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An Efficient Synthesis of (S)-2-Hexylthiodecanoic Acid

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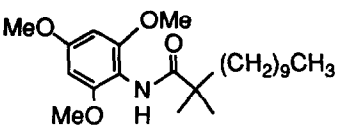
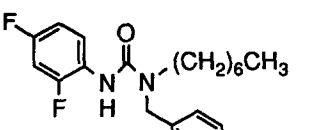
Abstract: A short synthesis of (S)-2-hexylthiodecanoic acid from racemic 2-hydroxydecanoic acid is described. This material is useful as a sidechain for ACAT inhibitors.

Recently, publications from several pharmaceutical firms described inhibitors of ACAT (acyl coenzyme A: cholesterol acyl transferase) as an approach to lowering plasma cholesterol concentrations. Two examples that have appeared in the literature, PD128042 (CI-976)[1] and CL 277,082[2], are depicted below. Common structural features of these inhibitors were a lipophilic alkyl sidechain coupled through a urea or amide linkage to an aromatic nucleus.

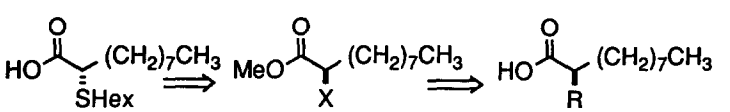


PD128042
(CI-976)



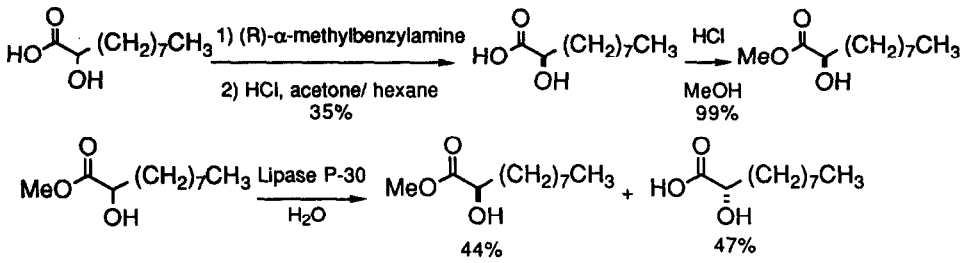
CL 277,082

Our own efforts in this area have centered on 2-hexylthiodecanoic acid as a side chain.[3] Because a potency difference was observed for (R) and (S)-2-hexylthiodecanamide, we required a synthesis of (S)-2-hexylthiodecanoic acid.



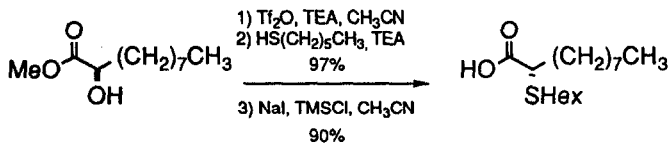
Scheme 1

Our approach is summarized in Scheme 1. We envisioned the incorporation of hexanethiol by displacement of a leaving group alpha to an optically active carboxylic acid derivative. While the enzymatic resolution of the N-chloroacetyl derivative of 2-aminodecanoic acid with *Aspergillus amino acylase* and its diazotization to give (S)-2-hydroxydecanoic acid was known, this resolution was run under extremely dilute conditions for several days.[4] There was no known chemical resolution of 2-hydroxydecanoic acid and synthetic approaches to optically active 2-hydroxydecanoic acid were multistep processes involving expensive reagents.[5] We developed two alternative resolutions: a classical diastereomeric salt resolution of 2-hydroxydecanoic acid with (R)-α-methylbenzylamine and lipase hydrolysis of racemic methyl ester[6], summarized in Scheme 2 .



Scheme 2

Having developed an efficient route to methyl (S)-2-hydroxydecanoate, we required the displacement alpha to the carbonyl to take place with clean inversion of stereochemistry. Displacements alpha to a carbonyl by thiol derivatives have been described in the literature[7] and reaction conditions were critical for obtaining material of high enantiomeric excess. The triflate, mesylate, and tosylate derivatives of ethyl 2-hydroxypropionate, studied by Effenberger, were displaced with benzylthiol and thiophenol using K_2CO_3 and acetonitrile.[7b] While these substitution reactions occurred on the triflate and mesylate with clean inversion of stereochemistry, they were carried out at room temperature for 20 hours and were done by prior isolation of the alkylating agent. We found the triflate could be generated in situ and rapidly displaced without isolation using a thiol tertiary amine base mixture, as depicted in Scheme 3.[8] This procedure produces methyl (S)-2-hexylthiodecanoate in 43% yield and 99% ee from methyl 2-hydroxydecanoate. The synthesis of the sidechain is completed by ester cleavage using TMSI[9].



