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Synthesis and characterization of enantiomers of 5- and 6-methyloctanoic acids

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Enantiomers of 5- and 6-methyloctanoic acids were synthesized in high configurational purity from 1,4-butanediol and 1,5-pentanediol, respectively. Each diol was alkylated with para-methylbenzyl bromide to form a monoether alcohol. The residual alcohol group was converted to a bromide that was then alkylated with valeric or butyric acid dianions, respectively, leading to α -branched acids that were resolved by fractional crystallization of diastereomeric α -phenylethylamides. Subsequently, the diastereomerically pure amides were reductively cleaved, the hydroxymethyl groups were reduced to methyl substituents, the para-methylbenzyl group was hydrogenolyzed, and the resulting alcohol was oxidized to the acid. Configurational assignments are described.

Keywords: asymmetric synthesis; lipase; diastereomer; NMR.

Introduction

The current agricultural interest in the chemistry of lipases, triacylglycerol hydrolases (EC 3.1.1.3), stems from their prospective applications in the synthesis of chiral insecticides [1], herbicides [2] and insect pheromones [3]; as well as projected uses involving the chemistry of fats and oils [4], biosurfactants [5] and peptides [6,7]. We recently developed procedures for synthesis of the enantiomers of 2-, 3- and 4-methyloctanoic acids [8] that are broadly applicable, and allow preparation of gram quantities of such compounds. These materials were viewed as useful to programs for studying lipases, in particular for assessing the consequences of altering lipase structure either by empirical methods, semisynthesis, or directed amino acid exchanges.

Although kinetic resolutions of chiral alcohols

Abbreviations: DMF, dimethylformamide; HMPT, hexamethylphosphoric triamide; LAH, lithium aluminum hydride; LDA, lithium diisopropylamide; NEA, naphthylethylamine; PEA, phenylethylamine; THF, tetrahydrofuran.

using lipases has been documented frequently [9], fewer instances of useful stereoselection based on acid chirality have been reported [10]. It seems likely that the associative binding of the enzyme to its substrate is more intimate with the acid, than with the alcohol, residue. Hence evaluation of kinetic parameters for lipase catalyzed reactions with a set of methyl branched alkanolic acids could prove useful in shedding some light on the nature of that binding. Determination of the configuration of such remotely branched carboxylic acids, however, is not a simple task, and one would not employ the racemic acids as substrates to study enzyme stereobias. We report here the preparations of 5- and 6-methyloctanoic acids in high configurational purity (>98%) by a route that has some generality, and that permits convenient analysis of configuration during the resolution of key intermediates.

Materials and methods

All commercial chemicals were reagent grade and were employed directly without further puri-

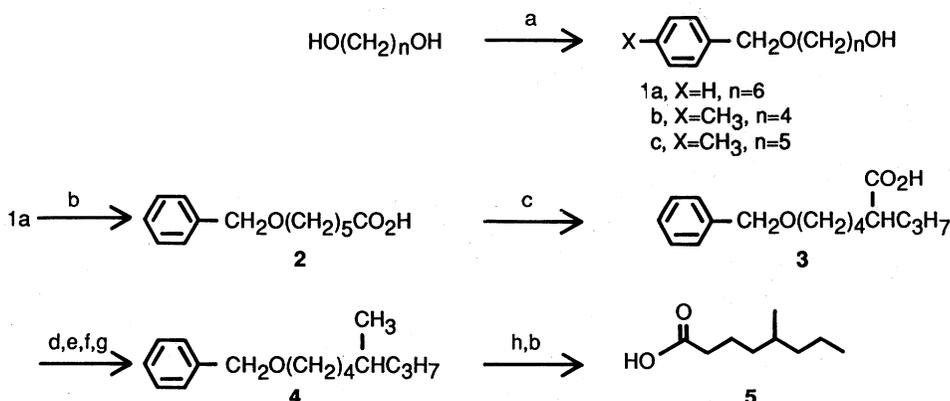
fication. Gas-liquid chromatography was performed with a Shimadzu GC-mini-2 instrument using an SPB-1 column (0.25 mm \times 30 m) with a 50:1 split ratio and helium carrier gas at a flow-rate adjusted to 18 cm/s. Infrared data were recorded with a Perkin-Elmer 1310 spectrophotometer using 3% solutions in carbon tetrachloride. Mass spectra were obtained with a Hewlett-Packard HP-5995 GC/MS system employing an OV-1 column (0.25 mm \times 30 m). $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectra were obtained using a JEOL JNM-GX 400 FT-NMR spectrometer with deuteriochloroform as the solvent and tetramethylsilane as internal standard. Thin-layer chromatography was performed with standard analytical plates of silica gel from Analtech (Newark, DE, USA). (*R*)- and (*S*)- α -phenylethylamine, PEA (Hexcel, Zeeland, MI, USA) and (*S*)- α -naphthylethylamine, NEA, (Norse Labs, Santa Barbara, CA, USA) were used directly. Combustion analyses were carried out by Micro-Analysis Inc., Wilmington, DE. Optical rotations were obtained with a Perkin-Elmer Model 241 polarimeter. Complete spectral data obtained for all new compounds were consistent with assigned structure. Selected spectra data are presented below; critical data for configuration assignments are given in Table III as part of the Discussion; $^{13}\text{C-NMR}$ spectra for compounds of Scheme 2 are provided in Table I at the end of the Experimental section.

