SYNTHESIS OF AN ORALLY ACTIVE PAF ANTAGONIST OF THE *N*-[4-(3-PYRIDINYL) BUTYL]PENTADIENAMIDE CLASS[a]

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Abstract - The PAF antagonist [R-(E,E)]-5-(4-methoxyphenyl)-*N*-[1-methyl-4-(3-pyridinyl)butyl]-2,4-decadienamide (**2**) was synthesized from (S)-α-methyl-3-pyridinebutanol (**14**), which was obtained either from ethyl lactate or by enantioselective kinetic hydrolysis of its racemate using the lipase derived from *Pseudomonas cepacia* (syn. *P. fluorescens).* Mesylation of **14**, followed by azide displacement and hydrogenation, produced amine (**7**), which was coupled with the *p*-nitrophenol ester (**8**) to give **2**. The direct coupling of (E,E)-5-(4-methoxyphenyl)-2,4-decadienoic acid (**27**) with azide (**24**) in the presence of tri-n-butylphosphine also gave **2**. Acid (**27**) was prepared by a vinylogous Reformatsky reaction between ketone (**25**) and methyl 4-bromocrotonate.

Platelet activating factor (PAF, **1**) is a family of 2(R)-acetylglycero-3-phosphorylcholine derivatives synthesized and secreted by a variety of cell types, such as platelets, mast cells, alveolar macrophages, neutrophils, endothelial cells, and basophils.[1] Because of the considerable evidence to implicate PAF in a variety of pathophysiological conditions, including bronchial asthma, ischemia, cutaneous inflammation, endotoxic shock, and gastric ulcers, there is an extensive effort to find specific and selective antagonists of PAF.[1,2] PAF also modulates the immune response by suppressing lymphocyte activity.[3] Using a variety of in vitro screening techniques, a number of natural and synthetic compounds have been found to attenuate the effects of PAF.[1,4] Of a series of *N*-[4-(3-pyridinyl)butyl]-5,5-disubstituted pentadienamides evaluated in these laboratories as PAF antagonists, **2** was found to be an orally active PAF antagonist with a high receptor affinity, a long duration of action, and the ability to inhibit thromboxane A_2 formation.[5]

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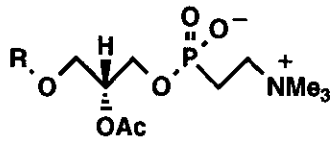
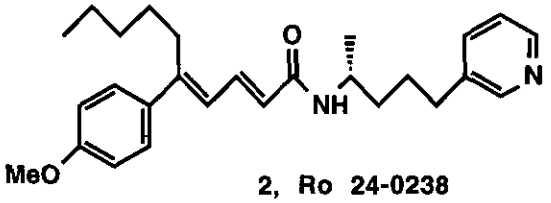
[a] Dedicated to Professor E. C. Taylor (Princeton University) on the occasion of his 70th birthday.

Compared to its (S)-enantiomer, **2** is three-fold more potent in vitro in inhibiting PAF-induced aggregation of canine platelets and 19-times more potent in PAF-induced bronchoconstriction by the oral route in guinea pigs. When administered intravenously at 10 mg/kg, **2** also produces rapid reversal of endotoxin-induced hypotension in rats.[6]



1, R = C_{16} - C_{18}



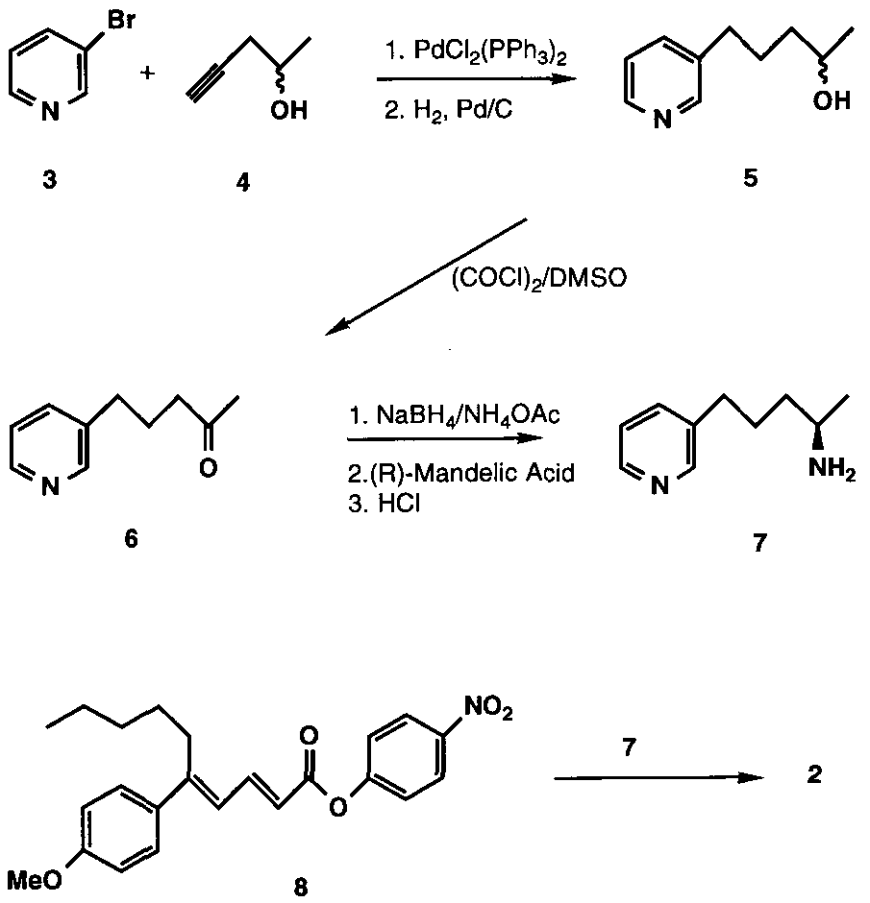
2, Ro 24-0238

The original synthesis of **2**,[5] which was accomplished in fourteen steps (see **Scheme 1** for the salient features of the synthesis), involved a palladium-mediated coupling of 3-bromopyridine with racemic 4-pentyn-2-ol (**4**) to give the alcohol (**5**). Swern oxidation of the latter gave ketone (**6**), which on reductive amination ($NaBH_4/NH_4OAc$), followed by fractional crystallization of the diastereomeric mandelamides derived from (R)-mandelic acid, gave the optically active amine (**7**) after hydrolysis. A single-crystal X-ray analysis of the (R,R)-mandelamide established the stereochemistry of **7**. Coupling of **7** with the *p*-nitrophenol ester of (E,E)-5-(4-methoxyphenyl)-2,4-decadienoic acid (**8**) then gave **2**.

Although this synthesis of **2** was suitable for preparing material needed for preliminary pharmacological screening, it was considered impractical to produce the large quantities of bulk drug substance required for toxicological and clinical testing. In the present paper, we describe a practical synthesis of **2** in which the important (R)-stereochemistry is secured either from (S)-lactic acid (**Scheme 2**) or by enzymatic resolution of alcohol (**5**) *via* lipase-catalysed hydrolysis of its butyrate (**19**) or by lipase-catalysed transesterification of **5** with butyric anhydride (**Scheme 3**). Conversion of the optically active alcohol (**14**) into amine (**7**) was accomplished by a series of straightforward reactions, i.e., mesylation, S_N2 displacement with azide, and reduction of the azido group (**Scheme 4**). In addition, the decadienoic acid moiety(**27**)was conveniently

assembled using a vinylogous Reformatsky reaction between ketone (**25**) and methyl 4-bromocrotonate (**Scheme 5**).

