Synthesis of a C-Phosphonate Disaccharide as a Potential Inhibitor of Peptidoglycan Polymerization by Transglycosylase

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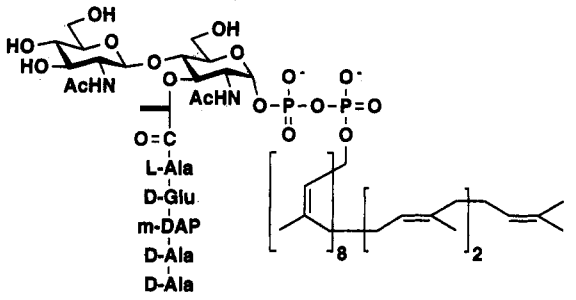
Summary: A phosphonate disaccharide 4, having structural features of both peptidoglycan monomer 1 and the active portion 2 of moenomycin A, was synthesized as a potential antibiotic and inhibitor of transglycosylase, an enzyme responsible for formation of the polysaccharide backbone of bacterial peptidoglycan.

Formation of the peptidoglycan cell wall layer in bacteria is a target of numerous antimicrobial agents (e.g., penicillin, cephalosporin, vancomycin).[1] However, most interfere with processing of the peptide portion and only very few, such as moenomycin A,[2,3] are believed to prevent polymerization of the polysaccharide chain.[4] This antibiotic, which is part of the flavomycin complex used in veterinary medicine, appears to inhibit transglycosylase,[5] a penicillin-binding protein responsible for catalyzing the connection of the lipid-bearing monomer units 1 of peptidoglycan.



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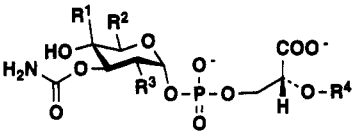
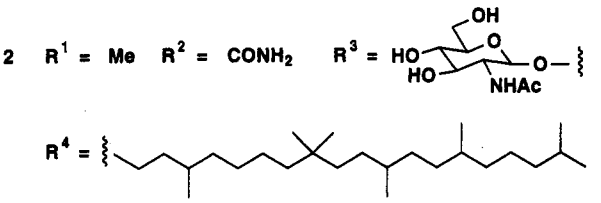
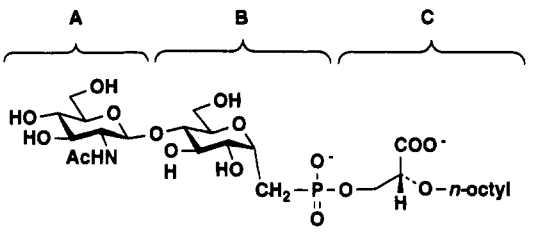
Extensive degradation studies indicate that the disaccharide derivative 2 of moenomycin retains virtually all of the activity of the parent compound.[3] Hecker and coworkers recently reported the syntheses of a series of monosaccharide analogues (e.g., 3), but these compounds appear to lack antibacterial activity.[6] Since synthetically accessible inhibitors of transglycosylase with better solubility than moenomycin A may be effective against organisms resistant to current therapy, we embarked on synthesis of C-phosphonate disaccharides such as 4 which combine features of both the active portion of this antibiotic (i.e., 2) and the natural transglycosylase substrate 1.





3 R^1 = H R^2 = CH_2OH R^3 = NHAc R^4 = n-C_5H_{11}

Compound 4 possesses a noncleavable sugar C-phosphonate moiety[7] and lacks the physiologically active[8] peptide chain which contributes to the multiple biological effects (e.g., immunoadjuvant properties) of peptidoglycan derivatives in mammals.[9] However, 4 does have many of



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the features expected for recognition by transglycosylase, namely, a disaccharide with a terminal *N*-acetylglucosamine unit, a lipid tail, and anionic groups which can apparently mimic a diphosphate. During normal transglycosylase-catalyzed polymerization, the growing terminus of the peptidoglycan polysaccharide chain is the glycosyl donor with a lipid-linked diphosphate as the leaving group.[1] Addition of the 4-hydroxyl of the *N*-acetylglucosamine unit of 1 (initially the acceptor) extends the chain by two sugar units and makes this disaccharide moiety the glycosyl donor for the next monomer unit (i.e., next unit of 1). Since the C-phosphonate functionality does not provide a cleavable leaving group, in addition to

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(7) For a recent review of C-glycoside syntheses see: Postema, M. H. D. *Tetrahedron* **1992**, *48*, 8545–8599.

