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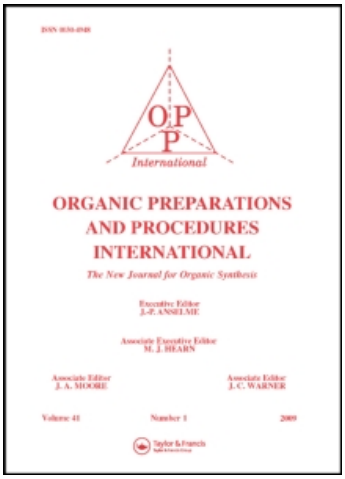

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ASYMMETRIC SYNTHESIS OF 2-,3-, AND 4-METHYLOCTANOIC ACIDS

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ASYMMETRIC SYNTHESIS OF 2-,3-, AND 4-METHYLOCTANOIC ACIDS

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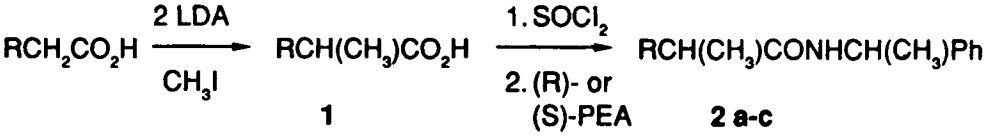
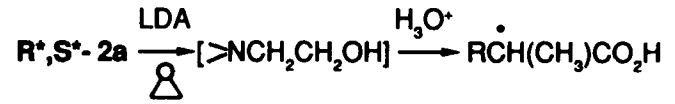
Our interest in the chemistry of lipases, enzymes that catalyze reactions of fatty acids and their derivatives, led us to prepare 2-,3-, and 4-methyl octanoic acids in high (> 97%) configurational purity.[1] Branched octanoic acids were chosen, because lipases appear to react well with octanoate esters generally;[2] methyl substituents were selected as stereoprobes for lipase reactivity, because such a substitutent would not act as a potential source of electrostatic interactions when associated with the enzyme. A number of methods of asymmetric synthesis of α-branched acids are available,[3] and we chose to employ a previously described general method involving diastereomer resolution[4] in the hope that the route could be extended to include diastereomeric derivatives formed from acids with asymmetric centers further removed from the carboxyl group. Ultimately, however, each desired acid was synthesized by resolution of an α-methyl acid, which was then elaborated to the required chain length.

Scheme 1



a) $R = C_6H_{13}$ **b)** $R = C_5H_{11}$ **c)** $R = C_4H_9$ PEA = α-Phenylethylamine



R*,S* = Relative configuration

Octanoic acid was converted to a dianion with lithium diisopropylamide (LDA) and alkylated with methyl iodide (Scheme 1). The resulting 2-methyloctanoic acid was converted via its acid halide, to amide 2a with either (R)-, or (S)-α-phenylethylamine (PEA). Pure (> 99%) diastereomers were obtained by recrystallization from ethanol monitored by gas-liquid chromatography

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(glc). Since the R*S* diastereomer is least soluble, and therefore more easily purified, we prepared the (R)-acid using the (S)-amine, and vice-versa. Each pure amide was deprotonated with LDA, and the resulting anionic nitrogen was alkylated with ethylene oxide. The hydroxyethylated adduct was then hydrolyzed with dilute acid. The hydrolytic cleavage is known to be facilitated by rearrangement of the amide to aminoester.[5] After distillation of the (R)- and (S)-2-methyloctanoic acids 1a, each was analyzed for configurational purity as an amide of PEA by glc.

We were only able to affect a partial chromatographic resolution of the diastereomeric PEA amides of racemic 3-methyloctanoic acid 1b, and could not obtain a crystalline adduct. The amides formed from α-naphthylethylamine (NEA), however, were chromatographically resolvable, and could be fractionally crystallized from ethanol. Because of the cost of the NEA, however, we opted to resolve 2-methylheptanoic acid instead, and then add the required additional carbon atom. Furthermore, and perhaps predictably, neither PEA nor NEA provided amides of 4-methyl-octanoic acid[1] that could be separated chromatographically to afford a basis for monitoring purification. Since the rigidity of the amide link provides the basis for chromatographic differentiation of such diastereomers,[6] we sought to extend that rigidity toward the asymmetric center. 4-Methyl-E-2-octenoic acid, obtained by condensing 2-methylhexanal with malonic acid, has a trans double bond inserted between the branched carbon and the carboxyl group. However, only the amide of NEA was resolved (high performance liquid chromatography, hplc), and fractionation was difficult.

