solids, and the solvent was removed. After sublimation at 100 °C, 0.5 mmHg,[38] the material exhibited the following: $^1$H NMR ($CDCl_3$) δ 1.16–1.42 (m, 11 H), 1.65–1.96 (m, 14 H); mass spectrum, *m/e* (relative intensity) 228 ($M^+$, 11.4). Anal. Calcd for $C_{13}H_{25}PO$: $M_r$, 228.1643. Found: $M_r$, 228.1687.

**General Procedures for Reaction of $LiCuMe_2$ with Alkyl Halide and Tosylate Probes.** Copper iodide (1 equiv) was transferred to a 50-mL flask in an oxygen-free glovebox. Freshly distilled THF was added, and the slurry of CuI in THF was cooled to 0 °C in an ice bath. Two equivalents of MeLi were added dropwise by syringe while stirring, and a colorless solution was formed. To this solution was added a concentrated solution of the halide or tosylate in THF. For reaction profile studies, samples were taken by syringe and quenched immediately with stirred cold solutions of saturated $NH_4Cl/NH_4OH$ (10 to 1) in glass vials which also contained the internal standard in hexane or pentane. After stirring for several minutes the water layer was removed and the nonaqueous layer washed with saturated $NH_4Cl$ solution and then $H_2O$. The samples were then either immediately analyzed by GLC or stored in screw-top glass vials at <–10 °C until analysis could be made. In some cases the whole reaction mixture was quenched with cold saturated $NH_4Cl$ solution under a nitrogen atmosphere at 0 °C and worked up similar to the above. New reactions were routinely submitted for analysis by GLC/mass spectroscopy to confirm product identification.

When additives were used, they were added as a concentrated THF solution immediately before the addition of the halide solution. In the solvent effect studies, the cuprate was formed as detailed above and the solvent removed by high vacuum in order to be replaced by the solvent mixtures to be studied. In the reactions using CuCN as the source of copper(I), the cuprates were prepared by the method used by Lipschutz.[18]

Control experiments by NMR using benzene as an internal standard showed that lithium dimethylcuprate was stable at 0 °C during the time periods studied and that DCPH and 1,4-cyclohexadiene were stable in the presence of cuprate during the time periods studied. It also was determined by GLC that DCPH and 1,4-cyclohexadiene do not react with the alkyl halides during the time periods of interest.

**Acknowledgment.** We are indebted to the National Science Foundation (Grant #CHE-8403024) for support of this work.

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# Enzymes in Organic Synthesis. 39.[1] Preparations of Chiral Cyclic Acid-Esters and Bicyclic Lactones via Stereoselective Pig Liver Esterase Catalyzed Hydrolyses of Cyclic Meso Diesters

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Pig liver esterase catalyzed hydrolyses of *meso*-dimethyl cyclopropane-, cyclobutane-, and cyclohexane-1,2-dicarboxylates are enantiotopically specific, giving acid–ester products that are readily converted into γ-lactones of >97% ee that are of value as chiral synthons. There is a dramatic change of stereospecificity on going from the cyclopropane and cyclobutane diesters to the cyclohexane substrate, with the cyclopentane diester hydrolysis representing the changeover point within the series. This reversal of enzyme stereospecificity is explicable in terms of a two binding-pocket active-site model. Hydrolyses of dimethyl oxirane-2,3-dicarboxylate and of cyclopropane-1,2-diacetates are also stereoselective, giving product ee's of up to 30–70%.

Enzymes are now widely recognized as practical catalysts for asymmetric synthesis, with their abilities to induce stereospecific transformations on symmetrical substrates being of particular importance.[2] Esterases are attractive in this regard because they operate without requiring expensive coenzymes. One such enzyme that is commercially available, and whose potential for discriminating between enantiotopic ester groups of prochiral substrates such as meso diesters has already begun to be exploited in the preparation of useful chiral synthons,[3,4] is pig liver esterase (PLE, EC 3.1.1.1). The results detailed in this paper on the stereoselectivity of PLE-catalyzed hydrolysis of the monocyclic meso diesters **1**–**7**[4] extend further the asym-

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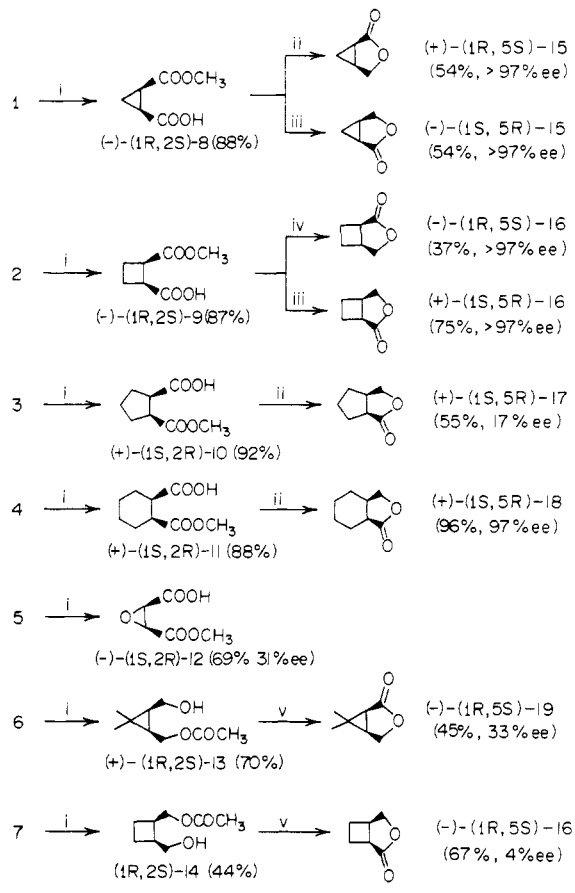
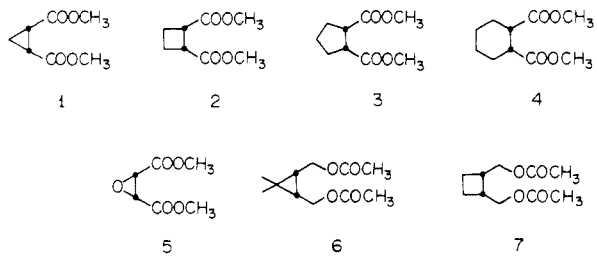
0022-3263/87/1952-4565$01.50/0 

**Scheme I**[a]




[a] Reagents: (i) PLE pH 7; (ii) $BH_3$; (iii) $LiBH_4$; (iv) 1. $ClCO_2Et$, 2. $NaBH_4$; (v) $KMnO_4$.

metric synthetic applicability of the enzyme, and also provide information on its limitations and its active-site binding regions.