Scheme 3

Having demonstrated a more efficient preparation of (R)-2-hydroxydecanoic acid and methyl ester followed by conversion to (S)-2-hexylthiodecanoic acid, this sidechain has been coupled to a variety of aromatic amine nuclei and their efficacy as ACAT inhibitors studied. This work is ongoing and full details will be reported by our colleagues in drug discovery in due course.[3]

Experimental Section:

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and were uncorrected. NMR spectra were recorded on a Bruker 300-MHz spectrometer in $CDCl_3$. Infrared spectra were recorded on a Perkin-Elmer 283B spectrophotometer. Flash chromatography was performed using Kieselgel 60 (230-400 mesh). Microanalyses were performed by the Pfizer Analytical Department. All reagents were used as received without further purification.

(R)-2-Hydroxydecanoic acid: 2-Hydroxydecanoic acid[10] (74 g, 0.393 mol) suspended in 1.8 L of 5% acetone in hexane was treated with R-(+)-α-Methylbenzylamine (50.7 mL, 47.6 g, 0.393 mol) at rt for 1.5 h. R-(+)-α-Methylbenzylammonium-(R)-2-hydroxydecanoate formed was recrystallized from a 10% solution of acetone in hexane (600 mL) to give R-(+)-α-Methylbenzylammonium-(R)-2-hydroxydecanoate (43.43g, 0.14

mol, 36%) as a white solid: mp 94-95°C; $[\alpha]_D$ = +17.7 (c =1, MeOH). Anal. Calcd. for $C_{18}H_{29}NO_3$: C, 69.87; H, 9.45; N, 4.53: Found: C, 69.83; H, 9.86; N, 4.50 %. R-(+)-α-Methylbenzylammonium-(R)-2-hydroxydecanoate (42.43 g, 0.137 mol) was placed in 140 mL of EtOAc, 140 mL of 1N HCl was added and the mixture stirred for 0.5 h. The organic phase was separated, washed with 30 mL portions of 1N HCl, brine and dried ($MgSO_4$). Following concentration, (R)-2-hydroxydecanoic acid (25.63g, 0.136 mol, 99%) was isolated as a white solid[11]: mp 77.5-78.5° C; $[\alpha]_D$ = -4.9 (c =1, $CHCl_3$); IR ($CHCl_3$) 3657, 3517, 3385, 1602, 1457, 1343, 1261, 1210, 1127, 1088, 1034, 893, 751 cm-1; ^1H NMR δ 4.25 (dd, 1 H, J = 4.2, 7.5 Hz), 1.83-1.25 (m, 14 H), .85 (t, 3 H, J = 5.4 Hz); ^{13}C NMR δ 179.57, 70.36, 34.04, 31.84, 29.39, 29.27, 29.23, 24.78, 22.65, 14.04. Anal. Calcd. for $C_{10}H_{20}O_3$: C, 63.80; H, 10.71: Found: C, 63.84; H, 10.84 %.

Methyl (R)-2-hydroxydecanoate: Lipase P-30 (Amano from *Pseudomonas fluorescens*) (1g, 5% by weight) was dissolved in 140 mL of H_2O and the pH of the solution adjusted to 7.5 with a 1 N solution of NaOH. Racemic methyl 2-hydroxydecanoate (20.12 g, 0.995 mol) was added and the pH controlled to maintain a range of 6-8. The reaction was stirred at rt for 10 h (total of 46.5 mL of 1 N NaOH added) and worked up by addition of MeOH (140 mL). The aqueous alcohol was extracted with hexane (3 x 200 mL) and dried ($MgSO_4$). Following concentration, methyl (R)-2-hydroxydecanoate (10.08 g, 0.049 mol, 50%) was obtained: $[\alpha]_D$ = -3.1 (c=1, MeOH). This enriched methyl (R)-2-hydroxydecanoate (9.95 g, 0.049 mol) was resubjected to the identical reaction conditions using Lipase P-30 (1.02 g, 10% by weight) in H_2O (140 mL). After 4 h, 5.4 mL of base had been added and the reaction was stopped by the addition of H_2O (50 mL) and MeOH (30 mL) and extracted with hexane (3 X 200 mL), the combined organic layers were filtered, washed with brine and dried ($MgSO_4$). Following concentration, the desired methyl (R)-2-hydroxydecanoate (8.64 g, 0.043 mol, 87%) was obtained: $[\alpha]_D$ = -3.8 (c=1, MeOH); IR ($CHCl_3$) 3665, 3535, 2853, 1601, 1439, 1377, 1262, 1220, 1130, 1089, 1000, 634 cm^{-1}; ^1H NMR δ 4.16 (m, 1 H), 3.75 (s, 3 H), 2.80 (m, 1 H), 1.77-1.24 (m, 14 H), .85 (t, 3 H, J = 6.50 Hz); ^{13}C NMR δ 175.71, 70.43, 52.14, 34.31, 31.75, 29.32, 29.22, 29.11, 24.69, 22.54, 13.92. Anal. Calcd. for $C_{11}H_{22}O_3$: C, 65.30; H, 10.96: Found: C, 65.00; H, 11.33 %. The optical purity was determined to be 99.2% ee by conversion to the MTPA ester[12, 4b] and analysing the ^{19}F NMR spectra.

