}C NMR δ_c 172.3 (C=O), 133.7 (CH_2=*CH*), 117.7 (CH_2=CH), 70.3 (C_3COH), 50.9 (OCH_3), 46.2 (=CHCH_2C) and 44.4 (CH_2C=O), 26.4 (CH_3COH).

Anal. Calcd for $C_8H_{14}O_3$: C, 60.73; H, 8.93. Found: C, 60.83; H, 8.94.

Ethyl 3-Hydroxy-3-methyl-5-hexenoate (6j). In a manner similar to that described for **6i**, **6j** was prepared in 50% yield from 15 g of 3-hydroxy-3-methyl-5-hexenoic acid, 500 mL of absolute ethanol, and 10 g of H_2SO_4: bp 52–55 °C (0.07 mm); ^{1}H NMR δ 5.6–6.2 (m, 1 H, CH_2=C*H*), 5.2 and 4.9–5.1 (finely split s and finely split m, 2 H, CH_2=CH), 4.19 (q, J = 7 Hz, 2 H, OCH_2CH_3), 3.7 (s, 1 H, OH), 2.48 (s, 2 H, CCH_2C=O), 2.30 (d, J = 7 Hz, 2 H, =CHCH_2C) 1.26 (t, J = 7 Hz, 3 H, OCH_2CH_3), 1.23 (s, 3 H, CH_3COH); ^{13}C NMR δ_c 172.3 (C=O), 133.6 (CH_2=CH), 117.9 (CH_2=CH), 70.4 (C_3COH), 60.1 (OCH_2CH_3), 46.3 (=CHCH_2C), 44.4 (CH_2C=O), 26.6 (CH_3COH), 13.8 (OCH_2CH_3).

Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.74; H, 9.51.

Hydrolysis of 3-Hydroxy-3-methylalkanoic Acid Methyl and Ethyl Esters with Pig Liver Esterase in Phosphate Buffer (Method A). Phosphate buffer was prepared by dissolving 3.48 g (20.0 mmol) of K_2HPO_4 in 20 mL of distilled water to give a solution having pH 8.9–9.0. To this buffer was added one vial (10 mg) of pig liver esterase to give a solution having pH 8.6–8.7. The substrate (10 mmol) was then added and the pH and time were recorded. The hydrolysis was allowed to progress until the pH had dropped to 7.2, corresponding to consumption of approximately 50% of the starting ester. The pH was then adjusted to 8.0 with 1 N NaOH and the aqueous solution extracted with 3 × 50 mL of ether. (Alternatively, the aqueous solution has been extracted continuously with CH_2Cl_2 for 24 h.) The organic phase was then dried over $MgSO_4$ and filtered, and the solvent was evaporated to provide the unhydrolyzed ester fraction, which may be analyzed for enantiomeric purity without further purification. The aqueous phase was acidified to pH 2 with 1 N H_2SO_4 than again extracted with 3 × 50 mL ether (or continuously with CH_2Cl_2 for 24 h). The organic phase was dried over $MgSO_4$ and filtered, and the solvent evaporated to provide the hydrolyzed ester fraction as the carboxylic acid. (The acetal acid, **7c** or **7d**, is unstable so is handled as discussed below.) The recovered acid was esterified with diazomethane in the usual way prior to analysis for enantiomeric purity.

Hydrolysis of 3-Hydroxy-3-methylalkanoic Acid Methyl and Ethyl Esters with Pig Liver Esterase Using the pH Stat (Method B). A reaction vessel designed to hold a pH electrode and an appropriate reaction volume was placed in a thermostated (±0.5 °C) bath and charged with 16.0 mL of distilled water. When the desired reaction temperature was reached, 400 μL of the pig liver esterase solution (see method A) was added. The calibrated syringe buret was filled with 0.547 N sodium hydroxide solution and the delivery tube placed in the reaction vessel. The pH of the reaction mixture was then manually adjusted to no less than 0.3 pH unit below the desired reaction pH, 1.50 mmol of the desired 3-hydroxy-3-methylalkanoic acid ester added, and the automatic titrator turned on. The reaction was allowed to proceed at constant pH until the desired extent of hydrolysis, as determined by the volume of standard based added, had been achieved. The reaction was then quenched by raising the pH above 9.5 with the NaOH solution. The alkaline solution was extracted once with 50 mL of ether and then the aqueous layer was saturated with NaCl and extracted with 4 × 50 mL of ether. (Saturating with salt prior to the first extraction leads to a more severe emulsion apparently from denaturation of the enzyme.) The combined ether extracts were decanted from any residual water, dried over $MgSO_4$ and the ether was removed on the rotary evaporator to give the unhydrolyzed ester fraction. The aqueous phase was adjusted to pH 1 with 6 N HCl or H_2SO_4 and then extracted with 5 × 50 mL of ether. The combined extracts were decanted away from residual water and the volume was reduced to approximately 100 mL. The ether solution of the carboxylic acid product was then treated with an ether solution of diazomethane until a permanent yellow color was observed. The color was discharged with acetic acid, the ether solution washed once with 50 mL of saturated brine and dried over $MgSO_4$, and the solvent evaporated to give the methyl ester of the acid formed in the enzymatic hydrolysis.