## Results

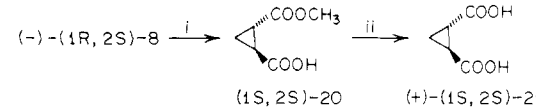
The meso diester substrates **1–7**, and the racemic lactones (±)-**15–19** required as ee reference standards, were prepared by unexceptional methods.

The viability of **1–7** as PLE substrates was established by measuring their rates of hydrolysis relative to that of ethyl butyrate. The observed rates for each were in the range of 4–7 (ethyl butanoate = 100), well in excess of the 0.02% of ethyl butanoate minimum needed to assure good preparative-scale results.[3g]

The PLE-catalyzed hydrolyses of **1–7** were carried out in 0.1 M phosphate buffer at pH 7, with the pH being maintained at this level by periodic addition of aqueous NaOH. Each reaction was terminated after the addition of 1 equiv of base, and the acid–ester **8–12** and hydroxy ester **13**, **14** products were isolated. These were then readily converted to the lactones **15–19**. The results are summarized in Scheme I.

The ee's of the enantiomerically pure lactones **15–18** were determined by NMR on the diol products of their

**Scheme II**[a]




[a] Reagents: (i) 1. KO-*t*-Bu, 2. HCl; (ii) $^-OH$.

reaction with excess MeLi.[5] The corresponding diols derived from each of the racemic lactones were used as reference standards. The ee of (-)-**12** was measured by NMR using the (+)-(*R*)-1-methylbenzylamine salt method of Schneider et al.[3e] The enantiomeric purities of (-)-**13** and (-)-**14** were determined by the NMR method[5] applied above to the diol derivatives of **15–18**.

The absolute configurations of the Scheme I compounds were assigned by comparison of the (+)- or (-)-lactones **15–19** with samples of established structures[6] and of the oxirane (-)-**12** from the literature assignment.[7] The absolute configuration of the cyclopropane acid–ester (-)-**8** was further confirmed by its conversion to the known (+)-**21**,[8] as shown in Scheme II.

All preparative-scale hydrolyses were also surveyed with chymotrypsin as the catalyst. Only with **5** as a substrate was transformation to the acid–ester observed. However, the acid–ester product (+)-**12** was of only 15% ee, and its 1*R*,2*S* configuration was opposite to that of acid–ester (-)-**12** obtained via PLE-catalyzed hydrolysis of **5** (Scheme I).

## Discussion

The stereospecificity of PLE-catalyzed hydrolyses studied is excellent for the cyclopropane, cyclobutane, and cyclohexane diesters **1**, **2**, and **4**, giving the enantiomerically pure acid–esters (-)-**8**, (-)-**9**, and (+)-**11**, respectively, in excellent yields. In contrast, only marginal stereoselectivity is observed in the hydrolysis of the cyclopentane substrate **3**.

There is a clear reversal of the stereospecificity of PLE within this series, with the enantiotopic specificity for the *S*-center ester groups of the cyclopropane and cyclobutane substrates switching to *R*-center ester hydrolysis for the cyclohexane case. The cyclopentane diester hydrolysis represents the changeover point, with only 17% *R*-center group enantiotopic distinction being manifest.

Chiral acid–esters such as **8**, **9**, and **11** represent attractive asymmetric synthons. They are complementary in oxidation states to those of related structures obtainable via horse liver alcohol dehydrogenase[6] and porcine pancreatic lipase[9] catalyzed reactions, and thus extend the range of availability of basic monocyclic chirons[10] of this type. Furthermore, acid–esters such as **8–14** are very versatile chiral building blocks in that they provide ready access to enantiomeric series of lactones **15–19** either by controlled reduction of the acid function with borane[11a]

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or by the mixed anhydride followed by the $NaBH_4$[11b] method (Scheme I).

The synthon potential of these chirons has already been recognized, with the cyclopropane lactone (−)-**15** being an attractive precursor for the South Sea pheromone,[12] the cyclobutane lactone (+)-**16** for the boll weevil pheromone, grandisol,[13] and the cyclohexene equivalent of (+)-**18** for iridoids,[14] brefeldins,[3f] and prostanoids.[3f]

The oxirane diester **5** was included because of its potential as a chiron precursor for the gypsy moth sex pheromone, disparlure.[15] Regrettably, the poor stereoselectivity of the PLE-catalyzed hydrolysis of **5** yielded the acid–ester (−)-**12** of too low an enantiomeric purity to be synthetically useful as a competitive chiron for disparlure synthesis, although it has been employed as a carbapenem precursor.[7] Interestingly, when methylene groups are introduced between the oxirane ring and the ester groups, the PLE-catalyzed hydrolysis becomes completely enantiotopically specific.[16]

The PLE-catalyzed hydrolysis of the 2,2-dimethylcyclopropyl diester equivalent of **1** for the preparation of lactone **19** has been explored previously[3d,e] as the basis of a potential route to pyrethroid precursors. Unfortunately, while the 70% ee of the (−)-**19** obtained via hydrolysis of the diacetate **6** in the current study is significant, it remains below the viable level for a pyrethroid chiron. The level of enantiotopic selectivity observed for the cyclobutane diester **7** hydrolysis was barely discernible (4% ee), thus confirming the unsuitability of PLE for stereospecific hydrolyses of diacetates of these types.[17]

The ee determinations and absolute configuration assignments were straightforward. The confirmation of the assignment of the cyclopropane acid–ester (−)-**8** as 1*R*,2*S* (Scheme II) was performed because the original determination, based on CD spectrum analysis of (−)-**15**,[6] had been queried and the opposite enantiomeric configuration assigned.[3e] Scheme II results provide unequivocal proof of the 1*R*,2*S* configuration of (−)-**9** and of the correctness of the first assignment.[18] It is noteworthy that the *R*-center stereoselectivity of hydrolysis of the oxirane diester **5**, while the same as that of its bishomo analogue,[16] is opposite to that of the structurally similar cyclopropane diester **1**, for which the *S*-center ester function is hydrolyzed.

