spectra assuming a Lorentzian line shape. The radicals were detected in the solid state and also in a DMSO solution maintained in an inert atmosphere. The solution was transfered to an ESR flat quartz cell and placed inside the microwave cavity of the spectrometer.

Cyclic voltammetry was carried out at a hanging Hg drop; the cell used for electroanalytical experiments contained a working volume of 50 mL. It contained the hanging Hg drop working electrode, Pt wire secondary electrode, and SCE reference which was isolated from the electrolyte by a fine glass frit. The solution was deaerated with N_2 before analysis. Electrochemical experiments were performed with a potentiostat and an integrator.

Compounds **2** were obtained in accord with the literature.[6] Solvents were purchased from Aldrich without previous purification, except THF, which was purified following well-known standard procedures, and dried.

General Electrolysis Procedure. Electrolyses were carried out in a concentric cell with two compartments separated by a circular glass frit (medium) diaphragm. A mercury pool (diameter 5 cm) was used as the cathode and a platinum plate as the anode. The catholyte was magnetically stirred. The reductions were carried out in DMSO–anhydrous lithium perchlorate, 0.1 M. Approximately 60 mL and 20 mL of this solution were placed into the cathodic and the anodic compartments, respectively. A flow of dry nitrogen was bubbled through the catholyte solution, and the temperature was kept at 15 °C by external cooling. Anhydrous potassium carbonate (3 g) was placed in the anode compartment to prevent the accumulation of electrogenerated acid.

Solutions of **2** (0.2 mmol) were electrolyzed under a constant cathodic potencial of −1.6V vs SCE (**2a**) and −1.7V vs SCE (**2b**, **2c**). The electricity consumption was 1 Faraday per mole of **2**.

Chemical Reduction Procedure. **2** (0.2 mmol) was placed into a Schlenk tube with a stoichiometric amount of sodium amalgam (5 mg of Na in 2 mL of Hg) under argon and 20 mL of dry THF was added. After 3 min the reaction was complete. The red solution was transferred to another Schlenk tube through a Teflon tube. The THF was evaporated under vacuum. A crude red solid was obtained. The small amount of starting material which had not reacted was extracted with hexane and a crystalline red product was obtained.

Ethyl 3-(*p*-Chlorophenyl)-5-phenyl-*N*-(*p*-methylbenzylidene)-2-aminofuran-4-carboxylate anion-radical (4a): MS *m/z* (relative intensity) 445 (9, M^+ + 2), 443 (24, M^+), 342 (5), 208 (24), 207 (10), 189 (10), 178 (10), 146 (11), 120 (11), 105 (100), 91 (14), 77 (55).

Ethyl 3-(*p*-Methylphenyl)-5-phenyl-*N*-(*p*-methylbenzylidene)-2-aminofuran-4-carboxylate anion-radical (4b): MS *m/z* (relative intensity) 423 (2, M^+), 322 (3), 276 (6), 200 (8), 145 (9), 143 (9), 132 (18), 120 (34), 105 (100), 91 (23), 77 (44).

Ethyl 3,5-Diphenyl-*N*-(*p*-methylbenzylidene)-2-aminofuran-4-carboxylate anion-radical (4c): MS *m/z* (relative intensity) 409 (28, M^+), 380 (9), 333 (12), 308 (6), 208 (31), 207 (10), 193 (17), 189 (11), 178 (21), 146 (17), 132 (12), 105 (100), 91 (18), 77 (66).

Methylation of 4. Compounds **4** were generated by the electrochemical procedure (above), starting with 0.2 mmol of **2**. The electrochemical cell was then opened to air and methyl iodide (1 mmol) added to the red solution. This solution was worked up by adding 250 mL of ice–water and extracting with ethyl ether (3 × 25 mL). The organic layer was again washed with water to take the DMSO residues off. After drying over anhydrous sodium sulphate, the ether was evaporated under vacuum.

5a: MS *m/z* (relative intensity) 476 (1.4, M^+ + 2), 474 (3.6, M^+), 460 (3), 458 (5), 445 (2), 443 (4), 414 (3), 341 (8), 208 (7), 207 (6), 178 (9), 146 (24.5), 105 (100), 91 (7), 77 (28).

