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Synthesis of *N*-acetylglucosamine thiazoline/lipid II hybrids

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Abstract—Potential inhibitors of transglycosylases involved in bacterial cell wall biosynthesis were synthesized by combining *N*-acetylglucosamine thiazoline, a potent inhibitor of β-hexosaminidase, with functional groups present in lipid II, the natural substrate of the transglycosylases.

Due to the emerging problem of antibiotic resistance in bacteria, there is increasing interest in the exploration of new antibiotic targets. Among the promising targets, the transglycosylase involved in bacterial cell wall biosynthesis is of particular interest, as the polysaccharide backbone of peptidoglycan appears to remain intact during the course of antibiotic resistance development, while the peptide moiety shows a high frequency of change.[1] The transition states of the reaction catalyzed by transglycosylase and that by *N*-acetyl-β-hexosaminidases have been considered to feature similar geometries and charge distributions (Fig. 1),[2] and this proposition has served as the basis for our inhibitor design. Since *N*-acetylglucosamine (GlcNAc) thiazoline **3** has been shown to be a potent competitive inhibitor of *N*-acetyl-β-hexosaminidase,[3,4] we have decided to use **3** as a core structure. Herein, we report the chemistry developed for the syntheses of several small molecules that combine thiazoline **3** with some of the structural features of lipid II, the natural substrate of the bacterial cell wall transglycosylases.

Our synthesis began with the protection of the 4- and 6-hydroxyl groups of thiazoline **3**[4] as a *p*-methoxybenzylidene (PMB) acetal (Scheme 1). This was followed by attachment of a lactic acid residue to the 3-hydroxyl group to afford muramic acid (MurNAc) derivative **4**. The yield of this reaction, albeit moderate, was comparable to other GlcNAc to MurNAc conversions.[5] A portion of the peptide side chain of lipid II was introduced into the molecule by EDCI promoted coupling with a suitably protected dipeptide to yield **5**. Subsequent deprotection of the PMB acetal turned out to be problematic. Treatment with aqueous acids led to faster

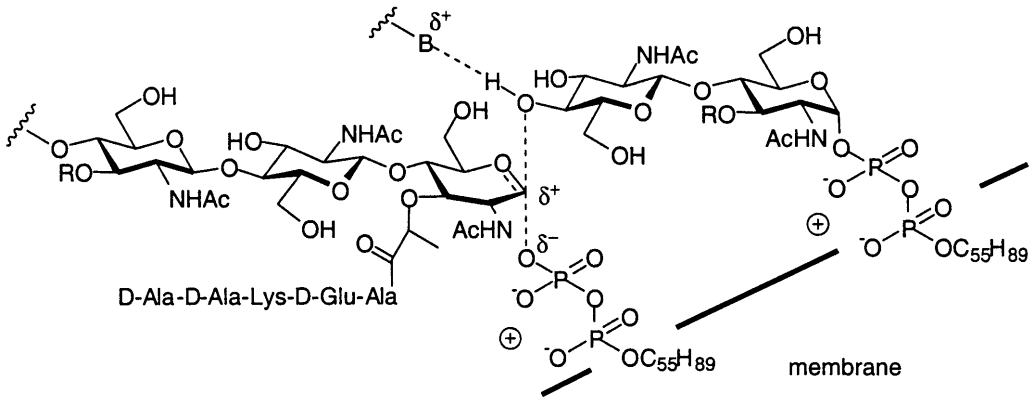

Figure 1. Proposed transition state of the transglycosylase reaction in bacterial peptidoglycan synthesis.

Keywords: carbohydrates; thiazolines; transglycosylase inhibitors.

