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Preparation of 3(*S*)-Ethyl-Heptanoic Acid from (*S*)-Limonene A Chiron Approach

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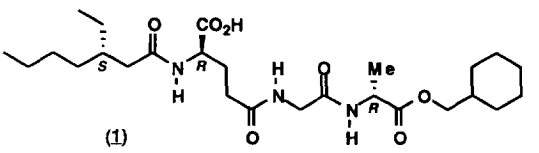
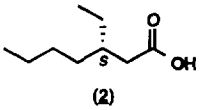
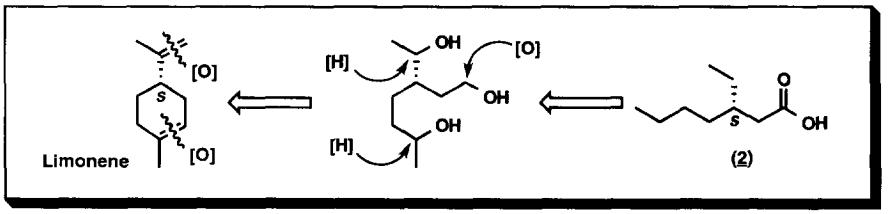
Abstract: Optically active 3-ethyl-heptanoic acid is readily synthesized from limonene.

The tripeptide (**1**) is a potent immunomodulator.[1] 3(*S*)-Ethyl-heptanoic acid (**2**) is the sidechain that caps the *N*-terminus of (**1**), and has been synthesized previously *via* asymmetric conjugate addition.[2,3] We are particularly interested in the chiron approach to the synthesis of optically active 3-ethyl-heptanoic acid using limonene as the starting material. Limonene is readily available in both enantiomeric forms of high optical purity.

One can envision making use of the built-in chirality of the isopropylidene group in (*S*)-limonene as the potential 3-(*S*) ethyl group by means of a one-carbon excision. Oxidative cleavage of the carbocyclic olefinic bond would provide the acyclic carbon back-bone with appropriate functionality at C-1.

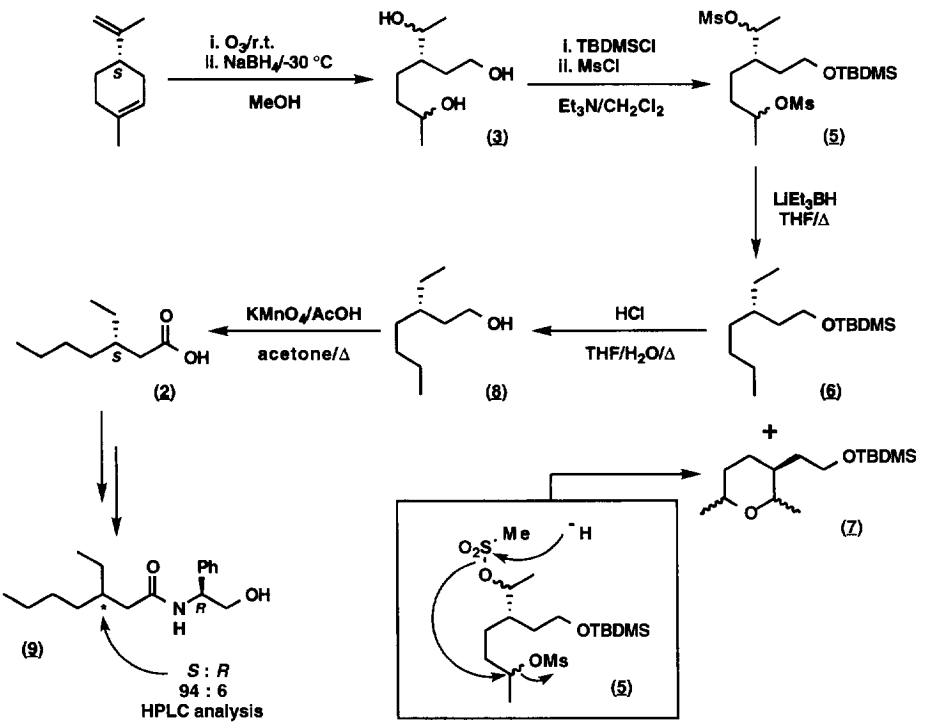






(*S*)-Limonene was subjected to ozonolysis followed by a reductive quench with sodium borohydride[4] to provide the triol (**3**) as a diastereomeric mixture (64-99%). Notably, the stereochemistry at these secondary hydroxy centers is irrelevant because they will be reduced to methylene groups at a later stage. The primary

