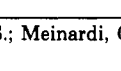
from the substituted camphor to give 7, which is attacked by thiophenoxide from the less hindered face to give trans product. Clauss et al.[3] also showed that 4-acetoxyacetidin-2-one reacts with 2 equiv of piperidine in the nonnucleophilic solvent acetonitrile to give 3-piperidinoacrylamide. It seemed probable that 7 was formed in this reaction too and that it was trapped by piperidine to give the product.

We extended this latter reaction to **5** in aqueous solutions of piperidine, reasoning that if 7 is an electrophilic intermediate in reactions of 1–6 (and other 4-substituted azetidin-2-ones) in aqueous solution, then added nucleophiles, e.g. piperidine, should compete with lyate species and trap it. When piperidine is the nucleophile, 3-piperidinoacrylamide should be the product. When reactions of **5** were carried out in piperidine buffer, pH 11.92, repetitive UV scans of the reaction mixture showed an increase in absorbance at $\lambda_{max}$ 280 nm, consistent with formation of *p*-chlorothiophenolate ion and 3-piperidinoacrylamide (Experimental Section). The difference spectrum corresponded to that of 3-piperidinoacrylamide. This reaction was not catalyzed by piperidine (Results) and the pseudo-first-order rate constant was correctly predicted from eq 2, pH and the constants of Table I (Results). When 4-acetoxyazetidin-2-one was allowed to react in piperidine buffer solution, a single absorption at 287 nm characteristic of 3-piperidinoacrylamide was obtained. For 1–6 these results support the rate-determining formation of 7 (Scheme I), which may be quickly trapped by piperidine. 4-Acetoxyazetidin-2-one similarly reacts and it seems likely that other 4-substituted azetidin-2-ones also react to give 7 transiently.[28]

Stirling et al.[2,13,14] studied olefin-forming elimination reactions with leaving groups whose ranks spanned ca. 16 powers of 10 in reactivity, and they concluded that there is no correlation between leaving tendency and $pK_a$ of conjugate acids of nucleofuges, except within a congeneric series such as 2-(aryloxy)ethyl phenyl sulfones for which $\beta_{lg} = -0.4$.[13] Similarly, there is no correlation between leaving tendency (log $k_2$) and $pK_a$ of conjugate acids of leaving groups for reactions of 1–6 and 4-(aryloxy)azetidin-2-ones. However, within each series of compounds a good correlation exists. Thus for 1–6, $\beta_{lg} = -0.89$, which may be compared with values of −0.65 and −0.75 for similar reactions of 4-(para-substituted phenoxy)azetidin-2-ones and 4-(para-substituted phenoxy)-3,3-dimethylazetidin-2-ones, respectively.[1] For azetidinones, these measures of mechanism suggest that transition states for loss of thiophenoxide ions from anions of 1–6 appear later along the reaction coordinate than do those of comparable phenoxy derivatives. This is in accord with the lower ranks of thiophenoxides than phenoxides in elimination reactions of 1–6 and analogous phenoxy compounds, despite the fact that thiophenols are 2 to 3 orders of magnitude more acidic than phenols.[5,14] Thus phenoxides leave 4–7 times more quickly than thiophenoxides in this system.

In regard to the lower ranks of thiophenoxides than phenoxides, back bonding of an electron pair into sulfur's d orbitals has been invoked to account for transition state stabilization in reactions of thiolates with $\alpha,\beta$-unsaturated compounds[16] and with carbonyl compounds.[17,18] For 1–6, such use of d orbitals could impart stability to ground states of the lactam anion




An alternative possibility for stabilization of ground states is suggested by results of ab initio SCF-MO calculations of thiomethyl anion, $HSCH_2^-$, that implicate polarization of sulfur rather than d orbital conjugation.[19] Van der Waals–London attraction[20] may also have a stabilizing role.

