Synthesis of Biologically Active Carbocyclic Analogues of *N*-Acetylmuramyl-L-alanyl-D-isoglutamine (MDP)†

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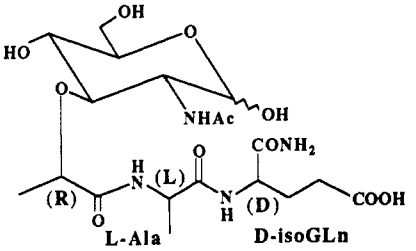
Summary: Two biologically active analogues of MDP containing pseudo-D-glucosamine have been synthesised using as key step the Ferrier rearrangement (carbohydrate → inosose). Several different procedures for carrying out this reaction have been compared.

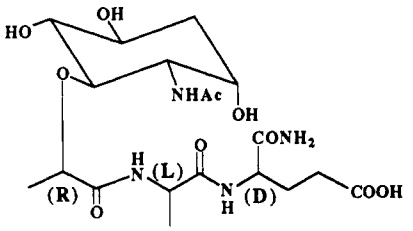
Sir: MDP (*N*-acetylmuramyl-L-alanyl-D-isoglutamine), a synthetic analogue of a fragment of bacterial peptidoglycan, is capable of replacing whole Mycobacteria in complete Freund's adjuvant.[1]

As part of a larger research program on "carbocyclic sugars", we were interested in replacing the D-glucosamine moiety of the immunostimulant MDP by a pseudo-D-glucosamine. Isosteric analogues of this type might confer interesting pharmacodynamic properties by virtue of their resemblance to the bacterial product and also because of an anticipated higher metabolic stability in vivo.



MDP

With these considerations in mind, we have initiated a synthetic effort aimed at the enantioselective and expeditious synthesis of a new class of immunomodulators. In this paper, we report our approaches to the construction of two biologically active analogues of MDP, 1 and 2. In both synthetic sequences, we adopted a strategy which proceeds through two stages. First, a rearrangement[2] of the exocyclic alkenes **8** and **15** into the corresponding cyclohexanones **9** and **16**, respectively, occurs with simultaneous retention of their stereogenic centers at carbons 2, 3, and 4. Second, the stereocontrolled conversion of the inososes **9** and **16** into cyclitols **12** and **19** provides key intermediates for the final coupling with the dipeptide L-Ala-D-isoglutamine benzyl ester **13**.



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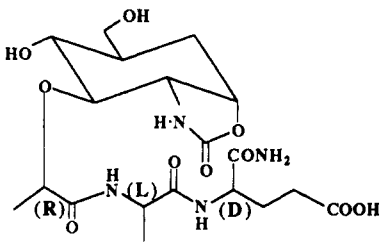

2

We envisaged the synthesis of **1** starting from 4,6-*O*-benzylidene muramic acid **3** (Scheme I), readily available from *N*-acetyl-D-glucosamine[3] as a mixture of α,β-methyl glycoside (ratio 9:1).

Acid **3** was transformed into its benzyl ester **4** with benzyl bromide–potassium carbonate in *N,N*-dimethylformamide. The choice of the benzyl ester as a temporary protecting group greatly facilitated the reductive cleavage of **11** into the acid **12** required for the final condensation. Acid hydrolysis of the acetal group in **4** afforded the diol **5**. Selective *p*-toluenesulfonylation at the primary hydroxyl group followed by acetylation yielded **6**. Substitution of the *p*-toluenesulfonyloxy group in **6** was readily achieved with potassium iodide in *N,N*-dimethylformamide to afford the crystalline **7**. This on treatment with silver fluoride in pyridine underwent the desired elimination to give the exocyclic olefin **8**. The overall yield was 34% from *N*-acetyl-4,6-*O*-benzylidene muramic acid **3**.

With the exocyclic alkene **8** containing the 3-*O*-lactyl side chain in hand, we were interested to find out whether the mercury(II) salt triggered Ferrier rearrangement[2] of sugar to inosose could be effected.