hydroxyl was selectively protected as the TBDMS ether (4)[5] whereas the remaining secondary hydroxyls were converted to the mesylates. These functionalizations of the hydroxyls were readily accomplished in one-pot by sequential treatment of the triol (3) with TBDMS chloride (one equivalent) and mesyl chloride to provide the crude bis-mesylate (5) quantitatively. Reductive removal[6] of the mesylates was successfully carried out by treatment with Super-Hydride® ($LiEt_3BH$) in refluxing THF to give the alkane (6) in good yield (70-82%).[7] Interestingly, the pyran (7) was also isolated as a side-product (5-27%).[8] The pyran may be derived mechanistically from hydride attack at the sulfur site[9] of the mesylate moiety, which contains branching at the β-carbon, and the remaining mesylate is then displaced intramolecularly by the resulting alkoxide. Heating the silyl ether (6) with aqueous hydrochloric acid in THF led to the removal of the silyl protecting group. The resulting alcohol (8) was subsequently oxidized by potassium permanganate to provide 3(*S*)-ethyl-heptanoic acid (2) in 75% yield. The optical purity of the acid (2) was determined by HPLC analysis of its corresponding (*R*)-phenylglycinol amide (9)[10] and found to be 94:6/*S*:*R*. Chiral GC assay[11] of the commercial (*S*)-limonene[12] reveals that it is a 93:7 mixture and suggests that there is no racemization in this process.



Experimental

Triol (3) Ozone was bubbled through a stirred solution of (*S*)-limonene (10 g, 73.4 mmol) in methanol (100 mL) at room temperature for 10 min. and the reaction mixture was then stirred for 20 min. The bubbling of ozone and stirring sequence were repeated three times. The reaction mixture was then bubbled with nitrogen for 5 min. to purge any excess ozone and cooled to -45 °C. Powdered sodium borohydride (6.5 g, 0.17 mol) was

added portionwise to the reaction mixture over 15 min. while the reaction temperature was maintained between -45 and -30 °C. The mixture was stirred at -30 °C for 10 min. then warmed to room temperature and stirred for 10 min. The reaction was quenched cautiously with slow addition of water to destroy excess sodium borohydride. Most of the methanol was removed by rotavap and the residue was poured into water, saturated with sodium chloride and extracted with ethyl acetate. The extract was dried over anhydrous Na_2SO_4 and concentrated to provide the triol (**3**) as a syrup (8.29 g, 64%). IR (thin film) 3356(s), 2934 cm^{-1}. ^{1}HNMR ($CDCl_3$) 3.89-3.32 (m, 6 H), 1.98-1.45 (m, 8 H), 1.32-1.13 (discernible d's, 6 H, J = 6.4 Hz). LC/MS (CI-NH_3) 194 (M+18), 177 (M+1).

TBDMS ether (**4**) A solution of the triol (**3**) (243 mg, 1.38 mmol) in dichloromethane (3 mL) and triethylamine (0.3 mL, 2.15 mmol) was stirred with anhydrous sodium sulfate (0.5 g) for 5 min. DMAP (9 mg) and TBDMS chloride (212 mg, 1.36 mmol) were then added, and the mixture was stirred at room temperature for 1 hr. The reaction mixture was poured into water and extracted with EtOAc. The extract was washed with saturated brine, dried over anhydrous Na_2SO_4 and concentrated to give the crude TBDMS ether (**4**) as a syrup (0.41 g, 100%). The crude ether was of good purity as judged by ^{1}HNMR and used directly in the next step. An analytical sample was prepared by silica gel column chromatography. IR (thin film) 3356(s), 2930, 2858 cm^{-1}. ^{1}HNMR ($CDCl_3$) 3.82-3.58 (m, 5 H), 1.83-1.21 (m, 8 H), 1.18 (discernible d's, 6 H, J = 6.2 Hz), 0.89 (s, 9 H), 0.06 (s, 6 H). LC/MS (CI-NH_3) 291 (M+1), 273, 176.