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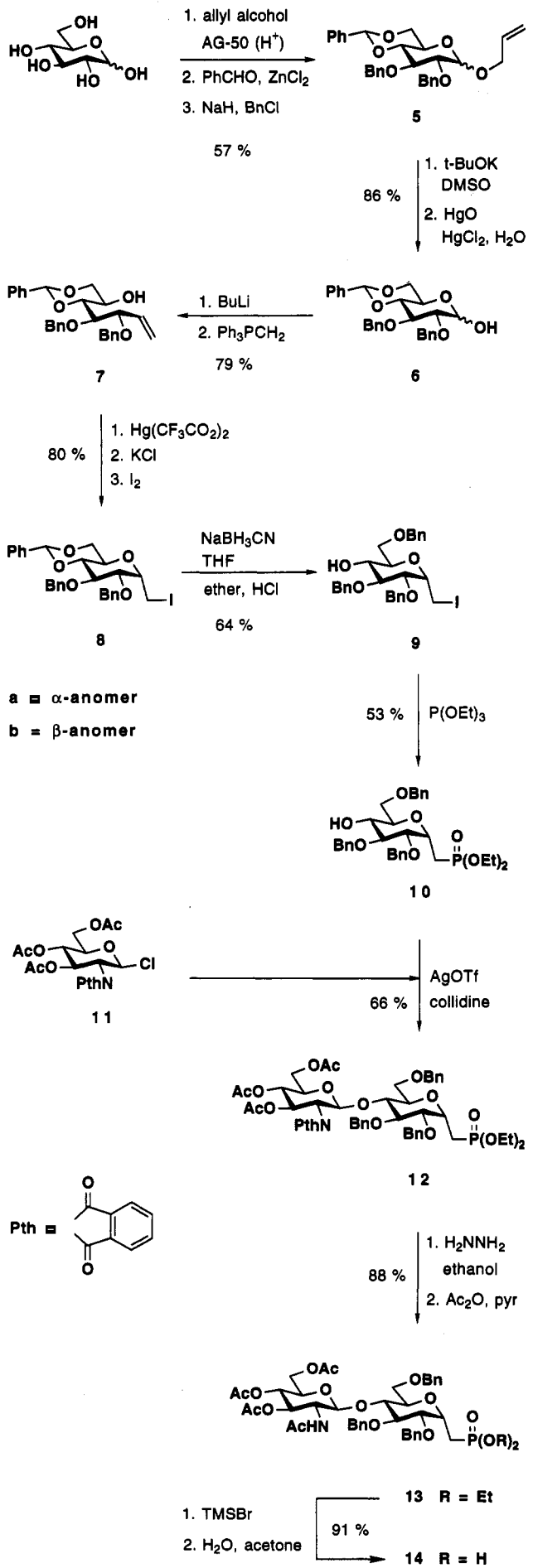
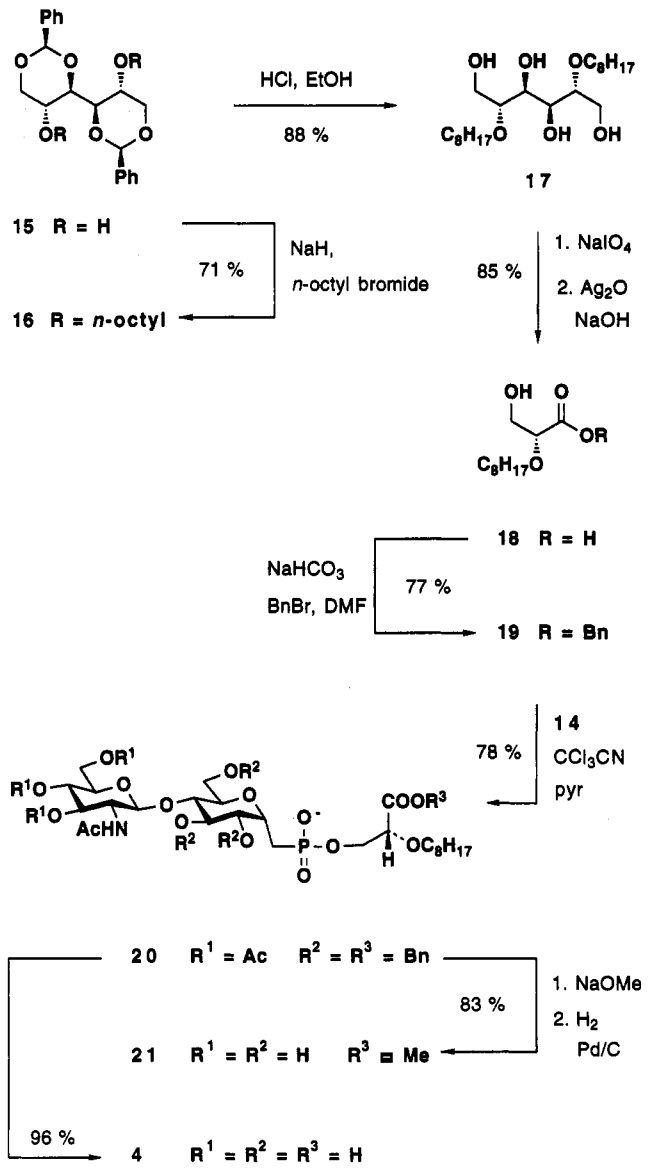
Scheme I