Esterification of 3-Hydroxy-5,5-dimethoxy-3-methylpentanoic Acid, Sodium Salt (Anion of 7c). A solution of the sodium salt of the acetal acid **7c** was obtained from pig liver esterase hydrolysis of 2.06 g of acetal ester **6c** followed by adjusting the pH to 8.0 and extracting with ether to remove unhydrolyzed ester. On the basis of the amount of unreacted ester recovered, it was estimated that the aqueous solution contained at most 1.4 g of the sodium salt of **7c**. To this aqueous phase was added 1.74 g (10 mmol) of K_2HPO_4, 50 mL of chloroform, 0.16 g of Adogen 464, and 1.47 g (12 mmol) of dimethyl sulfate. The two-phase mixture was stirred vigorously for 2 h at room temperature. The organic phase was removed, and the aqueous phase was extracted with 3 × 50 mL of ether. The combined organic phases were dried ($MgSO_4$) and evaporated to a yellow oil containing Adogen. This oil was introduced onto a chromatography column containing 5 g of silica gel and was eluted with 10 mL of ethyl acetate. The eluant was evaporated to 1.10 g of oil, which was analyzed by ^{1}H NMR and found to contain 0.5 g of acetal ester (*R*)-**6c** and 0.6 g of dimethyl sulfate. (The dimethyl sulfate did not interfere with the NMR analysis for enantiomeric purity.)

Conversion of Methyl (*S*)-3-Hydroxy-5,5-dimethoxy-3-methylpentanoate (6c) to (*S*)-Mevalonolactone. To 5.5 mL of *p*-dioxane was added 0.50 g (2.4 mmol) of (*S*)-**6c** having ≥96% ee of the *S* enantiomer and 18.5 mL of 0.1 N H_2SO_4. The mixture was stirred in a nitrogen atmosphere at ambient temperature for 4 h, then was saturated with salt, and was extracted with 4 × 25 mL of ether. The combined ether extracts were back extracted with 2 × 25 mL of saturated brine and dried over $MgSO_4$ and the solvent was evaporated to give 0.25 g (65% yield) of methyl 3-hydroxy-3-methyl-5-oxopentanoate as a colorless oil. The crude oil was dissolved in 20 mL of dry THF, and the 0.4 mL (0.8 mmol) of 2 M borane methyl sulfide in THF was added dropwise. After stirring for 24 h at ambient temperature, 3 mL of methanol was added dropwise to the reaction mixture. The solvents, methanol and trimethyl borate, which formed were evaporated on the rotary evaporator. The methanol addition/evaporation treatment was repeated with 3 × 2 mL of methanol and then the residual oil was dissolved in 8.0 mL of 0.05 N H_2SO_4 and allowed to stir for 2 h. The aqueous solution was continuously extracted with dichloromethane for 24 h, then the extract dried, and the solvent removed to give 0.04 g (13% based on the acetal) of mevalonolactone having ≥89% ee of the *S* enantiomer as determined by NMR in the presence of Eu(hfc).[18]

3-Hydroxy-3-methylpentanedioic Acid Monomethyl Ester. A suspension of 10 mg (1200 units) of pig liver esterase in 1 mL of 3.2 M ammonium sulfate buffer (pH 8) was added to 20 mL of 1.0 M potassium phosphate buffer (pH 8.8). To this solution was added 2.50 g (1.3 mmol) of dimethyl 3-hydroxy-3-methylpentanedioate (**4**). The resulting cloudy solution was stirred at 25 °C, and the pH was monitored periodically. After 2.5 h the pH had dropped to 6.9. The pH was raised to 8.5 by addition

of 1 N NaOH, and an additional 3.00 g (1.6 mmol) of 4 was added to the reaction mixture. After 7 h, the pH had dropped to 5.9. The pH was raised to 8.5 and an additional 2.50 g (1.3 mmol) of 4 was added. After 11 h, the pH had dropped to 6.1, the pH was raised to 8.5, and another 2.50 g (1.3 mmol) of 4 was added. After 5 h the pH had dropped to 6.7, the pH was raised to 8.5, and another 2.5 g (1.3 mmol) of 4 was added. After 8 h, the pH had dropped to 6.4, the pH was raised to 8.5, and another 2.0 g (1.1 mmol) of 4 was added. After 60 h, the pH had dropped to 6.2. The pH was raised to 7.8 and the solution was extracted with three 30-mL portions of ether to remove unhydrolyzed diester. The organic layers were discarded. The aqueous phase was acidified with 4 N HCl to pH 2.2, saturated with NaCl, and extracted with four 50-mL portions of ether. The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated to give 11.2 g (81%) of a slightly yellow oil.