5c: MS *m/z* (relative intensity) 440 (7, M^+), 424 (3), 409 (24), 380 (6), 333 (8.5), 208 (25), 207 (9), 193 (15), 191 (11), 189 (9), 178 (16), 146 (16), 132 (11), 115 (10), 105 (100), 91 (20), 77 (65).

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Registry No. **2a**, 108262-51-7; **2b**, 108262-49-3; **2c**, 108262-48-2; **4a**, 141509-80-0; **4b**, 141509-81-1; **4c**, 141509-82-2; **5a**, 141526-80-9; **5c**, 141526-81-0; DMSO, 67-68-5; sodium amalgam, 11110-52-4; methyl iodide, 74-88-4.

Enzymatic Hydrolysis of Ethyl 3-Hydroxy-3-phenylpropanoate: Observations on an Enzyme Active-Site Model

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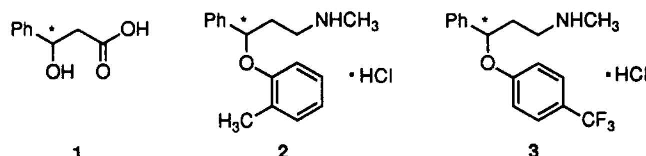
Optically active β-aryl-β-hydroxy acid derivatives are synthetically interesting, highly functionalized chiral synthons. The prototype, 3-hydroxy-3-phenylpropanoic acid (**1**), is of additional significance as a potential progenitor of optically pure tomoxetine hydrochloride (**2**) and fluoxetine hydrochloride (**3**). Both of these materials are important antidepressants,[1] with fluoxetine (Prozac, Eli Lilly Co.) exhibiting activity against such diverse conditions as anxiety, alcoholism, chronic pain, obesity, and bulimia.[1b] Preparation of these materials (or their known precursors) in optically pure form has attracted much interest,[2] although fluoxetine is currently marketed as the racemate.



Catalytic asymmetric reduction of the corresponding β-keto ester comprises the most efficient and general synthesis of β-hydroxy acid derivatives in high optical purity.[3] However, β-aryl derivatives such as ethyl benzoylacetate require long reaction times and afford diminished (but still high) optical purities compared to the alkyl species. Alternative asymmetric syntheses of 3-hydroxy-3-phenylpropanoate exhibiting varying degrees of enantioselectivity have been reported using chemical[4] and microbiological[2d,5] reduction, aldol,[6] Reformatsky,[7] Diels–

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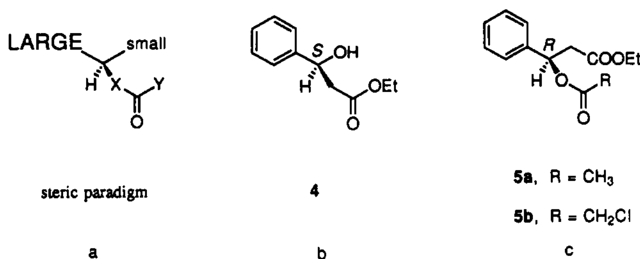
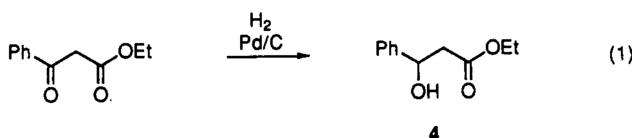


Figure 1.

Alder[8] and even organocopper conjugate addition[9] reactions, attesting to the attractiveness of this class of compounds. These latter reactions all have drawbacks, most notably the widespread need for stoichiometric chiral reagents. Clearly, the most efficient synthetic methods for the preparation of optically active materials such as this β-hydroxy ester are both simple and catalytic. We report here such a method for the chemoenzymatic preparation of both enantiomers of the parent compound, 3-hydroxy-3-phenylpropanoic acid, in high optical purity.