A comparison of $\rho$'s for 1–6 (1.95) and 4-(para-substituted phenoxy)azetidin-2-ones (2.2)[1] indicates that 1–6 experience a slightly smaller change in charge than phenoxy compounds in the transition states for the nucleofugic step, $k_2$ (Scheme I). This result finds a parallel in ionization of thiophenols and phenols for which $\rho$'s are 1.81[5] and 2.11,[15] respectively. Possibly, because of sulfur's large size and greater polarizability, sulfur in 1–6 carries a larger share of the charge in the transition state than does oxygen in analogous oxygen isosteres.

Our results show that phenoxides are higher ranked nucleofuges than analogous thiophenoxides and that a simple quantitative structure activity relationship, e.g. log $k_2$ vs $pK_a$, does not describe nucleofugality in these azetidin-2-ones. The possibility for developing such a QSAR seems small when the effect of replacing O or S by Se on reactivity is considered. Relative reactivity in the series is Se:O:S = 290:3.6:1.[21] For eliminations from 2-(arylseleno)-, 2-(aryloxy)-, and 2-(arylthio)ethyl phenyl sulfones,[2] the relative reactivities are 50:1.6:1.

**Acknowledgment.** Grateful acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society.

**Registry No.** 1, 31898-69-8; 2, 68960-59-8; 3, 129001-78-1; 4, 129287-21-4; 5, 68960-60-1; 6, 129287-22-5; $H_2NC(O)CH{=}CHO^-K^+$, 129314-70-1; $D_2$, 7782-39-0.

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## Lipase-Catalyzed Stereoselective Thiotransesterification of Mercapto Esters

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*Received February 16, 1990*

Hydrolytic enzymes such as lipases, esterases, and proteases have been used extensively as catalysts in enantioselective and regioselective synthesis.[1] Many chiral synthons like alcohols,[2] amines,[3] and acids[4] have been prepared in high optical purity via enzymatic hydrolysis in water, or via esterification, transesterification, and aminolysis in organic solvents. Surprisingly, very little attention has been paid to the enzymatic resolution of thiols, in spite of their importance as chiral building blocks. In this work we report that lipases can be used for the preparation of optically active thiols. Acetyl thioesters **1** and **2** were chosen as model compounds, because they are versatile intermediates in the synthesis of antihypertensive agents[5] and other drugs of clinical interest.[6]

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0022-3263/90/1955-5657$02.50/0 

**Table I. Enzymatic Resolution of Thiols 1 and 2**

| | | | | | thiol | | | | thioester | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| substrate | nucleophile | enzyme | time (h) | conv, (%) | yield (%) | $[\alpha]^{25}_D$[a] (deg) | cont | ee (%) | yield (%) | $[\alpha]^{25}$ (deg) | conf | ee (%) |
| 1 | $H_2O$[b] | lipase P | 1 | 60 | n.i.[E] | | | | 30 | −29.7[a] | S[d] | 45[e] |
| 1 | propanol[c] | lipase P | 24 | 60 | 32 | +16.1 | R | 54[g] | 31 | −61.3 | S | 93 |
| 1 | $H_2O$ | PPL | 5 | 60 | n.i. | | | | 28 | −13.1 | S | 20 |
| 1 | propanol | PPL | 72 | 51 | 39 | +26.2 | R | 88 | 42 | −62.7 | S | 95 |
| 2 | $H_2O$ | lipase P | 4 | 65 | n.i. | | | | 30 | −15.3[h] | S[i] | 11[j] |
| 2 | propanol | lipase P | 32 | 55 | 28 | +27.1 | R | 45[k] | 40 | −110 | S | 80 |

