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Synthesis of lipid A analogues containing glucose instead of glucosamine and their LPS-antagonistic activities

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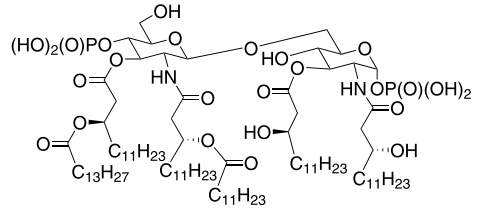
Abstract—Lipid A analogues containing glucose in substitution for glucosamine on the reducing end were synthesized, and the inhibitory activities on LPS-induced TNFα production (LPS-antagonistic activity) in vitro using human whole blood cells were measured. The IC_{50} values (nM) of these ten compounds, **8**, **14**, **21**, **31**, **40**, **51**, **57**, **62**, **67** and **72**, were 11.2, 15.4, 2.7, 0.1, 0.4, 1.3, 3.2, 3.2, 1.4 and 14.4, respectively. And also inhibitory activities (ID_{50}) on TNFα production toward galactosamine loaded C3H/HeN mice in vivo of compounds **21**, **31**, **57**, **62** and **67** were measured. The values of these compounds were 0.29, 0.50, 0.61, not dose-dependent and 0.33 mg/kg, respectively.

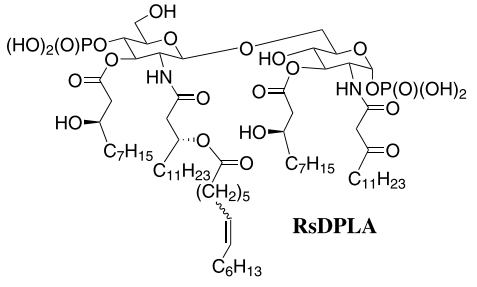
1. Introduction

The study of endotoxin has proceeded extensively[1] since Shiba and Kusumoto's[2] total synthesis of lipid A, a toxic component of endotoxin (lipopolysaccharide, LPS) existing in the outer surface membrane of Gram-negative bacteria. On the contrary, a nontoxic natural lipid A-related compound (RsDPLA)[3] was isolated from *Rhodobacter sphaeroides* by an Eisai group. This compound unlike lipid A has a unique structural feature, that is, it contains two amides composed of an unsaturated fatty acid ((*R*)-3-(7-tetradecenoyloxy)tetradecanoic acid) and a 3-oxotetradecanoic acid in its long fatty acid chains, and shows LPS-agonistic activity toward neither human nor mouse macrophages.[4] Furthermore, the Eisai group found that many RsDPLA-related compounds having an olefinic double bond in their molecules behave as LPS antagonists toward human and murine macrophages,[4] and E5564,[5] a compound related to RsDPLA, has been developed as a highly potent anti-septicemia drug (Fig. 1).

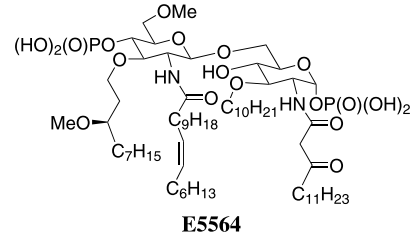
The active structures of all natural lipid A- and also RsDPLA-related compounds are constructed with an β(1-6)-linked glucosamine–glucosamine disaccharide moiety, and the configuration of the anomeric phosphate



Lipid A



RsDPLA



E5564

Figure 1. Structures of Lipid A, RsDPLA, and E5564.