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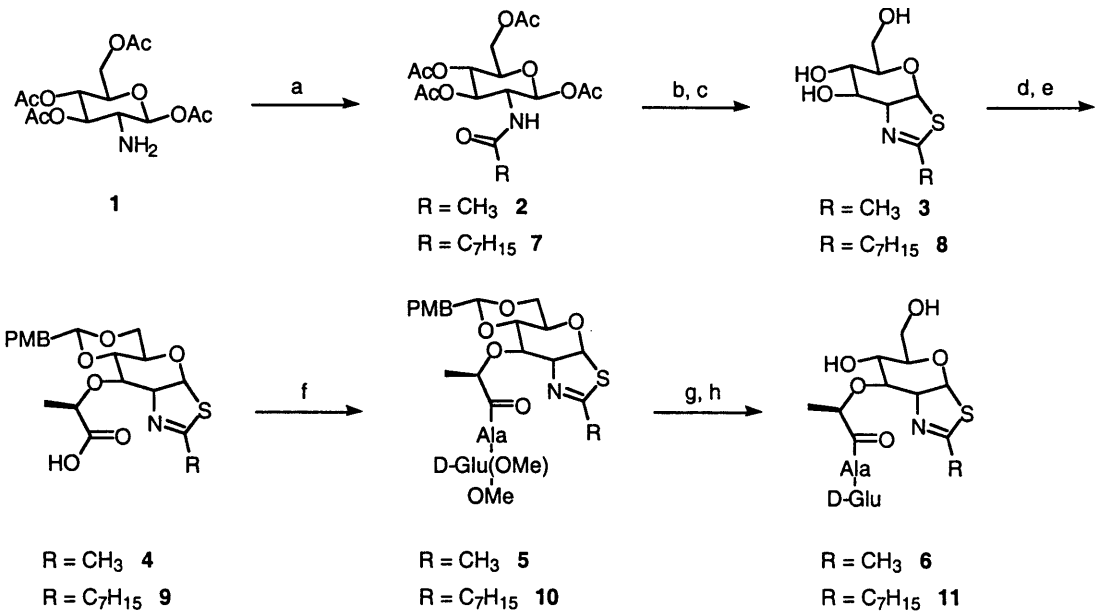
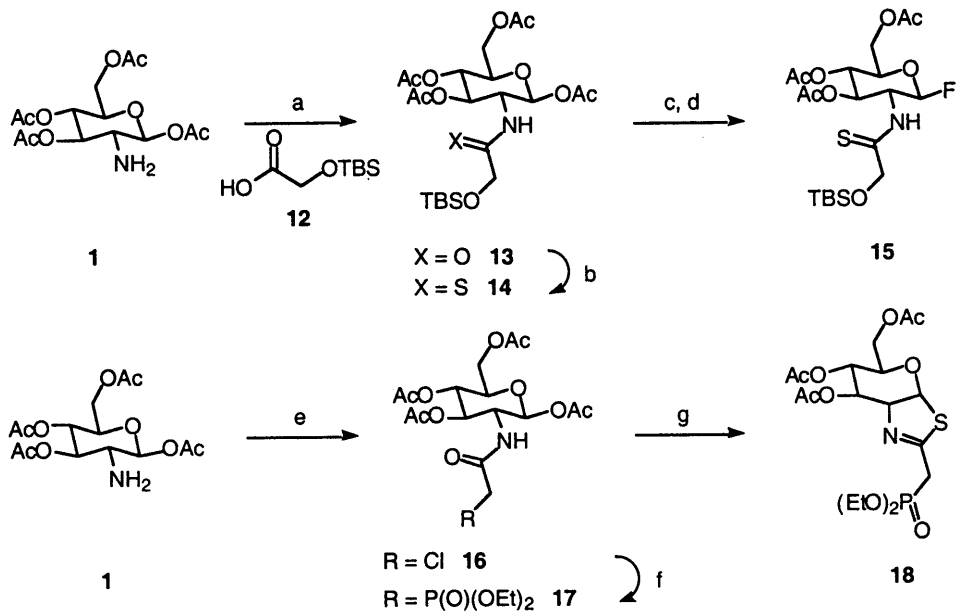
opening of the thiazoline ring than cleavage of the acetal, and oxidative conditions oxidized the sulfur atom of the thiazoline moiety. Eventually, it was found that ethanedithiol in the presence of one equivalent camphorsulfonic acid removed the benzylidene group efficiently. Cleavage of the methyl esters then afforded target molecule **6**.[6]

In order to mimic the oligoisoprenyl membrane anchor of lipid II, a long alkyl chain was incorporated into the core structure. Per-*O*-acetylated β-glucosamine **1**[7] was coupled to octanoic acid, followed by conversion of the amide bond to a thioamide, which was cyclized under the reaction conditions to thiazoline **8**. Compound **8** was then subjected to the reaction sequence outlined above, yielding target molecule **11**.