Bis-mesylate (**5**) A solution of the diol (**4**) (215 mg, 0.73 mmol) in dichloromethane (3 mL) and triethylamine (0.39 mL, 2.76 mmol) was cooled to 0 °C and treated with mesyl chloride (145 µL, 1.84 mmol). After stirring for 10 min. at 0 °C, the reaction mixture was poured into aqueous 5% $NaHCO_3$ solution and extracted with 1:1 EtOAc/hexanes. The extract was washed with saturated brine and dried over anhydrous Na_2SO_4. Removal of solvent provided the mesylate as a pale yellow oil (0.34 g, 100%). The bis-mesylate (**5**) was found to be rather labile and was used immediately in the next reaction. ^{1}HNMR ($CDCl_3$) 4.97-4.73 (m, 2 H), 3.68 (t, 2 H, J = 6.3 Hz), 1.88-1.25 (m, 6 H), 1.42 (discernible d, 3 H, J = 6.9 Hz), 1.40 (discernible d, 3 H, J = 6.4 Hz), 0.89 (s, 9 H), 0.05 (s, 6 H).

One-pot preparation of bis-mesylate (**5**) The triol (**3**) (1.8 g, 10.2 mmol) in a mixture of dichloromethane (25 mL) and triethylamine (2.8 mL, 20 mmol) was stirred with anhydrous sodium sulfate (5 g) for 10 min. TBDMS chloride (1.6 g, 10.3 mmol) was added and the reaction mixture was stirred at room temperature for 2 hrs. The reaction mixture was cooled to 0 °C, treated sequentially with triethylamine (4.2 mL, 30 mmol) and mesyl chloride (2 mL, 25 mmol) and stirred for 15 min. The mixture was poured into an aqueous 5% $NaHCO_3$ solution and extracted with 1:1 EtOAc/hexanes. The extract was washed with brine and dried over anhydrous Na_2SO_4. Removal of solvent provided the crude bis-mesylate (**5**) as a yellow syrup (5.03 g).

Alkane (**6**) A solution of the bis-mesylate (**5**) (250 mg, 0.56 mmol) in THF (2 mL) was treated with Super-Hydride® (1.7 mL, 1.7 mmol) and stirred at room temperature for 30 min. More Super-Hydride® (1 mL, 1 mmol) was added and the reaction mixture was heated under gentle reflux for 35 min. After cooling to room temperature, the mixture was quenched cautiously with water then extracted with hexanes. The extract was dried over anhydrous Na_2SO_4 and concentrated to an oil. The crude oil was subjected to silica gel chromatography eluted with hexanes to give the alkane (**6**) as a colorless oil (119 mg, 82%). Optical rotation $[\alpha]_D^{25}$ = +0.19 (c = 15.1 in $CHCl_3$) ^{1}HNMR ($CDCl_3$) 3.62 (t, 2 H, J = 7.0 Hz), 1.57-0.81 (m, 17 H), 0.89 (s, 9 H), 0.05 (s, 6 H). ^{13}CNMR ($CDCl_3$) 61.66, 36.50, 35.65, 32.95, 28.86, 26.05, 25.98, 23.09, 18.34, 14.14, 10.78. GC/MS (retention time 1.76 min.), 258 (M^+), 243, 201, 143, 125, 115.