Scheme II



potentially inhibiting transglycosylase, **4** could also "end cap" growing peptidoglycan polysaccharide chains if it is incorporated. The absence of a diphosphate also lends general metabolic and chemical stability to the structure.

The synthetic approach to **4** involves initial preparation and coupling of a protected D-glucose C-phosphonate (B) to a protected D-glucosamine (A), attachment of an alkylated glyceric acid moiety (C), and finally, deprotection. The known[10] glucose derivative **6** was prepared by an improved four-step procedure in 49% overall yield from D-glucose (Scheme I). Wittig reaction of the derived alkoxide produces **7**, which undergoes mercury-induced cyclization and iodination to form a separable mixture (4.3:1) of α- and β-anomers **8a** and **8b**, respectively (overall yield 80%).[11] Sodium cyanoborohydride reduction of the benzylidene group[12] in acidic ether–THF liberates the

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4-hydroxy group to give **9** (64%). Arbuzov reaction with triethyl phosphite completes the synthesis of the "B component" **10** (53%). Although it would appear that Wittig reaction of **6** with an appropriate phosphonate-bearing reagent [e.g., $(EtO)_2P(O)CH_2P(O)(OEt)_2$][13] could give a benzylidene precursor to **10** directly, Michael closure of the initial unsaturated phosphonates produced by such reagents in other systems proved problematic.[14] Coupling of **10** to the known[15] protected 1-chloroglucosamine derivative **11** in the presence of silver triflate[15a] affords disaccharide **12** (66%), which is easily converted to the corresponding *N*-acetyl derivative **13** by standard hydrazinolysis and acetylation.[15a] Removal of the ethyl groups from the phosphonate with bromotrimethylsilane proceeds in 91% yield to provide the "AB component" **14** ready for attachment of the lipid-bearing glyceric acid part.

The "C component" **19** is readily available by slight modification of the procedure originally devised[16] for related compounds by Schubert and Welzel and subsequently modified by the Pfizer group[6] (Scheme II). As expected, alkylation of dibenzylidenemannitol **15** with octyl bromide to give **16**, followed by deprotection to **17**, oxidative cleavage to **18**, and esterification affords **19** in 41% overall yield. Coupling of **19** to the disaccharide C-phosphonate **14** with trichloroacetonitrile[17] in pyridine completes formation of the target skeleton **20**. Hydrogenolysis of the benzyl groups followed by saponification of the esters proceeds in very high yield to generate the amphiphilic target analogue **4**. Reversal of the order of the deprotection steps produces the corresponding methyl ester **21**. This convergent synthetic approach is amenable to rapid production of numerous analogues bearing modifications at various sites. Current studies on the biological activity of **4** and related analogues will be reported later.

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Supplementary Material Available: Experimental procedures and spectra data for compounds **4–21** (18 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(14) For related examples see: Chung, S.-K.; Moon, S.-H. *J. Chem. Soc., Chem. Commun.* **1992**, 77–79.
(15) (a) Lemieux, R. U.; Takeda, T.; Chung, B. Y. *ACS Symp. Ser.* **1976**, *39*, 90–115. (b) Kantoci, D.; Keglevic, D.; Derome, A. E. *Carbohydr. Res.* **1987**, *162*, 227–235.
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