

(44 kDa) and the individual heme cofactors (10 kDa) to pass through, while retaining any aggregates formed by the enzyme–polymer hybrid.

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Active Immunization with a Glycolipid Transition State Analogue Protects against Endotoxic Shock**

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Septic shock is one of the ten leading causes of both infant and adult mortality in the United States and, according to the Centers for Disease Control and Prevention, directly resulted in over 30 000 deaths in 1999 alone. Lipopolysaccharide (LPS) released from the bacterial membrane after bacteriolysis is responsible for many of the toxic effects associated with gram-negative bacterial septic shock.^[1] Lipid A (**1**; the *E. coli* structural form is shown in Figure 1) is the main toxic determinant of LPS and is known to stimulate host macrophages to secrete increased amounts of various cytokines, which include tumor necrosis factor- α (TNF- α), interleukin-1 β , and interleukin-6.^[2] Immunomodulation of this inflammatory cascade has been suggested as a crucial but inadequately addressed element in the treatment of sepsis.^[3] While passive immunization with monoclonal antibodies directed against components of the inflammatory cascade or LPS itself^[4] have shown promise at the research level, these strategies have to date been ineffective in extensive clinical trials.^[5]

As a primary step in a strategy that may ultimately lead to a new immunomodulatory treatment for septic shock, we report that active immunization with keyhole limpet hemocyanin (KLH) glycoconjugates of novel bisphosphonate analogues of lipid X **2a,b** (see Figure 1) offers significant in vivo protection against a sublethal lipid A challenge.

Raetz^[6] has shown that the biological effects of the *E. coli* lipid A (**1**) require the presence of several key structural features: both phosphate groups, the glucosamine disaccharide, and all the fatty acyl chains, especially the 2'-lauroyl and 3'-myristoyl acyloxy residues (R' and R of **1** in Figure 1).

Our designed lipid A mimics (**2a,b**, Figure 1) incorporate the following features: 1) a glucosamine 4'-phosphate β -O-butyl lipid X saccharide analogue of lipid A; 2) truncated 2'- and 3'-acyloxy chains that contain both the lipid A R stereo-

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Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

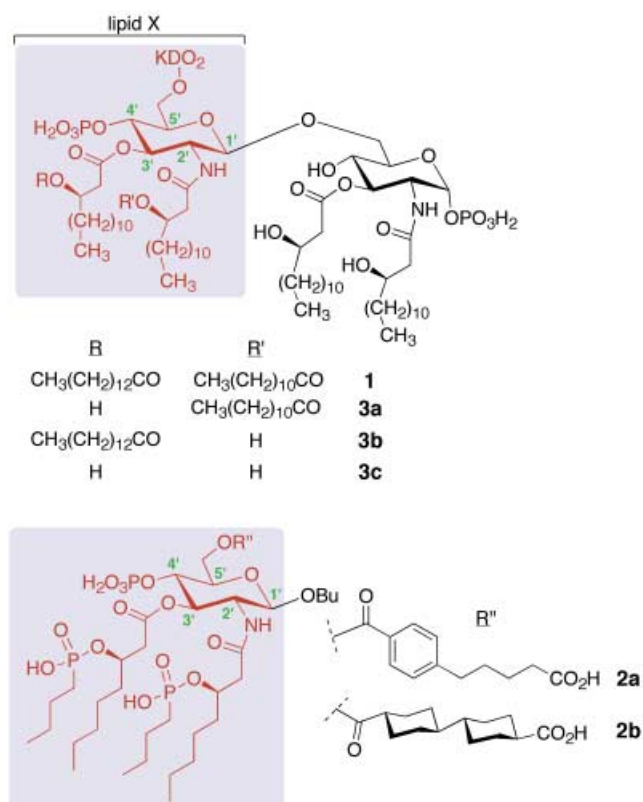


Figure 1. Bisphosphonates **2a,b** were synthesized as immunogens for active immunization to treat lipid A mediated endotoxemia. The derivatives **3a–c** are less toxic derivatives of lipid A. The lipid X component of **1** and its structural mimic in haptens **2a,b** are shown boxed. KDO = 3-deoxy-D-manno-octulosonate.

chemistry and a phosphonate group; 3) a flexible and a rigid linker moiety for attachment to a carrier protein.