[a] $[\alpha]^{25}_D$ (c = 1, $CHCl_3$). [b] All the hydrolytic reactions were performed in 0.05 N phosphate buffer, pH 7 (25 mL) at 25 °C; substrate, 11 mmol; enzyme, 150 mg. [c] Not isolated. [d] Determined on the basis of the specific rotation of (S)-(−)-1, obtained from commercially available (S)-(−)-3-(acetylthio)-2-methylpropionic acid. [e] Estimated by $^1H$ NMR in the presence of Eu(hfc)$_3$. [f] All the transesterification reactions were performed in 1-hexane (17 mL) and 1-propanol (50 mmol); substrate,s 11 mmol; enzyme, 2 g. [g] Determined on the basis of the optical purity of the (R)-(+)-1 obtained by chemical acetylation of the thiol. [h] $[\alpha]^{25}_{578}$ (c = 1, $CHCl_3$). [i] The specific rotation of (R)-(+)-2 is $[\alpha]^{25}_{578}$ = +137.5° (c = 1, $CHCl_3$).[7a] [j] Determined by $^{13}C$ NMR satellite/Eu(hfc) method.[7] [k] Determined by $^{31}P$ NMR method.[9]

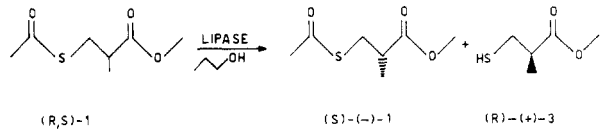


Figure 1.

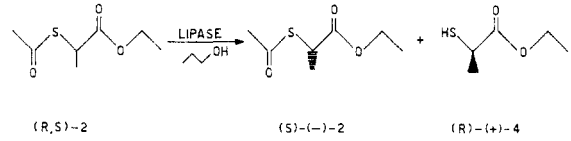


Figure 2.

Various chemical methods for the preparation of optically active thiols have been described, but they use sophisticated procedures, and they are not widely applicable to compounds that are prone to racemization.[7] Our experimental strategy was based on the ability of lipases to catalyze the hydrolysis of carboxylic esters. In order to find a stereoselective enzyme, we tested several commercially available lipases[8] for the hydrolysis of compounds **1** and **2**. The reactions were carried out at pH 7 and 25 °C. The pH was maintained constant by addition of 0.5 N aqueous NaOH. Periodically aliquots were withdrawn and analyzed by GLC and TLC. All the enzymes showed good activity on both substrates, but unfortunately a very poor stereoselectivity (Table I) and chemoselectivity. In all reactions we observed that both ester groups were hydrolyzing with the thioester unit being more susceptible.

It is known that enzymatic selectivity can dramatically change when going from water to organic solvents.[10] Therefore, the transesterification reaction of compounds **1** and **2** in organic solvents was investigated by using the same enzymes employed in the hydrolytic approach with 1-propanol as the nucleophile. Racemic **1**, or **2**, and 1-propanol in a molar excess were dissolved in hexane, powdered enzymes were added to the solution, and the suspensions were shaken on an orbital shaker at 200 rpm at 25 °C. The reactions were stopped at different degrees of conversion and worked up as described in the Experimental Section for the isolation of the products.

In the case of the primary thiol **1**, porcine pancreatic lipase and lipase P displayed good activity, with high chemoselectivity and stereoselectivity.[11] Both enzymes catalyzed only the thiotransesterification reaction (Figure 1) without affecting the ester moiety. Moreover, it was found that these enzymes reacted preferentially with the *R* enantiomer. Consequently, at the end of the reaction, the remaining thioester was enriched in the *S* form and the thiol was produced in the *R* form (Table I).

In the case of compound **2**, only lipase P catalyzed the thiotransesterification reaction (Figure 2), showing good chemoselectivity but a lower stereoselectivity than that observed for the primary thiol (Table I).

The enantiomeric excess of (*R*)-**3** was determined, after transformation to (*R*)-**1** by chemical acetylation, by using the 300-MHz $^1H$ NMR/Eu(hfc) method. The optical purity of (*S*)-**2** was determined by the 300-MHz $^{13}C$ NMR/Eu(hfc) method.[7a] Since the chemical acetylation of the thiol (*R*)-**4** to give (*S*)-**2** was accompanied by a partial racemization, enantiomeric excess of this compound was directly determined by the 300-MHz $^{31}P$ NMR method.[9]

The results of this study demonstrate that not only the stereoselectivity but also the chemoselectivity of lipases, in organic solvents, are radically different from those in water. In addition, we discovered that enantioselectivity is tightly related to the presence of the sulfur atom in the molecule. In fact when methyl (*R,S*)-3-acetoxy-2-methylpropionate (analogue to **1** but with an oxygen atom instead of the sulfur) was tested in the lipase P catalyzed transesterification reaction, at 50% conversion we isolated almost racemic starting material and methyl 3-hydroxy-2-methylpropionate.