Experimental

5-*p*-Methylbenzyloxy-1-pentanol, 1c (Scheme 1). Sodium hydride (7.2 g of 60% in oil dispersion, 0.15 mol) was washed with hexane under nitrogen. 1,5-Pentanediol (28.1 g, 0.27 mol) was added dropwise, and the resulting mixture was warmed to about 50°C for 0.5 h to complete the reaction. The *p*-methylbenzyl chloride (18.9 g, 0.135 mol), or bromide, was added and the resulting mixture was stirred overnight at 40–45°C. The mixture was diluted with ether and H_2O , and extracted with ether. The organic phase was washed thoroughly with H_2O to remove diol, dried (MgSO_4) and concentrated. Distillation provided a small forerun, and then a fraction bp 125–135°C (0.4 mm), 21.4 g (76%) of **1c**: IR (cm^{-1}): 3640, 3580–3620, 1090; GLC: $k' = 4.46$ at 180°C; $^1\text{H-NMR}$ (δ): 1.45 and 1.6 (6H, CH_2s), 2.34 (3H, s, ArCH_3), 3.47 (2H, m, $\text{CH}_2\text{CH}_2\text{OCH}_2$), 3.64 (2H, m, CH_2OH), 4.46 (2H, s, OCH_2Ar), 7.3 (4H, m, ArH).

Similarly were prepared **1a**: 73%, bp 127–135°C (0.5 mm); and **1b**: 75%, bp 127–141°C (0.5 mm).

6-Benzyloxyhexanoic acid, 2. A solution of CrO_3 (9.0 g, 90 mmol) in 8 ml of conc H_2SO_4 was diluted with H_2O to 35 ml and added dropwise to a stirred solution of **1a** (13.6 g, 65.4 mmol) in 50 ml of acetone at 0–5°C until the oxidant's color persisted. The mixture was stirred for an additional 1 h, diluted with 150 ml



Scheme 1 (a) Sodium hydride, *p*-X-benzyl bromide; (b) chromium trioxide; (c) 2 lithium diisopropylamide, *n*-propyl bromide; (d) lithium aluminum hydride; (e) methanesulfonyl

chloride, triethylamine; (f) sodium iodide, acetone; (g) lithium triethylborohydride; (h) hydrogen, palladium on carbon.

of H₂O and extracted thoroughly with ether. The organic phase was washed with water and then the acid product was extracted into 1.25 N NaOH. Subsequently, the aqueous alkaline phase was acidified (2N HCl), and the product was extracted with ether; the solution was dried and concentrated. Distillation afforded 9.2 g (64%) of 2: bp 154–164°C (0.5 mm); IR (cm⁻¹): 3500–2500, 3030–3090, 1708, 1100, GLC: k' = 2.08 at 220°C.

2-Propyl-6-benzyloxyhexanoic acid, 3. Acid 2 (8.0 g, 36.0 mmol) was converted to a dianion using 2 equiv of lithium diisopropylamide, LDA, (11.1 ml of diisopropylamine and 45 ml of 1.6 M butyllithium in hexane) in 75 ml of dry tetrahydrofuran (THF) containing 25 ml of hexamethylphosphoric triamide, HMPT, (0 to 25°C, 1 h). The mixture was cooled to -78°C, and *n*-propyl bromide (3.6 ml, 40 mmol) was injected. The resulting mixture was stirred overnight at 25°C. The mixture was diluted with 100 ml of 2N HCl and extracted thoroughly with ether. The organic phase was washed with H₂O, dried and concentrated. Distillation gave 9.5 g (92%) of 3: bp 169–173°C (0.6 mm); IR (cm⁻¹): 3500–3200, 3100–3040, 1705, 1100; GLC: k' = 3.54 at 220°C; ¹H-NMR (δ): 0.88 (3H, t, CH₃), 3.4 (2H, t, CH₂CH₂O), 4.5 (2H, s, OCH₂Ar), and 7.3 (5H, s, ArH).

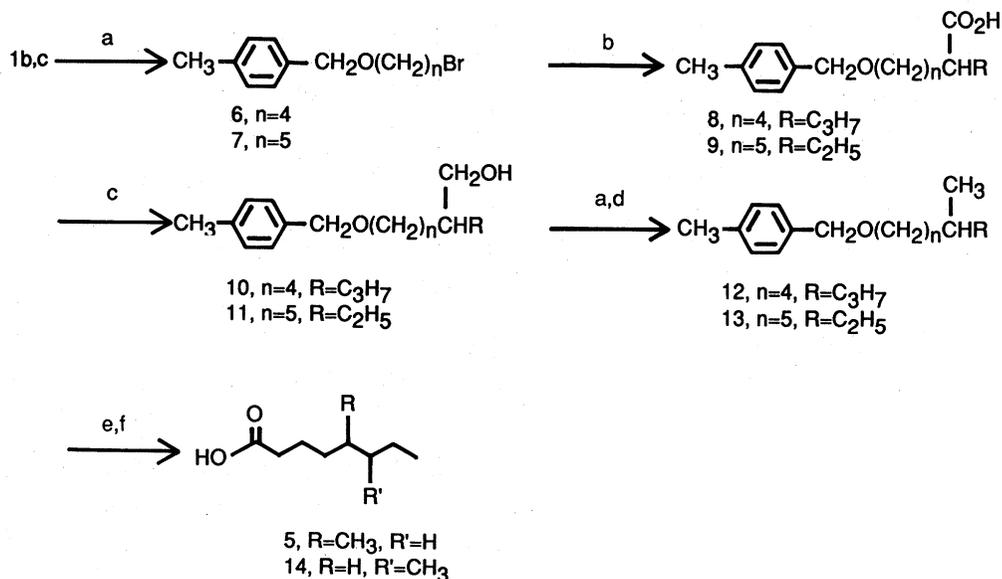
5-Methyl-1-octanol benzyl ether, 4. To a slurry of lithium aluminum hydride (LAH) (0.57 g, 15 mmol) in 15 ml of THF, was added the acid 3 (2.68 g, 10 mmol) in 10 ml THF. The mixture was refluxed for 2 h, and then worked up in the usual manner to obtain the corresponding alcohol, 2-propyl-6-benzyloxy-1-hexanol, 1.37 g (54%): bp 129–131°C (0.12 mm); IR (cm⁻¹): 3600–3150, 3030, 1095; GLC: k' = 3.06 at 220°C; ¹H-NMR (δ): 0.88 (3H, t, CH₃), 3.4 (2H, t, CH₂CH₂O), 3.5 (2H, d, CHCH₂OH) 4.5 (2H, s, OCH₂Ar), 7.3 (5H, s, ArH).

