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TETRAHEDRON: *ASYMMETRY*

An efficient synthesis of (*R*)-3-hydroxytetradecanoic acid

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Abstract

A short, efficient synthesis of (*R*)-3-hydroxytetradecanoic acid, a key component of bacterial endotoxins, using (*R*)-oxirane acetic acid ethyl ester as the source of chirality is described. The method is general and can be used in the preparation of other chiral 3-hydroxy acids.

(*R*)-3-Hydroxytetradecanoic acid is the most common fatty acid constituent of the lipid A component of bacterial lipopolysaccharides (LPS) (Fig. 1). The lipid A is responsible for most of the endotoxic activities of LPS.[1,2]

Although several methods have been reported for the formation of 3-hydroxy acids,[3] current syntheses for (*R*)-3-hydroxytetradecanoic acid either give products in low optical purity,[4] in low yield[5] or are limited to small scale preparations.[6] 3-Hydroxytetradecanoic acid of very high optical purity is essential for

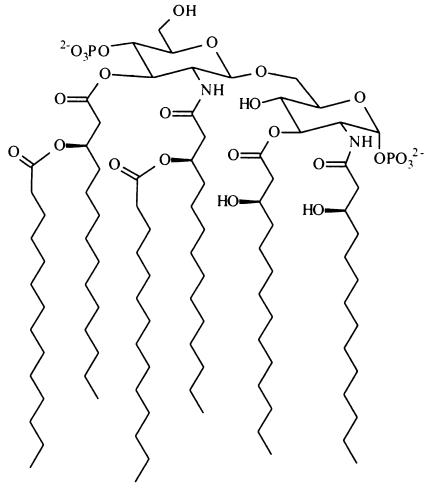

Figure 1. The structure of a typical bacterial lipid A

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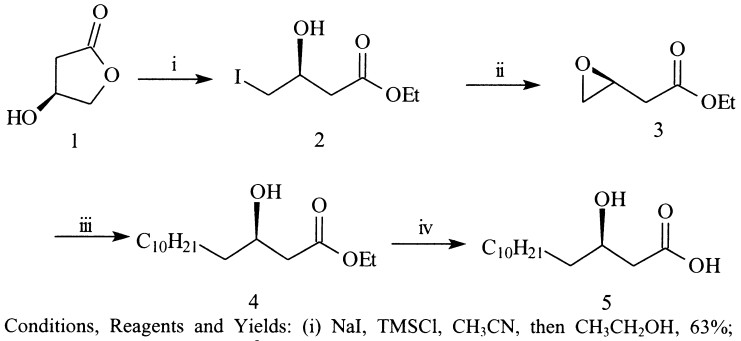
the synthesis of lipid A because at least four such fatty acid residues are present. A synthesis employing a fatty acid preparation that was 93% optically pure would yield a lipid A product that was only 75% pure containing 16 isomers. Here we report an efficient synthesis for (*R*)-3-hydroxytetradecanoic acid in high enantiomeric excess from (*S*)-3-hydroxy-γ-butyrolactone (**1**).[7,8] It should be useful in the preparation of other chiral 3-hydroxy acids. As shown in the scheme, (*S*)-3-hydroxy-γ-butyrolactone was treated with NaI–TMSCl–CH_3CN[9] at room temperature to give the iodohydrin **2**. This was converted to the oxiraneacetic acid ester **3** by treatment with Ag_2O in CH_3CN at room temperature.[10] Compound **3** was selectively ring-opened with decyl magnesium bromide and CuI in anhydrous THF at −30°C to give (*R*)-3-hydroxytetradecanoic acid ethyl ester **4** in 97% yield[11] [99.3% ee; NMR spectrum of (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl ester[12]]. Finally, the 3-hydroxy ester was saponified to give (*R*)-3-hydroxytetradecanoic acid **5**.



1 2 3 4 5

Reaction Conditions, Reagents and Yields: (i) NaI, TMSCl, CH_3CN, then CH_3CH_2OH, 63%; (ii) Ag_2O, CH_3CN, 94%; (iii) CuI, n-$C_{10}H_{21}MgBr$, THF, -30°C, 97%; (iv) KOH in 90% ethanol, 76%.

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11. To a suspension of CuI (3.81 g, 20.0 mmol) in 50 mL anhydrous THF (dry nitrogen) was added dropwise decylmagnesium bromide (40 mL, 1.0 M in ether) at −30°C with stirring. After 30 min, the epoxide **3** (2.60 g, 20.0 mmol) in 10 mL anhydrous THF was added dropwise and the reaction mixture was stirred for 1 h at −30°C. It was then allowed to reach

room temperature and was stirred overnight. The reaction was quenched with saturated NH_4Cl in water and the phases separated. The aqueous layer was extracted three times with ether. The combined ether extracts were washed with saturated NaCl solution, dried (Na_2SO_4), concentrated and separated on a silica column. The yield was 97%. IR ($CDCl_3$): 3027 (s), 2928 (s), 2857 (s), 1213 (s), 1208 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.15 (2H, q, J=7.2 Hz), 3.97 (1H, m), 2.48 (1H, dd, J=16.5, 3.0 Hz), 2.37 (1H, dd, J=16.5, 9.0 Hz), 1.40 (2H, m), 1.23 (21H, br, s), 0.86 (3H, t, J=6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 173.15, 68.01, 60.65, 41.24, 36.47, 31.88, 29.60, 29.55, 29.50, 29.32, 25.45, 22.66, 14.14, 14.09; HRMS Exact mass: calcd for $C_{16}H_{33}O_3$, $[M+H]^+$, 273.2430. Found 273.2438.

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