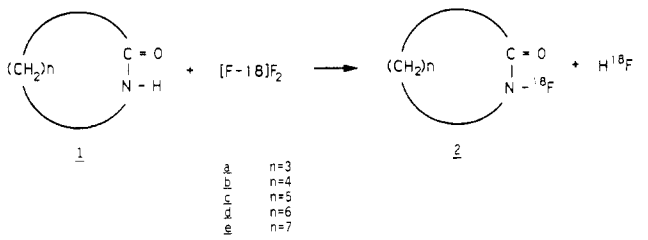
Table I. Formation of *N*-[^{18}F]Fluorolactams

[^{18}F]fluorolactam	isolated chemical yield,[a]	^{19}F NMR,[b] ppm
2a	76 (41)	-69.98
2b	61 (33)	-50.66
2c	79 (42)	-42.56
2d	71 (48)	-65.93
2e	33 (19)	-66.64

[a] Isolated chemical yields of *N*-fluorolactams are based on fluorine gas, the limiting reagent. Radiochemical yields (corrected for decay) are given in parentheses and are calculated from chromatographic data (HPLC and TLC). It should be noted that in this reaction the theoretical maximum radiochemical yield is only 50% since half of the activity is lost as H^{18}F during the formation of **2**. [b] After complete decay of the radioisotope at -20 °C (~24 h), the fluorolactams could be analyzed by ^{19}F NMR spectroscopy. These chemical shift values are identical with the literature values.[11,12]

Scheme I



cyclic amides (neat or in aqueous solution) with 100% F_2 has been reported to yield *N*-fluorolactams in low yields.[11] In this work we report that the yields of fluoroamides are excellent when the cyclic amides **1a-e** are reacted in freon with diluted ^{18}F-labeled fluorine (0.05% in neon)[13] (Table I and Scheme I).

Also, the [^{18}F]fluorolactams **2** reacted generally smoothly with various Grignard reagents to give the fluoro derivatives **4** (Table II). The mechanism for this reaction is currently under investigation. It is likely, however, that the fluorine in **2** could become slightly electron deficient due to its p-orbital electrons back-bonding into the π-electron system of the amide,[12,14,15] enabling fluorination of basic anions, e.g. Grignard reagents. On the other hand, the fluorolactams **2** failed to produce any aryl fluorides when treated with phenyllithium. This is probably due to the major side reaction of β-elimination of HF from **2** by the very strong basic anions such as phenyl lithium.[12]

In summary, we have shown that a number of *N*-fluorolactams can be prepared from readily available amides in good yields. The mild, regiospecific, and facile reaction of these *N*-fluoro derivatives with Grignard reagents are the attractive features of these electrophilic substitution reactions. The full range and limitations of these fluorination reactions are yet to be evaluated. However, *N*-fluorolactams show great promise as fluorinating agents because of their easy accessibility from F_2 and its ^{18}F-radiolabeled counterpart and they complement other related reactions reported recently.[5,6,8]

Experimental Section

Proton-decoupled ^{19}F NMR spectra in $CDCl_3$ were recorded on a Bruker WM 500 spectrometer with Freon as an internal standard. High-pressure liquid chromatography was carried out on Waters-590 solvent delivery module (Ultrasphere ODS Column, 75% CH_3OH and 25% water). The effluent from the column was monitored with a 254-nm UV detector (Altex Model 153) and a radioisotope detector (Beckman Model 170). GLC analyses were carried out with a Perkin-Elmer Model 900 gas chromatograph [DC-710 (10%) column; He Carrier gas]. Radio TLC analyses were performed with an automatic TLC analyzer [Berthold Model LB 2832; silica gel plates; hexane-ether (1:1)].

Table II. Fluorination of Grignard Reagents with *N*-[^{18}F]Fluorolactams

$$2 + RMgBr \rightarrow R^{18}F$$
$$3 \qquad 4$$

[^{18}F]fluorolactam	Grignard reagent, R =	yields,[a] %
2a	phenyl	1-2
2b	phenyl	8
2c	phenyl	20
	p-tolyl	30
	1-naphthyl	51
	cyclohexyl	19
2d	phenyl	19

[a] Isolated yields based on *N*-fluorolactams. Products identified by HPLC, GLC, and ^{19}F NMR analyses (after decay of the isotope).