Keywords: LPS-antagonist; RsDPLA.
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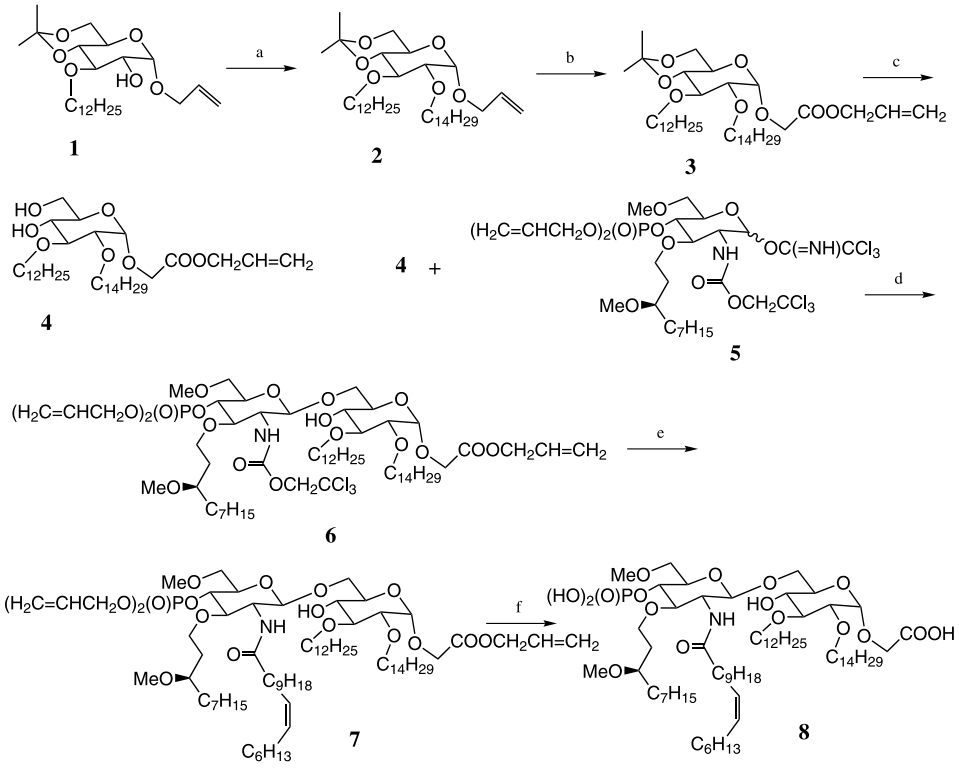
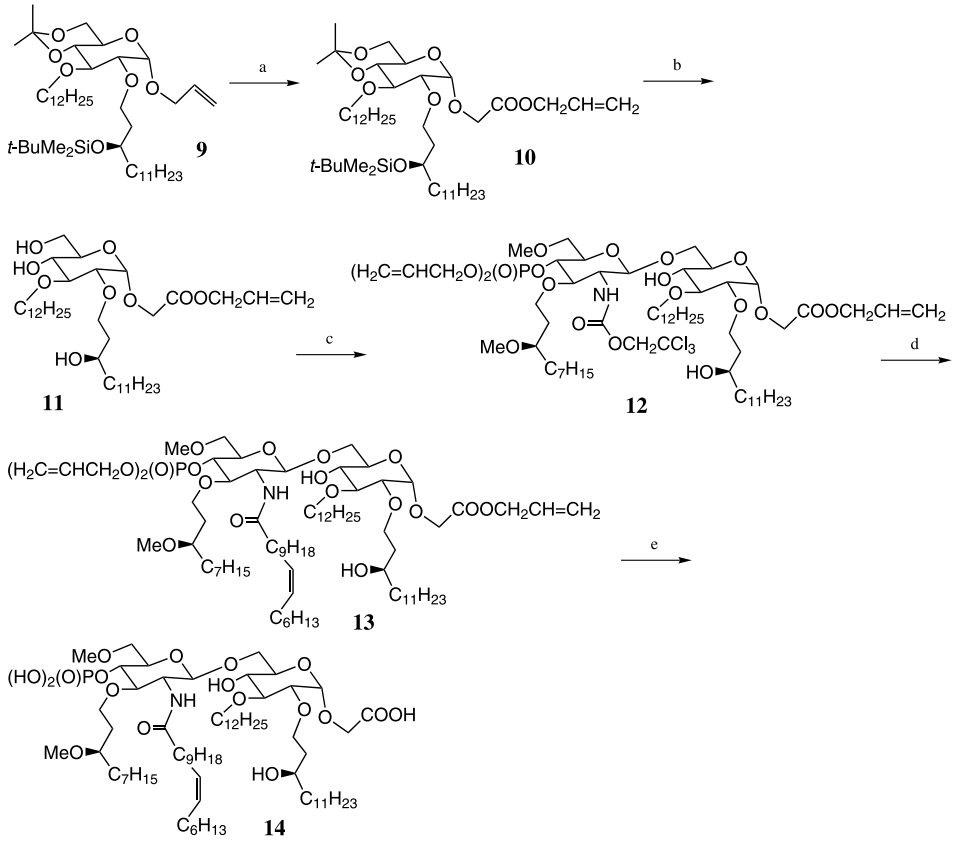


Scheme 1. Reagents and conditions: (a) tetradecyl methanesulfonate, NaH, DMF, rt, 16 h, 75%; (b) $RuO_2.xH_2O$, $NaIO_4$, $MeCN–CCl_4–H_2O$ (2:2:3), rt, 3 h, then allyl bromide, Et_3N, DMF, rt, 16 h, 72%; (c) $AcOH–H_2O$ (4:1), 65 °C, 2 h, 71%; (d) TMSOTf, MS 4A, CH_2Cl_2, −40 °C, 1 h, 43%; (e) (1) Zn, AcOH–THF (1:1), rt, 4 h; (2) (*Z*)-11-octadecenoyl chloride, $NaHCO_3$, $THF–H_2O$ (5:1), rt, 30 min, two steps 77%; (f) $(PPh_3)_4Pd$, PPh_3, Et_3N, HCOOH, THF, under N_2, 55 °C, 4 h, 95%.



Scheme 2. Reagents and conditions: (a) RuO_2 hydrate, $NaIO_4$, $MeCN–CCl_4–H_2O$ (2:2:3), rt, 3 h, then allyl bromide, Et_3N, DMF, rt, 16 h, 69%; (b) $AcOH–H_2O$ (4:1), 65 °C, 2 h, 60%; (c) **5**, TMSOTf, MS 4A, CH_2Cl_2, −40 °C, 1 h, 45%; (d) (1) Zn, AcOH–THF (1:1), rt, 4 h; (2) (*Z*)-11-octadecenoyl chloride, $NaHCO_3$, $THF–H_2O$ (5:1), rt, 30 min, 67%; (e) $(PPh_3)_4Pd$, PPh_3, Et_3N–HCOOH, THF, under N_2, 55 °C, 4 h, 55%.