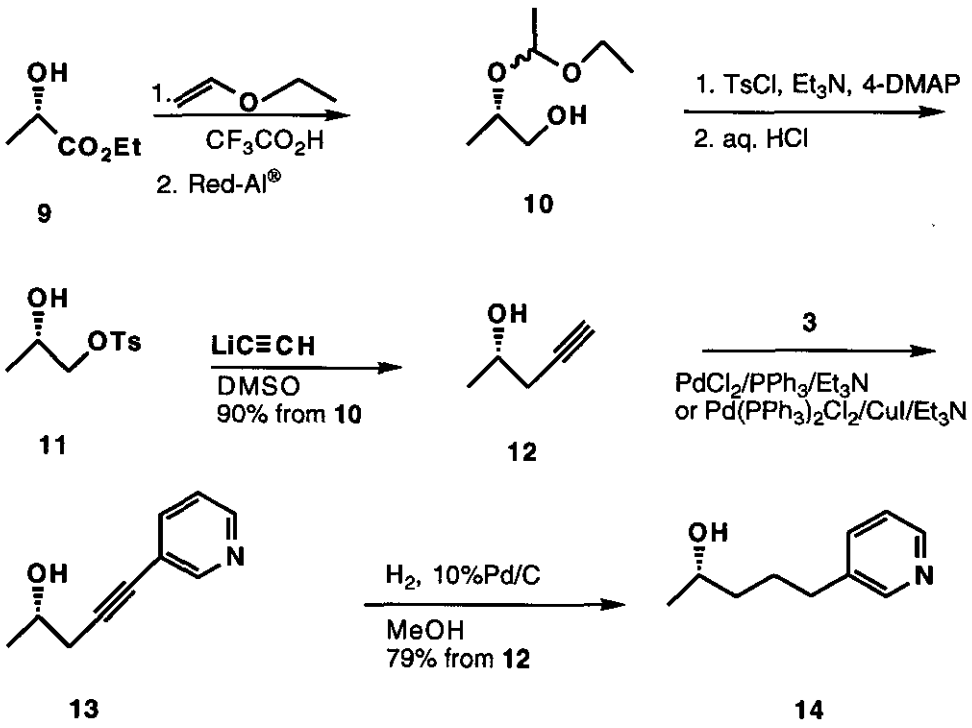
Scheme 1



As outlined in **Scheme 2**, the alcohol group of (S)-ethyl lactate was protected with ethyl vinyl ether and the ester function was reduced with Red-Al® to give the alcohol (**10**), which, after tosylation and removal of the acetal protecting group with aqueous hydrochloric acid, gave the known tosylate (**11**).[7] The latter was reacted with freshly prepared lithium acetylide in DMSO to give (S)-4-pentyn-2-ol (**12**)[8] in 90% yield from **10**, with an enantiomeric excess (e.e.) of >99.5%. The enantiomeric excess was determined by capillary gc of the derived Mosher ester.[9] Formation of **12** presumably occurred *via* (S)-propylene oxide.[7] Coupling of **12** with

3-bromopyridine was achieved using $PdCl_2(PPh_3)_2$-CuI-Et_3N as described by Guthrie *et al.*,[5] or, preferably, using $PdCl_2$-PPh_3, to give alcohol (**13**), which on hydrogenation gave **14**, in 79% yield from **12**.

Scheme 2



Although the route to **14** from ethyl lactate proceeded in high overall yield (55%), certain technical difficulties encountered on scale-up, particularly the isolation of **12** and the Pd-mediated coupling, led us to examine other routes to **14**. A route starting from ethyl nicotinate was subsequently selected for scale-up (**Scheme 3**). A Claisen condensation[10] between ethyl nicotinate and γ-valerolactone in the presense of sodium methoxide, followed by decarboxylation with dilute sulfuric acid, gave alcohol (**17**) in 90% yield. Huang-Minlon reduction of **17** gave **5**. The acetate (**18**) and butyrate (**19**) esters of **5** were prepared and subjected to enzymatic kinetic hydrolysis using NaOH in the presence of the lipase derived from *Pseudomonas cepacia* (syn. *P. fluorescens*, P-30, Amano Co.).[11] With each ester, two cycles were required to produce the product with satisfactory enantiomeric purity. This purity was established by hydrolysis of the unhydrolysed ester ($MeOH/K_2CO_3$), conversion to the Mosher ester, and examination by capillary gc. The acetate gave the

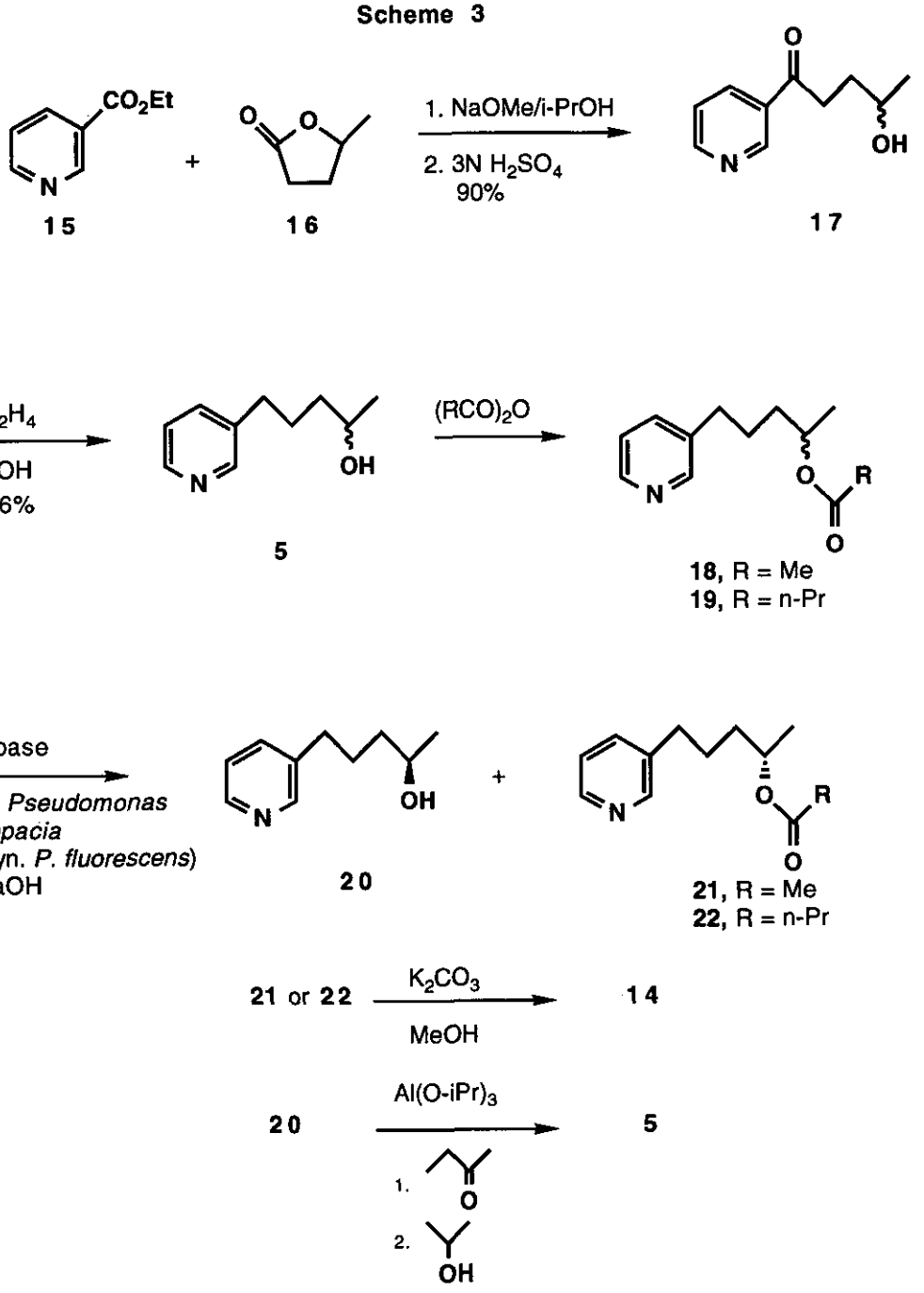
desired alcohol (**14**) in 28% yield with an e.e. of 97%, while the butyrate gave **14** in 38.7% yield with an e.e. of 99%. The (R)-alcohol (**20**) produced from the enzymatic hydrolysis was recycled using a combined Oppenauer oxidation/Meerwein-Pondorf-Verley reduction sequence with aluminum isoproxide in butanone and then in 2-propanol.