General Procedure for the Preparation of [^{18}F]Fluorolactams (2). In a typical experiment, 50 mCi of [^{18}F]F_2 (specific activity 1 Ci/mmol; i.e. containing 50 μmol of nonradioactive $^{19}F_2$)[13] diluted with 100 mmol of neon was bubbled into a solution of the amide **1** (65 μmol) in freon (15 mL) at 0 °C over a period of 15 min. The solvent was evaporated at room temperature by bubbling dry argon, and the oily product was dissolved in 2 mL of dry ether. If necessary, the [^{18}F]fluorolactams **2** could by purified by HPLC.[12] However, it could be used in the next step without purification. The isolated chemical yields as well as radiochemical yields are reported in Table I.

General Procedure for the Reaction of [^{18}F]Fluorolactams with Grignard Reagents. To the [^{18}F]fluorolactam (20 μmol), as prepared above, the Grignard reagent **3** (65 μmol in 1 mL of ether) was added, vortexed for 1 min, and quenched with 1 N NH_4Cl solution (1 mL). The product **4** was isolated by semipreparatory HPLC. The overall process was carried out in less than 60 min, and the yields for the isolated ^{18}F-labeled products are given in Table II.

Acknowledgment. This work was supported in part by Department of Energy contract DE-AC03-76-SF00012, NIH Grants R01-NS-20867 and P01-NS-15654, NIMH Grant 01-MH-37916, and donations from the Hereditary Disease Foundation and the Jennifer Jones Simon Foundation.

Registry No. **1a**, 616-45-5; **1b**, 675-20-7; **1c**, 105-60-2; **1d**, 673-66-5; **1e**, 935-30-8; **2a**, 126063-29-4; **2b**, 126063-30-7; **2c**, 126063-31-8; **2d**, 126063-32-9; **2e**, 126063-33-0; **3** (R = Ph), 100-58-3; **3** (R = *p*-Tolyl), 4294-57-9; **3** (R = 1-naphthyl), 703-55-9; **3** (R = cyclohexyl), 931-50-0; **4** (R = Ph), 3857-04-3; **4** (R = *p*-tolyl), 2070-54-4; **4** (R = 1-naphthyl), 126063-34-1; **4** (R = cyclohexyl), 126063-35-2; $^{18}F_2$, 13981-56-1.

(13) For small scale experiments it was convenient to use [^{18}F]F_2 to increase the sensitivity of detection and accuracy of the determination of reaction yields. For the preparation of [^{18}F]F_2, see: Casella, V.; Ido, T.; Wolf, A. P.; Fowler, J. S.; MacGregor, R. R., Ruth, T. J. *J. Nucl. Med.* **1980**, *21*, 750.

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Cleavage of Aldehyde Hydrazonium Iodides under Mild Conditions. A Convenient Route to Chiral Nitriles of High Enantiomeric Purity

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The combination of chiral recognition and dipole-dipole forces can have great impact on self-assembly and ordering transitions in organic phases. A remarkable example discovered not long ago was the organization of chiral

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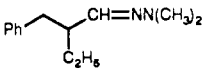
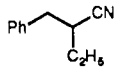
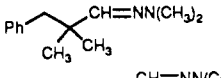
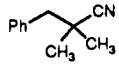
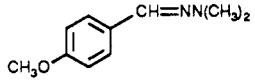
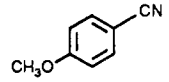
Table I. Conversion of Dimethylhydrazones to Nitriles[a]

starting hydrazone	product[b]	reaction time, min	yield, %
n-$C_6H_{13}CH{=}NN(CH_3)_2$	n-$C_6H_{13}CN$	60	76
		90	96
		150	83
		90	85

[a] See method A. [b] Products were characterized by 300-MHz ^1H NMR, IR, and mass spectrometry; correct spectroscopic data were obtained for all products.[8]

rodlike molecules into smectic ferroelectric liquid crystals.[1] In this context, the large dipole moment of nitriles makes them interesting functional groups for the study of chiral–dipolar forces among organic molecules. We have therefore set out to investigate an efficient, enantiocontrolled route to introduce the nitrile function at a stereogenic center.