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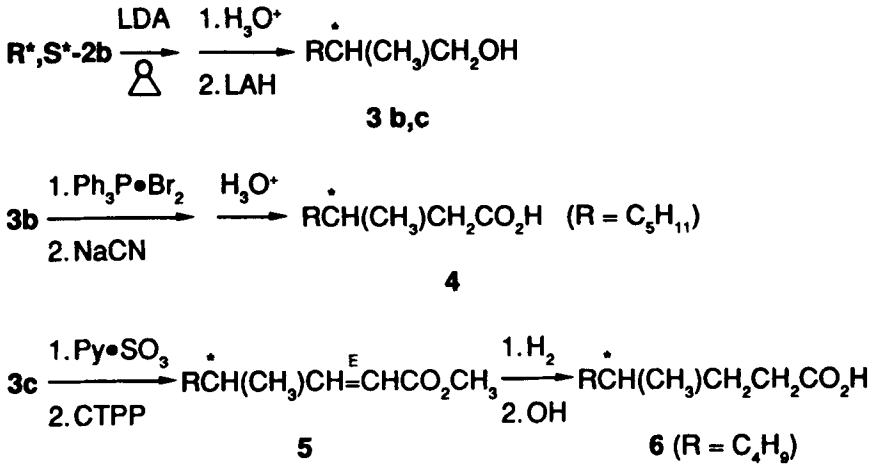
The 2-methylheptanoic acid 1b was synthesized and purified by resolving amides PEA in complete analogy to the route described for 2-methyloctanoic acid. Each diastereomeric amide 2b was N-hydroxyethylated (Scheme 2), the adducts were treated with dilute acid in THF, and the resulting mixture of aminoester and acid was reduced with LAH to give (R)- and (S)-2-methyl-heptanols 3b. Although it has been established that this sequence does not jeopardize configuration, the (R)-alcohol was oxidized to the acid using Jones Reagent[7] and the acid then transformed to an amide of PEA for glc analysis. No loss in configurational purity was observed. The alcohols were converted to bromides, treated with sodium cyanide and then hydrolyzed to yield (R)- and (S)-3-methyloctanoic acids 4. These acids were then analyzed again for configurational purity as amides of (S)-NEA.

In order to prepare the 4-methyloctanoic acids, racemic 2-methylhexanoic acid 1c was synthesized, the amides of PEA were resolved. The N-hydroxyethylated adducts were reductively cleaved to give (R)- and (S)-2-methylhexanols 3c[8] (Scheme 2). Oxidation to the aldehydes with pyridine sulfur trioxide (Parikh oxidation)[9] was followed by condensation with carbomethoxymethylene triphenylphosphorane[10] to produce (R)- and (S)-4-methyl-E-2-octenoic acid, methyl esters 5. These were analyzed for configurational purity by oxidative cleavage with permanganate to 2-methylhexanoic acids that were then converted to amides of PEA for glc analysis. The unsaturated esters were then hydrogenated, and saponified to produce (R)- and

(S)-4-methyl octanoic acids 6.

Scheme 2



CTPP = Carbomethoxy triphenylphosphorane
R*,S* = Relative configuration

EXPERIMENTAL SECTION

All chemicals and solvents were reagent grade or better. IR spectra were recorded on a Perkin-Elmer 1310 Spectrophotometer using 3% solutions in CCl_4 of $CHCl_3$. ^1H NMR spectra were obtained on a Bruker 400 MHz spectrometer using $CDCl_3$ solutions and shifts are reported in ppm δ to TMS. Mass spectra were determined using a Hewlett-Packard 5995 GC-MS system interfaced with an OV-1 capillary column (0.25 mm ID x 12 m). Gas liquid chromatography (glc) was accomplished using a Shimadzu GC-Mini 2 instrument with either an SP-2340, or SPB-1, column (0.25 mm ID x 30 m) with flame ionization detection and He as carrier gas with a 50:1 split ratio. High performance liquid chromatography (hplc) was performed with a Spectra-Physics SP-8800 pump, and a Waters Associates R 401 detector with an LC-Si column, or an LC-18 column (4.6 mm ID x 25 cm). Thin layer chromatography (tlc) was determined using Silica gel G (0.25 mm) from Analabs, Inc. Optical rotations were measured with a Perkin-Elmer Model 241 Polarimeter. Combustion analyses were obtained from Micro-Analysis, Inc. of Wilmington, DE.