Lipase-catalysed enantioselective acylation of **5** was also examined using the conditions (benzene, n-butyric anhydride) reported by Biandi *et al.*[12] At 0.4 molar concentration of **5**, **14** was isolated directly from the reaction medium in 38% yield with an e.e. of 95%. Although replacing benzene with the industrially more desirable toluene gave satisfactory results on a 10-g scale, scale-up of this process produced **14** with low e.e. Acetic anhydride, trichloroethyl butyrate, and trifluoroethyl butyrate, were also studied in the enantioselective acylation of **5**, but these were found inferior to n-butyric anhydride. An obvious improvement in the synthesis of **14** using the Claisen condensation would be to start with (S)-γ–valerolactone. Although many synthetic approaches to this lactone have been reported,[13] in our hands these were found to be technically laborious and impractical on a large scale. Yeast reduction of ketone (**6**)[5] was also examined by us, but this gave alcohol (**14**) in only 28% yield with an e.e. of 86.6%.[14]

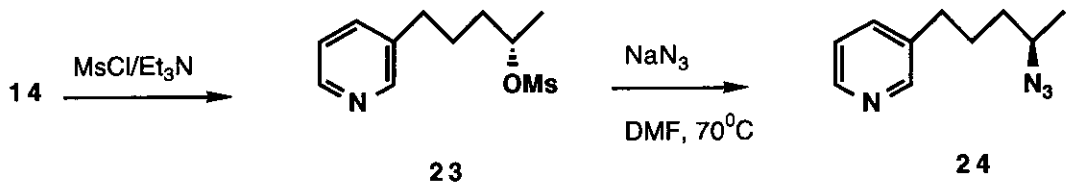
With alcohol (**14**) now readily available, its conversion into the amine (**7**) without loss of enantiomeric purity was undertaken. This was accomplished in a straightforward manner (**Scheme 4**). Mesylation ($MsCl/Et_3N$) of **14**, followed by displacement of the mesylate with sodium azide in DMF, afforded **24**, hydrogenation of which gave the amine (**7**) in 72% yield from **14**. The enantiomeric purity of **7** was determined to be 98.7% by capillary gc examination of the derived Mosher amide. Coupling of amine (**7**) with ester (**8**) gave **2**, identical with a sample prepared by Guthrie *et al.*[5] The direct coupling of azide (**24**) with acid (**27**) to give **2** was also achieved when the reaction was carried out in the presence of tri-n-butylphosphine.

As the reported[5] synthesis of acid (**27**) from ketone (**25**) employed five steps, shorter routes to **27** were examined. To our surprise, **25** failed to react with the anions derived from the Wittig salt (**28**) and from the phosphonate (**29**). Similarly, **25** failed to react with the anion generated from methyl crotonate with $NaNH_2$, and with the dianion derived from crotonic acid.[15] However, a vinylogous Reformatsky reaction[16] (Zn/Me_3SiCl/THF) between (E/Z)-4-bromocrotonate and **25**, followed by dehydration and saponification afforded crystalline (E,E)-acid (**27**) in 60-65% yield. An additional 10% of product could be obtained from the mother liquor.

Scheme 3


CO2Et
N
15
+
O
O
16
1. NaOMe/i-PrOH
2. 3N H2SO4
90%
O
OH
N
17
N2H4
KOH
86%
OH
N
5
(RCO)2O
O
R
O
N
18, R = Me
19, R = n-Pr
Lipase
ex Pseudomonas cepacia
(syn. P. fluorescens)
NaOH
OH
N
20
+
O
R
O
N
21, R = Me
22, R = n-Pr
21 or 22
K2CO3
MeOH
14
20
Al(O-iPr)3
1.
O
2.
OH
5

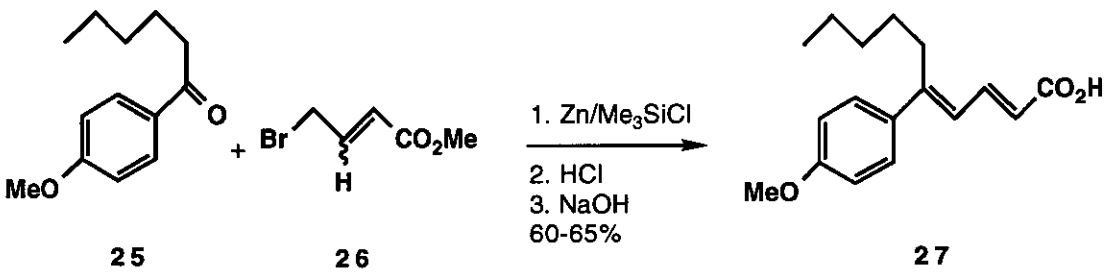
Scheme 4



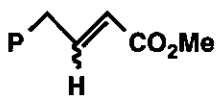
23 **24**

7

Scheme 5



25 **26** **27**



28, P = $P^+Ph_3Br^-$

29, P = $(MeO)_2P(O)$

EXPERIMENTAL

General. Unless otherwise indicated, ir and nmr spectra were determined in $CHCl_3$ and $CDCl_3$, respectively. ^1H- and ^{13}C-nmr spectra were recorded at 200 and 50.4 MHz, respectively. Assignments of ^{13}C nmr are based on chemical shifts (δ, ppm), off-resonance, and DEPT spectra, and are tentative. Coupling constants (J) are given in Hz. Optical rotations were determined at 25 °C. Thin layer chromatoplates (silica gel) were purchased from Merck (Darmstadt); spots were visible under short wave-length uv light or made visible by spraying with 10% phosphomolybdic acid in ethanol and heating the plates.