Most of the synthetic methods summarized above generate the β-hydroxy acid asymmetry from a prochiral precursor. A biocatalytic resolution procedure is a conceptually different but viable alternative for the simultaneous preparation of both enantiomers of 3-hydroxy-3-phenylpropanoate provided three criteria are met. First, the desired racemate must be easily prepared. Second, the biocatalytic step should be highly enantioselective and optical purity enhancement of the products should be simple. Third, there should be a convenient method for the separation of the resolved species.

A simple preparation of the racemate of ethyl 3-hydroxy-3-phenylpropanoate (**4**) was the initial requirement. An aldol reaction between ethyl acetate and benzaldehyde (LDA, THF) or, most preferably, simple catalytic hydrogenation (50 psi H_2, 5% Pd/C, ethanol) of commercially available ethyl benzoylacetate readily afforded **4** (eq 1).



Ethyl 3-hydroxy-3-phenylpropanoate has been hydrolyzed with moderately high enantioselectivity using relatively large amounts of α-chymotrypsin.[10] We sought an improved reaction (both rate and enantioselectivity) using commercially more convenient microbial lipases. However, the choice of enzyme and specific substrate must be carefully considered, as evidenced by the poor enantioselectivity observed in the attempted resolution of ethyl 3-hydroxy-3-phenylpropanoate using pig liver esterase.[11] To enhance the probability of high enantioselectivity, we focused on the readily available lipase from *Pseudomonas sp.*, since a rudimentary active-site postulate[12] could guide substrate design. This active-site model, first proposed by Laumen[12a] and later modified by others,[12b–d] is presented in Figure 1a as its simple substrate steric paradigm. It is interesting to note that this model is certainly an empirical construct and says little about the actual structure of the active site. For example, the steric model can be applied in similar fashion (where Ph = large and CH_3 = small) to both α-phenethyl acetate (X = O, Y = CH_3) and methyl 3-phenylbutyrate (X = CH_2, Y = OCH_3),[12a] although the leaving alcohol groups in these cases point in opposite directions (making equal interactions with the protonating general acid difficult). Despite these mechanistic inconsistencies, the active site steric model is empirically useful for either type of substitution pattern. This diversity allows consideration of two potential reactivity sites on the ethyl 3-hydroxy-3-phenylpropanoate backbone for enzymatic resolution, either the terminal ester moiety or an acyl derivative of the hydroxyl substituent. Examination of the active-site model and contemplation of earlier examples suggested that hydroxy ester **4** would probably be a poor substrate for this enzyme, since a hydrophilic hydroxyl group capable of hydrogen-bonding and even hydration would be directly attached to the chiral center and would necessarily take the place of a normally small hydrophobic moiety, most often a methyl group (Figure 1b).[12,13] However, using an ester derivative of the alcohol **4** as the functional handle would provide a carbethoxy analog of α-phenethyl acetate for which the enzyme from *Pseudomonas sp.* reacts essentially enantiospecifically.[12a,13a,b] This simple analysis suggested that the acetyl derivative of ethyl 3-hydroxy-3-phenylpropanoate should match the steric requirements (Ph = large; CH_2COOEt = small) of the enzyme (Figure 1c).

The acetate **5a**, prepared from **4** (Ac_2O, Et_3N, CH_2Cl_2), was submitted to enzymatic hydrolysis using lipase PS-30 from *Pseudomonas sp.* (Amano International Enzyme Co.) in aqueous pH 7 phosphate buffer kept at constant pH 7.00 by automatic titration. Although the enzymatic reaction exhibited very high *R* enantioselectivity, the hydrolysis was very slow and surprisingly afforded *R*-hydroxy acid **1** (94% ee)[14] instead of hydroxy ester **4** as the product along with recovered *S*-**5a** (96% ee),[15] for an apparent enantioselectivity *E* value of >100.[16] The expected product **4** was surmised to be a reaction intermediate, since the enzymatic hydrolysis of a derivative with enhanced acyl reactivity, chloroacetate **5b**, initially afforded *R*-**4** that was further hydrolyzed to **1**. Of particular interest was the reduced optical purity of the final product **1** (86% ee)[14] compared to intermediate **4** (>95% ee)[17] when isolated from an incomplete **5b** enzymatic hydrolysis. Although double resolution of **5** due to the two hydrolysis steps was not ob-

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(14) The enantiomeric excess of **1** was determined by conversion to methyl ester **6** (see Experimental Section), derivatization with (*S*)-MTPA chloride,[19] and ^{1}H NMR analysis.