The application of the thiotransesterification reaction on different thiol-containing substrates is currently under investigation.

## Experimental Section

$^1H$ NMR spectra were recorded in $CDCl_3$ solution, using $(CH_3)_4Si$ as internal standard. $^{13}C$ NMR spectra were recorded in $CDCl_3$ solution, using $CDCl_3$ as internal standard. $^{31}P$ NMR were recorded in $CDCl_3$ solution, using 85% $H_3PO_4$ as external standard. GLC analyses were carried out with a 2 m × 4 mm SP 2100 3% column. Lipase P from *Pseudomonas cepacia* (30 units/mg) was purchased from Amano Chemical Co., porcine pancreatic lipase (13 units/mg) was purchased from Sigma Chemicals Co., and lipase of from *Candida cylindracea* (360 units/mg) was purchased from Sankyo Co. Ltd.

**Methyl (*R,S*)-3-(Acetylthio)-2-methylpropionate (1).** Methyl methacrylate (20 g, 200 mmol) was added dropwise to thioacetic acid (25 g, 330 mmol). The mixture was allowed to react for 6 h at 95 °C, and then was distilled under reduced pressure. The fraction boiling at 115–130 °C (3–4 mm) was collected, giving

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(11) Lipase from *C. cylindracea* was also active in the transesterification reaction, but at 70% of conversion we obtained a mixture of 30% of **1**, 35% of **3**, 30% of propyl 3-mercapto-2-methylpropionate, and 5% of propyl 3-(acetylthio)-2-methylpropionate. All the other tested lipases showed no activity on compound **1**.

30 g (85% yield) of (*R,S*)-1; $^1$H NMR ($CDCl_3$) $\delta$ 3.68 (3 H, s), 3.15–2.98 (2 H, m), 2.73–2.62 (1 H, m), 2.31 (3 H, s), 1.22 (3 H, d). Anal. Calcd for $C_7H_{12}O_3S$: C, 47.71; H, 6.86; S, 18.19. Found: C, 47.50; H, 7.00; S, 18.22.

**Ethyl (*R,S*)-2-Mercaptopropionate (4).** 2-Mercaptopropionic acid (20 g, 189 mmol) and *p*-toluenesulfonic acid (200 mg, 1 mmol) were dissolved in ethanol (200 mL). The solution was refluxed for 16 h, and the solvent was evaporated. The residue was dissolved in ether, washed with 5% aqueous sodium hydroxide, dried ($Na_2SO_4$), and evaporated to dryness, affording 25 g (98% yield) of (*R,S*)-4; $^1$H NMR ($CDCl_3$) $\delta$ 4.17 (2 H, q), 3.50 (1 H, m), 2.13 (1 H, d), 1.52 (3 H, d), 1.28 (3 H, t). Anal. Calcd for $C_5H_{10}O_2S$: C, 44.75; H, 7.51; S, 23.89. Found: C, 44.61; H, 7.55; S, 23.95.

**Ethyl (*R,S*)-2-(Acetylthio)propionate (2).** Acetyl chloride (16 g, 205 mmol), dissolved in anhydrous diethyl ether, was added dropwise to a solution of (*R,S*)-4 (26 g, 194 mmol) and triethylamine (30 g, 208 mmol) in anhydrous diethyl ether (300 mL). The mixture was stirred overnight at room temperature. The precipitate was filtered off, and the solution was washed with 5% hydrochloric acid and dried ($Na_2SO_4$). The solvent was evaporated, and the residue was purified by chromatography on silica gel, using hexane/ether (95:5) as eluant, affording 25.9 g (76% yield) of (*R,S*)-2; $^1$H NMR ($CDCl_3$) $\delta$ 4.10 (1 H, q), 4.06 (2 H, q), 2.28 (3 H, s), 1.46 (3 H, d), 1.22 (3 H, t). Anal. Calcd for $C_7H_{12}O_3S$: C, 47.71; H, 6.86; S, 18.19. Found: C, 47.63; H, 6.77; S, 18.24.