(S)-2-(1'-Ethoxyethoxy)-1-propanol (10). To a stirred, cooled (ice-bath) solution of 227 ml (2.0 mol) of (S)-ethyl lactate and 574 ml (6.0 mol) of ethyl vinyl ether (distilled from K_2CO_3 at 40 °C) was added 4.2 ml of CF_3CO_2H. The mixture was stirred at 0 °C for 3 h and then refrigerated overnight, allowed to warm to room temperature, and treated with 21.8 ml of Et_3N. Stirring was continued for 30 min and most of the excess ethyl vinyl ether was removed in vacuo at room temperature. The residue was diluted with 700 ml of Et_2O, washed with 800 ml of H_2O, 400 ml of brine, dried ($MgSO_4$), and evaporated in vacuo at 30 °C to give 391.8 g of the acetal, which was used without further purification. A solution of 274.3 g (ca. 1.4 mol) of this material in 275 ml of Et_2O was added to a stirred solution of 500 ml (1.75 mol) of sodium bis(2-methoxy)aluminum dihydride (Red-Al®) (3.5 M in toluene) at a rate so as to maintain a slow reflux. After the addition was complete, stirring was continued at room temperature for 2.0 h, and excess hydride was destroyed by the dropwise addition of 55 ml of EtOH in 55 ml of Et_2O. The mixture was washed with 1.2 l of 28% NaOH solution, 1.0 l of brine, dried ($MgSO_4/K_2CO_3$), and concentrated in vacuo at 30 °C. Distillation gave 161.7 g (78%) of **10**, bp 82-85 °C (16 Torr.); $[\alpha]^{25}D$ + 43.26° ($CHCl_3$, c=1.0518); ir 3590, 3420 cm^{-1}; ^1H nmr δ 1.12/1.17 (3 H, d, J=7), 1.21 (3 H, t, J=7), 3.40-4.70 (4 H, m, OCH_2), 3.82 (1 H, m, CHO), 3.71-3.81 (1 H, m, OC(H)O); ms *m/z* 73 (M^+-75), 45 (100). Anal. Calcd for $C_7H_{16}O_3$: C, 56.73; H, 10.88. Found: C, 56. 60; H, 10.41.

(S)-1,2-Propanediol-1-tosylate (11). To a stirred, cooled (ca. 5 °C) solution of 161.6 g (1.09 mol) of **10**, 198 ml of Et_3N and 13.3 g (0.109 mol) of 4-dimethylaminopyridine in 1.6 l of CH_2Cl_2, was added 228.7 g (1.2 mol) of *p*-toluenesulfonyl chloride. The mixture was stirred at 0-5°C for 4 h, poured into 1.0 l of ice-water, and extracted with CH_2Cl_2 (2 x 400 ml). The organic extracts were combined and washed with 900 ml of 1N

HCl, 1.0 l of brine, and dried ($MgSO_4$). Evaporation gave an oil, which was dissolved in 800 ml of THF, 110 ml of water and 8.08 ml of conc. HCl, and the mixture was stirred vigorously for 2.2 h. The THF was removed in vacuo, and the residue was dissolved in 1.0 l of CH_2Cl_2 and washed with 1.0 l of water, 800 ml of satd $NaHCO_3$, 800 ml of brine, and dried ($MgSO_4$). Evaporation at 35°C (5 Torr.) gave 249.1 g of a gum, pure enough for use in the next step. A sample crystallized from ether-pentane gave **11** as crystals, mp 32-34 °C (lit.,[7b] mp 31-32 °C), $[\alpha]^{25}_D$ + 11.61° ($CHCl_3$, c=0.9646) (lit.,[7b] $[\alpha]_D$ + 12.2°, $CHCl_3$, c=1.1); uv (EtOH), 223 (ε=2,420), 255 (ε=460), 263 (ε=530), 266 (ε=540), 272 (ε=505); ir ($CHCl_3$) 3600, 1362, 1189, 1172 cm^{-1}; ^1H nmr δ 1.17 (3 H, d, J=7), 2.16 (1 H, d, J=5 Hz, OH), 2.45 (3 H, s), 3.85 (1 H, br d, J=7), 3.99 (1 H, d, J=7), 4.01 (1 H, m, CHO), 7.35 (2 H, d, J=7), 7.80 (2 H, d, J=7); ^{13}C nmr δ 18.56 (CH_3), 21.44 (CH_3), 85.13 (CH), 74.65 (CH_2), 127.28 (CH), 129.90 (CH), 130.13, 132.34 (Ar, s), 145.00 (s); ms *m/z* 230 (M^+, 0.1). Anal. Calcd for $C_{10}H_{14}O_4S$: C, 52.16; H, 6.13; S, 13.92. Found: C, 51.97; H, 6.21; S, 13.70.

(S)-4-Pentyn-2-ol (12). A 5-l, 3-necked, round-bottomed flask equipped with a mechanical stirrer, gas inlet tube, Claisen adapter, and a dry ice condenser, was cooled to -78 °C, and charged with ca. 2.0 l of liquid ammonia. Acetylene, purified by passing through three traps, was introduced into the flask as 28.0 g (4.0 mol, 12.7 mm diameter rods) of lithium was added piece-wise under argon. When all the lithium had reacted, the flow of acetylene was stopped, the acetylene inlet tube was replaced with a thermometer, and the dry-ice condenser was removed. DMSO (1.0 l) was added and the ammonia was evaporated (steam bath) until the temperature of the mixture reached 30 °C. The mixture was cooled to 15 °C and treated with a solution of 249.1 g (1.09 mol) of crude (S)-1,2-propanediol-1-tosylate (**11**) from the preceding experiment in 175 ml of anhyd. DMSO at a rate such that the temperature did not exceed 17 °C. The mixture was stirred at 15 °C for 30 min, and at room temperature for 2.0 h, then poured slowly onto ca. 1.0 l of ice, and filtered. The filter cake was washed with Et_2O (3 x 100 ml) and the combined filtrate and washings were continuously extracted with Et_2O for 64 h. The extract was dried ($MgSO_4$) and evaporated to give an oil, which was distilled through a 50 cm Vigreaux column to give 82.5 g (90%) of **12**, bp 55-80 °C/22 Torr., $[\alpha]^{25}_D$ = - 17.01° (Et_2O, c=26.1326) (lit.,[8] $[\alpha]_D$ = - 20.00°, Et_2O, c=0.265.); ir 3615, 3585, 3305, 2115 cm^{-1}; ^1H nmr δ 1.27 (3 H, d, J=7), 2.07 (1 H, s), 2.30 (1 H, d, J=5 Hz, OH), 2.31-2.40 (2 H, m), 3.99 (1 H, q, J=6); ms *m/z* 69 (M-15).

Determination of the Enantiomeric Purity of 12. A solution of 21.5 mg (0.25 mol) of (S)-4-pentyn-2-ol in 30 drops (ca. 23 μl) of CCl_4 was treated with 76 mg (0.30 mmol, *ca.* 55 μl) of (S)-2-methoxy-2-

(trifluoromethyl)phenylacetyl chloride[9] and 10 drops of pyridine. The mixture was left at room temperature overnight, diluted with H_2O and extracted into 10 ml of Et_2O. The organic phase was washed with 7.5 ml of cold dil HCl, satd $NaHCO_3$, and brine. The extract was dried ($MgSO_4$) and evaporated, and the residue was dissolved in a few mls of CH_2Cl_2. Capillary gc analysis of this showed only one peak (>99.5% e.e.), whereas the corresponding Mosher ester derived from racemic 4-pentyn-2-ol gave 2 peaks of equal areas.