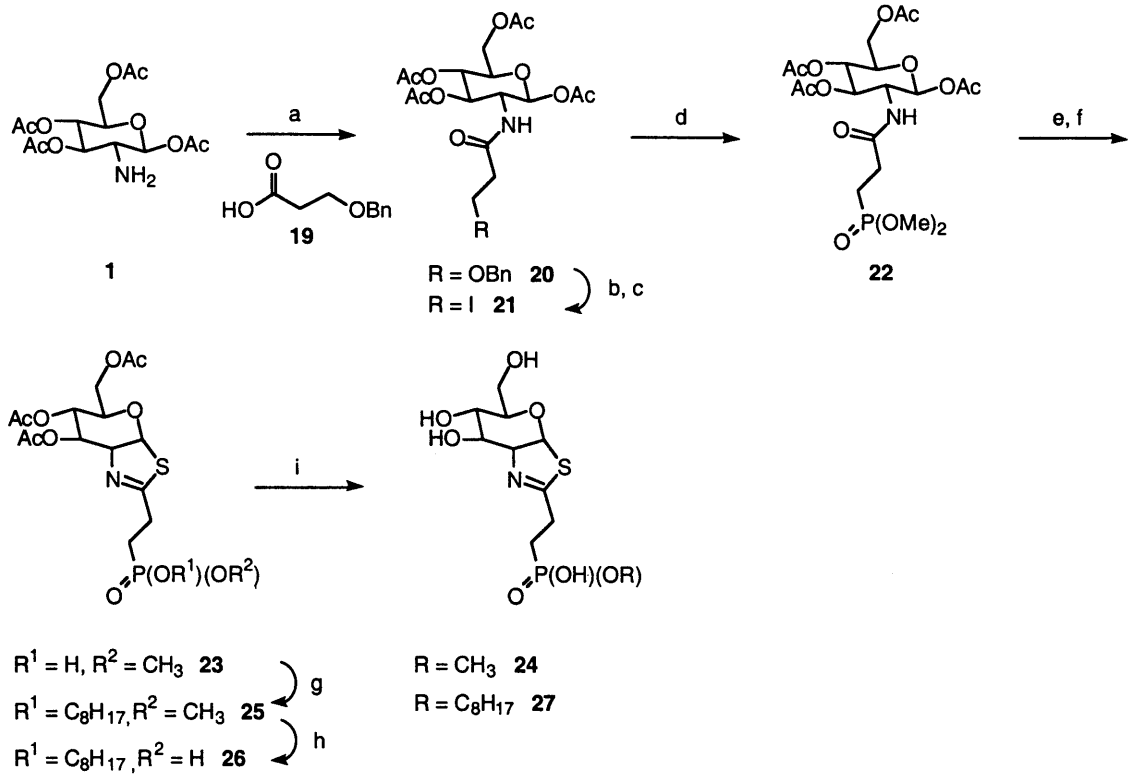
Another consideration of the transglycosylation reaction is the electrostatic and hydrogen bonding interactions between the pyrophosphate moiety of the



Scheme 1. (a) Octanoic acid, EDCl, DMAP, CH_2Cl_2, 95%; (b) Lawesson's reagent, toluene, 65°C, 98% (**2**), 88% (**7**); (c) TEA, $MeOH/H_2O$, 93% (**2**), quant. (**7**); (d) PMB dimethyl acetal, CSA, CH_3CN, 68% (**3**), 82% (**8**); (e) (*S*)-chloropropionic acid, NaH, THF, 55% (**3**), 23% (**8**); (f) Ala-D-Glu(OMe)-OMe, EDCl, HOBt, NMM, CH_2Cl_2/DMF, 71% (**4**), 95% (**9**); (g) ethanedithiol, CSA, CH_3CN, 86% (**5**), 88% (**10**); (h) LiOH, $MeOH/H_2O$, 80% (**5**), 90% (**10**).



Scheme 2. (a) EDCl, DMAP, CH_2Cl_2, 85%; (b) Lawesson's reagent, toluene, 80°C, 71%; (c) N_2H_4–HOAc, DMF, 78%; (d) DAST, CH_2Cl_2, −78°C, 35% (e) chloroacetic anhydride, pyridine, 69%; (f) $P(OEt)_3$, NaI, CH_3CN, 65°C, quant; (g) Lawesson's reagent, toluene, 65°C, 74%.



Scheme 3. (a) EDCl, DMAP, CH_2Cl_2, 91%; (b) H_2, 10% Pd/C, MeOH, quant.; (c) NIS, PPh_3 resin, DMF, 80%; (d) $P(OMe)_3$, 80°C, 2 days, 89%; (e) Lawesson's reagent, toluene, 65°C, 81%; (f) PhSH, TEA, THF, quant.; (g) *n*-octanol, DEAD, PPh_3, CH_2Cl_2, 73%; (h) PhSH, TEA, THF, quant.; (i) TEA, $MeOH/H_2O$, 51% (**23**), 90% (**26**).

substrate and the enzyme.[8] It is therefore desirable to include a charged group in the inhibitor design. Toward this end, **1** was coupled to TBS-protected hydroxyacetic acid **12** to provide amide **13** (Scheme 2). Surprisingly, reaction of **13** with Lawesson's reagent gave the uncyclized thioamide **14** instead of the desired thiazoline. Even activation of the anomeric position to fluoride **15** did not force ring closure. This lack of reactivity is most likely due to a reduction in nucleophilicity of the thioamide by the neighboring oxygen substituent of the protected hydroxyl group.