The alcohol was converted to a methanesulfonate ester by treatment with 1.1 equiv of methanesulfonyl chloride and 1.2 equiv of triethylamine in methylene chloride (0–10°C). The mixture was stirred for 1 h at 25°C, and was then worked up by washing with water, drying (MgSO₄) and concentrating. The crude

mesylate was converted to the iodide by refluxing in acetone with 2 equiv of NaI for 2 h. After the usual work up, the crude iodide was dissolved in dry THF under nitrogen and cooled in ice/MeOH. Two equiv of LiEt₃BH (1.0 M in THF) was injected and the mixture was then stirred at 25°C for 2 h. The excess hydride was destroyed by adding 3N NaOH and 30% H₂O₂ (exothermic!): 2.4 ml of each per ml of 1.0 M reductant employed. The product was extracted with hexane; the extract was dried and concentrated. Distillation gave 4 (1.05 g, 45% yield from 3): bp 80–85°C (0.13 mm); IR (cm⁻¹): 3090–3030, 1097; GLC: k' = 1.73 at 220°C; ¹H-NMR (δ) 0.9 (6H, m, CH₃), 3.4 (2H, t, CH₂CH₂O), 4.5 (2H, s, OCH₂Ar), 7.3 (5H, s, ArH).

(±)-*5-Methyloctanoic acid, 5.* Ether 4 (2.1 g, 9.0 mmol) was hydrogenolyzed in 12 ml of abs ethanol containing 1 drop of conc HCl and 25 mg of 20% Pd/C at 3 atm. The crude 5-methyl-1-octanol was obtained by diluting the reaction mixture with H₂O and extracting with hexane. The alcohol was distilled (bp 112–115°C, 51 mm), and subsequently oxidized with CrO₃ in acetone as described above for the oxidation of 1a. The racemic acid was obtained (1.4 g, 76%): bp 44–52°C (0.10 mm); IR (cm⁻¹): 3600–3500, 1705; GLC: k' = 3.65 at 120°C; ¹H-NMR (δ): 0.88 (~6H, m, CH₃), 1.3 and 1.65 (m, aliph CH, CH₂), 2.34 (~2H, t, CH₂CO₂H).

4-Bromo-1-butanol, p-methylbenzyl ether, 6 (Scheme 2). Alcohol 1b (30.4 g, 0.154 mol) was dissolved in 400 ml of THF containing triethylamine (23.8 ml, 0.171 mol) and cooled to <10°C. Methanesulfonyl chloride (13.3 ml, 0.171 mol) was added dropwise using 10 ml of THF as a rinse. LiBr (39.2 g, 0.45 mol) was added and the mixture was stirred 16 h at 25°C. The reaction mixture was then diluted with water and extracted with hexane. The combined organic phase was washed with brine, then water; dried and concentrated. Distillation gave 36.2 g (92%) of 6: bp 108–115°C (0.25 mm); mp 21.5–22°C (pentane); IR (cm⁻¹): 3090–3000, 1095; GLC: k' = 2.09 at 220°C; ¹H-NMR (δ): 1.66–1.78 (2H, m, CH₂), 1.93–2.0 (2H, m, CH₂), 2.34 (3H, s, ArCH₃), 3.43 (2H, t, J =



Scheme 2 (a) Methanesulfonyl chloride, triethylamine, lithium bromide in tetrahydrofuran; (b) RCH₂CO₂H converted to a dianion with lithium diisopropylamide; (c) resolve the acids by fractional crystallization of α -phenethylamides; treat

lithiated amides with methyl chloroformate; reduce the acyl urethans with lithium aluminum hydride; (d) lithium triethylborohydride; (e) hydrogen, palladium on carbon; (f) chromium trioxide.

6.4, OCH₂CH₂), 3.48 (2H, t, J = 6.1, BrCH₂CH₂), 4.46 (2H, s, OCH₂Ar), 7.15 and 7.21 (4H, d, J = 7.3, ArH).

Similarly was prepared 5-bromo-1-pentanol, *p*-methylbenzyl ether, **7**: bp 110–132°C (0.4 mm); spectra data equivalent to **6**.