(S)-5-(3-Pyridinyl)-4-pentyn-2-ol (13). (A) Procedure using PPh_3PdCl_2/CuI. A stirred solution of 155 g (0.981 mol) of 3-bromopyridine and 134 g (185 ml) of Et_3N in 300 ml of CH_2Cl_2 was deaerated with argon for 25 min. Under argon, 6.89 g (0.0098 mol) of bis(triphenylphosphine)palladium dichloride (Strem Chemical) and 1.87 g (0.0098 mol) of cuprous iodide were added. The mixture was warmed to a gentle reflux and a solution of 82.53 g (0.981 mol) of **12** in 200 ml of CH_2Cl_2 was slowly added during 8 h. Stirring was continued at reflux for a further 3 h, and the mixture was left at room temperature overnight. It was poured into 400 g of ice and acidified with 150 ml of conc HCl. The organic phase was separated and the aqueous phase was washed with CH_2Cl_2 (2 x 100 ml). The aqueous phase was cooled in an ice bath, made basic with 150 ml of 40% NaOH solution, and extracted with CH_2Cl_2 (2 x 200 ml). The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated to give 169.3 g of a dark oil. Most of the unreacted 3-bromopyridine was removed by evaporation at 100 °C/0.1 mm for 1 h. Distillation of a portion gave an analytical sample of **13**, bp 115 °C/0.1 Torr.; $[\alpha]^{25}_D$ - 17.51° (EtOH, c=0.992); ir 3610, 2240, 2220, 702 cm^{-1}; ^1H nmr δ 1.32 (3 H, d, J=7), 2.62, (2 H, dd, J=4, 2), 4.10 (1H, d, J=7), 7.23 (1 H, dd, J=4, 2), 7.68 (1 H, d, J=4), 8.49 (1 H, d, J=2), 8.62 (1 H, s); ms *m/z* 161 (M^+, 7), 146 (M^+ - 15), 117 (100).

(B). Procedure Using $PdCl_2/PPh_3$. A 500-ml, four-necked, round-bottomed flask equipped with a mechanical stirrer, argon inlet, condenser, and a 125-ml dropping funnel was charged with 39.5 g (0.25 mol) of 3-bromopyridine, 3.93 g (0.015 mol) of triphenylphosphine, and 75 ml of Et_3N (dried over KOH pellets). The mixture was deaerated by bubbling argon through the solution for 20 min. Palladium (II) chloride (877 mg, 0.005 mol) was added and the mixture was heated to reflux. A solution of 21.0 g (0.025 mol) of **12** in 75 ml of Et_3N, which had been deaerated for 5-10 min, was added dropwise during *ca.* 6 h, and the mixture was stirred at reflux for an additional 6 h. It was cooled to room temperature, poured onto ca. 200 mL of iced water, acidified with conc HCl, and extracted with CH_2Cl_2 (2 x 50 ml). The combined organic extracts were back-extracted with 25 ml of H_2O, added to the acidic phase, and made basic with 50 ml of 40% NaOH. The

organic phase was separated and the aqueous phase was extracted with EtOAc (2 x 100 ml). The combined organics were washed with brine (2 x 100 ml), dried ($MgSO_4$), and evaporated to give 44.11 g of **13**, essentially homogeneous by tlc (10% MeOH in CH_2Cl_2).

(S)-α-Methyl-3-pyridinebutanol (14). A solution of 145.8 g (0.9 mol) of crude **13** in 750 ml of MeOH was hydrogenated over 6.0 g of 10% palladium on charcoal at 100 psi and 25°C for 16 h. An additional 6.0 g of the catalyst was added and the hydrogenation was continued for a further 4 h. The catalyst was removed by filtration, the solvent was concentrated, and the residue was distilled to give 128.3 g (79% yield from **12**) of **14**, bp 115-120 °C/0.3 Torr.; $[\alpha]^{25}_D$ = + 15.64° (EtOH, c=0.8565); ir 3615, 711 cm^{-1}; ^1H nmr δ 1.15 (3 H, d, J=7), 1.40-1.50 (2 H, m), 1.60-1.80 (2 H, m), 2.41 (1 H, s, OH), 2.60 (2 H, t, J=7), 3.80 (1 H, q, J=7), 7.15 (1 H, dd, J=7, 4), 7.45 (1 H, d, J=7), 8.40 (2 H, s); ms *m/z* 164 (M^+-H), 105 (100). Anal. Calcd for $C_{10}H_{15}NO$: *C, 72.69; H, 9.15; N, 8.27. Found: C, 72.61; H, 8.86; N, 8.27.*

(R,S)-4-Hydroxy-1-(3-pyridinyl)-1-pentanone (17). Powdered NaOMe (54.0 g, 1.0 mol) was added to 1.5 l of 2-propanol and the mixture was stirred at reflux while a solution of 100.7 g (0.67 mol) of ethyl nicotinate and 86.6 g (0.87 mol) of (R,S)-γ-valerolactone was added dropwise during 1.0 h. The mixture was stirred at reflux for an additional hour, and the solvent was removed by distillation under vacuum at 100 °C. To the resulting solid was added 1.5 l of 3N H_2SO_4 and the distillation was continued until the internal temperature reached 100 °C. The mixture was boiled under reflux at 100 °C overnight, cooled to 0 °C, and made basic to pH 9 with *ca.* 800 ml 6N NaOH (exothermic). The mixture was extracted with EtOAc (3 x 500 ml), dried (Na_2SO_4), and concentrated to give 108 g (90%) of **17** as a dark oil: ^1H nmr (400 MHz) δ 1.27 (3 H, d, J=6.2, CHC*H*$_3$), 1.82-2.04 (2 H, m, C*H*$_2$CHOH), 2.82 (1 H, br s, OH), 3.17 (3 H, m, $COCH_2$), 3.92 (1 H, m, C*H*CH_3), 7.41 (1 H, m, β-pyrH), 8.25 (1 H, γ-pyrH), 8.75 (1 H, m, α-pyrH), 9.16 (1 H, α-pyrH); ir 3615, 1728, 1689, 702 cm^{-1}; ms m/z 179 (EI, M^+). Anal. Calcd for $C_{10}H_{13}NO_2$: C, 66.51; H, 7.31; N, 7.82. Found: C, 67.01; H, 7.55; N, 7.77.

(R,S)-α-Methyl-3-pyridinebutanol (5). To a flask equipped with a Dean-Stark trap was added 108.0 g (0.60 mol) of **17**, 1.5 l of diethylene glycol and 61.0 g (65 ml, 1.22 mol) of hydrazine hydrate. The mixture was heated to 140-150 °C for 1.5 h. After tlc (EtOAc) indicated conversion of **17** to its hydrazone, 45.0 g (0.802 mol) of KOH was carefully added portionwise (ca. 10 min), during which there was evolution of N_2. The mixture was heated at 140-150 °C for an additional 3 h, cooled, and poured into 3.0 l of H_2O. The mixture

was extracted with CH_2Cl_2 (5 x 600 ml), washed with H_2O (3 x 100 ml), dried (Na_2SO_4), and concentrated to give 85.4 g (86%) of **5** as a yellow oil: ^{1}H nmr (400 MHz) δ 1.19 (3 H, d, J=6.2, CHC*H*$_3$), 1.43-1.57 (2 H, m, CH_2), 1.61-1.82 (2 H, m, CH_2), 2.63 (2 H, t, J=7.2, ArCH_2), 3.78-3.94 (2 H, C*H*OH, CHO*H*), 7.25 (1 H, β–pyrH), 7.41 (1 H, m, γ-pyrH), 8.25 (1 H, m, α-pyrH), 9.16 (1 H, α-pyrH); ir 3615, 1728, 1689, 702 cm^{-1}; ms (EI) *m/z* 179.