The asymmetric alkylation chemistry of chiral hydrazones developed by Enders[2] appeared to offer great potential for a general and direct route to the desired nitriles. However, the strongly basic conditions[3,4] or high temperature[5] involved in previously known methods for conversion of hydrazones to nitriles would likely reduce enantiomeric purity. One example is the treatment of an α- or a β-branched hydrazone with an activated amide base to bring about direct elimination to the nitrile.[3] Alternatively, conversion of hydrazones to their methiodide derivatives followed by treatment with sodium methoxide in refluxing methanol is reported to give good yields of nitriles.[4] We report herein a convenient procedure to transform methiodide derivatives to nitriles under mildly basic conditions. Furthermore we demonstrate here the application of this procedure to the synthesis of nitriles with absolute stereocontrol.

Treatment of dimethylhydrazones with excess methyl iodide followed by reaction with neat 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) at room temperature produced nitriles as shown in eq 1. The elimination reaction failed

$$RCH{=}NN(CH_3)_2 \xrightarrow[2.\ DBU/25\ ^\circ C]{1.\ CH_3I} RCN \qquad (1)$$

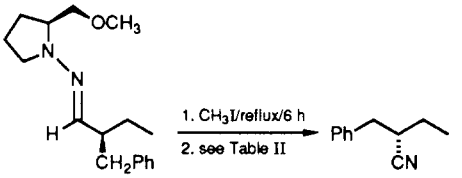
with tertiry amine bases like pyridine (neat/25 °C), 4-(dimethylamino)pyridine (CH_2Cl_2/40 °C), and 1,4-diazabicyclo[2.2.2]octane (CH_2Cl_2/40 °C). Yields for several nitriles are summarized in Table I. These results show that the method is general for aromatic nitriles as well as aliphatic nitriles having primary, secondary, or tertiary substitution at the α-carbon. Yields are high and the reaction is complete in less than 3 h.

Table II. Conversion of 1 to 2[a]

solvent	base (equiv)	temp, °C	reaction time, h	chemical yield, %	ee,[b] %
CH_2Cl_2	DABCO (5.0)	40	2	nr	-
CH_2Cl_2	DMAP (2.0)	40	12	nr	-
-	DBU (5.5)	20	0.2	83	28
CH_2Cl_2	DBU (4.0)	0	5.5	68	46
THF	DBU (1.2)	0	3.0	77–85	75–80

[a] See Method B. [b] See ref 6.

We attempted to convert the diastereomerically enriched hydrazone 1 (de = 80–82%) to the corresponding chiral nitrile as shown in eq 2. Results of selected experiments



1 (de = 80 – 82%) 2 (2)

are given in Table II. When DBU was used stoichiometrically it was necessary to remove methyl iodide completely in order to avoid low chemical yields.[7] The elimination could be conducted in THF at 0 °C with essentially no racemization at the α-carbon, but different conditions were required for the structurally similar hydrazones **3** (de > 95%). These monomers, synthesized in our laboratory,[8] required low temperatures and concentrated solutions of the amidine base in THF (see Table III). The amidine base 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) proved superior to DBU with respect to enantiomeric excess, and there is a smooth rise in enantiomeric excess with decreasing reaction temperatures.

Under the conditions of the elimination the configuration at the nitrile α-carbon is completely stable. Thus, racemization is presumed to occur by epimerization of the hydrazonium salt prior to elimination. It has previously

(1) Meyer, R. B.; Liebert, L.; Strzelecki, L.; Keller, P. *J. Phys.* **1975**, *36*, L69.

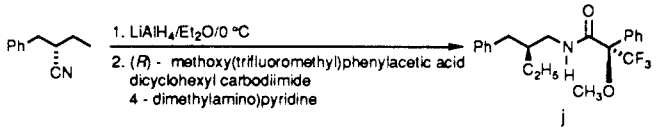
(2) For reviews on the chemistry of RAMP and SAMP-hydrazones, see: (a) Enders, D. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Chapter 4. (b) Enders, D. *Nach. Chem. Tech. Labor.* **1984**, *33*, 882. (c) Enders, D. In *Selectivity—A Goal for Synthetic Efficiency*; Trost, B. M., Bartmann, W., Eds.; Verlag Chemie: Weinheim, 1984; p 65. (d) Enders, D; Schubert, H. *Angew. Chem.* **1984**, *96*, 368.

(3) Cavigny, T.; Le Bargne, J. F.; Larcheveque, M.; Normant, H. *Synthesis* **1976**, 237.

(4) Smith, R. F.; Walker, L. E. *J. Org. Chem.* **1962**, *27*, 4372.

(5) Arbuzov, A. E. *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 2297.