**Enzymatic Hydrolysis of Methyl (*R,S*)-3-(Acetylthio)-2-methylpropionate (1).** To a magnetically stirred suspension of (*R,S*)-1 (2 g, 11 mmol) in 0.05 N phosphate buffer, pH 7 (25 mL), at 25 °C was added porcine pancreatic lipase (150 mg), and the pH was maintained at 7 with 0.05 aqueous sodium hydroxide. The hydrolysis was allowed to proceed to 60% of conversion (5 h). The reaction mixture was extracted with ether. The organic layer was washed with 5% aqueous sodium hydroxide, dried ($Na_2SO_4$), and then evaporated to dryness. Chromatography on silica gel using hexane/ether (95:5) as eluant afforded 570 mg (28% yield) of (*S*)-(−)-1: $[\alpha]^{25}_D$ = −13.1° (*c* = 1, $CHCl_3$), ee = 20%.

**Enzymatic Thiotransesterification of Methyl (*R,S*)-3-(Acetylthio)-2-methylpropionate (1).** To a solution of (*R,S*)-1 (2 g, 11 mmol) and 1-propanol (3 g, 50 mmol) in hexane (17 mL) was added porcine pancreatic lipase (2 g), and the suspension was stirred at 25 °C. After 72 h (51% conversion), the enzyme was filtered off, and the solution was diluted with water and extracted with ether. The organic layer was dried ($Na_2SO_4$) and evaporated to dryness. Chromatography on silica gel with hexane/ether (95:5) as eluant afforded 840 mg (42% yield) of (*S*)-(−)-1 [$[\alpha]^{25}_D$ = −62.7° (*c* = 1, $CHCl_3$), ee = 95%] and 590 mg (39% yield) of (*R*)-(+)-methyl 3-mercapto-2-methylpropionate (3) [$[\alpha]^{25}_D$ = +26.2° (*c* = 1, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$ 3.69 (3 H, s), 2.83–2.55 (3 H, m), 1.48 (1 H, t), 1.23 (3 H, d)]. Anal. Calcd. for $C_5H_{10}O_2S$: C, 44.75; H, 7.51; S, 23.89. Found: C, 44.90; H, 7.48; S, 23.79.

**Acetylation of (*R*)-(+)-Methyl 3-Mercapto-2-methylpropionate (3).** (*R*)-3, $[\alpha]^{25}_D$ = +26.2° (*c* = 1, $CHCl_3$) (500 mg, 3.7 mmol), was dissolved in acetic anhydride (2 mL). The solution was stirred for 8 h at 60 °C. The mixture was diluted with ether and washed with aqueous sodium carbonate. The organic layer was dried ($Na_2SO_4$) and evaporated to dryness. Chromatography on silica gel with hexane/ether (95:5) as eluant afforded 550 mg (83% yield) of (*R*)-(+)-1; $[\alpha]^{25}_D$ +58.2° (*c* = 1, $CHCl_3$), ee = 88%.

**Enzymatic Hydrolysis of Ethyl (*R,S*)-2-(Acetylthio)-propionate (2).** To a magnetically stirred suspension of (*R,S*)-2 (2 g, 11 mmol) in 0.05 N phosphate buffer, pH 7 (25 mL) at 25 °C, was added lipase P (150 mg), and the pH was maintained at 7 with 0.05 N aqueous sodium hydroxide. The hydrolysis was allowed to proceed to 65% of conversion (4 h). The reaction mixture was extracted with ether, dried ($Na_2SO_4$), and evaporated to dryness. Chromatography on silica gel, using hexane/ether (98:2) as eluant, afforded 600 mg (30% yield) of (*S*)-(−)-2; $[\alpha]^{25}_{578}$ = −15.3° (*c* = 1, $CHCl_3$), ee = 11%.