Acetate of (R,S)-α-Methyl-3-pyridinebutanol (18). A mixture of 100 g (0.61 mol) of **5** and 171 ml (1.82 mol) of Ac_2O was stirred at room temperature for 24 h, poured onto ca. 1 l of ice, and stirred for 45 min. The mixture was extracted with CH_2Cl_2 (2 x 400 ml), washed with sat. $NaHCO_3$ (4 x 250 ml), dried (Na_2SO_4), and evaporated to give 110 g of **18** as a light brown oil: ^{1}H nmr (400 MHz) δ 1.21 (3 H, d, J=6.2, $CHCH_3$), 1.52 (2 H, m, CH_2), 1.71 (2 H, m, CH_2), 2.03 (3 H, s, OAc), 2.62 (2 H, m, CH_2Ar), 4.94 (1 H, CHOAc), 7.23 (1 H, β-pyrH), 7.51 (1 H, m, γ-pyrH), 8.45 (2 H, d, J=2.8, α–pyrH); ms *m/z* 207 (M^+). Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.53; H, 8.27; N, 6.76. Found: C, 69.00; H, 8.36; N, 6.71.

Butyrate of (R,S)-α–Methyl-3-pyridinebutanol (19). With rapid stirring, 158.0 g (1.0 mol) of butyric anhydride was added during 5 min to a mixture of 110 g (0.67 mol) of **5** at room temperature, producing a slight exotherm (to *ca.* 40 °C). The mixture was stirred for 1 h, warmed to 50 °C for 2 h, cooled to room temperature, poured onto ice, and stirred with aqueous $NaHCO_3$ until the aqueous layer remained basic. The mixture was extracted with CH_2Cl_2 (2 x 500 ml), dried (Na_2SO_4), and evaporated to give 140.0 g of **19** as a light brown oil. Chromatography on silica gel with 1:1 hexane:EtOAc removed non-polar impurities and gave 131.6 g (84%) of **19**: ^{1}H nmr (400MHz) δ 0.94 (3 H, t, J=7.4, CH_2CH_3), 1.21 (3 H, d, J=6.3, $CHCH_3$), 1.54-1.72 (6 H, m, CH_2), 2.26 (2 H, t, J=7.3, CH_2CO), 2.62 (2 H, m CH_2Ar), 4.94 (1 H, CHOCOBu), 7.23 (1 H, m, β-pyrH), 7.48 (1 H, m, γ-pyrH), 8.44 (2 H, d, J=2.8, α–pyrH); ir 1722, 712 cm^{-1}; ms *m/z* 235 (M^+). Anal. Calcd for $C_{12}H_{17}NO_2$: C, 71.45; H, 9.00; N, 5.95. Found: C, 71.08; H, 9.22; N, 6.04.

Lipase-Catalysed Hydrolysis of 19. To a 3-necked, 1-l flask equipped with a mechanical stirrer and pH probe/controller connected to a reservoir containing 2N NaOH was added 77.7 g (0.33 mol) of **19** and 400 ml of 10% pH 7.0 buffer. The pH controller was set to maintain a pH of 7.4. The reaction mixture was placed in a constant temperature bath at 45 °C and 8.0 g of lipase ex *Pseudomonas cepacia* (*P. fluorescens,* P-30, Amano Corp.) was added to the rapidly stirred mixture. After 8 days, uptake of base ceased at 51% of theory. The mixture was filtered through Celite, the filtrate was extracted with hexane (3 x 750 ml), and the combined

extracts were washed with H_2O (3 x 500 ml) to remove traces of the alcohol (**20**), and dried (Na_2SO_4). Evaporation gave 35.2 g (45.3% yield) of ester (**22**), which was hydrolysed (K_2CO_3/MeOH, see below) to give crude **14**. Convertion of a portion into the Mosher ester and examination by capillary gc indicated an e.e. of 93.2%. The combined aqueous layers were extracted with CH_2Cl_2 (4 x 750 ml), and the combined extracts were dried (Na_2SO_4) and evaporated to give 26.6 g (48.8%) of alcohol (**20**), with an e.e. of 80.8%. Crude **14** (33.5 g) from the first cycle hydrolysis was resuspended in 16 ml of pH 7.0 buffer and hydrolysed with 2N NaOH in the presence of 5.0 g of lipase *Pseudomonas cepacia* (P-30 Amano) as described previously. After 5 days, 5.0 ml of NaOH was consumed. Work up of the reaction as described above gave 30 g (38.7% after the two cycles) of ester (**22**), which was hydrolysed with 75.0 g of K_2CO_3 in 125 ml of MeOH overnight. After dilution with 300 ml of H_2O, extraction with CH_2Cl_2 (3 x 300 ml), drying, evaporation and distillation, bp 115-120 °C/ 0.3 Torr., 20 g of **14** was obtained. Capillary gc analysis of the Mosher ester of **14** gave an e.e. of 99.6%, $[\alpha]_D$ = + 13.81° (c=1.0, EtOH).

Lipase-Catalysed Hydrolysis of Acetate 18. The acetate (**18**) was hydrolysed using the procedure described for **19**, to give, after hydrolysis (K_2CO_3/MeOH), a sample of alcohol (**14**) having an e.e. of 81.0% as determined by capillary GC of the derived Mosher ester. After a second cycle enzymatic hydrolysis, the derived ester (**21**) was hydrolysed to give **14** with an e.e. of 97.2%.

Lipase-Catalysed Butyration of 5 with Butyric Anhydride. *Into a 50-ml round-bottomed flask was placed* 1.65 g (0.01 mol) of **5**, 25 ml of benzene, and 0.5 g of lipase ex *Pseudomonas cepacia* (*P. fluorescens*, P-30, Amano) adsorbed on Celite. The mixture was stirred at room temperature overnight, filtered, and the filter pad was washed with 10 ml of benzene. Concentration of the filtrate, washing with water, and chromatography of the residue on silica gel (7:3 hexane:EtOAc) gave 0.63 g (38% yield) of **14**, $[\alpha]_D$ = + 12.5° (EtOH, c=1.00), 95.0% e.e. as determined from gc analysis of the Mosher ester; 1.36 g of the (R)-enriched butyrate was obtained.

Yeast Reduction of Ketone 6. To a rapidly stirred solution of 50 g of dextrose in 250 ml of H_2O in an open beaker was added 28 g of baker's yeast (*Saccharomyces cerevisiae*, Fleishmann's). After 1 h, evolution of CO_2 commenced. A solution of 2.0 g (0.013) of **6** in 2.0 ml of EtOH was added and the mixture was stirred for 5 days, during which five 2-g portions of dextrose was added. The mixture was filtered through Celite, washed with H_2O (3 x 150 ml) and the filtrate and washings were extracted with CH_2Cl_2 (4 x 300 ml). The

extract was dried (Na_2SO_4), and evaporated to give 0.52 g (25% yield) of **14**, $[\alpha]_D$ = + 9.7° (c=1.0, EtOH), with an e.e. of 86.6%.

Oxidation-Reduction of 20 to Give 5. A mixture of 10 g (0.061 mol) of **20** in 500 ml of butanone and 25 g (0.12 mol) of aluminum isopropoxide was stirred at reflux under argon for 36 h and then concentrated. The residue was dissolved in 500 ml of 2-propanol, 15 g of aluminum isopropoxide was added, and the mixture was stirred at reflux for 24 h. It was diluted wtih 350 ml of H_2O and filtered. The filtrate was extracted with CH_2Cl_2 (2 x 400 ml), dried (Na_2SO_4), and evaporated to give 11.4 g of an oil, which was chromatographed on silica gel (1:1 hexane:EtOAc) to give 8.7 g (87% yield) of **5**.