(6) Enantiomeric excess was measured by reduction of the nitrile with $LiAlH_4$ followed by conversion of the corresponding primary amine to its MTPA amide,



j

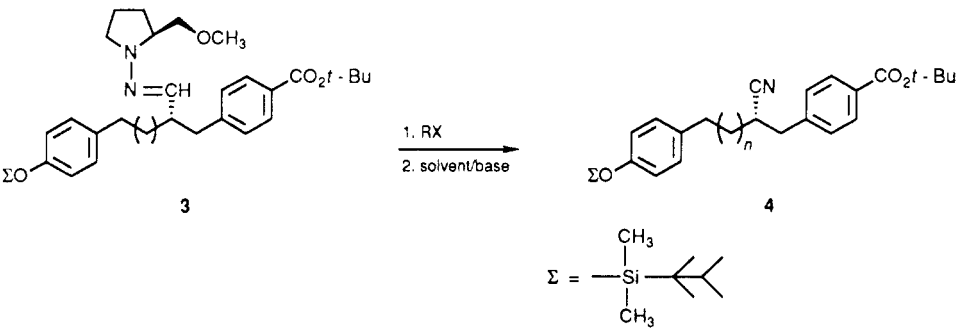
^1H NMR analysis of i in the presence of tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium ($Eu(fod)_3$) provided % ee.

(7) Presumably, excess CH_3I consumes DBU via the Menschutkin reaction.

(8) Moore, J. S. Ph.D. Thesis, University of Illinois, 1988.

(9) Enantiomeric excess was measured by using the chiral shift reagent (+)-$Eu(hfc)_3$ in CD_3CN. Nonequivalence in the ^1H NMR spectrum was observed for the methyl protons of the *tert*-butyl ester group. The accuracy and reliability of this procedure was checked by ^{13}C NMR analysis of the MTPA amide obtained by reduction of **4** as outlined in ref 6. The two methods agreed within 5%.

Table III[a]



entry	n	RX	solvent	base (equiv)	temp, °C	reaction time, h	chemical yield, %	ee,[b] %
1	3	CH_3I	PhH	DBU (1.2)[c]	5	3.0	80	34
2	3	CH_3I	-	DBU[d]	0	0.25	86	25
3	3	CH_3I	THF	DBU[e]	-20	0.5	96	45
4	3	CH_3I	THF	DBN[e]	-20	0.5	78	56
5	4	C_2H_5I	THF	DBN[e]	-40	2	77	72
6	4	$(CH_3O)_2SO_2$	THF	DBN[e]	-40	2	71	56
7	3	CH_3I	THF	DBN[e]	-78	3	71	88

[a] New compounds were characterized by proton and carbon NMR, and mass spectrometry and elemental analysis. [b] See ref 9. [c] See method B. [d] See method A. [e] A 4.2 M solution of the base was used.

been shown[2a] that alkylation of (*S*)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP) hydrazones with methyl iodide occurs unselectively at both the pyrrolidine and sp^2-hybridized nitrogens. Indeed we have observed a pair of doublets of nearly equal intensity between 8.5 and 9.5 ppm in the ^1H NMR spectrum of the methiodide of hydrazone **3**. Presumably, these doublets arise from the two alkylation products mentioned above. Alkylation at the sp^2 nitrogen would be expected to give an unreactive intermediate with respect to basic elimination. However, yields of purified nitriles are always observed to be much greater than those predicted from NMR data, thus suggesting that alkylation is reversible under the conditions of elimination. Also, using different alkylating agents it is possible to modify the regioselectivity. For example, reaction of **3** with ethyl iodide (reflux/24 h) yields a ratio of 4.6:1 in favor of pyrrolidine alkylation[10] while dimethyl sulfate (CH_2Cl_2/40 °C/24 h) predominantly alkylates the sp^2 nitrogen (0.8:1). Comparison of entries 5 and 6 in Table III shows that improved yield and higher enantiomeric purity are obtained when the elimination is conducted on hydrazonium salts derived from ethyl iodide instead of dimethyl sulfate. This is reasonable since ethyl iodide gives significantly greater levels of the pyrrolidine alkylation product which can eliminate directly. The acidity at the α-carbon for hydrazones alkylated at the sp^2 nitrogen is probably enhanced over that of the pyrrolidine alkylated compounds.

In summary, we believe that the mild procedures developed here, in conjunction with Enders' alkylation chemistry, may be utilized as a convenient route to nitriles of high enantiomeric purity. Application of these procedures to the stereocontrolled synthesis of nitrile-containing monomers and polymers will be reported in a subsequent publication.