**Enzymatic Thiotransesterification of Ethyl (*R,S*)-2-(Acetylthio)propionate (2).** To a solution of (*R,S*)-2 (2 g, 11 mmol) and 1-propanol (3 g, 50 mmol) in hexane (17 mL) was added lipase P (2 g), and the suspension was stirred at 25 °C. After 32 h (55% conversion), the enzyme was filtered off, and the solution was diluted with water and extracted with ether. The organic layer was dried ($Na_2SO_4$) and evaporated to dryness. Chromatography on silica gel with hexane/ether (98:2) as eluant afforded 800 mg (40% yield) of (*S*)-(−)-2 [$[\alpha]^{25}_{578}$ = −110° (*c* = 1, $CHCl_3$), ee = 80%] and 426 mg (28% yield) of (*R*)-(+)-4 [$[\alpha]^{25}_D$ = +27.1° (*c* = 1, $CHCl_3$), ee = 45%].

**Registry No.** (*R,S*)-1, 97101-46-7; (*S*)-(−)-1, 86961-08-2; (*R*)-(+)-1, 86961-07-1; (*R,S*)-2, 128899-61-6; (*S*)-(−)-2, 128822-70-8; (*R*)-(+)-3, 86961-09-3; (*R*)-(+)-4, 103616-07-5; (*R,S*)-4, 66707-26-4; methyl methacrylate, 80-62-6; thioacetic acid, 507-09-5; 2-mercaptopropionic acid, 79-42-5; lipase P, 9001-62-1.

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# An Asymmetric Synthesis of Aporphine and Related Alkaloids via Chiral Formamidines. (+)-Glaucine, (+)-Homoglaucine, and (−)-8,9-Didemethoxythalisopavine

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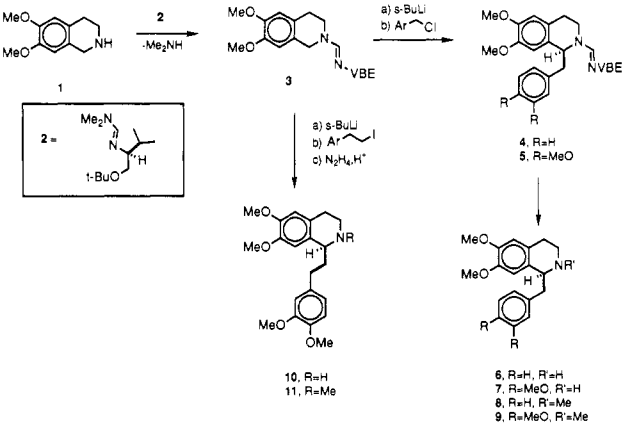
*Received March 23, 1990*

The use of chiral formamidines as a tool for reaching a number of chiral nonracemic alkaloids has been demonstrated in earlier reports from this laboratory.[1] The fact that they are prepared in either racemic fashion or as pure enantiomers makes the formamidine methodology a rather viable route to these systems and other elaborated amines.[2]

We now report further developments in this area by describing our synthesis of the natural aporphine (+)-glaucine (**12**), the homoaporphine (+)-homoglaucine (**13**), and the isopavine (−)-didemethoxythalisopavine (**15**), all reached in high enantiomeric excess starting from the readily available dimethoxytetrahydroisoquinoline **1**.[3] The




synthetic route followed was similar to that reported earlier[1] and required the attachment of the chiral auxiliary via the dimethylamino-substituted formamidine **2**. Thus, heating **1** and **2** in toluene gave the requisite formamidine **3** in 90–92% yield. The key asymmetric step in the entire sequence was implemented by metalation of **3** with *sec*-butyllithium at −78 °C followed by cooling the resulting lithio anion to −100 °C and adding the appropriate aryl-alkyl halide. In this fashion we obtained two adducts **4** and **5** prepared from addition of benzyl chloride and 3,5-

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(3) Aldrich Chemical Company, Milwaukee, WI.

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