Treatment of **8** with a catalytic amount of mercury(II) sulfate in a 5 mM solution of sulfuric acid in aqueous dioxane over 2 h at 80 °C afforded a 9:1 mixture of the deoxyinososes **9** and **10** in 62% yield.[8] The major cyclohexanone **9** ($[\alpha]^{20}_D = +21°$, $c = 0.7$, CH_2Cl_2), purified by silica gel column chromatography using as eluent ethyl acetate, was regioselectively reduced with lithium *tert*-butoxyaluminium hydride in THF at 0 °C to the corresponding diol, which was peracetylated in situ to produce the triacetate **11** ($[\alpha]^{20}_D = +42°$, $c = 1.14$, CH_2Cl_2) in 76% yield from the inosose **9**. Hydrogenolytic cleavage of the ester **11** in ethanol in the presence of 10% palladium on charcoal as catalyst smoothly removed the benzyl protecting group to give the carbocyclic noranalogue of mu-

† Dedicated to the memory of Professor Edgar Lederer.
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(8) All new compounds have been fully characterized by spectroscopic data and elemental analysis within accepted limits.

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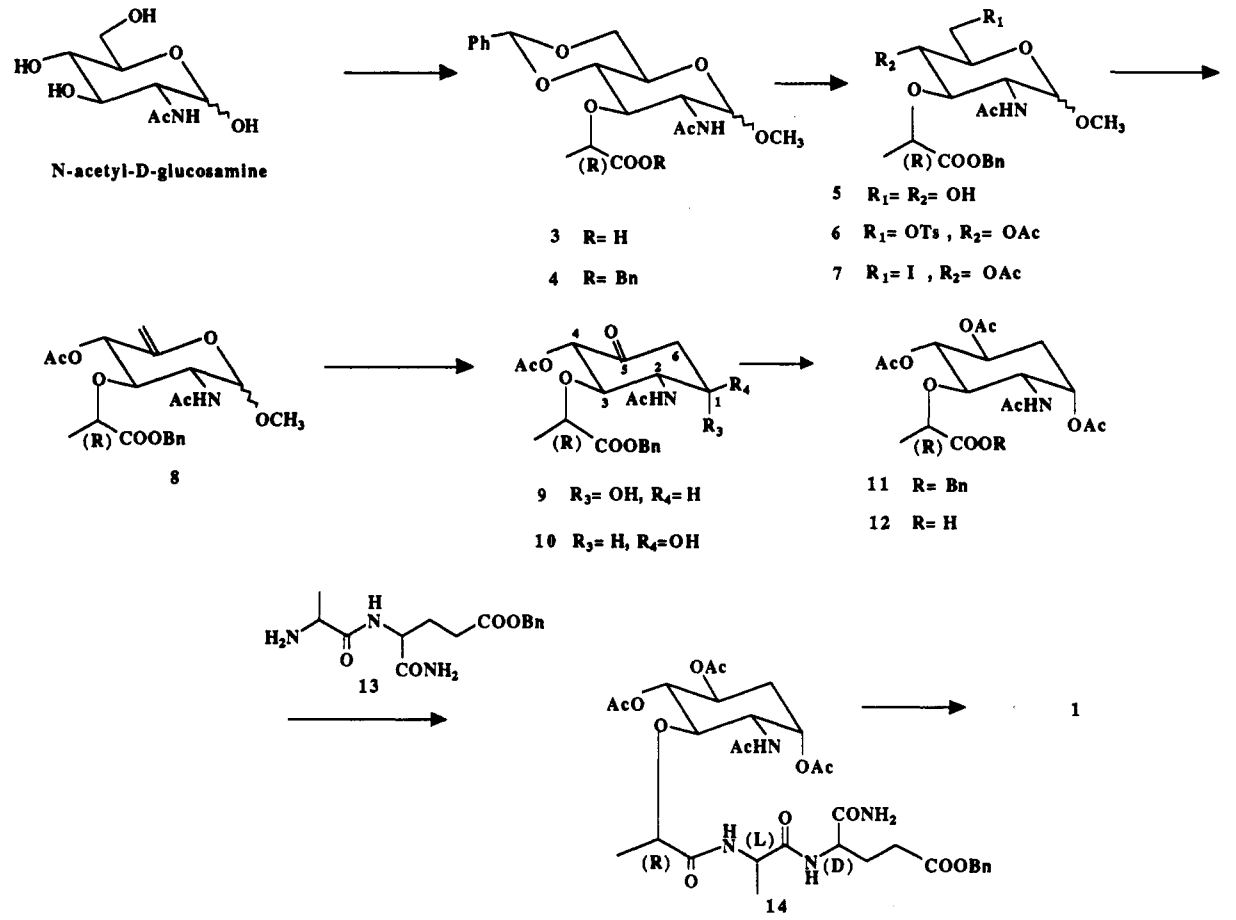
Scheme I