2-Propyl-6-*p*-methylbenzyloxyhexanoic acid, 8. Valeric acid (18.5 ml, 0.17 mol) was converted to a dianion with 2.1 equiv of LDA as described for the alkylation of acid **2** above in HMPT-THF, and alkylated with the bromoether **6** (64.5 g, 0.24 mol). After the usual workup procedure that separated acidic from neutral fractions, the crude acid **8** was obtained (32.4 g, 68.5%). Because the acid tended to decompose on distillation, it was characterized and employed directly: IR (cm⁻¹): 3600–3400, 1702, 1092; GLC: k' = 5.43 at 220°C; ¹H-NMR (δ): 0.90 (3H, t, J = 6.7, CH₃), 1.24–1.64 (11H, m), 2.34 (3H, s, ArCH₃), 3.44 (2H, t, J = 6.71, CH₂CH₂O), 4.45 (2H, s, OCH₂Ar), 7.14 and 7.21 (4H, d, ArH).

Similarly prepared was 2-ethyl-7-*p*-methylbenzyloxyheptanoic acid, **9**: bp 174–179°C (0.4

mm), decomposes at 210°C. Spectral data equivalent to **8**.

Synthesis of α -phenylethylamides and purification of diastereomers. The racemic acid, **8** or **9**, was converted to the acid chloride in anhydrous ether using 1.2 equiv of thionyl chloride, SOCl₂, and 0.1 equiv of dimethylformamide, DMF, at 25°C for 1 h. The mixture was freed of solvent and unreacted SOCl₂; then added dropwise as a solution in CH₂Cl₂ to a solution of 1.2 equiv each of triethylamine and (*R*)- or (*S*)- α -phenylethylamine in CH₂Cl₂ at 0–10°C. After 1 h at 25°C, the mixture was washed with 2N HCl, H₂O, dried, and concentrated. The crude oil was crystallized from ethanol (approx. 5:1), and was obtained in >98% diastereomeric purity after 4–5 crystallizations in approx. 50% theoretical yield. The *R***R**-diastereomer is the less soluble isomer for acid **8**, and the *R***S**-diastereomer was obtained pure from acid **9**. Thus for **8**, (*R*)-2-propyl-6-*p*-methylbenzyloxyhexanoic acid, (*R*)-1-phenylethylamide: mp 64°C; IR (cm⁻¹): 3440, 3088, 1672, 1093, GLC: k' = 5.70 at 280°C (k' for *R,S* = 5.94; α =

1.043); $^1\text{H-NMR}$ (δ): 0.90 (3H, t, $J = 7.3$, CH_2CH_2), 1.24—1.40 (6H, m), 1.48 (3H, d, $J = 6.7$, $\text{CH}-\text{CH}_3$), 1.51—1.63 (4H, m), 1.98 (1H, m, $\text{O}=\text{CCH}$), 2.34 (3H, s, ArCH_3), 3.37 (2H, m, OCH_2CH_2), 4.42 (2H, s, OCH_2Ar), 5.16 (1H, m, NCH), 5.60 (1H, d, NH), 7.12 and 7.26 (4H, d, *p*-methylbenzyl ArH), 7.30—7.32 (5H, m, phenyl ArH).

For **9**, (*R*)-2-ethyl-7-*p*-methylbenzyloxyheptanoic acid (*S*)-1-phenylethylamide: mp 76—77°C; spectral data equivalent; GLC: $k' = 5.96$ at 280°C (k' for *R,R* = 5.68; $\alpha = 1.049$).

Recovered amides richer in the more soluble diastereomer were re-racemized in ethylene glycol (2 ml/g) with KOH (1 g/10 ml) at 160°C for 48 h.

Anal Calcd for $\text{C}_{25}\text{H}_{35}\text{NO}_2$: C, 78.69; H, 9.25; N, 3.67. Found (**8**-amide): C, 78.21; H, 9.39; N, 3.58; (**9**-amide): C, 78.01; H, 9.25; N, 3.67.

(*R*)- and (*S*)-2-Propyl-6-*p*-methylbenzyloxy-1-hexanol, **10**. Diastereomerically pure amide of **8** (8.40 g, 22.0 mmol) was treated in 80 ml of THF with 1.1 equiv of 2.5 M butyllithium under nitrogen at -78°C . Methyl chloroformate (1.7 ml, 22 mmol) was added, and the mixture was stirred for 2 h without external cooling. The resulting acyl urethane (IR (cm^{-1}): 1760, 1725; TLC (15% ethyl acetate-hexane): $R_f = 0.44$; R_f of amide = 0.16) was isolated by workup with H_2O and ether. The crude material was treated with LAH (2 g, excess) in 20 ml of THF at 0—6°C for 0.5 h to selectively cleave the acyl-N bond, then under reflux for 2 h to reduce the product urethane to $\text{N}-\text{CH}_3$. The reduction mixture was worked up with 1.25 N NaOH, and filtered by suction with thorough rinsing by ether. The filtrate was washed with H_2O , 2N HCl, H_2O ; then dried and concentrated. Distillation provided 4.35 g (75%) of **10**: bp 142—149°C/0.3 mm; (*R*): $[\alpha]_D^{20} = +0.38$ ($c = 1.08$, CHCl_3); (*S*): $[\alpha]_D^{20} = -0.83$ ($c = 1.09$, CHCl_3); IR (cm^{-1}): 3640, 3090, 1095; GLC: $k' = 3.10$ at 240°C; $^1\text{H-NMR}$ (δ): 0.90 (3H, t, $J = 6.7$, CH_3), 1.2—1.6 (approx. 11H, m), 2.34 (3H, s, ArCH_3), 3.45 (2H, t, $J = 6.7$, OCH_2CH_2), 3.54 (2H, bs, CHCH_2OH), 4.46 (2H, s, OCH_2Ar), 7.15, 7.22 (4H, d, ArH).