Experimental Section

Preparation of 2-Ethyl-3-phenylpropanal Dimethylhydrazone. A dry, 200-mL, three-neck flask fitted with a septum and argon inlet was thoroughly purged with argon and charged with diisopropylamine (3.06 mL, 21.9 mmol) and dry THF (21.3 mL). After cooling to 0 °C, a 1.44 N solution of *n*-butyllithium (15.18 mL, 21.9 mmol) was added dropwise. The mixture was stirred for 5 min at 0 °C and cooled to −78 °C, and butanal dimethylhydrazone (21.3 mmol) was added dropwise as a neat liquid. Stirring at −78 °C was continued for 30 min, and then the temperature was allowed to slowly rise to 0 °C. After 20 min at 0 °C, a pale yellow precipitate was noticed. Stirring was continued for a total of 1 h at 0 °C, and then the flask was cooled to −78 °C. A solution of benzyl bromide (2.78 mL, 1.1 equiv) in THF (4.3 mL) was added dropwise. After 30 min at −78 °C, the temperature was allowed to gradually rise to 0 °C and stirring was continued for 4 h further. At this point, the mixture was transferred to a separatory funnel along with ether (80 mL) and saturated sodium bicarbonate (70 mL). The layers were separated, and the organic phase was washed with brine (1 × 70 mL) and water (1 × 70 mL). The organic layer was dried over Na_2SO_4, concentrated, and purified by column chromatograhy (silica gel, 8% Et_2O in CH_2Cl_2).

Conversion of Hydrazones to Nitriles. Method A. The *N,N*-dimethylhydrazone (1 mmol) was refluxed with 2 mL of freshly distilled CH_3I for 3–8 h in a bath regulated between 50 and 55 °C. Excess CH_3I was removed by rotary evaporation, and the yellow residue was treated with 2 mL of dry DBU. After 1–2.5 h of rapid stirring, the homogeneous solution was poured onto pentane and washed with 1 N HCl and water. The pentane solution was dried ($MgSO_4$) and concentrated, leaving spectroscopically pure nitriles.

Method B. The SAMP hydrazone **1** (1 mmol) was refluxed as described above for 6 h with 2.5 mL of CH_3I. Excess CH_3I was removed, leaving a viscous yellow oil. The residue was taken up in 2 mL of dry THF and was again concentrated by rotary evaporation. After repeating this process three more times to completely remove CH_3I, 2 mL of THF was added, the mixture was cooled to 0 °C, 1.2 mmol of DBU was added dropwise, and the contents were stirred at this temperature 3 h. The solution was poured onto pentane and washed with 1 N HCl and water. Drying over $MgSO_4$ and removal of solvent left the nonracemic nitrile. Purification by flash chromatography on silica gel could be performed without changing enantiomeric excess.

Method C. The SAMP hydrazone **3** (1.0 mmol) was refluxed as described above with 6.5 mL of CH_3I for 6 h. Excess CH_3I was removed as described in method B. The residue was taken up in 3.4 mL of dry THF. A solution of 7.4 mL of dry DBN and 3.4 mL of THF was cooled to −78 °C and stirred rapidly as the solution of the methiodide was added dropwise over a period of 5 min. After stirring for 3 h at this temperature, the mixture was poured onto pentane, extracted with cold 1 N HCl, and washed

(10) The further downfield resonance (9.5 ppm) was assigned to the aldehyde proton of the hydrazonium product alkylated at the sp^2 nitrogen.

with water. The organic layer was dried ($MgSO_4$) and concentrated, leaving the crude nitrile, which could be purified by flash chromatography.

Acknowledgment. This work was initially supported by 3M Company and subsequently by the U.S. Department of Energy, Grant No. DE AC02 76ER01198. A Ph.D. Fellowship Award from AT&T Bell Laboratories for J. S. Moore is gratefully acknowledged. We are also grateful to the UIUC Molecular Spectroscopy Laboratory of the School of Chemical Sciences for use of their facilities.