(15) The enantiomeric excess of **5a** was determined by hydrolysis to hydroxy acid **1** and analysis as above.[14]

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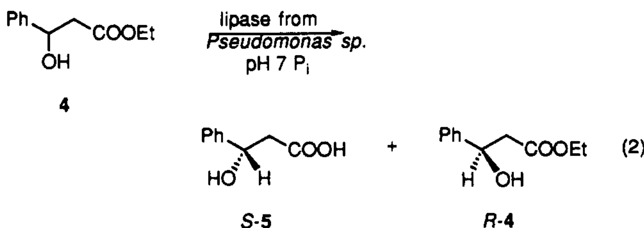
(17) The enantiomeric excess of **4** was determined by ^{1}H NMR analysis of its (*R*)-MTPA ester.[19]

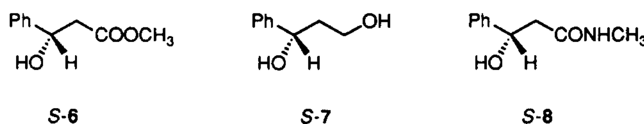
served (the overall *R* enantioselectivity of the hydrolysis of **5a** was apparently defined by the first hydrolysis step), the optical purity differences of **4** and **1** indicated that the sequential hydrolysis of **5** and then **4** possessed, to some extent, opposite enantioselectivities. In fact, analysis as pictured in Figure 1b would account for *S* enantioselectivity in the hydrolysis of **4**, despite the discouraging active-site considerations detailed above. This paradox concerning the required electronic character of the small substituent suggested that an investigation of the enzymatic hydrolysis of hydroxy ester **4** using the lipase from *Pseudomonas sp.* would be enlightening. In addition, a potential synthetic strategy based on an enantioselective hydrolysis of **4** rather than **5** would have significant substrate preparation, reaction simplicity, and product isolation advantages.

The enzymatic hydrolysis of **4** using the lipase from *Pseudomonase sp.* (aqueous pH 7 phosphate buffer, constant pH 7.00) was more than an order of magnitude faster than that of **5a**, demonstrating kinetic competence of **4** during **5a** hydrolysis. The enantioselectivity of the enzymatic hydrolysis was surprisingly high, exhibiting an *E* value of 37 with the *S* enantioselectivity inherently required by the active-site model as pictured in Figure 1b (recovered (+)-**4** compares with known *S*-(−)-**4**).[4a] The enhanced rate and reduced enantioselectivity of the enzymatic hydrolysis of **4** compared to that of **5** accounts for the lack of sequential configurationally opposite resolutions in the enzymatic hydrolysis of **5**.

For product optical purity optimization, the enzymatic hydrolysis of **4** was halted just before 40% conversion as measured by base uptake to afford a mixture of *S*-**1** and residual substrate *R*-**4** (eq 2). A simple separation of these species, the next requirement, was conveniently achieved by aqueous base extraction. The isolated *S*-**1** thus recovered possessed 93% ee[14] and could be readily recrystallized to optical purity. Continuing the enzymatic hydrolysis of recovered *R*-**4** with the lipase from *Pseudomonas sp.* for an additional 20% conversion afforded *R*-**4** of >98% ee[17] after extractive separation from the **1** generated. Thus optically pure *S*-**1** and *R*-**1** (available from *R*-**4** by simple base hydrolysis) can be readily obtained through a simple sequence of reactions, suggesting that the active site of this enzyme would accept the hydrophilic hydroxyl group in place of a hydrophobic methyl group. This unexpected versatility greatly expands the scope of substrates considered acceptable to this enzyme.