Similarly prepared were (*R*)- and (*S*)-2-ethyl-7-*p*-methylbenzyloxy-1-heptanol, **11**: bp 138—

146°C (0.25 mm); (*S*): $[\alpha]_D^{20} = +9.33$ ($c = 1.05$, CHCl_3); GLC: $k' = 3.13$ at 240°C; spectral data analogous to **10**.

Samples of alcohols **10** and **11** were oxidized (CrO_3 , acetone) to the corresponding acids. (*R*)-**10** gave (*R*)-**8**: $[\alpha]_D^{20} = -3.50$ ($c = 1.03$, CHCl_3); (*S*)-**10** gave (*S*)-**8**: $[\alpha]_D^{20} = +3.18$ ($c = 1.01$, CHCl_3); (*S*)-**11** gave (*S*)-**9**: $[\alpha]_D^{20} = +6.70$ ($c = 1.00$, CHCl_3). The sample of (*R*)-**9** was contaminated with some of the urethane and was not employed for these experiments.

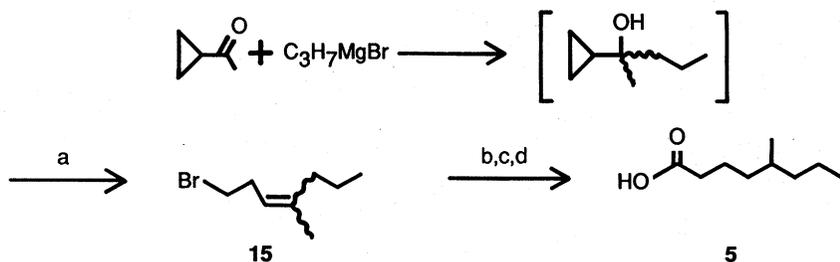
(*R*)- and (*S*)-5-Methyl-1-octanol, *p*-methylbenzyl ether, **12**. The alcohol **10** (3.58 g, 13.6 mmol) was converted to a bromide using methanesulfonyl chloride/triethylamine/LiBr in CH_2Cl_2 as described above for **6**, and then reduced with LiEt_3BH in THF as described for **4**. Distillation gave 2.83 g (79%) of **12**: bp 104—108°C (0.3 mm); (*R*): $[\alpha]_D^{20} = -1.09$ ($c = 1.10$, CHCl_3); (*S*): $[\alpha]_D^{20} = +1.06$ ($c = 1.04$, CHCl_3); IR (cm^{-1}): 3090, 1098; GLC: $k' = 1.96$ at 240°C; $^1\text{H-NMR}$ (δ): 0.82, 0.89 (6H, m, CH_3), 1.1—1.6 (11H, m), 2.34 (3H, s, ArCH_3), 3.44 (2H, t, $J = 6.7$, OCH_2CH_2), 4.46 (2H, s, OCH_2Ar), 7.15 and 7.23 (4H, d, ArH).

Similarly, **11** was converted to **13**: bp 111—115°C (0.35 mm); (*R*): $[\alpha]_D^{20} = -5.45$ ($c = 1.06$, CHCl_3) (contaminated); (*S*): $[\alpha]_D^{20} = +6.89$ ($c = 1.10$, CHCl_3).

(*R*)- and (*S*)-5-Methyloctanoic acid, **5**. Ether **12** (2.7 g, 10.2 mmol) was hydrogenolyzed in abs ethanol over 20% Pd/C as described above for the reduction of **4** to give, after distillation, 1.6 g (100%) of 5-methyl-1-octanol: bp 113—115°C (30 mm); IR (cm^{-1}): 3640; (*R*): $[\alpha]_D^{20} = -0.68$ ($c = 1.02$, CHCl_3); (*S*): $[\alpha]_D^{20} = +1.06$ ($c = 1.043$, CHCl_3); GLC: $k' = 2.52$ at 120°C; $^1\text{H-NMR}$ (δ): 0.81—0.90 (6H, m, CH_3), 1.0—1.6 (11H, m), 3.65 (2H, t, $J = 6.5$, $\text{CH}_2\text{CH}_2\text{OH}$).

Similarly prepared was 6-methyl-1-octanol: bp 101—105°C (30 mm); (*R*): $[\alpha]_D^{20} = -8.99$ ($c = 1.09$, CHCl_3); (*S*): $[\alpha]_D^{20} = +9.33$ ($c = 1.05$, CHCl_3); spectral data analogous to the above.

Oxidation of these alcohols to the carboxylic acids with CrO_3 in acetone as described previously gave 5-methyloctanoic acid, **5**, (70—75%): bp 44—52°C (0.10 mm); IR (cm^{-1}): 3600—3500, 1705; (*R*): $[\alpha]_D^{20} = -1.10$ ($c = 1.09$, CHCl_3); (*S*): $[\alpha]_D^{20} = +1.31$ ($c = 1.07$, CHCl_3);



Scheme 3 (a) Hydrobromic acid, 0–25°C; (b) sodium cyanide; (c) hydrogen, palladium on carbon; (d) 50% sulfuric acid, reflux.

GLC: $k' = 3.65$ at 120°C; and 6-methyloctanoic acid, **14**: bp 85–89°C (0.4 mm); rep. bp 146–147°C (13 mm) (**11**); (*R*): $[\alpha]_D^{20} = -8.20$ ($c = 1.00$, CHCl_3); (*S*): $[\alpha]_D^{20} = +8.90$ ($c = 1.09$, CHCl_3); (*S*)-isomer reported (+) with no value assigned [12].