Registry No. 1, 126063-56-7; 2, 126063-57-8; 3 (n = 3), 126063-58-9; 3 (n = 4), 126063-59-0; 4 (n = 3), 126063-60-3; 4 (n = 4), 126063-61-4; $H_3C(CH_2)_5CH{=}NNMe_2$, 67660-53-1; $PhCH_2CH(Et)CH{=}NNMe_2$, 126063-54-5; $PhCH_2C(Me)_2CH{=}NNMe_2$, 126063-55-6; $4\text{-}MeOC_6H_4CH{=}NNMe_2$, 14371-13-2; $H_3C(CH_2)_5CN$, 629-08-3; $phCH_2CH(Et)CN$, 53244-13-6; $PhCH_2C(Me)_2CN$, 35863-45-7; $4\text{-}MeOC_6H_4CN$, 874-90-8; $H_3C(CH_2)_2CH{=}NNMe_2$, 10424-98-3; $PhCH_2$-(*S*)-CH(Et)-CH_2NHCO-(*R*)-C(Ph)(OMe)CF_3, 126063-62-5.

Lipase-Catalyzed Irreversible Transesterification Using Enol Esters: Resolution of Prostaglandin Synthons 4-Hydroxy-2-alkyl-2-cyclopentenones and Inversion of the 4*S* Enantiomer to the 4*R* Enantiomer

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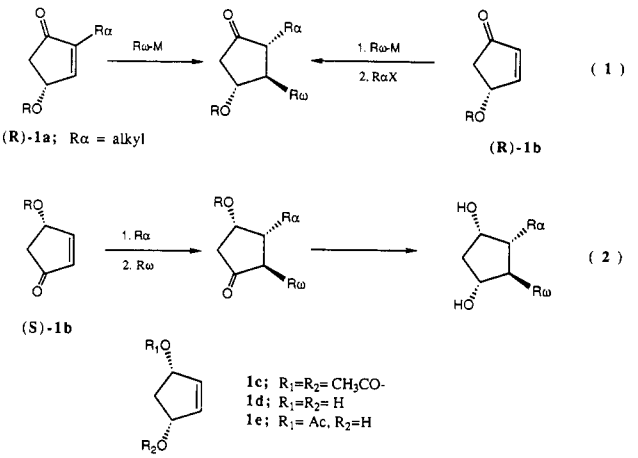
A common strategy for synthesis of prostaglandins (PGs) and their analogues is conjugate addition of ω-side chain (lower chain) to 4(*R*)-alkoxy-2-alkyl-2-cyclopentenones [(*R*)-**1a**][1] or to 4(*R*)-alkoxy-2-cyclopentenone [(*R*)-**1b**] followed by trapping with an electrophile (upper chain) suitable for construction of the α-side chain[2] (eq 1). A new strategy based on nucleophilic addition of the upper chain to the enantiomer of (*R*)-**1b** followed by electrophilic addition of the lower chain has recently been reported by Danishefsky et al. (eq 2).[3] Both (*R*)- and (*S*)-**1b** are available via enzyme-catalyzed enantioselective hydrolysis of the meso-diester **1c**[4] or transesterification of **1d**.[5] To



prepare enantiomerically pure **1a** with 4*R* absolute configuration, several methods are available which require either chemical resolution[6] or a lengthy process from a chiral intermediate.[7] As our interest in the development of an efficient method for the practical preparation of enantiomerically pure (4*R*)-**1a** from the corresponding racemates for use in synthesis of PGs,[8] we report here the enzymatic resolution of **1a** using lipases as catalyst and enol esters as solvents and as irreversible transesterification reagents. This irreversible enzymatic process has proven to be more efficient and often more enantioselective than other transesterification processes.[9] The high enantioselectivity of the process also allows conversion of the undesired *S* byproduct with high stereospecificity to the desired *R* enantiomer via Mitsunobu chemistry. With regard to the resolution strategy, transesterification instead of hydrolysis was chosen because the readily available starting materials contain an ester group which complicates the hydrolysis process (Scheme I).

Compounds **2a** and **2b** are appropriate intermediates for the synthesis of some PG analogues used for the treatment of peptic ulcer disease.[10] Several lipases, including that from Pseudomonas species (PSL), Candida cylindracea (CCL), porcine pancreas (PPL), and Aspergillus niger (ANL), and cholesterol esterase and subtilisin, all available commercially, were examined for the resolution of **2a**. It was found that all of the enzymes were selective in acylating the *R* isomer of the starting enone compound, and PPL gave the best enantioselectivity.

The resolution of **2b** was then undertaken. Of several lipases and organic solvents tested, it was found that PPL (free or immobilized on Amberlite XAD-8) in neat vinyl acetate gave the best result in terms of enantioselectivity

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