Although some inversions of enzyme stereospecificity within a structurally related series of substrates are known, the reversal observed in the hydrolyses of **1–4** is one of the most dramatic. Furthermore, reversal of stereospecificity within a structurally related series of substrates appears to be more general for PLE than for other enzymes, with certain acyclic[19a,20] and other cyclic diesters[3g] exhibiting similar behavior. These stereospecificity reversals are satisfactorily interpreted in terms of an active site possessing two hydrophobic binding sites, one small and one large. Hydrophobic groups bind preferentially at the smaller site until they exceed its dimensions,[21] whereupon

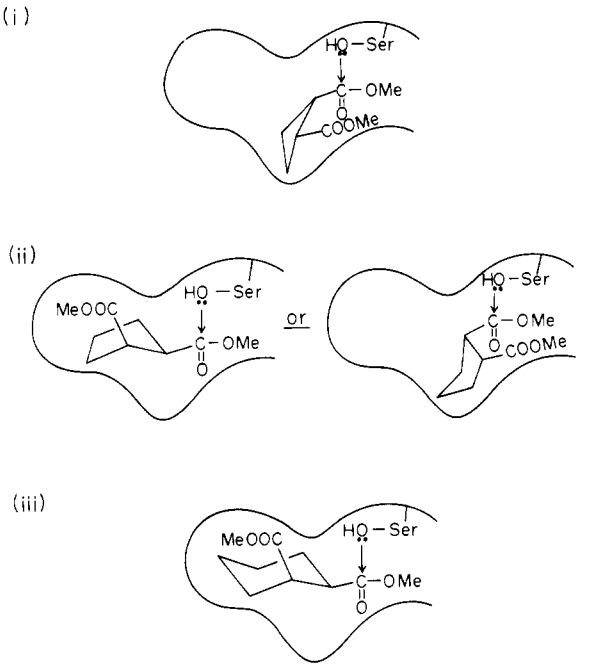


**Figure 1.** Active-site orientations of diesters **2–4**. The ester group to be hydrolyzed must locate adjacent to the nucleophilic hydroxyl group of the catalytically vital serine residue. Two binding sites, 1 and 2, capable of accommodating hydrophobic substrate groups, are situated nearby. Hydrophobic residues of a substrate will locate preferentially in the smaller site 1 in order to maximize hydrophobic bonding.[21] This is depicted in (i) for the cyclobutane diester **2**, which locates the *S*-center carbomethoxy group adjacent to the serine nucleophile as required for the observed acid–ester (−)-(1*R*,2*S*)-**9** formation. (ii) The cyclopentyl moiety of **3** marginally exceeds the dimensions of site 1, and binding in the larger site 2 becomes slightly more favored. The marginal preference of site 2 binding, in which the *R*-center ester group locates adjacent to the serine hydroxyl, is manifest by the 17% ee of the (+)-(1*S*,2*R*)-**10** acid–ester product. (iii) For the cyclohexane diester **4**, the steric requirements of the cyclohexyl group cannot be accommodated by site 1, and it must therefore bind entirely in the larger site 2. This results in exclusively *R*-center ester hydrolysis to (+)-(1*S*,2*R*)-**11**. The equatorial orientation of the ester group attacked by the serine hydroxyl has been established.[19b]

they are obliged to locate in the larger pocket. The situation for substrates **2–4** is depicted in Figure 1. The dimensions and locations of these binding sites relative to the catalytic groups are now being delineated in a systematic manner using computer modelling. A detailed active-site model of predictive value is emerging[22] and will be reported shortly.

## Experimental Section

The instrumentation, general purification, and analytical procedures used were the same as described previously.[19] PLE (EC 3.1.1.1) was Sigma Chemical Co. Type II (Lot 123F-0240). All NMR spectra were determined in $CDCl_3$ unless indicated otherwise.

**Preparations of Diester Substrates 1–7. Dimethyl *cis*-cyclopropane-1,2-dicarboxylate (1)** was prepared by the method of McCoy:[23] bp 60 °C (0.5 mmHg) [lit.[23] bp 59 °C (0.6 mmHg)]; IR (film) $\nu$ 1735 $cm^{-1}$; $^1H$ NMR $\delta$ 1.03–1.90 (2 H, m), 1.90–2.28 (2 H, m), 3.68 (6 H, s); $^{13}C$ NMR $\delta$ 11.03 (t), 20.74 (d), 51.27 (q), 169.66 (s).

**Dimethyl *cis*-cyclobutane-1,2-dicarboxylate (2)** was obtained by Fisher esterification of *cis*-cyclobutane-1,2-dicarboxylic

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acid (Aldrich) with methanol and concentrated $H_2SO_4$: bp 85–90 °C (3 mmHg) [lit.[24] bp 85 °C (3 mmHg)]; IR (film) $\nu$ 1738 $cm^{-1}$; $^1H$ NMR $\delta$ 1.95–2.60 (4 H, m), 3.18–3.63 (2 H, m), 3.68 (6 H, s); $^{13}C$ NMR $\delta$ 21.10 (t), 39.66 (d), 50.49 (q), 172.46 (s).

**Dimethyl *cis*-cyclopentane-1,2-dicarboxylate (3)** was made by the method of Fuson and Cole:[25] bp 70 °C (6 mmHg) [lit.[26] bp 116–117 °C (12 mmHg)]; IR (film) $\nu$ 1735 $cm^{-1}$; $^1H$ NMR $\delta$ 1.58–2.25 (6 H, m), 2.87–3.22 (2 H, m), 3.67 (6 H, s); $^{13}C$ NMR $\delta$ 23.07 (t), 27.87 (t), 46.03 (d), 50.43 (q), 173.17 (s).

**Dimethyl *cis*-cyclohexane-1,2-dicarboxylate (4)**[27] was prepared by the route of Cope and Herrick:[28] bp 75 °C (0.55 mmH) [lit.[28] bp 110–112 °C (5 mmHg)]; IR (film) $\nu$ 1740 $cm^{-1}$; $^1H$ NMR $\delta$ 1.40–1.60 (4 H, m), 1.70–2.00 (4 H, m), 2.60–3.00 (2 H, m), 3.66 (6 H, s).

**Dimethyl *cis*-2,3-oxiranedicarboxylate (5)** was prepared by the procedure of Payne and Williams:[29] bp 65 °C (0.3 mmHg) [lit.[29] bp 240–244 °C (760 mmHg)]; IR (film) $\nu$ 1752 $cm^{-1}$; $^1H$ NMR $\delta$ 3.73 (2 H, s), 3.82 (6 H, s); $^{13}C$ NMR $\delta$ 51.71 (d or q), 51.80 (q or d), 165.00 (s).