(±)-5-Methyloctanoic acid, **5** (Scheme 3). Methyl cyclopropyl ketone (9.9 ml, 0.10 mol) and the Grignard Reagent obtained from *n*-propyl iodide (11.7 ml, 0.12 mol) and magnesium (5.8 g, 0.24 mol) were allowed to react in ether (ice cooling) as the first step of Julia's method for preparing homoallylic halides [13]. The crude intermediate carbinol was rearranged with cold 48% HBr (30 ml) and worked up with pentane. The crude product was passed through Brockman neutral alumina (20 g) with 100 ml of pentane, the solvent was removed and the crude bromide **15** was then treated with NaCN (6.1 g, 0.13 mol) in 50 ml of DMSO at 45–50°C for 16 h. After the usual workup, the displacement product, 5-methyl-4-octenitrile, was distilled to give 6.8 g (55%): bp 40°C (0.3 mm); IR (cm^{-1}) 2260. The double bond was reduced over 0.11 g of 20% Pd/C in 50 ml of abs ethanol containing 2 drops of HCl, and monitoring by GLC: k' of unsaturated nitrile = 3.2; k' of saturated nitrile = 2.7 (120°C). The reduced material was extracted from the H₂O-diluted reaction mixture with hexane. The extract was washed with H₂O, dried, and concentrated. The saturated nitrile was then hydrolyzed by heating it in 25 ml of 50% H₂SO₄ under reflux for 4 h. After the usual workup, the 5-methyloctanoic acid was obtained by distillation: 5.5 g (35% overall),

identical in all respects with the other preparations described.

Synthesis of α-naphthylethylamides of acids 8 and 9 (16–19, Table II). Each enantiomer of **8** and **9** (100 μl) was allowed to react with SOCl₂ (0.2 ml) and DMF (10 μl) in 10 ml of anhydrous ether as described above. The crude acid halide was freed of solvent and unreacted SOCl₂ and then added in CH₂Cl₂ to a solution of 100 μl each of (*S*)-α-naphthylethylamine and triethylamine in CH₂Cl₂ (10 ml) to form the amide. After the usual workup, the crude amide was eluted from silica gel (1 g) with ether, and recrystallized from ethanol: IR (cm^{-1}) 3440, 3095, 1670, 1095; mp: **16**, 117°C; **17**, 120–121°C; **18**, 121–122°C; **19**, 117–118.5°C.

Results and Discussion

Readily available α,ω-diols served as starting materials for the general routes to branched fatty acids outlined in Schemes 1 and 2. The key step in each route involves the resolution of an α-branched acid and was accomplished by fractional crystallization of amides formed from (*R*)- or (*S*)-α-phenylethylamine (PEA), and subsequent liberation of the enantiomerically purified carboxylic acids as the corresponding carbinols. While racemic acids could be prepared by either route, the enantiomeric acids were most easily synthesized by the method shown in Scheme 2. The preparation of racemic 5-methyloctanoic acid exemplifies Scheme 1; additionally, this material was prepared by an independent path that is specifically useful for 5-substituted (racemic) alkanolic acids (Scheme 3).

TABLE I

¹³C-NMR shifts.

Compound	C=O	Aromatic	C—O, C—X	Aliphatic
1b		137.2, 135.5, 129.0, 127.8	72.8, 69.9, 62.0	30.1, 26.9, 21.2
1c		137.2, 135.5, 129.0, 127.7	72.8, 70.1, 62.8	32.5, 29.4, 22.4, 21.1
6		137.3, 135.3, 129.0, 127.7	72.8, 69.0	33.7, 29.7, 28.3, 21.2
7		137.2, 135.5, 129.0, 127.7	72.5, 69.8	33.7, 32.6, 28.9, 25.0, 21.1
8	182.9	137.4, 135.5, 129.1, 127.9	73.0, 70.1	45.2, 34.5, 32.0, 29.8, 24.3, 21.4, 20.7, 14.1
10		135.5, 132.6, 129.0, 127.8	72.8, 70.1, 65.6	40.2, 33.2, 30.7, 30.1, 23.5, 21.1, 20.0, 14.4
12		137.0, 135.6, 129.0, 127.7	72.7, 70.3	39.3, 36.9, 32.4, 30.1, 23.6, 21.1, 20.1, 19.6, 14.4
5	179.7			39.1, 36.3, 34.2, 32.2, 22.2, 20.0, 19.5, 14.4
14	180.2			36.2, 34.2, 34.1, 29.4, 26.5, 25.0, 19.1, 11.3

1,5-Hexanediol was converted to a monobenzyl ether **1a** (Scheme 1, $n = 6$) and then oxidized to a carboxylic acid **2**. The acid was treated with two equivalents of lithium diisopropylamide (LDA) to prepare the dianion, which was then alkylated with *n*-propyl bromide giving **3**. The carboxyl group was reduced with lithium aluminum hydride (LAH) to the carbinol; this was treated sequentially with methanesulfonyl chloride (MsCl)/triethylamine, then NaI in acetone converting the alcohol to the iodide. Lithium triethylborohydride (LiEt₃BH) was

employed to complete the reduction of carboxyl to methyl, **4**. The benzyl group was hydrogenolyzed, and the resulting 5-methyl-1-octanol was oxidized to the racemic acid, **3**.