In order to circumvent this problem, a less electronegative heteroatom was introduced as substituent on the thiazoline ring. Compound **1** was reacted with chloroacetic anhydride. The chloride **16** was then converted under Arbuzov conditions to phosphonate **17**. This substate was readily cyclized to thiazoline **18** when submitted to Lawesson's reagent. Unfortunately, **18** was found to be very unstable and deprotection of the phosphonate moiety could not be achieved under Lewis acidic or basic conditions.

At this point, it was decided to remove the heteroatom substituent from the proximity of the thiazoline ring by an additional methylene group spacer. Coupling of **1** to **19** was followed by deprotection of the benzyl ether and conversion of the resulting hydroxyl group to halogen (Cl, Br, I) substituents (Scheme 3). Of the three halogenides, only iodide **21** reacted in the Arbuzov reaction to yield **22**. Phosphonate **22** was then converted to the corresponding thiazoline and monodeprotected with thiophenol in the presence of triethyl amine to provide **23**. This procedure was followed by hydrolysis of the acetate esters to give **24**.[9] A membrane anchor was also attached to phosphonate **23**, by coupling to octanol in a Mitsunobu reaction. Deprotection of **25** afforded target molecule **27**.

Investigation of the activities of molecules **6**, **11**, **24** and **27** as inhibitors of the bacterial cell wall transglycosylases is under way.

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6. Compound **6**: ^1H NMR (500 MHz, D_2O) δ 6.31 (1H, d, $J=7.0$ Hz, H1), 4.60 (1H, m, $GluH_\alpha$), 4.44 (1H, q, $AlaH_\alpha$, $J=7.2$), 4.34 (1H, q, $LacH_\alpha$, $J=6.8$), 4.16 (1H, dd, $J=8.4$, 4.4, H4), 4.12 (1H, dd, $J=3.7$, 2.2 Hz, H3), 3.80–3.77 (2H, m, H2,6), 3.64 (1H, dd, $J=12.3$, 6.8 Hz, H6′), 3.31 (1H, ddd, $J=9.1$, 6.9, 2.3 Hz, H5), 2.29 (3H, d, $J=2.6$ Hz, Me), 2.18 (2H, m, $GluH_\gamma$), 2.06 (1H, m, $GluH_\beta$), 1.88 (1H, m,

GluH$_{\beta'}$), 1.45 (3H, d, $J=7.0$ Hz, AlaH$_{\beta}$), 1.43 (3H, d, $J=6.6$ Hz, LacH$_{\beta}$); ^{13}C NMR (125 MHz, D$_2$O) δ 182.4, 178.8, 175.8, 174.2, 172.2, 88.3, 79.3, 76.8, 76.0, 73.9, 68.4, 62.1, 55.4, 49.9, 34.3, 29.0, 19.9, 18.9, 17.6; HR-MS (MALDI) calcd for $C_{19}H_{29}N_3O_{10}S$ [M+Na$^+$] 514.1466, found 514.1480.

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9. Compound **24**: ^{1}H NMR (500 MHz, D$_2$O) δ 6.34 (1H, d, $J=7.0$ Hz, H1), 4.46 (1H, t, $J=5.7$ Hz, H4), 4.25 (1H, dd, $J=4.6$, 3.5 Hz, H3), 3.78 (1H, dd, $J=12.5$, 2.2 Hz, H6), 3.63 (1H, dd, $J=12.5$, 7.0 Hz, H6), 3.62 (1H, m, H2), 3.55 (3H, d, $J=10.3$ Hz, OMe), 3.39 (1H, ddd, $J=9.2$, 7.0, 2.4 Hz, H5), 2.79–2.73 (2H, m, NHCOCH_2CH$_2$P), 1.98–1.89 (2H, m, NHCOCH$_2$CH_2P); ^{13}C NMR (125 MHz, D$_2$O) δ 88.0, 78.3, 74.6, 72.1, 69.9, 62.1, 51.7; MS (ESI) pos. 328 [MH$^+$], 350 [MNa$^+$]; neg. 326 [M–H]$^-$.