The optically pure hydroxy acid **1** could be conveniently converted to the corresponding esters **4** and **6** without loss of optical purity (EtI or MeI, respectively, $KHCO_3$, acetone, reflux). These optically pure acid and ester synthons can be directly converted to two known precursors of optically pure fluoxetine and tomoxetine, diol **7**[2b] from reduction of optically pure **1** (BH_3, THF) and amide **8** as documented from **4**.[2d]



Experimental Section

General. Solvents and reagents were used as received from Kodak Laboratory and Research Products, J. T. Baker Chemical Company, or Aldrich Chemical Company. pH 7 phosphate buffer was obtained from VWR. Lipase PS-30 from *Pseudomonas sp.* was obtained from Amano International Enzyme Company. Microanalyses were performed by the Analytical Sciences Division, Kodak Research Laboratories. All melting points are uncorrected.

Ethyl 3-Hydroxy-3-phenylpropanoate (4). Ethyl benzoylacetate (19.21 g, 0.10 mol) was dissolved in 95% ethanol (100 mL) in a Parr bottle. The bottle was purged with nitrogen and 5% palladium on carbon (960 mg; 5 wt %) was added. The vessel was placed under 45 psi H_2 and shaken on a Parr apparatus for 14 h at which time H_2 uptake had halted and TLC analysis indicated no starting material. The reaction mixture was suction-filtered through Celite with a top sand layer (to prevent channels) and eluted with ether. The filtrate was concentrated to afford **4** (19.17 g; 99%), which exhibited spectral data identical to those previously reported.[5a]

Enzymatic Hydrolysis of Ethyl 3-Hydroxy-3-phenylpropanoate. Racemic **4** (7.77 g, 40.0 mmol) was combined with pH 7 phosphate buffer (35 mL) and placed on an automatic titrator, and the pH was adjusted to 7.00. Lipase PS-30 from *Pseudomonas sp.* (400 mg) was added and the hydrolysis commenced. The reaction mixture was maintained at pH 7.00 by automatic titration and followed by the uptake of 1.000 N NaOH. After 6.5 h at room temperature, 15.71 mL of 1.000 N NaOH had been consumed (39.3% conversion) and the reaction was halted. The reaction mixture was diluted with aqueous $NaHCO_3$ and extracted three times with ether. After a single back-extraction with saturated aqueous $NaHCO_3$, the combined organic solution was set aside.

The combined aqueous solution was acidified to pH 1 with 3 N HCl and extracted two times with ether and once with ethyl acetate. The extracts were dried ($MgSO_4$) and concentrated to afford 2.60 g (39%) of *S*-(−)-**1**, 93% ee,[14] as a white solid. This material was recrystallized from warm *tert*-butyl methyl ether (25 mL) by the addition of hexanes (25 mL) and cooling to −20 °C. Optically pure *S*-**1** (2.15 g, 32%) was collected as white needles, mp 117–119 °C: ^{1}H NMR (CD_3CN) δ 7.6–7.2 (m, 5 H), 5.07 (t, 1 H, J = 6.65 Hz), 4.9 (s, 2 H), 2.68 (d, 2 H, J = 6.73 Hz); IR (KBr, cm^{-1}) 3500–2400 (s, b), 1700 (s), 1595 (w), 1505 (w); EIMS *m/e* 166 (M^+), 148 ($M^+ - H_2O$); $[\alpha]^{22}_D$ −18.9° (*c* 2.27, EtOH), lit.[10] (*R*)-**1**, $[\alpha]^{22}_D$ +21.1° (*c* 2.2% EtOH).[10] Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07; N, 0.0. Found: C, 65.28; H, 6.00; N, <0.3.