***cis*-1,2-Bis(acetoxymethyl)-3,3-dimethylcyclopropane (6)**[30] was obtained by $LiAlH_4$ reduction of dimethyl cyclopropane-1,2-dicarboxylate[31] followed by acetylation: bp 40 °C (0.05 mmHg); IR (film) $\nu$ 1741 $cm^{-1}$; $^1H$ NMR[32] $\delta$ 1.08 (3 H, s), 1.12 (3 H, s), 0.80–1.33 (2 H, m), 2.04 (6 H, s), 3.90–4.30 (4 H, m); $^{13}C$ NMR $\delta$ 14.29 (q, $CH_3$ cis to $CH_2OAc$), 18.98 (s), 20.30 (q), 24.98 (q, $CH_3$ trans to $CH_2OAc$), 61.26 (t), 170.20 (s).

***cis*-1,2-Bis(acetoxymethyl)cyclobutane (7)** was made by a modification of the method of Blomquist and Verdal.[33] Dimethyl *cis*-cyclobutane-1,2-dicarboxylate (**2**; 2 g, 11.6 mmol) was added slowly with stirring at 20 °C to $LiAlH_4$ (880 mg, 23.2 mmol) in dry THF (50 mL) and the mixture stirred for a further 4 h. Acetic acid (5 mL) was then added dropwise with stirring, and acetic anhydride (50 mL) was added. The THF was removed by distillation, and the residual mixture was refluxed for 1 day, cooled, filtered, and rotoevaporated. Kugelrohr distillation of the residual oil gave the desired diacetate **7** (2.16 g, 93% yield): bp 90 °C (2.5 mmHg) [lit.[33] bp 79–80 °C (0.5 mmHg)]; IR (film) $\nu$ 1742 $cm^{-1}$; $^1H$ NMR $\delta$ 1.57–2.33 (4 H, m), 2.03 (6 H, s), 2.83–3.10 (2 H, m), 3.90–4.37 (4 H, m); $^{13}C$ NMR $\delta$ 19.81 (q), 20.83 (t), 34.36 (d), 63.66 (t), 169.71 (s).

**PLE-Catalyzed Hydrolyses of Diesters 1–7.** The following general procedure was used: PLE (n units) was added to a slowly stirred solution of diester in 0.1 M $KH_2PO_4$ of pH 7 at 20 °C. The pH was maintained at 7 by pH-stat-controlled addition of 1 M aqueous NaOH. The hydrolysis was permitted to continue until 1 equiv of base had been taken up. The reaction mixture was immediately washed with $Et_2O$ (6 × 50 mL) and the emulsion that formed in the aqueous phase eliminated by vacuum filtration. The aqueous phase was then acidified to pH 2 with 2 M hydrochloric acid and was then extracted with EtOAc (5 × 50 mL). Evaporation of the dried ($MgSO_4$) EtOAc solution followed by Kugelrohr distillation yielded the products, as follows.

Hydrolysis of **dimethyl *cis*-cyclopropane-1,2-dicarboxylate** (**1**; 1.0 g, 6.3 mmol) in buffer (80 mL) with PLE (870 units) for 8 h gave methyl hydrogen (−)-(1*R*,2*S*)-cyclopropane-1,2-dicarboxylate (**8**; 800 mg, 88% yield): mp 81–83 °C (lit.[34] (±) mp 51–52 °C); $[\alpha]^{25}_D$ −13.4° (*c* 0.97, $CHCl_3$); IR ($CHCl_3$) $\nu$ 1712, 1741, 2500–3600 $cm^{-1}$; $^1H$ NMR $\delta$ 1.07–1.87 (2 H, m), 1.93–2.33 (2 H, m), 3.72 (3 H, s), 11.28 (1 H, s); $^{13}C$ NMR $\delta$ 11.75 (t), 20.84 (d), 21.98 (d), 51.96 (q), 170.12 (s, $COOCH_3$), 175.24 (s, COOH).

Hydrolysis of **dimethyl *cis*-cyclobutane-1,2-dicarboxylate** (**2**; 2.9 g, 16.9 mmol) in buffer (80 mL) with PLE (1200 units) for 7 h yielded methyl hydrogen (−)-(1*R*,2*S*)-cyclobutanedicarboxylate (**9**; 2.43 g, 87% yield): mp 85 °C (0.15 mmHg) [lit.[33] bp 111–112 °C (13 mmHg)]; $[\alpha]^{25}_D$ −3.0 (*c* 2.11, $CHCl_3$); IR (film) $\nu$ 1705, 1735, 2380–3600 $cm^{-1}$; $^1H$ NMR $\delta$ 2.05–2.65 (4 H, m), 3.22–3.75 (2 H, m), 3.72 (3 H, s), 11.58 (1 H, s); $^{13}C$ NMR $\delta$ 21.05 (t), 21.19 (t), 39.63 (d), 39.70 (d), 50.78 (q), 173.19 (s), 178.07 (s).

Hydrolysis of **dimethyl *cis*-cyclopentane-1,2-dicarboxylate** (**3**; 770 mg, 4.1 mmol) in buffer (80 mL) with PLE (800 units) for 5 h afforded methyl hydrogen (+)-(1*S*,2*R*)-cyclopentane-1,2-dicarboxylate (**10**; 650 mg, 92% yield): bp 105 °C (0.5 mmHg); $[\alpha]^{25}_D$ 1.0° (*c* 1, $CHCl_3$); IR (film) 1705, 1735, 2380–3600 $cm^{-1}$; $^1H$ NMR $\delta$ 1.51 (6 H, m), 3.17–3.30 (2 H, m), 3.65 (3 H, s), 11.65 (1 H, s); $^{13}C$ NMR $\delta$ 23.56 (t), 28.43 (t), 46.33 (d), 51.34 (q), 174.04 (s), 179.90 (s).