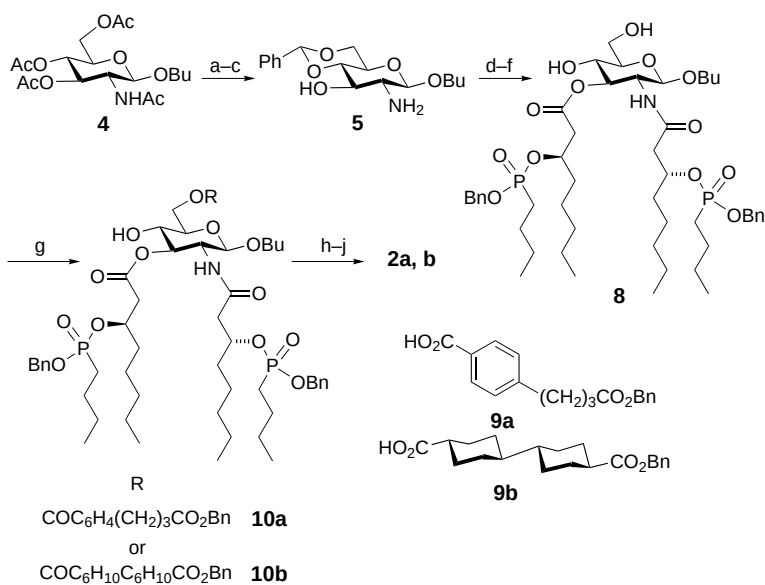
It was anticipated that active immunization of mice with the KLH-**2a,b** glycoconjugates would produce serum antibodies that could either bind to and neutralize lipid A (as a result of the structural similarity of **2a,b** with **1**) or that may catalyze the hydrolysis of the key 2'- and or 3'-acyloxyacyl ester linkages of **1**, which thus generates the functionally inactive lipid A derivatives **3a–c**. For the latter reason, the phosphonate groups were incorporated into **2a,b** as stable mimics of the presumed tetrahedral intermediates formed during hydroxide-catalyzed ester hydrolysis (Figure 1).^[7] Truncated lipid chains were used to minimize micelle formation and aid antibody recognition of the glucosamine core and phosphoryl components of the 2'- and 3'-acyloxy side chains.

Given that carbohydrates have notoriously poor immunogenicity,^[8] the linker was seen as a key locus at which to incorporate an immunostimulatory chemical motif that would facilitate the immunogenicity of the associated carbohydrate core. In this regard, we have studied the immunogenicity imparted by possession of either a flexible (*para*-substituted benzoic acid, see R'')

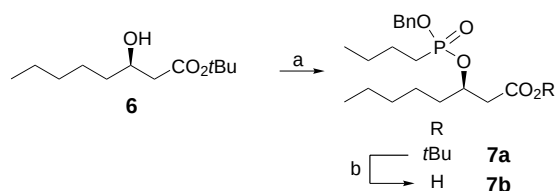
in Figure 1 **2a**) or rigid (1,1'-bis(cyclohexyl)-substituted carboxylic acid **2b**) spacer group.

Our synthesis of the phosphonates **2a** and **2b** is highly convergent and efficient (Scheme 1 and 2).^[9] Thus, transesterification of the known β -butyl glycoside **4**^[10] with catalytic sodium methoxide in methanol, followed by protection of the two free hydroxy groups as a benzylidene group and deprotection of the *N*-acetate with hydrazine, at elevated temperatures, furnished the aminoalcohol **5** (Scheme 1). The side chain, which bears the quintessential phosphonate ester moiety, was prepared from the known enantiomerically pure β -hydroxy ester **6**^[11] (Scheme 2). The mixed phosphonate diester **7a** was prepared as a 1:1 mixture of diastereomers^[12] by an initial tetrazole-catalyzed monoaddition of the alcohol **6** to *n*-butyl phosphonic dichloride and subsequent addition of benzyl alcohol.^[13] Removal of the *tert*-butyl ester from **7a** provided the key side-chain acid **7b**. Subsequent coupling of **7b** to the amino alcohol **5** (DCC, DMAP), followed by acetal deprotection, afforded the diol **8**. Selective acylation of the C6 hydroxy group of **8** using DCC with either **9a** or **9b**^[14] installed the flexible or rigid linkers, respectively. Transformation of the C4 hydroxy group of **10a** or **10b** into a phosphite group with Watanabe's reagent, followed by oxidation with *m*CPBA and complete hydrogenolysis furnished the desired haptens **2a** and **2b**. Glycoprotein conjugates of KLH, for active immunization, and bovine serum albumin (BSA), for serum titer measurement, were prepared by coupling haptens **2a,b** to the ϵ -amino groups of the protein lysine residues by activation to their sulfo-*N*-hydroxysuccinimido esters as previously described.^[15]

The protective effect of active immunization with KLH-**2a** and KLH-**2b** against a lipid A challenge was investigated using an in vivo mouse model (three strains: Swiss-Webster