The initial organic solution set aside above was dried ($MgSO_4$) and concentrated to afford 4.51 g (58%) of *R*-**4**, which was resubmitted to the above reaction conditions. After 43 h the enzymatic hydrolysis had consumed 7.613 mL of 1.000 N NaOH (20% further conversion) and was halted by the addition of saturated aqueous $NaHCO_3$ and extracted three times with ether. The combined extracts were dried ($MgSO_4$) and concentrated to afford 2.82 g (36% overall) of *R*-(+)-**4**, >98% ee.[17] All achiral properties of **4** are as described previously:[5a] $[\alpha]^{20}_D$ +44.0° (*c* 1.015, $CHCl_3$), lit.[4a] for *S*-(−)-**4**, $[\alpha]^{22}_D$ −40.8° (*c* 1.03, $CHCl_3$).[4a]

(*R*)-3-Hydroxy-3-phenylpropanoic Acid (*R*-1). Ester *R*-**4** recovered from the enzymatic hydrolysis (1.00 g, 5.15 mmol) was dissolved in methanol (10 mL). A 10% aqueous solution of sodium hydroxide (10 mL; excess) was added and the reaction mixture was stirred at room temperature overnight, at which time no ester was detectable by TLC analysis. The reaction mixture was diluted with ether and extracted three times with saturated sodium bicarbonate. The ethereal solution was discarded and the combined aqueous extracts were acidified to pH 1 with 3 N HCl and extracted twice with ether and twice with ethyl acetate. The combined organic extracts were dried ($MgSO_4$) and concentrated to afford 850 mg (99%) of *R* acid **1**. This was recrystallized from warm *tert*-butyl methyl ether (8 mL; 10 mL/g) by the addition of one volume of hexanes and chilling to afford 686 mg (80%) of optically pure *R*-(+)-**1**, mp 117–119 °C, >98% ee.[14] All achiral properties of **1** are as reported above; $[\alpha]^{22}_D$ +18.7° (*c* 2.195, EtOH).

Methyl (*S*)-3-Hydroxy-3-phenylpropanoate (*S*-6). Optically pure *S*-**1** (20.0 g, 0.12 mol) was dissolved in acetone (60 mL). To this were added potassium bicarbonate (24 g, 0.24 mol; 2 equiv)

and iodomethane (15 mL, 0.24 mol; 2 equiv). The reaction mixture was heated at 60 °C for 24 h to completely consume 1 according to TLC analysis. The reaction mixture was concentrated to small volume, diluted with water, and extracted three times with ether. The combined extracts were dried ($MgSO_4$) and concentrated to afford 21.2 g (98%) of *S*-6. The spectral characteristics of 6 were identical to those reported;[6a] $[\alpha]^{24}_D$ −18.8° (*c* 4.735, EtOH), lit.[18] for *R*-6, $[\alpha]^{24}_D$ +18.3° (*c* 4.78, EtOH).

Ethyl (*S*)-3-Hydroxy-3-phenylpropanoate (*S*-4). By a similar procedure to that described for 6 above, *S*-1 (337 mg, 2.03 mmol) was treated with potassium bicarbonate (2.0 g, 20 mmol; 10 equiv) and iodoethane (1.6 mL; 20 mmol; 10 equiv) in 2.5 mL of acetone at reflux for 36 h to afford *S*-4 (327 mg; 83%). All achiral properties of 4 are as described previously;[5a] $[\alpha]^{20}_D$ −50.8° (*c* 1.070, $CHCl_3$).

(*S*)-1-Phenyl-1,3-propanediol (*S*-7). Optically pure hydroxy acid *S*-1 (1.66 g, 10.0 mmol) was dissolved in THF (20 mL) and cooled to 0 °C. A 1.0 M solution of borane in THF (21 mL, 21 mmol; 2.1 equiv) was added (frothing) and the reaction mixture was warmed to room temperature for 1 h to completely consume 1 as determined by TLC analysis. Aqueous sodium hydroxide was added and the mixture was heated to 60 °C for 3 h to cleave the borate. The mixture was cooled to room temperature and extracted three times with ether. The combined extracts were dried ($MgSO_4$) and concentrated to afford 1.59 g of crude *S*-(−)-7 that solidified upon chilling (−20 °C). This was dissolved in methylene chloride (7.5 mL, 5 mL/g) and hexanes (7.5 mL, one volume) was added. This resulted in a phase separation which upon cooling (−20 °C) overnight afforded *S*-7 (1.47 g; 97%) as white needles, mp 63–65 °C: ^{1}H NMR ($CDCl_3$) δ 7.4–7.2 (m, 5 H), 4.869 (dd, 1 H, *J* = 4.04 Hz, *J* = 8.52 Hz), 3.789 (m, 2 H), 3.6 (s, 1 H), 3.14 (s, 1 H), 2.05–1.8 (m, 2 H); IR (KBr, cm^{-1}) 3350 (s, b), 1605 (w), 1485 (w); EIMS *m*/*e* 152 (M^+), 134 ($M^+ - H_2O$), 107 ($M^+ - CH_2CH_2OH$); $[\alpha]^{21.5}_D$ −70.5° (*c* 1.015, $CHCl_3$), lit.[6h] for *S*-7,[6h] $[\alpha]^{21.5}_D$ −63.0° (*c* 0.958, $CHCl_3$). Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95; N, 0. Found: C, 70.98; H, 7.80; N, <0.3.