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Registry No. 4, 56652-39-2; (*S*)-**5**, 56652-40-5; (±)-**6a**, 87173-15-7; (*S*)-**6a**, 60665-97-6; (±)-**6b**, 87137-46-0; (*S*)-**6b**, 87173-16-8; (±)-**6c**, 87137-47-1; (*S*)-**6c**, 87173-17-9; (*R*)-**6c**, 87173-23-7; (±)-**6d**, 87137-48-2; (*S*)-**6d**, 87173-18-0; (±)-**6e**, 87137-49-3; (*S*)-**6e**, 87173-19-1; (±)-**6f**, 87137-50-6; (*S*)-**6f**, 87173-20-4; (±)-**6g**, 87137-51-7; (±)-**6h**, 87137-52-8; (±)-**6i**, 87137-53-9; (*S*)-**6i**, 87173-21-5; (±)-**6j**, 87137-54-0; (*S*)-**6j**, 87173-22-6; (*R*)-**7a**, 36567-73-4; (*R*)-**7b**, 87137-55-1; (*R*)-**7c**, 87137-56-2; (*R*)-**7e**, 87137-57-3; (*R*)-**7i**, 87137-58-4; PLE, 9013-79-0; *tert*-butyl 3-hydroxy-3-methyl-5-hexenoate, 87137-59-5; (*S*)-mevalonolactone, 19022-60-7.

(*N*-Alkylthiocarbamoyl)thionophosphonic Acid Esters[1]

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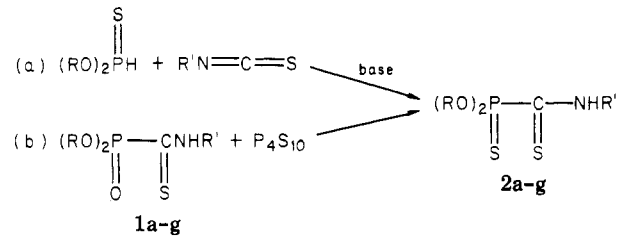
The title compounds **2** were prepared by the reaction of dialkyl thiophosphites and alkyl isothiocyanates. The diphenyl derivative **2f** was also prepared by heating the phosphoryl analogue **1f** with P_4S_{10}. The spectral differences between the present series **2** and the known phosphoryl series **1** are discussed. Both thiono functions of **2a**, **2c**, and **2e** react with methyl iodide, producing the phosphoryl-containing, synthetically useful zwitterion **7**.

Our interest in the chemistry of thiocarbamoyl phosphonic acid esters **1**[1,2] as possible precursors for different α-substituted phosphonates led us to investigate the analogous series of thiophosphoryl compounds **2**, which to our knowledge have not yet been described.

Two synthetic methods (Scheme I) were tried for the synthesis of **2**: (a) base-catalyzed reaction of dialkyl or diaryl thiophosphite with alkyl isothiocyanate and (b) "Thionation" of the phosphoryl analogues **1** with phosphorus pentasulfide. Since the thiophosphites are somewhat inconvenient to prepare[3,4] and to handle, we tried to develop method b which circumvents the usage of thiophosphites, but only in the case of conversion of **1f** to **2f** did the thionation reaction prove satisfactory. In all other cases only small amounts of the desired products could be identified (usually only by their TLC spots), whereas most of the starting materials were degraded to tars.

Five bases were used for catalyzing reaction a: sodium ethoxide and sodium methoxide as their appropriate alcoholic solutions, sodium hydride, potassium *tert*-butoxide, and triethylamine. It seems that even though all were applicable, sodium hydride or preferably sodium alkoxides were of advantage in the synthesis of the aliphatic esters

Scheme I[a]



[a] a, R = CH_3, R' = CH_3; *b*, R = CH_3, R' = benzyl; **c**, R = C_2H_5, R' = CH_3; d, R = C_2H_5, R' = benzyl; e, R = *n*-C_4H_9, R' = CH_3; f, R = phenyl, R' = CH_3; g, R = phenyl, R' = benzyl.

2a–e, while triethylamine proved to be the best for the synthesis of the aromatic esters **2f,g**. The same pattern was also found in the preparation of compounds **1**,[2] except that the thiophosphites are less selective in their choice of bases. This lower selectivity can be explained if it is assumed that the thiophosphites are more acidic than the phosphites, so they are ionized more readily by bases.

Following the addition of some of the base an exothermic reaction took place, instantly producing a yellow color. TLC, taken as soon as the reaction subsided, revealed a considerable amount of **2** accompanied by the remaining thiophosphite. The reaction mixture was then heated to 75 °C for 10–20 min. Higher temperatures and long heating periods resulted in a brown coloration and lower yields. The products could be not be distilled and were isolated by chromatography as yellow viscous oils, except for **2f** which crystallized. The yields were in the range of

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