Synthesis of Diastereomerically Pure Amides (2).- 2-Methyloctanoic, heptanoic and hexanoic acids, 1a, b, and c, respectively were synthesized by the general method of Pfeffer and Silbert.[11] The yields were 90-95% and the acids had the following bps: 1a, 93-95°/0.7 mm; 1b, 88-94°/0.5 mm; 1c, 70-73°/0.05 mm. Preparation of amides of (R)- and (S)-α-phenylethylamine (PEA), and resolution of the diastereomers by several recrystallizations from ethanol has been described previously as a general procedure,[4] and it has been employed specifically to prepare (R)- and (S)-1c.[8] Application of the technique for 1a and 1b, however, has not. Each diastereomer represented by structures 1a, b, c was obtained in > 98% purity. Compound (glc data for the SPB-1 column, yield of R*S* isomer, mp.): 2a (k' [210°]; R*R*, 4.90; R*S*, 5.43; α = 1.10 g, 50-52% of theoretical; 100-101°); 2b (k' [210°]; R*R*, 3.35; R*S*, 3.56; α = 1.063, 37-40%; 88-90°). For 2a, IR: 3440, 3000, 1655 cm^{-1}; ^1H NMR: δ 0.86 (t, 3H), 1.13 (d, ~3H, J

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= 7.2), 1.2 (m, ~12H), 1.48 (d, 3H, J = 6.8), 2.3 (m, 1H), 7.3 (m, 5H) ppm; GCMS $(m/e)^+$: 261 $(M)^+$, 177 $(P - C_6H_{12})^+$, 105 $(C_5H_6CH_2)^+$. Spectral properties of 2b were analogous and GCMS $(m/e)^+$: 247 $(M)^+$, 177 $(M-C_5H_{10})^+$, 105 $(C_5H_6CH_2)^+$. Optical rotations for PEA-amides (compound, diastereomer, rotation, solvent, concentration: 2a, R-acid, S-amine, $[\alpha]_D$ -91.6, $CHCl_3$, 1.01; 2b, R-acid, S-amine, $[\alpha]_D$ - 95.41°, $CHCl_3$, 0.50; 2c, S-acid, R-amine, $[\alpha]_D$ + 73.52, $CHCl_3$, 1.01.

Compound 2a Anal. Calcd for $C_{17}H_{27}NO$: C, 78.11; H, 10.41; N, 5.36
Found : C, 78.11; H, 10.44; N, 5.77

Compound 2b Anal. Calcd for $C_{16}H_{25}NO$: C, 77.68; H, 10.19; N, 5.66
Found : C, 77.82; H, 10.48; N, 5.94

(R)- and (S)- 2-Methyloctanoic Acids 1a.- The R(acid)S(Pea)-amide, 2a (3.0 g, 11.5 mmol) was added to a solution of LDA (1.1 equiv) prepared from butyllithium and diisopropylamine, and stirred for 0.25 hr. The solution was cooled at 0-5° and ethylene oxide (1.1 ml, 22 mmol) was injected. The mixture was stirred overnight and then after dilution with water, extracted with ether in the usual way. The crude N-hydroxyethylated product (IR: 3540, 1630 cm^{-1}) was treated with 50 ml of 2N HCl and sufficient dioxane to dissolve the compound as it was heated under reflux for 5 hrs. Glc monitoring indicated the absence of hydroxyethylated amide after 2 hrs and disappearance of presumed aminoester that had been formed after 5 hrs. The product acid was recovered from the cooled reaction mixture by dilution with water and extraction with hexane. After drying with $MgSO_4$ and removal of the solvent, the acid was distilled: (R)-1a; 1.50 g; bp. 93-95°/0.5 mm; $[\alpha]_D$- 16.53° ($CHCl_3$, c = 1.21; lit. value corresponding to 42% ee: $[\alpha]_D$- 6.94° (neat, = 1); [12] glc analysis of the PEA amide indicated 97.8% ee, i.e., no more than 1.1% of the R-acid present. Similarly was obtained (S)-1a: $[\alpha]_D$ + 16.12° ($CHCl_3$, c = 1.179); glc analysis of PEA-amide showed > 97% ee.

