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ASYMMETRIC SYNTHESIS OF (3R)-ALKANOYLOXYTETRADECANOIC ACIDS-COMPONENTS OF BACTERIAL LIPOPOLYSACCHARIDES

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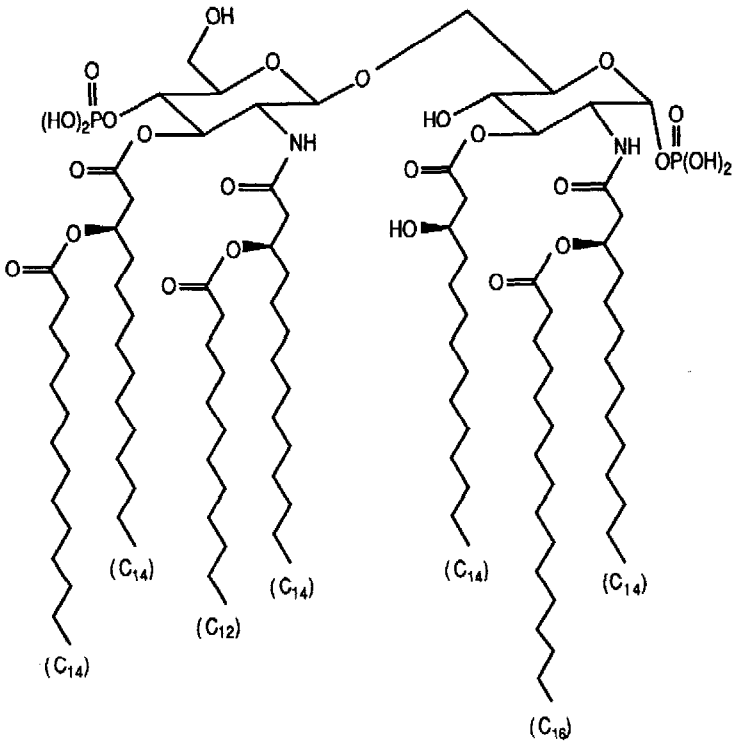
Summary - An efficient general synthesis of (3R)-alkanoyloxytetradecanoic acids has been developed by asymmetric allylboration, acylation followed by oxidation of the homoallylic esters.

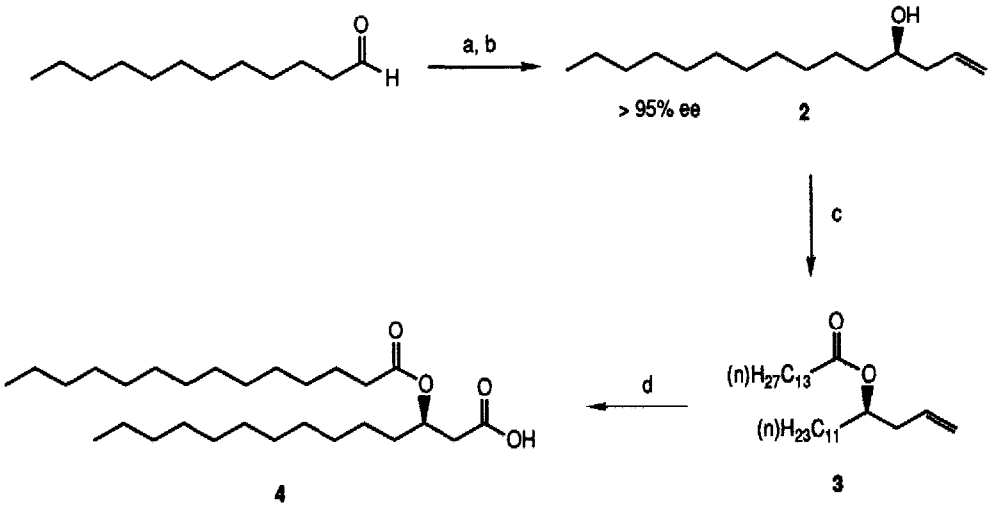
Lipopolysaccharides are diverse, complex macromolecules present on the outer cell membranes of the gram negative bacteria such as *Salmonella minnesota*, *Salmonella typhirium* , *Escherichia coli*, etc. These are highly potent compounds which mediate a variety of immunological responses following the bacterial infection.[1] Most of the biological activities of lipopolysaccharides reside in a relatively small portion of the molecule known as Lipid A (**1**).[2] The structure of Lipid A is marked by the presence of two β(1,6)-linked D-glucosamine units with highly polar phosphate groups at 1 and 4' positions. (3R)-Alkanoyloxytetradecanoic acid or (3R)-hydroxytetradecanoic acid moieties are bound to 2, 3, 2', 3' positions of the disaccharide through amide and ester linkages. The nature and length of the hydrocarbon chain depends on the bacterial origin of the Lipid A. The biological significance of 3-alkanoyloxytetradecanoic acid has been demonstrated by the structure activity relationship study of Lipid A analogs.[3] We have developed a highly general asymmetric synthesis of this biologically important class of 3-alkanoyloxytetradecanoic acids in >95% enantiomeric purities.



1 Lipid A (*Salmonella minnesota)*

There are methods available for enantioselective synthesis of 3-hydroxy acids.[4] However, most of them involve either enzymatic or chemical reductions of the corresponding 3-keto esters. Consequently, these methods require synthesis of 3-keto esters. The enantioselective synthesis of (3R)- and (3S)-alkanoyloxytetradecanoic acids disclosed in this communication is highly efficient and makes use of readily available reagents.