Hydrolysis of **dimethyl *cis*-cyclohexane-1,2-dicarboxylate**[27] (**4**; 1.31 g, 6.6 mmol) in buffer (150 mL) with PLE (2400 units) for 5 days gave methyl hydrogen (+)-(1*S*,2*R*)-cyclohexane-1,2-dicarboxylate (**11**; 1.07 g, 88% yield) bp 100 °C (0.2 mmHg); $[\alpha]^{25}_D$ +4.7° (*c* 0.87, $CHCl_3$); IR (film) $\nu$ 1723, 1740, 2400–3600 $cm^{-1}$; $^1H$ NMR $\delta$ 1.30–1.50 (4 H, m), 1.70–2.10 (4 H, m), 2.70–3.00 (2 H, m), 3.70 (3 H, s), 10.9 (1 H, s).

Hydrolysis of **dimethyl *cis*-2,3-oxiranedicarboxylate** (**5**; 1.0 g, 6.3 mmol) in buffer (80 mL) with PLE (800 units) for 4.5 h yielded methyl hydrogen (−)-(1*S*,2*R*)-2,3-oxirane-1,2-dicarboxylate (**12**; 631 mg, 69% yield, 31% ee) bp 70 °C (0.05 mmHg); $[\alpha]^{25}_D$ −3.69° (*c* 1.65 $CHCl_3$); IR ($CHCl_3$) $\nu$ 1728, 1742, 2300–3500 $cm^{-1}$; $^1H$ NMR $\delta$ 3.80 (2 H, s), 3.85 (3 H, s), 9.67 (1 H, s); $^{13}C$ NMR $\delta$ 52.38 (d), 52.83 (q), 166.51 (s), 168.81 (s). Substitution of $\alpha$-chymotrypsin as the enzymic catalyst for the **6** → **12** reaction gave (+)-(1*R*,2*S*)-**12** (61% yield, 15% ee), $[\alpha]^{25}_D$ +1.84° (*c* 1.63, $CHCl_3$).

Hydrolysis of ***cis*-1,2-bis(acetoxymethyl)-3,3-dimethylcyclopropane** (**6**; 150 mg, 0.7 mmol) in buffer (35 mL) with PLE (260 units) for 4.5 h gave, after chromatography on silica gel (hexane/$Et_2O$, 1:1 elution), (+)-(1*R*,2*S*)-1-(acetoxymethyl)-2-(hydroxymethyl)-3,3-dimethylcyclopropane (**13**; 92 mg, 70% yield, 33% ee); $[\alpha]^{25}_D$ +6.25° (*c* 0.8, $CHCl_3$); IR (film) $\nu$ 1739, 3410 $cm^{-1}$; $^1H$ NMR (200 MHz, $CCl_4$) $\delta$ 0.91–1.13 (2 H, m, X parts of 2 ABX systems), 1.06 (3 H, s), 1.12 (3 H, s), 2.00 (3 H, s), 2.60 (1 H, s, OH), 3.53 (1 H, C$H_2$OH, 4 lines of B of ABX, $J$ = 8.00, 11.64 Hz), 3.64 (1 H, C$H_2$OH, 4 lines of A of ABX, $J$ = 6.94, 11.64 Hz), 4.10 (2 H, C$H_2$OAc, 2 lines of AB of ABX, $J$ = 7.62 Hz); $^{13}C$ NMR $\delta$ 14.75, 19.12, 19.91, 24.82, 28.60, 29.28, 59.14, 62.09, 171.14.

Hydrolysis of ***cis*-1,2-bis(acetoxymethyl)cyclobutane** (**7**; 700 mg, 3.5 mmol) in buffer (80 mL) with PLE (470 units) for 5.5 h gave *cis*-1-(acetoxymethyl)-2-(hydroxymethyl)cyclobutane (**14**; 350 mg containing 13% starting material and 9% diol, 44% yield, 4% ee): $[\alpha]^{25}_D$ 0° (*c* 2.8, $CHCl_3$); IR (film) $\nu$ 1740, 3430 $cm^{-1}$; $^1H$ NMR (200 MHz, $CCl_4$) $\delta$ 1.61–1.80 (2 H, m, X parts of 2 ABX systems), 2.02 (3 H, s), 1.93–2.17 (2 H, m), 2.50 (1 H, s, OH), 2.50–2.83 (2 H, m), 3.52 (1 H, C$H_2$OH, 4 lines of B of ABX, $J$ = 5.62, 10.98 Hz), 3.67 (1 H, $CH_2$OH, 4 lines of A of ABX, $J$ = 8.04, 10.98 Hz), 4.10 (1 H, $CH_2$OAc, 4 lines of B of ABX, $J$ = 6.95, 11.31 Hz), 4.20 (1 H, $CH_2$OAc, 4 lines of A of ABX, $J$ = 7.70, 11.31 Hz); $^{13}C$ NMR $\delta$ 20.36 (q), 20.99 (t), 21.19 (t), 34.43 (d), 37.74 (d), 52.25 (t), 64.55 (t), 170.69 (s).

**Conversions of Acid-Esters 8–11, 13, and 14 to Their Corresponding Lactones 15–19. (1*R*,5*S*)-3-Oxabicyclo-[3.1.0]hexan-2-one [(+)-15].** Methyl hydrogen *cis*-(1*R*,2*S*)-cyclopropane-1,2-dicarboxylate [(−)-**8**, 124 mg, 0.86 mmol] was dissolved under $N_2$ with stirring in dry THF (2 mL) at −10 °C and $BH_3$·$Me_2S$ (0.7 mL of 0.2 M THF solution, 1.4 mmol) added via a syringe. The mixture was then allowed to warm to 20 °C and stirred under $N_2$ for a further 6 h. MeOH (3 mL) was then added and the mixture rotoevaporated. This methanol-addition procedure was repeated twice more. Kugelrohr distillation of the residue gave methyl *cis*-2(*S*)-(hydroxymethyl)-1(*R*)-cyclopropanecarboxylate (90 mg, 80% yield): bp 20 °C (0.05 mmHg); $[\alpha]^{25}_D$ −64.4° (*c* 1.16, $CHCl_3$); IR (film) 1729, 3409 $cm^{-1}$; $^1H$ NMR $\delta$ 0.87–1.33 (2 H, m), 1.33–1.93 (2 H, m), 2.97 (1 H, s, OH), 3.67 (3 H, s), 3.40–4.10 (2 H, m); $^{13}C$ NMR $\delta$ 11.52 (t), 17.03 (d), 23.08 (d), 51.47 (q), 59.88 (t), 173.64 (s). This hydroxy ester (88 mg, 0.67 mmol) in dry benzene (20 mL) containing *p*-TsOH (2 mg) was refluxed for 8 h in a Dean–Stark apparatus. Rotoevaporation of the solvent followed by chromatography on silica gel (pen-

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tane/$Et_2O$, 2:5, elution) yielded (+)-(1*R*,5*S*)-3-oxabicyclo-[3.1.0]hexan-2-one (**15**; 45 mg, 67% yield, >97% ee): bp 60 °C (1 mmHg); $[\alpha]^{25}_D$ +61.1° (*c* 0.72, $CHCl_3$); IR (film) $\nu$ 1770 $cm^{-1}$; $^1H$ NMR $\delta$ 0.66–1.50 (2 H, m), 1.70–2.50 (2 H, m), 3.98–4.56 (2 H, m); $^{13}C$ NMR $\delta$ 11.85 (t), 16.97 (d), 17.21 (d), 69.11 (t), 176.11 (s).