(S)-α-Methyl-3-pyridinebutanol methanesulfonate (23). A solution of 128.3 g (0.777 mol) of alcohol (**14**) in 135 ml (98.3 g, 0.97 mol) of Et_3N and 1.10 l of CH_2Cl_2 was cooled to 0 °C and treated dropwise with a solution of 69 ml (102.3 g, 0.893 mol) of methanesulfonyl chloride. The mixture was stirred at this temperature for 30 min, poured into 400 ml of H_2O, the organic phase was separated, and the aqueous phase was reextracted with 100 ml of CH_2Cl_2. The combined organics were washed with 200 ml of brine, dried ($MgSO_4$), and evaporated to give 201.7 g of **23**; uv (EtOH) 203 (ε=5,980), 256 (ε=2,600), 262 (ε=3010), 269 (ε=2210) nm; ir 1355, 1332, 1172, 712 cm^{-1}; ^1H nmr δ 1.41 (3 H, s, J=7), 1.62-1.85 (4 H, m), 2.63 (2 H, m), 2.99 (3 H, s), 4.82 (1 H, q, J=7), 7.22 (1 H, dd, J=6, 4), 7.51 (1 H, d, J=4 Hz), 8.45 (2 H, s); ms *m/z* 147 (M^+ - $HOSO_2CH_3$, 15). Anal. Calcd for $C_{11}H_{17}NO_3S$: C, 54.30; H, 7.04; N, 5.76; S, 13.18. Found: C, 54.57; H, 6.90; N, 5.95; S, 12.88.

(R)-3-(4-Azidopentyl)pyridine (24). A solution of 201.7 g (0.827 mol) of mesylate (**23**) in 1.30 l of DMF was added to 101.0 g (1.55 mol) of sodium azide and the mixture was stirred under argon at 70 °C for 2.5 h. It was cooled to room temperature, poured into 1.25 l of ice-water and extracted with EtOAc (1 x 500 ml, 3 x 150 mL). The extract was washed with 100 ml of H_2O, 100 ml of brine, dried ($MgSO_4$) and used directly in the next step. In a separate experiment the extract was evaporated to give an oil. Distillation of a portion gave **24** as an oil, bp 115 °C/0.1 Torr.; uv (EtOH) 204 (ε=6380), 246 (ε=2,720), 262 (ε=3,160), 269 (ε=2,800) nm; nmr 2105, 711 cm^{-1}; ^1H nmr δ 1.25 (3 H, d, J=7), 1.45-1.55 (2 H, m), 1.62-1.80 (2 H, m), 2.63 (2 H, t, J=7), 3.45 (1 H, q, J=7), 7.20 (1 H, dd, J=6, 4), 7.50 (1 H, d, J=4), 8.45 (2 H, s); ms *m/z* 189 (M^+ - H, 2), 147 (70), 92 (100). Anal. Calcd for $C_{10}H_{18}N_4$: C, 63.13; H, 7.42; N, 29.45. Found: C, 62.89; H, 7.46; N, 29.30.

(R)-α-Methyl-3-pyridinebutanamine (7). The EtOAc extract of the crude azide (**24**) from the preceding experiment was hydrogenated over 100 g of Raney® nickel at 25 °C and 50 psi during 18 h. Removal of the catalyst and solvent, and distillation of the residue gave 92.0 g of amine (**7**), as an oil, bp 83-86 °C/0.1 mm; ^{1}H nmr δ 1.01 (3 H, d, J=7), 1.22 (2 H, br s, NH_2), 1.33 (2 H, t, J=7), 1.61 (2 H, m), 2.57 (2 H, t, J=7) 2.85 (1 H, q, J=7 Hz), 7.14 (1 H, d, J=7), 7.16 (1 H, d, J=7), 7.44 (1 H, d, J=7), 8.38 (2 H, br s).

Determination of Enantiomeric Purity of 7. A 71.5 mg (0.435 mmol) sample of the amine(**7**)prepared above in 0.5 ml of CH_2Cl_2 was treated with 60.1 mg of Et_3N (0.594 mmol, 83 μl) and 102.8 mg (0.406 mmol, 74 μl) of (S)-2-methoxy-2-(trifluromethyl)phenylacetyl chloride[9] and the mixture was stirred at room temperature for 1 h. Work-up in the usual manner and examination of the product by gc gave a purity of 98.71%. The corresponding racemic amine gave a pair of Mosher amides, which on gc analysis gave two peaks of almost equal areas.

4'-Methoxyhexanophenone (25). To a stirred, cooled (-10 °C) solution of 135.0 g (1.01 mol) hexanoyl chloride and 108.14 g (1.0 mol) of anisole in 1.0 l of CH_2Cl_2 was added 145.2 g (1.10 mol) of $AlCl_3$ in portions at a rate so as to maintain the temperature between -5 °C and +5 °C. The resulting red mixture was stirred at 0 °C for 2.0 h and poured cautiously into ca. 2 kg of ice. The mixture was stirred for 15 min and the organic phase was separated. The aqueous phase was re-extracted with CH_2Cl_2 (2 x 250 ml), and the combined organic extracts were washed with 1.0 l of H_2O, 1.0N NaOH (2 x 1.0 l), brine (2 x 1.0 l), and dried ($MgSO_4$). Evaporation at 40 °C gave an oil, which was crystallized from hexane at 0 °C to give 129.8 g (63% yield) of **25**, mp 34-35 °C; uv 216 (ε=12,000), 270 (ε=15,700) nm; ir 1673, 1601, 1576 cm^{-1}; ^{1}H nmr δ 0.89 (3 H, t, J=7), 1.35 (4 H, br t, J=7), 1.65 (2 H, t, J=7), 2.89 (2 H, t, J=7), 3.85 (3 H, s), 6.91 (2 H, d, J=9), 7.92 (2 H, d, J=9); ^{13}C nmr δ 13.88 (CH_3), 22.48 (CH_2), 24.21 (CH_2), 31.51 (CH_2), 38.12 (CH_2), 55.31 (OCH_3), 113.60 (Ar, d), 131.12 (Ar, d), 130.42 (Ar, s), 163.9 (Ar, s), 119.0 (CO); ms *m/z* 206 (M^+, 5), 135 (M-C_5H_{11}, 100). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8,79. Found: C, 75.57; H, 8.53.

Methyl 4-Bromocrotonate (26). A stirred solution of 216.4 ml (2.0 mol) of methyl crotonate, 409.4 g (2.3 mol) of *N*-bromosuccinimide and 6.0 g (24 mmol) of benzoyl peroxide in 600 ml of CCl_4 was heated at reflux for 20 h and then cooled to 15 °C. The mixture was filtered and the filter cake was washed with 400 ml of CCl_4. Evaporation of the combined filtrate and washing, and distillation of the residue through a 6" Vigreaux

column gave 291.1 g (70% yield) of methyl 4-bromocrotonate, bp 65-75 °C/2.0 Torr. ^{1}HNmr indicated a mixture of (E)- and (Z)-isomers (*ca.* 1:1).