Methyl (S)-2-hexylthiodecanoate: Methyl (R)-2-hydroxydecanoate (202.3 g, 1.00 mol) was dissolved in 5 L of dry CH_3CN. Triflic anhydride (185 mL, 310 g, 1.10 mol) was added slowly followed by triethylamine (TEA) (150 mL, 111 g, 1.10 mol) at such a rate that the internal temperature stayed below -20 °C. The reaction was stirred for 15 min after the TEA addition. Hexanethiol (193 mL, 162 g, 1.30 mol) was added rapidly followed by slow addition of TEA (181 mL, 131g, 1.30 mol). The reaction was warmed to rt and stirred for 1 h. The CH_3CN was azeotroped with EtOAc, washed with H_2O (3 L) and 1 L of brine. The organic layer was dried ($MgSO_4$) and concentrated to an oil. The oil was filtered through silica gel [15 g silica/g crude product] and eluted with hexane and then flushed with 30:1 hexane / EtOAc to give methyl (S)-2-hexylthiodecanoate (295 g, 0.97 mol, 97%) as a colorless oil: $[\alpha]_D$ = -70.0 (c=1, MeOH); IR (neat) 2946, 2921, 2855, 1727, 1602, 1456, 1377, 1191, 1012 cm^{-1}; ^1H NMR δ 3.71 (s, 3 H), 3.21 (dd, 1 H, J =7 , 8 Hz), 2.55 (m, 2 H), 1.88-1.15 (m, 22 H), .95 (m, 6 H); ^{13}C NMR δ 173.46, 52.05, 46.64, 31.81, 31.46, 31.37, 31.30, 29.30, 29.17, 28.51, 27.38, 22.63, 22.50, 14.06, 13.99. Anal. Calcd. for $C_{17}H_{34}O_2S$: C, 67.50; H, 11.33: Found: C, 67.60; H, 11.45%.

(S)-2-Hexylthiodecanoic acid: To a 12 L flask equiped with a condenser and overhead stirrer was added methyl (S)-2-hexylthiodecanoate (302.5 g, 1.00 mol) , and 3 L of dry CH_3CN. To this solution was added NaI (600 g, 4.00 mol) and I_2 (25.4 g, 0.10 mol) followed by TMSCl (543 g, 635 mL, 5.00 mol). The reaction was heated to an internal temperature of 55 °C. After 12 h, TMSCl (130 g, 152 mL, 1.20 mol) was added and heating continued for 8 h . The reaction was cooled to 0 °C, 6 L of hexane added, followed by 1 L of icewater and the layers were allowed to separate. The combined CH_3CN / water layers were extracted with hexane (2 x 6 L). The combined hexane layers washed with H_2O (1 L), 0.1 M $Na_2S_2O_3$ (2 x 3 L) and 3 L of 1:1 brine/water, dried ($MgSO_4$), filtered and concentrated to give (S)-2-hexylthiodecanoic acid (260 g, 0.90 mol, 90%) a colorless oil: $[\alpha]_D$ = -59.4 (c=1, MeOH); IR (neat) 3091.5, 2955.4, 2925.9, 2871.3, 1704.2, 1465.8, 1414.5, 1285.2, 1260.9 cm^{-1}; ^1H NMR δ 3.19 (m, 1 H), 2.63 (m, 2 H), 1.95-1.18 (m, 22 H), .95 (m, 6 H); ^{13}C NMR δ 179.72, 46.71, 31.96, 31.79, 31.51, 31.27, 29.45, 29.34, 28.65, 27.45, 22.78, 22.65, 14.21, 14.13. Anal. Calcd. for $C_{16}H_{32}O_2S$: C, 66.61; H, 11.18: Found: C, 66.72; H, 10.94 %. The optical purity of (S)-2-hexylthiodecanoic acid was determined to be 99% ee by conversion to the acid chloride and coupling to R-(+)-1-(1-napthyl)ethylamine and analysis of the amide by HPLC.[13]

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13. This technique was used by Dr. George Chang at Pfizer Central Research and we thank him for his assistance.