Scheme 1. Reagents and conditions: a) NaOMe cat., MeOH, 93%; b) α -dimethoxytoluene, cat. TsOH, DMF, 82%; c) N_2H_4 , EtOH, 130°C, 80%; d) DCC, cat. 4-pyrrolidino-pyridine, **7b**, CH_2Cl_2 ; e) 80% AcOH (aq); f) **9a** or **b**, DCC, cat. DMAP, 82%; g) *N,N*-diethyl-1,5-dihydro-3*H*-2,4,3-benzodioxaphosphepin-3-amine, cat. 1*H*-tetrazole, CH_2Cl_2 ; h) *m*CPBA, 64% (2 steps); i) H_2 , 10% Pd-C, EtOH/MeOH/ H_2O 2:2:1; j) NEt_3 (100%), 60°C, 51% (2 steps). Ts = *p*-toluenesulfonyl, DMAP = *N,N*-dimethyl-4-aminopyridine, *m*CPBA = *m*-chloroperbenzoic acid, DCC = dicyclohexyl carbodiimide.



Scheme 2. Reagents and conditions: a) *n*-butylphosphonyl dichloride, 4*H*-tetrazole, **6** followed by BnOH (excess) (95%); b) 50% TFA in CH₂Cl₂ (87%). Bn = benzyl, TFA = trifluoroacetic acid.

(SW), 129Gix⁺, and A/J; *n*=8). The procedure involved preimmunization with either KLH-**2a** or **2b** (equivalent to 20 µg of glycoconjugate on day 1, day 7, and day 14) with ALUM (aluminum hydroxide gel) as adjuvant. Control groups received KLH (20 µg) with ALUM. Anti-BSA-**2a** and **2b** immunoglobulin G serum titers were measured by ELISA on day 21 and ranged from 14 300 ± 1600 (A/J, KLH-**2b** antigen) to 3200 ± 800 (A/J, KLH-**2a** antigen; Table 1). Significant cross-reactivity was observed between the antibodies generated to the glycoconjugates, which suggests that the major epitope on **2a** and **2b** is the lipid X analogue and not the immunogenic side chain (Table 1). Interestingly, in all three murine strains investigated, the serum titers against hapten **2b**, which contains the rigid *trans,trans*-bis(cyclohexyl) linker, were significantly higher than those achieved with the flexible linker **2a** (*n*=8, *p* < 0.05, Table 1); this offers strong support for the use of this new linker to improve hapten immunogenicity. In fact, the immunostimulatory effect of the bis(cyclohexyl) linker, when coupled with the cross-reactivity described above, results in higher observed serum titers for BSA-**2a** in mice immunized with KLH-**2b** rather than KLH-**2a** (Table 1).^[16]

It is well-documented that decreased TNF-α production during lipid A challenge correlates well with survival during murine gram-negative sepsis.^[17] Therefore, the extent of protection following active immunization with KLH-**2a** and KLH-**2b** was assessed by comparative serum analysis of TNF-α concentrations in the immunized and control groups. The immunized mice (see above) were subjected to a bolus sublethal challenge of lipid A (*E. coli* O111:B4, 20 µg in sterile saline, intravenous, day 24) and their serum TNF-α levels were measured 1.5 h after treatment. The lipid A associated elevation in serum TNF-α levels in the control group (which was immunized with only KLH) was significantly abrogated in all three strains that were immunized with KLH-**2a** or **2b** (129Gix⁺–100.0 ± 0.3% (KLH) versus 6.5 ± 2.0% (KLH-**2a**), 6.4 ± 2.8% (KLH-**2b**). SW–100.0 ± 5.8% (KLH) versus 16.4 ± 14.8% (KLH-**2a**), 10.3 ± 0.1% (KLH-**2b**). A/J–100.0 ± 2.9% (KLH) versus 33.0 ± 0.2% (KLH-

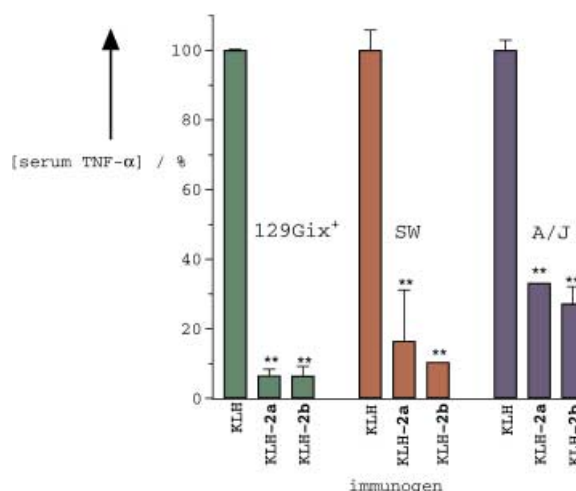


Figure 2. Serum TNF-α levels measured by ELISA 1.5 h after sublethal intravenous *E. coli* O111:B4 lipid A (20 µg) challenge in mice (■ 129 Gix⁺, ■ SW, ■ A/J) after active immunization with either KLH (control), KLH-**2a** or KLH-**2b**. Data are reported as the mean value ± S.E.M (*n*=8, ** denotes a *p* value < 0.05 relative to mice immunized with KLH alone).