With this route established, we wished to resolve the acid **3** using a previously described general method that makes use of the available (*R*)- and (*S*)- α -PEA that tend to yield crystalline amides of α -branched acids [14]. However, we were not able to obtain a solid adduct from this acid bearing a benzyl ether blocking group. Replacement with a *p*-methylbenzyl substituent

TABLE II

Comparisons of benzyl and *p*-methylbenzyl ethers protecting groups.

Group	pH		Organometals			Reduction		Other		
	1 ^b	2	3	4	5	6	7 ^a	8	9	10
Benzyl	U	M	U	M	U	M	R	U	R	R
<i>p</i> -Methylbenzyl	U	M	M	R	U	M	R	U	R	R

U = unreactive, M = moderate stability, R = reactive

^aBenzyl reacts significantly faster than *p*-methylbenzyl.^b(1) pH = 1, reflux, 4 h; (2) pH = 12, RT, 16 h; (3) LDA, THF, RT, 0–5 h; (4) LDA, THF/HMPT, RT, 0.5 h; (5) Zn, HCl, RT, 1 h; (6) BH₃, THF, RT, 16 h; (7) LAH, THF, reflux, 16 h; (8) 48% HBr, RT, 2 h; (9) H₂CrO₄, acetone, RT, 2 h; (10) HBr, acetic acid, 80–90°C, 1 h.

solved that specific problem, but alkylation of acid **2** with the new blocking group was unsuccessful. Deprotonation to the dianion was complicated by deprotonation of the *p*-methylbenzyl group (a deep blue solution formed immediately beyond the addition of one equivalent of LDA), and no simple alkylation products were observed.

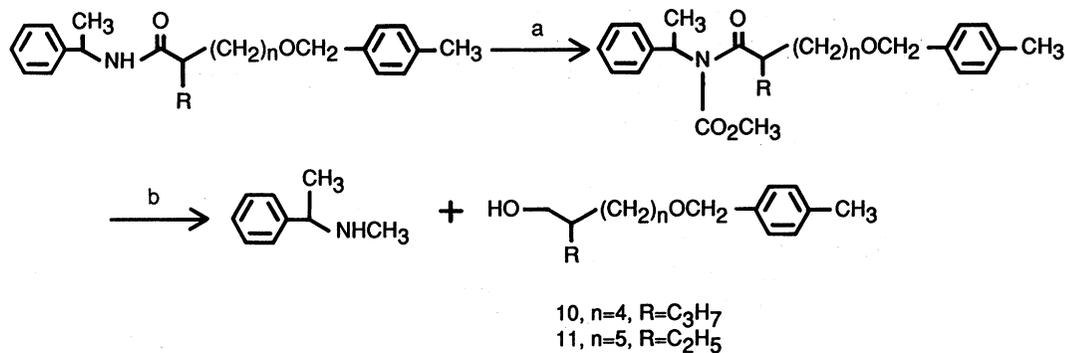
An alternate approach was taken (Scheme 2) in which the mono-*p*-methylbenzyl ether of 1,4-butanediol was converted to a bromide, **6**. The transformation of the hydroxyl group to a bromide was conveniently conducted in one flask by treatment with methanesulfonyl chloride-triethylamine and excess LiBr in tetrahydrofuran. Alkylation of the dianion of valeric acid with **6** produced the α -branched acid **8**. Compound **8** was converted to α -PEA amides that were crystalline and could be recrystallized to diastereomeric purity. The pure diastereomers were then reductively cleaved to the (*R*)- and (*S*)-alcohols **10** as discussed below. Alternatively, the racemic acid **8** could be reduced by LAH directly to give racemic **10** as indicated in Scheme 2. The enantiomeric alcohols **10** were then reduced (carbinol \rightarrow methyl) as described previously to give (*R*)- and (*S*)-**12**. Removal of the *p*-methylbenzyl group followed by oxidation gave the enantiomers of 5-methyloctanoic acid, **5**. Similarly, 1,5-pentanediol was transformed via bromoether **7** to the acid **9**. This acid was then resolved (see below), the enantiomeric carbinols were reduced to methyl branched ethers, **13**; and after hydrogenolysis, the liberated alcohol was oxidized to produce the enantiomers of 6-methyloctanoic acid, **14**.

Since the reagents are readily available and the steps involved are relatively straightforward, gram quantities of these acids may be prepared. The utility of this second route is limited by the resolvability of acids analogous to **8** and **9**, which will likely be a case-by-case matter affected by the relative sizes of the alkyl substituents and any additional functional groups present on those residues. We also wish to note that although substituted benzyl groups with altered chemical reactivity are sometimes used to protect alcohols [15], we are unaware of prior use of sub-

stitution in this protecting group to induce crystallinity. Its reactivity is comparable to that of the benzyl group, although some differences exist. Table II briefly surveys the susceptibility of both types of ether to a number of common chemical reagents. Also, in connection with the recent interest in homogeneous nucleophile exchange, e.g. Cl for Br [16], and continuing concern for simplifying the conversion of alcohol to alkyl halide [17], the one-pot transformation in THF is pertinent. This reaction was complicated by alkyl chloride formation (from the triethylammonium chloride present) when hexamethylphosphoric triamide (HMPT) had been added in an effort to accelerate the desired displacement. The formation of alkyl chloride occurred by replacement of bromide as well as by the competitive displacement of the methanesulfonate ester. Control experiments using 1-halodecanes indicated that in homogeneous solution (THF/HMPT, 5:1) the equilibrium ratio of 1-chloro- to 1-bromodecane was 74:26, and was achieved in 2–3 h at 25°C. The chloride, therefore, can easily be prepared using an excess of LiCl; the corresponding bromide can be obtained using excess LiBr and THF alone under reflux. The LiCl is less soluble, and the mixture becomes heterogeneous as reaction progresses, in analogy to the Finkelstein Reaction [18]. Equilibrations of Cl and I (75:25) and Br and I (60:40) were also conducted.