**(1*S*,5*R*)-3-Oxabicyclo[3.1.0]hexan-2-one [(−)-15].** Aqueous LiOH (0.97 mL of 1 M solution, 0.97 mmol) was added at 20 °C to methyl hydrogen *cis*-(1*R*,2*S*)-cyclopropane-1,2-dicarboxylate [(−)-**8**; 140 mg, 0.97 mmol] in water (2 mL). After the mixture was stirred for 30 min, it was rotoevaporated and dried for 2 h at 120 °C (0.15 mmHg). Dry THF (15 mL) was added under $N_2$ and the mixture stirred overnight to loosen the salt from the sides of the flask. $LiBH_4$ (35 mg, 1.6 mmol) in dry $Et_2O$ (10 mL) was added via a syringe and the mixture refluxed for 2 h. Methanol (5 mL) was added, and the mixture was refluxed for a further 30 min and then cooled to 20 °C. Aqueous 0.1 M $KH_2PO_4$ buffer (pH 7, 15 mL) was then added, and the organic solvents were rotoevaporated. The aqueous phase was acidified to pH 2 with 2 M hydrochloric acid and extracted with EtOAc (6 × 15 mL). The dried ($Na_2SO_4$) EtOAc solution was rotoevaporated and purified as described above for (+)-**15** to give (−)-(1*S*,5*R*)-3-oxabicyclo[3.1.0]hexan-2-one (**15**; 77 mg, 54% yield, >97% ee) bp 60 °C (1 mmHg); $[\alpha]^{25}_D$ −60° (*c* 0.4, $CHCl_3$) [lit.[6] bp 100 °C (10 mmHg); $[\alpha]^{25}_D$ −61.8° (*c* 6, $CHCl_3$)]; spectral properties as for (+)-**15**.

**(1*R*,5*S*)-3-Oxabicyclo[3.2.0]heptan-2-one [(−)-16].** Ethyl chloroformate (distilled from BaO, 1 mL, 10.5 mmol) was added with stirring to methyl hydrogen *cis*-(1*R*,2*S*)-cyclobutane-1,2-dicarboxylate [(−)-**9**; 318 mg, 2 mmol] and $Et_3N$ (0.5 mL, 3.8 mmol) in dry $CH_2Cl_2$ (15 mL) at 20 °C. After it was stirred for a further 10 min, the solution was rotoevaporated and the residual oil Kugelrohr distilled to give the corresponding mixed anhydride diester in quantitative yield: bp 80 °C (0.05 mmHg); IR (film) $\nu$ 1712, 1793 $cm^{-1}$; $^1H$ NMR $\delta$ 1.35 (3 H, t, $J$ = 7.2 Hz), 2.00–2.71 (4 H, m), 3.26–3.92 (2 H, m), 3.73 (3 H, s), 4.34 (2 H, q, $J$ = 7.2 Hz); $^{13}C$ NMR $\delta$ 13.43 (q), 21.47 (t), 39.90 (d), 40.29 (d), 51.47 (q), 65.18 (t), 148.39 (s, COOCOOEt), 167.08 (s, COOCOOEt), 172.47 (s, COOMe). To this mixed anhydride in dry $CH_2Cl_2$ (140 mL) was added at 5 °C with stirring $NaBH_4$ (1.1 g, 29.1 mmol) in MeOH (9 mL). The mixture was stirred for 20 min while warming to 20 °C and was then poured into saturated aqueous NaCl. The organic phase was separated and the aqueous phase extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic phases were dried ($Na_2SO_4$), rotoevaporated, and redissolved in $Et_2O$ (2 mL), and this solution was added to silica gel in $Et_2O$ to effect cyclization to the lactone. Rotoevaporation of the filtered ether solution followed by chromatography on silica gel (pentane/$Et_2O$, 1:2, elution) and Kugelrohr distillation gave (−)-(1*S*,5*R*)-3-oxabicyclo[3.2.0]heptan-2-one (**16**; 127 mg, 37% yield, >97% ee): bp 120 °C (20 mmHg); $[\alpha]^{25}_D$ −107.1° (*c* 1.1, $CHCl_3$); IR (film) $\nu$ 1770 $cm^{-1}$; $^1H$ NMR $\delta$ 1.73–2.87 (4 H, m), 2.87–3.53 (2 H, m), 4.03–4.63 (2 H, m); $^{13}C$ NMR $\delta$ 22.78 (t), 24.68 (t), 33.72 (d), 37.45 (d), 73.47 (t), 180.21 (s).

**(1*S*,5*S*)-3-Oxabicyclo[3.2.0]heptan-2-one [(+)-16].** The acid–ester (−)-(1*R*,2*S*)-**9** (344 mg, 2.15 mmol) was reduced with $LiBH_4$ as described above for (−)-(1*S*,5*R*)-**15** to yield (+)-(1*S*,5*R*)-**16** (180 mg, 75% yield, >97% ee): bp 120 °C (20 mmHg); $[\alpha]^{25}_D$ +106.7° (*c* 3.1, $CHCl_3$) [lit.[6] bp 100 °C (10 mmHg); $[\alpha]^{25}_D$ +118.7° (*c* 10, $CHCl_3$)]; spectral properties as for (−)-**16**.