2a), 27.2 ± 5.0% (KLH-**2b**; *n*=8, *p* < 0.05); Figure 2). This profound reduction of serum TNF-α levels (ranging from 94.6–72.8%) in the KLH-**2a** or **2b** active-immunization approach protects the host in vivo against the lipid A challenge. Preliminary studies have revealed that mice immunized with KLH-**2a** and KLH-**2b** possess serum antibodies that recognize *E. coli* (*E. coli* O111:B4) lipid A (see Table 1). However, a question still remains as to whether the protection conferred during the active immunization is caused by clearance of lipid A from serum by antibody binding and/or antibody-catalyzed destruction. This issue is under investigation.^[18]

This study shows for the first time that active immunization with a bisphosphonate lipid X analogue can offer significant protection against the effects of *E. coli* lipid A in a murine model. This preliminary result brings into focus a potential new immunopharmacotherapeutic approach that may ultimately offer significant help in the treatment of the serious and lethal clinical septic shock syndrome.

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Table 1. Serum titers^[a] following immunization with either KLH-**2a** or KLH-**2b**.

Strain	Titer [× 10 ³]		KLH- 2a immunogen		KLH- 2b immunogen	
	BSA- 2a	BSA- 2b	Lipid A ^[b]	BSA- 2a	BSA- 2b	Lipid A
129Gix ⁺	4.8 ± 1.6	2.8 ± 0.4	1.2 ± 0.4	9.6 ± 1.2	13.9 ± 2.0 ^[c]	1.2 ± 0.3
SW	4.8 ± 1.2	2.1 ± 0.8	0.8 ± 0.4	8.2 ± 1.2	11.6 ± 2.0 ^[c]	2.0 ± 0.4
A/J	3.2 ± 0.8	1.2 ± 0.4	0.8 ± 0.2	4.1 ± 0.8	14.3 ± 1.6 ^[c]	0.8 ± 0.2

[a] For experimental details of the ELISA procedures see the Supporting Information. Preimmunization control titers against KLH-**2a** or KLH-**2b** in all three strains were zero. [b] Lipid A from *E. coli* (O111:B4). [c] These values have a significant difference in serum titer between BSA-**2b** and BSA-**2a** in the same strain after immunization with KLH-**2b** or KLH-**2a**, respectively (*n*=8, *p* < 0.05).

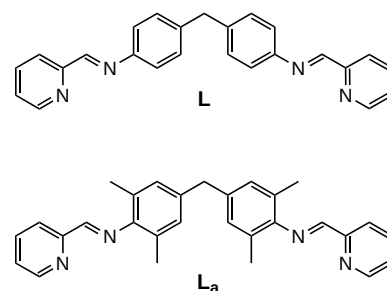
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Assembly of a Nanoscale Chiral Ball through Supramolecular Aggregation of Bowl-Shaped Triangular Helicates**

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Biological systems provide many intricate and elegant examples of the use of self-assembly through noncovalent recognition events to generate large functional arrays. Chemists have also been attempting to mimic this approach by using supramolecular interactions to construct a wide range of arrays of defined size and architecture (albeit on a smaller size scale).^[1] Metallo-supramolecular chemistry in particular has been a popular and effective tool.^[2] However, in common with other supramolecular systems synthesis of building blocks (in this case of the ligands) by the formation of *covalent* bonds places restrictions on the size of the architectures that have been generated. This situation represents a potential barrier to progress in this field. One approach to address this problem is to use multiple recognition events in sequence. Thus, an initial event generates a supramolecular structure which is then aggregated into a larger array in a second supramolecular event.^[3–6] As in the assembly of “simple” supramolecular structures, a challenge is to control the aggregation such that a discrete array (rather than a polymeric array) is obtained. We have been exploring the use of shape to control such aggregation and we recently reported the use of imine-based ligands to form arc-shaped double-helicates which aggregate into a discrete circular array as a result of their curved topography.^[4] We have been investigating whether the same approach can be applied to form three dimensional (rather than planar) structures and herein we report the assembly of a supramolecular ball from commercially available components by this approach.

We have shown that the reaction of ligand **L** with metal ions capable of tetrahedral coordination leads to a solution equilibrium of two dimeric isomers; a helicate (*rac* isomer)



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