Alcohol (**8**) The TBDMS ether (**6**) (106 mg, 0.4 mmol) in a mixture of THF (2 mL) and water (1 mL) was treated with concentrated HCl (0.3 mL). After stirring at room temperature for 45 min., the mixture was heated under gentle reflux for 30 min. then cooled. The mixture was poured into water, neutralized with $NaHCO_3$ and extracted with 1:1 EtOAc/hexanes. The extract was dried over anhydrous Na_2SO_4 and concentrated to a colorless oil, which was purified by silica gel column to give the alcohol (**8**) as a colorless oil (62 mg, 100%). Optical rotation $[\alpha]_D^{25}$ = -0.36 (c = 5.9 in $CHCl_3$). IR (thin film) 3327(br s) cm^{-1}. ^{1}HNMR ($CDCl_3$) 3.62 (t, 2 H, J = 7.1 Hz), 1.96 (bs, 1 H, exchangeable OH), 1.54-1.46 (m, 2 H), 1.33-1.23 (m, 9 H), 0.89-0.80 (m, 6 H). ^{13}CNMR ($CDCl_3$) 61.15, 36.44, 35.59, 32.87, 28.80, 25.95, 23.06, 14.08, 10.67. GC/MS (retention time 0.87 min.), 142, 126, 98, 84.

3(*S*)-Ethyl-heptanoic acid (**2**) A mixture of the alcohol (**8**) (0.32 g, 2.2 mmol) and potassium permanganate (1.4 g, 8.8 mmol) in acetone (3 mL), acetic acid (0.9 mL) and water (6 mL) was heated at 90 °C for 11 hrs. After cooling, the brown mixture was diluted with hexanes (10 mL) and 5% aqueous HCl, followed by addition of solid $NaHSO_3$ (1.3 g) in portions with vigorous stirring. The resulting colorless mixture was extracted with hexanes. The extract was washed with saturated brine and dried over anhydrous Na_2SO_4. Removal of solvent provided the acid (**2**) as a colorless oil (264 mg, 75%). IR (thin film) 1709 cm^{-1}. ^{1}HNMR ($CDCl_3$) 2.28 (d, 2 H, J = 6.9 Hz), 1.79 (m, 1 H), 1.43-1.27 (m, 8 H), 0.88 (m, 6 H). ^{13}CNMR ($CDCl_3$) 180.32, 38.61, 36.21, 32.95, 28.73, 26.21, 22.87, 14.05, 10.72. GC/MS (retention time 1.01 min.), 159 (M+1), 141, 129, 115, 101, 98.

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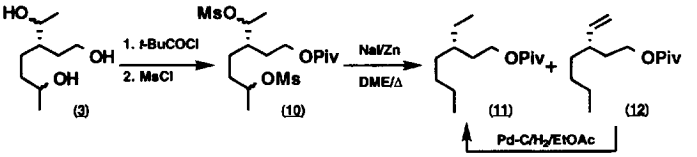
7. An alternate deoxygenation protocol was also explored. The primary hydroxyl of the triol (3) was first protected as a pivaloate, and the remaining secondary hydroxyls were converted to the corresponding bis-mesylate (10). On heating the bis-mesylate (10) with a large excess of sodium iodide and zinc dust in refluxing DME (Fujimoto, Y.; Tatsuno, T. *Tetrahedron Lett.* **1970**, 3325-3326), an inseparable mixture of the desired alkane (11) and the terminal alkene (12) was isolated (72%). The alkene (12) can be readily converted to the desired alkane (11) by means of hydrogenolysis. This approach was not pursued further because it incurs an extra step into the process.



8. It appears that the amount of the pyran (7) generated is dependent on the concentration and rate of heating of the reaction. A significant amount of (7) was obtained when the reaction was conducted at higher concentrations (0.28M). Better results were achieved when the reaction mixture of 0.15M concentration was first stirred at room temperature then slowly heated to reflux. The use of a sterically more hindered sulfonate, i.e. isopropanesulfonate (ref. 9b), may provide an alternative solution.
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10. The acid (2) was converted to the amide (9) *via* its acid chloride with (*R*)-2-phenylglycinol. HPLC assay (column: 5μm silica gel, 25cm; mobile phase: 70/30 chloroform/hexanes plus 0.5% of methanol; detection: UV 253nm) of the amide (9) showed a ratio of 94.4:5.6 between the (*S*,*R*) and the (*R*,*R*) diastereomers.
11. The optical purity of the (*S*)-limonene used in this sequence was determined to be 93:7 by chiral GC assay (column: Chrompak CP cyclodex B, 25m x 0.25μm). This GC assay was kindly provided by Mr. D. A. Cole of Analytical R&D, Pfizer Inc. Central Research, Groton.
12. Purchased from Aldrich Chemical Company.

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