ramic acid **12**. Without isolation the acid was condensed in the presence of *N*-hydroxysuccinimide and dicyclohexylcarbodiimide with the dipeptide[4] L-Ala-D-isoglutamine benzyl ester **13** to produce **14** (mp 202 °C, $[\alpha]^{20}_D$ = +20°, *c* = 2.17, CH_3OH) in 78% yield. Finally, the four ester groups in **14** were readily hydrolyzed with potassium hydroxide in aqueous dioxane to yield the desired target molecule **1** ($[\alpha]^{20}_D$ = +34°, *c* = 1.0, CH_3OH).

The deoxyinososse[5] **16** and a derivative of pseudo-D-glucosamine[6] **19** were the starting materials of choice for the synthesis of the second target molecule **2**. The synthetic strategy (Scheme II) was based on previous experience within our laboratory.

The development of effective approaches for the preparation of pseudo-D-glucosamine from deoxyaminocyclohexanones **16** or **17** is of interest not only in connection with our projected synthesis of a new type of immunostimulant but also because it would fill a gap that exists in current organic methodology.

The conversion of alkene **15** into the aminocyclohexanones **16** and **17** was initially effected[7] with a catalytic amount of palladium(II) chloride in 5 mM sulfuric acid in aqueous dioxane at 80 °C over 2 h. This mild procedure afforded a 70% yield of a mixture of two products in a 60:40 ratio. The structures of the major product **16** and the minor diastereoisomer **17** were rigorously established.[8] Recently **16** was described by Adam[9] using an identical procedure.

However, when the carbohydrate–carbocycle rearrangement was repeated on the hex-5-enopyranoside **15** (mp 74–75 °C, $[\alpha]^{20}_D$ = +53°, *c* = 1.33, $CHCl_3$) using mercury(II) sulfate as catalyst, the two diastereoisomers **16** and **17** were obtained in 78% yield in a ratio of 85:15. The major compound was shown to be **16** ($[\alpha]^{20}_D$ = −23°, *c* = 1.52, $CHCl_3$) and the minor product was identified as **17** ($[\alpha]^{20}_D$ = −21°, *c* = 1.88, CH_2Cl_2).

Elaboration of the advanced key intermediate **23** began with the conversion of cyclohexanone **16** to the oxazolidone containing a pseudo-D-glucosamine **19** by a two-step sequence recently described by us.[6]

Treatment of **16** with the Wittig reagent (methoxymethylene)triphenylphosphorane afforded the vinyl ether **18** with the concomitant formation of the oxazolidinone ring. The vinyl ether **18** was subsequently oxymercurated using mercury(II) acetate in acetonitrile–water, followed by reduction with sodium borohydride to produce a 65% yield of two products **19** and **20** in a ratio of 85:15. The major compound was the suitably functionalized crystalline pseudo-D-glucosamine **19** required for the synthesis of the triol **21**.

The benzyl protected pseudo-D-glucosamine **19** was subjected to dissolving metal reduction (Li, NH_3–THF, −78 °C over 1 h) using *tert*-butyl alcohol as proton source to give triol **21** in good yield. This effective method for removing the benzylic N–C and O–C bonds was discovered after numerous unsuccessful attempts to effect catalytic hydrogenolysis with palladium on charcoal.

Triol **21** was readily transformed into its crystalline 4,6-*O*-benzylidene acetal **22** (mp 196–197 °C, $[\alpha]^{20}_D$ = +28°, *c* = 2.30, CH_3OH) with benzaldehyde and anhydrous zinc chloride as catalyst. Attachment of the lactyl ether side chain to the hydroxyl at C-3 was best achieved by treatment with (*S*)-chloropropionic acid in *N*,*N*-dimethylformamide in the presence of sodium hydride, which afforded the acid **23** ($[\alpha]^{20}_D$ = +136°, *c* = 0.34, CH_3OH) in 72%