(E,E)-5-(4-Methoxyphenyl)-2,4-decadienoic Acid (27). A 2-l, creased, 3-necked, round-bottomed flask equipped with a mechanical stirrer, an Ar inlet tube, and a thermometer, was charged with 22.9 g (0.35 g-atom) of zinc dust, 250 ml of anhyd. THF, and 11.55 g (13.5 ml, 0.106 mol) of chlorotrimethylsilane. The mixture was stirred at room temperature for 20 min and treated dropwise during 30 min with a solution of 51.57 g (0.25 mol) of **25** and 59.7 g (0.3 mol) of (E/Z)-methyl 4-bromocrotonate in 250 ml of anhyd. THF. The temperature was kept between 30-35 °C during the addition. Stirring was continued at this temperature for 1.0 h, 75 ml of 6N HCl was added and the mixture was stirred at 60 °C for 2 h. It was evaporated to remove most of the THF and the residue was extracted into 500 ml of toluene. The extract was washed with brine (150 ml), EDTA (150 ml), sat. $NaHCO_3$ (150 ml), brine (150 ml), dried ($MgSO_4$), and evaporated to give the crude methyl ester, contaminated with *ca.* 15% of the starting ketone. The crude ester in methanol (500 ml) was stirred at reflux with 2.5N NaOH (175 ml) for 1.0 h and then concentrated. Water (250 ml) was added and the mixture was extracted with 300 ml of a 2:1 mixture of Et_2O in toluene. The aqueous phase was separated and acidified with 70 ml of 6N HCl and extracted with 500 ml of CH_2Cl_2. The extract was washed with 250 ml of brine, dried ($MgSO_4$), and evaporated to give 75 g of crude **27**, which was crystallized from 200 ml of isopropyl ether to give 42 g (61.2%) of **27** as pale yellow crystals, mp 127-128 °C; uv (EtOH) 238 (ε=8,700), 324 (ε=28,500); ir 3250, 3000-2500 (br), 1680, 1600 cm^{-1}; ^{1}H nmr δ 0.88 (3 H, t, J=7), 1.30 (4 H, m), 1.45 (2 H, t, J=7), 2.75 (2 H, t, J=7), 3.83 (3 H, s), 5.95 (1 H, d, J=15), 6.47 (1 H, d, J=12), 6.90 (1 H, d, J=9), 7.43 (1 H, d, J=9), 7.83 (1 H, dd, J=12, 15); ^{13}C nmr ($CDCl_3$) δ 13.97 (CH_3), 22.42 (CH_2), 29.34 (CH_2), 30.14 (CH_2), 31.67 (CH_2), 55.19 (OCH_3), 113.90 (CH), 119.58 (CH), 123.22 (CH), 127.71 (CH), 131.10 (Ar, s), 143.05 (CH), 151.91 (s), 159.95 (s), 173.27 (CO); ms *m/z* 274 (M^+). Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.28; H, 8.02.

(E,E,)-5-(4-Methoxy)-2,4-decadienoic acid 4-nitrophenyl ester (8). To a stirred, cooled (0-5 °C) solution of 27.44 g (0.10 mol) of **27** and 16.69 g (0.12 mol) of 4-nitrophenol in 125 ml of CH_2Cl_2 was added 21.66 g (0.105 mol) of DCC in 65 ml of CH_2Cl_2. The mixture was stirred at room temperature overnight and filtered. The filtrate was evaporated and the residue was purified by flash chromatography (silica gel, 70-230 mesh) with 3:2 CH_2Cl_2:hexane. Evaporation of the solvents and crystallization of the residue from 2-propanol gave

34 g (86% yield) of **6** as pale yellow crystals, mp 75-77 °C; uv (EtOH) 270 (ε=14,000), 343 (ε=36,300) nm; ir 1725, 1522, 1348 cm^{-1}; ^1H nmr δ 0.85 (3 H, t, J=7), 1.29 (6 H, m), 2.76 (2 H, t, J=7), 3.83 (3 H, s), 6.11 (1 H, d, J=15), 6.54 (1 H, d, J=12), 6.91 (2 H, d, J=9), 7.34 (2 H, d, J=9), 7.44 (2 H, d, J=9), 7.94 (1 H, dd, J=15, 12), 8.28 (2 H, d, J=9); ^{13}C nmr δ 13.94 (CH_3), 22.39 (CH_2), 29.38 (CH_2), 30.10 (CH_2), 31.61 (CH_2), 55.18 (CH_3), 113.96 (CH), 117.91 (CH), 122.47 (CH), 122.63 (sp^2, s), 122.88 (CH), 124.99 (CH), 127.76 (CH), 132.80 (sp^2, s), 143.97 (CH), 144.02 (sp^2, s), 153.07 (sp^2, s), 156.00 (sp^2, s), 160.16 (sp^2, s), 164.72 (CO); ms m/z 395 (M^+, 30), 257 (100). Anal. Calcd for $C_{23}H_{25}O_5$: C, 69.86; H, 6.37; N, 3.54. Found: C, 70.00; H, 6.51; N, 3.58.

[R-(E,E)]-5-(4-Methoxyphenyl)-N-[1-methyl-4-(3-pyridinyl)butyl]-2,4-decadienamide (2):

A. From Coupling of Amine 7 with Ester 8. A stirred solution of 5.3 g (32.26 mmol) of **7** and 12.76 g (32.26 mmol) of **8** in 47 ml of THF was stirred under argon at room temperature for 18 h and then heated at reflux for 3 h. The mixture was evaporated and the residue was extracted into 240 ml of CH_2Cl_2. The extract was washed with 0.5N NaOH (3 x 125 ml), dried ($MgSO_4$) and evaporated to give 15 g of an oil. Crystallization from Et_2O (18 h) gave 10.45 g (77% yield) of **2**, mp 88-89 °C; $[\alpha]^{25}_D$ = - 26.52° (MeOH, c=1.0408); (lit.,[5] mp 88-89 °C, $[\alpha]_D$ = - 28.48°, MeOH, c=1.00); ir (KBr) 3300, 1650, 1601 cm^{-1}; ^1H nmr δ (3 H, t, J=7), 1.14 (3 H, d, J=6), 1.27 (4 H, m), 1.35 (2 H, m), 1.50 (2 H, m), 1.65 (2 H, m), 2.65 (4 H, m), 3.79 (3 H, s), 4.14 (1 H, m, C<u>H</u>NH), 5.47 (1 H, d, J=8, NH), 5.85 (1 H, d, J=14), 6.35 (1 H, d, J=12), 6.85 (2 H, d, J=9), 7.18 (1 H, q, J=8, β-pyrH), 7.35 (2 H, d, J=9), 7.46 (1 H, d, J=8, γ-pyrH), 7.66 (1 H, dd, J=14, 12), 8.41 (2 H, s, α-pyrH); ^{13}C nmr δ 13.91 (CH_3), 20.95 (CH_3), 22.38 (CH_2), 27.62 (CH_2), 29.08 (CH_2), 29.95 (CH_2), 31.61 (CH_2), 32.62 (CH_2), 36.36 (CH_2), 44.70 (CH), 55.23 (CH_3), 113.69 (CH), 123.27 (CH), 123.52 (CH), 123.88 (CH), 127.36, 133.70 (Ar, s), 135.80 (CH), 136.73 (CH), 137.43 (s), 147.05 (CH), 148.61 (s), 149.60 (CH), 159.32 (s), 165.98 (CO).

B. From Coupling of Azide (24) with Acid (27). A stirred mixture of 630 mg (3.31 mmol) of azide (**24**), 1.0 g (3.04 mmol) of acid (**27**), 0.91 ml of tri-n-butylphosphine in 20 ml of cyclohexane under argon was heated at reflux for 20 h, concentrated and extracted with 100 ml of CH_2Cl_2. The extract was washed with satd. $NaHCO_3$ followed by 1.0 N HCl. The acid wash was re-extracted with CH_2Cl_2, and the combined extracts were washed with satd. $NaHCO_3$, dried ($MgSO_4$), and evaporated to give an oil. Flash chromatography (silica gel, 230-400 mesh) with CH_2Cl_2 as eluent gave, after evaporation of the solvent and

crystallization of the residue from ether-hexane (overnight), 537 mg of **2**, mp 86-88 °C, $[\alpha]^{25}_{D}$ = -26.6°(MeOH, c=0.861).

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