Although the route in Scheme 2 is useful for enantiomers of selected alkylalkanoic acids, it is less efficient for the racemic acids. A simple approach to 5-substituted acids is shown in Scheme 3. Methylcyclopropyl ketone was allowed to react with *n*-propyl magnesium iodide, and the crude product was treated with cold HBr to give the homoallylic bromide, **15**. Cyanide displacement, followed by reduction of the double bond and hydrolysis of the nitrile group gave 5-methyloctanoic acid, **5**.

Finally, the resolution of acids **8** and **9**, with attendant configuration assignment, was accomplished by a process described previously [14] in which amides were prepared from the racemic acid chlorides using (*R*)- or (*S*)-PEA. Several crystallizations from ethanol produced a pure



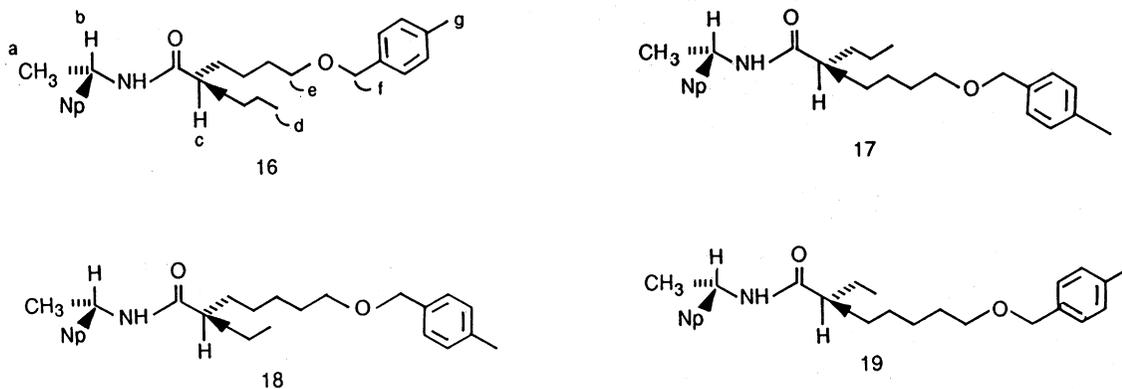
Scheme 4 (a) Butyllithium, methyl chloroformate; (b) lithium aluminum hydride.

diastereomer (>98%) as judged by GLC. The recovered amide fractions that were now enriched in the more soluble diastereomer could be racemized by extended treatment with strong base, namely ethylene glycol/KOH/160°C. This allows one to recycle the materials, and to increase the recovery of the less soluble

diastereomer. The most convenient manner in which to cleave the purified diastereomer was to carbomethoxylate the amide nitrogen by treating the compound with an equivalent each of n butyllithium and methyl chloroformate (Scheme 4) [19]. The resulting acyl urethan reacted with LAH in THF to produce the enantiomeric alco-

TABLE III

NMR data for α -naphthylethylamides.



Compound	Config.	GLC ^a	CDCl ₃ NMR shifts (ppm)						
			a	b	c	d	e	f	g
16	R,S	2	1.66	5.95	1.93	0.79	3.42	4.44	2.34
17	S,S	1	1.67	5.95	1.92	0.89	3.23, 3.29	4.34	2.32
18	R,S	2	1.66	5.96	1.83	0.79	3.42	4.44	2.33
19	S,S	1	1.68	5.96	1.82	0.92	3.30	4.38	2.33

^aElution order of PEA amide.

hols, **10** and **11**. These alcohols were then oxidized to the acids, **8** and **9**, and were converted to the original amides with either of the enantiomeric PEAs to ascertain configurational purity. The configurations of the acids were then determined. The rotations of the acids were obtained ((*R*)-2-methyloctanoic acid, for example, is $[-]$ [20]), and amides of (*S*)- α -naphthylethylamine were prepared in order to compare proton NMR shifts of key protons. The data are summarized in Table III. These amides were expected to exhibit a strong solution conformation preference [21] that would cause significant upfield shifts of protons opposed by the naphthyl ring [22]. Acid enantiomers whose rotations were positive and were, therefore, expected to have the (*S*) configuration, formed amides with (*S*)- α -naphthylethylamine in which the methyl group of the short aliphatic chain gave a normal signal at 0.89 ppm. The corresponding shifts for the (*R,S*)-diastereomer, however, appeared at 0.79 ppm. Such a displacement of that signal was expected if the conformations of the diastereomers in solution are as depicted. The signals for each PhCHN were as expected [22], and the corresponding signal for O=C—CHRR' appeared at 1.82—1.93 ppm. Interestingly, the effect of the naphthyl group is sufficiently pronounced that it extended to the —CH₂OCH₂— signals; relative shifts were also consistent with the configuration assignments. In summary, the gas chromatographic resolution orders of the PEA amides, the ¹H-NMR shift differences of the diastereomeric pairs of NEA amides, and the rotations of the subject branched acids were consistent with the assignments of configuration for **8** and **9**.

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