**(1*S*,5*R*)-3-Oxabicyclo[3.3.0]octan-2-one [(+)-17].** Reduction of methyl hydrogen *cis*-(1*S*,2*R*)-cyclopentane-1,2-dicarboxylate [(+)-**10**; 150 mg, 0.87 mmol] with $BH_3{\times}Me_2S$ as described above for (+)-**15**, plus additional chromatographic purification on silica gel (pentane/$Et_2O$, 1:12, elution), afforded (+)-(1*S*,5*R*)-**17** (60 mg, 55% yield, 17% ee): bp 120 °C (10 mmHg); $[\alpha]^{25}_D$ +12.8° (*c* 0.73, $CHCl_3$) [lit.[6] bp 60 °C (0.25 mmHg); $[\alpha]^{25}_D$ +96.9° (*c* 1, $CHCl_3$)]; IR (film) $\nu$ 1765 $cm^{-1}$; $^1H$ NMR $\delta$ 1.06–2.40 (6 H, m), 2.63–3.33 (2 H, m), 3.80–4.76 (2 H, m); $^{13}C$ NMR $\delta$ 24.82 (t), 29.95 (t), 32.99 (t), 38.33 (d), 43.81 (d), 72.86 (t), 180.25 (s).

**(1*S*,5*R*)-8-Oxabicyclo[4.3.0]nonan-7-one [(+)-18].**[27] Reduction of methyl hydrogen *cis*-(1*S*,2*R*)-cyclohexane-1,2-dicarboxylate [(+)-**11**; 179 mg, 0.96 mmol] with $BH_3{\cdot}Me_2S$ as described above for (+)-**15** gave (+)-(1*S*,5*R*)-**18** (110 mg, 96% yield, >97% ee): bp 90 °C (2 mmHg); $[\alpha]^{25}_D$ +32.2° (*c* 0.34, $CHCl_3$) [lit.[6] bp 86 °C (2 mmHg); $[\alpha]^{25}_D$ +48.8° (*c* 0.5, $CHCl_3$)]; IR (film) $\nu$ 1770 $cm^{-1}$; $^1H$ NMR $\delta$ 1.00–2.20 (8 H, m), 2.40–2.90 (2 H, m), 3.80–4.30 (2 H, m); $^{13}C$ NMR $\delta$ 26.1, 26.6, 27.0, 29.0, 39.0, 43.0, 74.9, 180.9.

**Preparation of (−)-16 from Hydroxyacetate 14.** To *cis*-1-(acetoxymethyl)-2-(hydroxymethyl)cyclobutane (**14**; 120 mg, 0.7 mmol) in 1 M $KH_2PO_4$ buffer (pH 7, 70 mL) was added $KMnO_4$ (333 mg, 2.1 mmol) and the mixture heated for 2 h at 55 °C. $Na_2S_2O_5$ was then added until the violet color disappeared. The mixture was filtered and the brown residue washed with hot water (5 mL), and the cooled (20 °C) combined aqueous phases were washed with $Et_2O$ (6 × 50 mL). The aqueous layer was then brought to pH 13 with NaOH and stirred for 2 h at 20 °C. The mixture was then saturated with NaCl, acidified to pH 2 with 12 M hydrochloric acid, and extracted with EtOAc (4 × 50 mL). The EtOAc solution was dried ($MgSO_4$) and rotoevaporated, and the residue was chromatographed on silica gel (pentane/$Et_2O$, 1:10, elution) and finally Kugelrohr distilled to give (−)-(1*R*,5*S*)-3-oxabicyclo[3.2.0]heptan-2-one (**16**; 52 mg, 67% yield, 4% ee based on **14**): bp 100 °C (10 mmHg); $[\alpha]^{25}_D$ −5.1° (*c* 0.87, $CHCl_3$).

**(1*R*,5*S*)-6,6-Dimethyl-3-oxabicyclo[3.1.0]hexan-2-one [(−)-19].** *cis*-(1*R*,2*S*)-2-(Acetoxymethyl)-1-(hydroxymethyl)-3,3-dimethylcyclopropane (**13**; 80 mg, 0.43 mmol) was oxidized with $KMnO_4$ as described for (−)-**16** above to afford (−)-(1*R*,5*S*)-**19** [24 mg, 45% yield, 33% ee based on (+)-**13**]: bp 105 °C (10 mmHg); $[\alpha]^{25}_D$ −18.8° (*c* 0.95, $CHCl_3$) [lit.[6] bp 100 °C (10 mmHg); $[\alpha]^{25}_D$ −36.6° (*c* 1.4, $CHCl_3$)[35]].

**Enantiomeric Excess Determinations.** The ee's of the enantiomerically pure lactones (+)- and (−)-**15** and **16** and (+)-**18** and of the enantiomerically enriched (+)-**17** were determined by $^1H$ NMR as described previously[5] on the diol products of their reactions with methyllithium in the presence of $Eu(tfc)_3$.[5] The ee of the epoxy acid–ester (−)-**12** was established by examination of its $^1H$ NMR spectrum in the presence of (+)-1(*R*)-methylbenzylamine.[3e] The ee values of (−)-**13** and (+)-**14** were determined by the method of ref 5. In all of the above, the corresponding racemates were used as reference standards.

**Absolute Configuration Determinations.** The absolute configurations of all lactones **15**–**19** had been established previously.[6] The absolute configuration of the epoxy acid–ester (−)-**12** was taken from the literature assignment.[7]

For the cyclopropyl series, the validity of the previous[6] absolute configuration assignments were confirmed by the Scheme II correlations as follows.

To methyl *cis*-(1*R*,2*S*)-cyclopropane-1,2-dicarboxylate [(−)-**8**, 40 mg, 0.28 mmol] in dry THF (3 mL) containing 18-crown-6 (5 mg) was added, at 20 °C under $N_2$, potassium *tert*-butoxide (64 mg, 0.56 mmol). The mixture was stirred at 20 °C under $N_2$ for 1 day and 1 M hydrochloric acid (0.6 mL) added. The organic phase was then separated and rotoevaporated. The residue (1*S*,2*S*)-**20** was dissolved in NaCl-saturated 0.01 M hydrochloric acid (8 mL) and extracted with EtOAc (4 × 6 mL). The dried ($MgSO_4$) EtOAc solution was rotoevaporated and 1 M aqueous NaOH (4 mL) added. The mixture was refluxed for 30 min and then cooled, and NaCl-saturated 1 M hydrochloric acid (5 mL) was added. Extraction with EtOAc (4 × 8 mL) followed by concentration of the dried ($MgSO_4$) EtOAc solution yielded crystals that were washed with *n*-pentane and then with pentane/$CH_2Cl_2$ (1:1) and then dried at 40 °C (0.05 mmHg) to give *trans*-(1*S*,2*S*)-cyclopropane-1,2-dicarboxylic acid [(+)-**21**; 18 mg, 50% yield, >97% ee]: mp 160–163 °C $[\alpha]^{25}_D$ +206.4° (*c* 0.29, MeOH) (lit.[8a] mp 161–163 °C; $[\alpha]^{25}_D$ +200° (MeOH),[8b,c] $[\alpha]^{25}_D$ +208.2 EtOH[8a]); IR ($CH_3CN$) $\nu$ 1730, 2450–3600 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) $\delta$ 1.02–1.48 (2 H, m), 1.65–2.12 (2 H, m), 11.0–13.0 (1 H, br s); $^{13}C$ NMR (DMSO-$d_6$) $\delta$ 12.59 (t), 19.82 (d), 170.75 (s).