The strategy involves asymmetric allylboration[5] of 1-dodecanal, acylation of the resulting homoallylic alcohol followed by the permanganate[6] oxidation of the olefinic moiety to carboxylic acid. The acylation prior to the permanganate oxidation not only protects the hydroxy group during oxidation but also allows placement of the desired acyl group on 3-hydroxyl. Thus, asymmetric allylboration of 1-dodecanal with allyldiisopinocampheylborane (derived from (+)-α-pinene) provided, after oxidation of the intermediate borinate, (4R)-1-pentadecen-4-ol **2** in 75% isolated yield and >95% ee.[7,8] The alcohol **2** was acylated with tetradecanoyl chloride in pyridine to give (4R)-tetradecanoyloxy-1-pentadecene **3** in 94% yield. The phase transfer catalyzed permanganate oxidation of **3** was readily effected to provide (3R)-tetradecanoyloxytetradecanoic acid **4** in 66% overall yield from 1-dodecanal (Scheme 1).

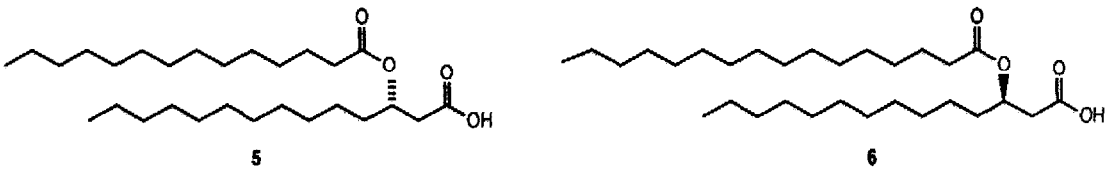


a) Allyldiisopinocampheylborane (derived from (+)-α-pinene). b) 3M sodium acetate/H_2O_2.
c) Tetradecanoyl chloride/pyridine. d) $KMnO_4$

Scheme 1

Similarly, (3S)-tetradecanoyloxytetradecanoic acid **5** was prepared in 64% overall yield and >95% ee from 1-dodecanal and allyldiisopinocampheylborane derived from (-)-α-pinene.

Synthesis of (3R)-hexadecanoyloxytetradecanoic acid **6** was readily achieved in 67% overall yield from *n*-dodecanal following the sequence of reactions for **4**, except that hexadecanoyl chloride was used as acylating agent in place of tetradecanoyl chloride.



A typical experimental procedure is as follows:

(4R)-Pentadecen-4-ol **2**: In a 250 mL R.B. flask equipped with septum inlet, a bent tube adapter and magnetic stirring bar were placed, under nitrogen atmosphere, chlorodiisopinocampheylborane (9.6 g, 30 mmol) in anhydrous ether (30 mL). The solution was cooled to

-40 °C, treated slowly with allyl magnesium bromide (1.1M, 22.7 mL, 25 mmol) and then allowed to warm up to 25 °C over a 1 h period. The reaction mixture was cooled to -78 °C and *n*-dodecanal (freshly distilled, 4.41 mL, 20 mmol) in anhydrous ether (10 mL) was slowly added over a 10 min. period. The reaction mixture was further stirred at -78 °C for 6 h, allowed to warm up to 0 °C, treated with acetaldehyde (10 mL, 180 mmol) at 0 °C and then allowed to stir at 25 °C for 18 hr. The mixture was oxidized with sodium acetate (3M, 20 mL, 60 mmol) and hydrogen peroxide (30%, 10 mL). The residue after workup was chromatographed and distilled, b.p. 96 °C/0.05 mm, to provide **2** (3.39 g, 75% yield).

(4R)-Tetradecanoyloxy-1-pentadecene **3**: To a solution of **2** (4.52 g, 20 mmol) in a mixture of dichloromethane (50 mL) and pyridine (10 mL) was added slowly tetradecanoyl chloride (freshly distilled 6.54 mL, 24 mmol) and allowed to stir at 25 °C for 18 h. The residue after workup was chromatographed to provide **3** (8.19 g, 94% yield).

(3R)-Tetradecanoyloxytetradecanoic acid **4**: In a 250 mL R.B. flask equipped with magnetic stirring bar was placed potassium permanganate (8 g, 50 mmol) in water (75 mL) and cooled to 0 °C. Meanwhile **2** (6.54 g, 15 mmol) and Aliquat®336 (100 mg) were dissolved in a mixture of hexane (75 mL) and glacial acetic acid (15 mL). The solution was then slowly added to potassium permanganate. The mixture was vigorously stirred at 0 °C for the 3 h. The excess permanganate was decomposed with the addition of sodium sulfite (9.0 g), stirred for 5 min. and then acidified with 1:1 HCl (18 mL). The residue after workup was chromatographed to provide **4** (6.39 g, 94% yield).

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7. Spectral data for all the compounds is in agreement with the assigned structures.
8. The homoallylic alcohol **2** and its enantiomer were converted into their corresponding Mosher esters and found to be pure by ^{1}H and ^{13}C NMR analysis. Attempted separation of the Mosher esters on HPLC was unsuccessful.

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