(R)- and (S)-3-Methyloctanoic Acids (4).- Amide 2b (from the R-acid and S-PEA, 4.5 g, 18.2 mmol) was deprotonated with LDA and hydrxyethylated with propylene oxide (2.9 ml, 36.3 mmol) as described above. The latter is a useful alternative to ethylene oxide; it is easier to dry, store and use. The crude product was heated under reflux for 5 hrs in THF (100 ml) containing $HClO_4$ (13.5 ml) and saturated with water. The cooled mixture was diluted with brine and extracted with CH_2Cl_2. The organic phase was washed with brine, dried and concentrated. The residue was added in a small amount of THF to a slurry of LAH (3.4 g) in THF (50 ml), and then warmed gently at 40° for 16 hrs.The reduction mixture was worked up with 1.25 N NaOH and ether, filtered through Celite and the organic phase was then washed sequentially with 2N HCl and water. After drying, the solvent was removed and alcohol 3b was distilled: bp. 94-96°/30 mm, 0.96 g (41%). The alcohol was treated with triphenylphosphine dibromide [8.5 mmol prepared from Ph_3P (2.3 g) and Br_2 (1.4 g) in CH_2Cl_2, 30 ml] at 25° for 2 hrs. MeOH (1 ml) was added and the solvent was evaporated. The resulting mixture was treated with NaCN (1.2 g) in DMSO (15 ml) at 50° for 16 hrs. The mixture was diluted and extracted with hexane. The

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organic phase was washed with water, dried; and the solvent was removed to yield the crude nitrile (IR: 2260 cm^{-1}). The nitrile was hydrolyzed in 50% H_2SO_4 (7.5 ml) under reflux for 4 hrs. The product prganic acid was then recovered in the usual manner to yield 0.72 g (25% from 2b) of (R)-4, bp. 90-95°/0.5 mm, $[\alpha]_D$ + 5.50° ($CHCl_3$, c = 1.237). Similarly was obtained (S)-4 (22%); $[\alpha]_D$ = -6.52° ($CHCl_3$, c = 1.134). Glc elution orders are reversed for β-methyl-substituted acid diastereomers, and signs of rotation are reversed for the acids.

(R)- and (S)-4Methyloctanoic Acids (6).- Diastereomerically pure amides 2c were N-hydroxylated and then treated with (1) dilute HCl in THF and (2) LAH as described above to produce (R)- and (S)-2-methyl hexanols, 3c.

The alcohol, (R)-3c (1.53 g, 13.2 mmol) was treated with pyridinesulfur trioxide (6.24 g, 69.2 mmol) and triethylamine (12.9 ml, 92.4 mmol) in DMSO (30 ml) at 25° for 2 hrs. The mixture was cooled in ice and diluted with 2N HCl (100ml), then extracted with petroleum ether (bp 35-40°). The organic phase was washed several times with water, dried and carefully concentrated to avoid losing the aldehyde. The crude aldehyde was treated with carbomethoxymethylene triphenylphosphorane (4.41 g, 13.2 mmol) in benzene (50 ml) under reflux for 1 hr. The solvent was removed, and the residue was extracted with hexane. The hexane solution was then concentrated and the residue distilled to give (R)-4-methyl-E-2-octanoic acid, methyl ester, (R)-5, (1.10 g, 65.8%) bp. 109-112°/30 mm, lit. bp 88-93°/20 mm[1] identical spectrally to material previously reported.[13]

The ester (0.58 g, 3.4 mmol) was hydrogenated with 20% Pd/C (0.2 g) in ethanol (10 ml) at 3 atm. When the ester had been reduced (glc monitoring), it was recovered by diluting the reaction mixture with water and extracting the product with hexane. The saturated ester was saponified with 1:1 methanol-6N KOH (30 ml) under reflux for 2 hrs. The organic acid was recovered by extracting the acidified mixture with ether. Distillation gave (R)-6, 0.24 g (45%), bp. 166-172°/25 mm, lit. bp 94-98°/0.5 mm,[14] $[\alpha]_D$ - 1.53° ($CHCl_3$, c = 1.114). Similarly was obtained (S)-6: $[\alpha]_D$ + 1.45° ($CHCl_3$, c = 1.106).

Analysis for configuration was performed on the unsaturated esters 5 in the following manner: the ester, 85 mg, was stirred vigorously in 10 ml of acetone containing $NaHCO_3$ (25 mg) and $KMnO_4$ (316 mg) at 25-30° for 3 hrs. The acetone was stripped, the residue was taken up in 6 ml of 0.33N H_2SO_4 (0.3 g) and extracted with ether. The ethereal layer was washed with water, dried and concentrated to give the corresponding 2-methylhexanoic acid which was then converted to an amide of PEA in the usual fashion. Each sample was judged to be > 95.4% ee implying less than 2% racemization had occurred either in the synthesis of 5, or during the oxidative cleavage performed for the analysis.

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