Registry No. *S*-1, 36567-72-3; *R*-1, 2768-42-5; (±)-4, 86286-51-3; *R*-4, 72656-47-4; *S*-4, 33401-74-0; *S*-6, 36615-45-9; *S*-7, 96854-34-1; ethyl benzoylacetate, 94-02-0.

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Access to Unstabilized Secondary Vinylphosphines by Chemoselective Reduction of Vinylphosphinates or by P-Alkylation of the Primary Vinylphosphine

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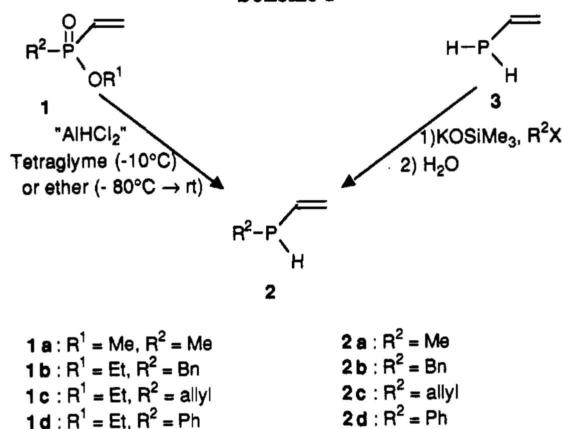
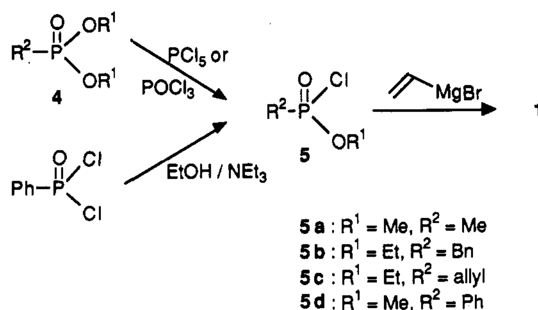
Primary and secondary alkenylphosphines, because of their multifunctionalities, present considerable potential as organophosphine ligands and for hydrophosphorylation reactions.[1,2] Among these derivatives, the vinylphosphines which can be furthermore considered as potential precursors of η^3 phospha–allyl–metal complexes[3] and phosphaalkenes[4] have been very poorly investigated. The lack of development of their chemistry came probably from the fact that they were long thought to be intrinsically unstable because of the high reactivity of the P–H bond toward their own unsaturation. The low yield obtained in the synthesis of some unstabilized derivatives was regarded as a confirmation of this assumption.[5–7] The fact that simple primary vinylphosphines, which were recently obtained by vacuum gas-phase thermolysis[8] from their corresponding anthracenic adducts, show a reasonable stability should encourage further development of their chemistry. We have already reported a preparative-scale synthesis of unstabilized primary vinylphosphines by a chemoselective reduction of the corresponding vinylphosphonic esters.[9] Since only few kinetically stabilized secondary vinylphosphines were described in the literature,[3c,4] a more general approach was needed. We present herein two routes to these species which involve chemoselective reduction of vinylphosphinic esters 1 (method A) or P-alkylation of the free vinylphosphine parent com-

Scheme I



Scheme II



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