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**Registry No.** **1**, 826-34-6; **2**, 2607-03-6; **3**, 4841-91-2; **4**, 1687-29-2; **5**, 56958-97-5; **6**, 67488-75-9; **7**, 98515-98-1; **8**, 88335-87-9; **9**, 88335-88-0; **9** (mixed anhydride diester), 110045-72-2; **10**,

(35) Mukaiyama, T.; Yamashita, H.; Asami, M. *Chem. Lett.* **1983**, 385 report $[\alpha]^{25}_D$ −72.8° (*c* 1.4, $CHCl_3$) for 81% ee material.

88335-90-4; **11**, 88335-91-5; (−)-**12**, 110115-15-6; (+)-**12**, 110115-16-7; **13**, 98516-02-0; (±)-**14**, 98516-05-3; *meso*-**14**-diol, 54445-64-6; (−)-**15**, 75658-86-5; (+)-**15**, 89395-28-8; (−)-**16**, 88335-95-9; (+)-**16**, 75658-85-4; **17**, 75658-84-3; **18**, 65376-02-5; **19**, 82442-72-6; **20**, 88335-96-0; **21**, 14590-54-6; pig liver esterase, 9016-18-6; *cis*-cyclobutane-1,2-dicarboxylic acid, 1461-94-5; dimethyl *cis*-cyclopropane-1,2-dicarboxylate, 20315-30-4; methyl *cis*-2(*S*)-(hydroxymethyl)-1(*R*)-cyclopropanecarboxylate, 110115-17-8.

# Simple Preparation of α-Acyl α-Arylthio Oximes (*N*-Hydroxy-2-oxoalkanimidothioates): Ambident Reactivity of α-Nitro Ketones

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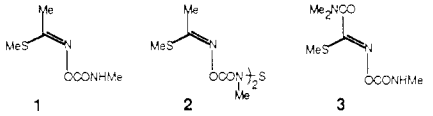
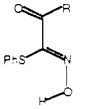
A one-step synthesis of α-acyl α-phenylthio oximes by nucleophilic dehydration of α-nitro ketones is described. Treatment of the α-nitro ketones **7a–c** (prepared by reaction of the sodium salt of nitromethane **6** with the acylimidazoles **5a–c**) with thiophenol and titanium tetrachloride in the presence of triethylamine gave the phenyl *N*-hydroxy-2-oxoalkanimidothioates **4a–c** in good yield. These products are potentially useful intermediates for the synthesis of analogues of the well-known pesticides, methomyl, thiodicarb, and oxamyl. Interestingly, when the α-nitro ketones **7a–c** are treated with thiophenol in the presence of boron trifluoride, only thioketalization is observed and the thioketals **8a–c** are produced. The stereochemistry of the oxime hydroxyl in the crystal was shown to be syn to the phenylthio group, i.e., *Z* stereochemistry, by a single-crystal X-ray structure determination. A reasonable mechanistic explanation is presented to explain the reaction pathway.

Methyl carbamate derivatives of a variety of oximes exhibit strong pesticidal activities. For example, the α-methylthio oxime carbamates—methomyl **1**, thiodicarb **2**, and oxamyl **3**—are potent acaricidal–insecticidal and nematicidal agents.[3-7] A major drawback to the use of



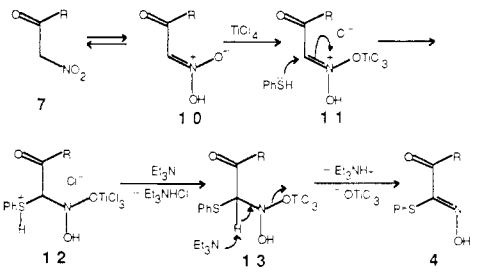
1 2 3

these compounds as commercial insecticides is their high mammalian toxicity. A large amount of effort has been expended in structure–activity and analogue studies in order to improve the effectiveness of these compounds as pesticides and to lower their toxicity.[3] However, few, if any, α-acyl derivatives of α-alkylthio or α-arylthio oximes have ever been prepared. We now report a very efficient synthesis of three α-acyl α-phenylthio oximes, **4a–c**, in only two steps from simple acylimidazoles with a key nucleophilic step that is sensitive to the Lewis acid used.

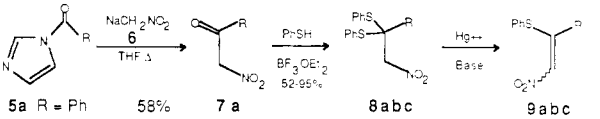


**4a** R = Ph
**4b** R = Et
**4c** R = Me

**Scheme I**



For another project in our laboratory, we required a quick route to β-phenylthio nitroolefins and chose to prepare them from α-nitro ketones via the corresponding dithioketals.[8] Thus the acylimidazoles **5a–c** were reacted with the preformed sodium salt of nitromethane **6** in THF to give good yields (60–80%) of the α-nitro ketones **7a–c**.



| | | |
|---|---|---|
| **5a** R = Ph | 58% | **7a** |
| **5b** R = Et | 70% | **7b** |
| **5c** R = Me | 80% | **7c** |

Formation of the bis(phenylthio) ketals **8a–c** occurred in excellent crude yields (isolated yields 52–95%) by treatment of **7** with thiophenol and boron trifluoride etherate.[8] These in turn were converted into the desired substituted functionalized olefins **9a–c** by treatment with mercuric salts and base.[8]

However, when a solution of the α-nitro ketone **7a** in dry THF at 25 °C was mixed with 1 equiv of titanium tetrachloride and then treated with a mixture of thiophenol and

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