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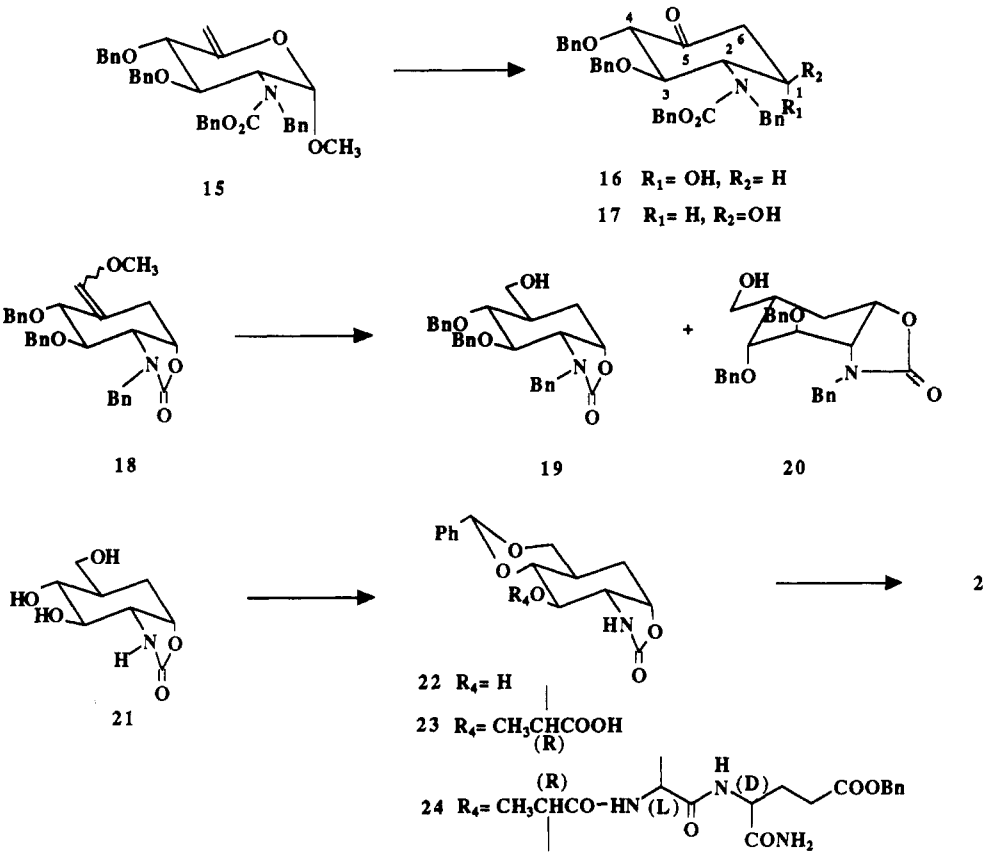
Scheme II



yield. As previously, this acid underwent smooth condensation with the dipeptide L-Ala-D-isoglutamine benzyl ester **13** in the presence of *N*-hydroxysuccinimide and dicyclohexylcarbodiimide to give the crystalline **24** (mp = 233–234 °C, $[\alpha]^{20}_D$ = +57°, *c* = 0.4, CH_3OH) in 78% yield.

Finally, hydrogenolysis (Pd–C 10%) of **24** afforded the crystalline **2**, our second target molecule (mp 142–143 °C, $[\alpha]^{20}_D$ = +53°, *c* = 4.28, H_2O) in 84% yield.

The biological activity of this new class of immunostimulant will be the subject of a forthcoming paper.

Host–Guest Properties of New Water-Soluble Calixarenes Derived from *p*-(Chloromethyl)calixarenes

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Summary: Water-soluble, cationic, and anionic calix[6]arenes were synthesized from *p*-(chloromethyl)calix[6]arene as a key intermediate: the formation of aqueous host–guest-type complexes was confirmed by spectroscopic methods.

Sir: "Calixarenes" are cyclic oligomers made up of benzene units like "cyclodextrins" are made up of glucose units.[1,2] One may expect, therefore, that they can serve as building blocks for designing new functionalized host molecules.[2-4] However, evidence supporting the formation of host–guest complexes in solution has been elusive despite the availability of convenient one-step syntheses of calixarenes.[1,2,5] In order to obtain evidence for complexes in aqueous solution, we previously synthesized a series of water-soluble calixarenes that have hydrophilic sulfonate groups on the upper rim of a hydrophobic calixarene cavity.[6,7] With the aid of hydrophobic forces in water, these compounds form host–guest-type complexes with several organic guest molecules.[6-9] The results indicate the capability of calixarenes to act as host molecules in aqueous media. Here,

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