(592 mg, 85% yield). The solid was identified as 6 (trifluoroacetate salt) by mass spectrometry: MS (CI, NH_3) m/z (%) 219 (100) $(M + 1)^+$.

An aqueous solution of a small sample of L-6A was left at ambient temperature for 3-4 h and was then analyzed by RPHPLC, which showed L-5A as the only hydrolysis product.

The amino lactone salt (531 mg, 1.6 mmol) was dissolved in anhydrous DMSO (17 mL). *N*-(Ethoxycarbonyl)phthalimide (363 mg, 1.66 mmol) was added, followed by triethylamine (0.23 mL, 1.66 mmol), and the reaction mixture was stirred at ambient temperature. After 30 h, the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 × 150 mL). The organic layer was washed with water (4 × 100 mL) and with saturated brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo. The major band was separated on a preparative silica plate (EtOAc–hexanes, 6:4 v/v) and the product (L-7A) crystallized from acetone as a white solid (100 mg, 18% yield): mp 277–280 °C (lit. mp, Table I); TLC showed that the compound was essentially unaffected by brief fusion; ^1H NMR (CD_3CN) δ 2.88–3.02 (m, 2 H, β-CH_2, $J_{\alpha\beta1}$ = 11.1 Hz, $J_{\alpha\beta2}$ = 9.8 Hz, $J_{\beta1\beta2}$ = 13.4 Hz), 5.56–5.63 (dd, 1 H, α-CH, $J_{\alpha\beta1}$ = 11.0 Hz, $J_{\alpha\beta2}$ = 10.0 Hz), 6.97–7.55 (m, 4 H, indolic aryl H's), and 7.83–7.93 (m, 4 H, phthaloylic aryl H's); MS (CI, NH_3) m/z (%) 349 (20) $(M + 1)^+$, 366 (60) $(M + 18)^+$; $[\alpha]^{22}_D$ −147° (*c* 0.97, acetone). Anal. Calcd for $C_{19}H_{12}N_2O_5$: C, 65.52; H, 3.45; N, 8.04. Found: C, 65.76; H, 3.54; N, 7.88.

Similarly, L-5B was converted into the amino lactone L-6B in trifluoroacetic acid. RPHPLC showed that only L-5B was formed on hydrolysis of L-6B and that stereochemistry had not been altered by lactonization. The amino lactone was then converted into L-7B as described for L-7A: mp 259–262 °C (lit. mp, Table I); on melting, L-7B showed major conversion to L-7A or D-7B by TLC; ^1H NMR (CD_3CN) δ 2.68–2.77 and 3.06–3.14 (m, 2 H, β-CH_2, $J_{\alpha\beta1}$ = 9.4 Hz, $J_{\alpha\beta2}$ = 12.8 Hz, $J_{\beta1\beta2}$ = 12.7 Hz), 5.61–5.68 (dd, 1 H, α-CH, $J_{\alpha\beta1}$ = 9.5 Hz, $J_{\alpha\beta2}$ = 12.2 Hz), 6.97–7.61 (m, 4 H, indolic aryl H's), and 7.83–7.92 (m, 4 H, phthaloylic aryl H's); MS (CI, NH_3) m/z (%) 349 (100) $(M + 1)^+$, 366 (50) $(M + 18)^+$, 305 (35) $(M + 1 - CO_2)^+$; $[\alpha]^{22}_D$ −204° (*c* 0.35, acetone). Anal. Calcd for $C_{19}H_{12}N_2O_5$: C, 65.52; H, 3.45; N, 8.04. Found: C, 65.28; H, 3.50; N, 7.95.

Acknowledgment. Mass and NMR spectra were provided by the Laboratory of Analytical Chemistry of this Institute. We are indebted to Dr. Virender M. Labroo of this Laboratory and Prof. Michael M. King of George Washington University for valuable advice and discussion.

Synthesis of Compounds Designed To Inhibit Bacterial Cell Wall Transglycosylation

Scott J. Hecker,* Martha L. Minich, and Karen Lackey

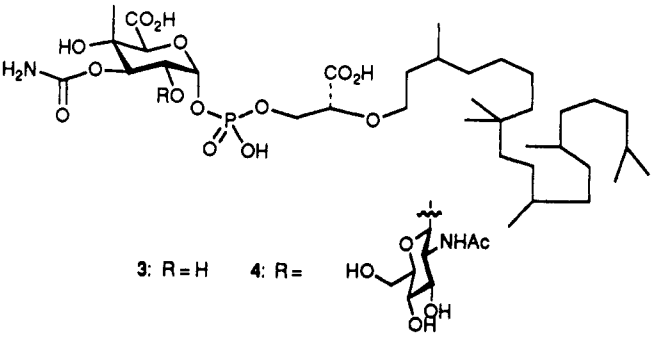
Pfizer Central Research, Groton, Connecticut 06340

Received March 6, 1990

Methods for preparation of compounds designed to inhibit the transglycosylation step in bacterial cell wall biosynthesis are described. Two hybrid structures (**5** and **31**) are synthesized, which combine features of the transglycosylase substrate with those of the natural product moenomycin, a known transglycosylation inhibitor. The compounds are synthesized by a convergent route involving the coupling as a phosphate diester of a protected sugar portion with a glycerate–lipid synthon. Details of the syntheses of the sugar and glycerate precursors are discussed.

The transglycosylation step in bacterial cell wall biosynthesis, responsible for the construction of the polyglycan chains of peptidoglycan (Figure 1), has received little attention from medicinal chemists in the search for new antibacterial agents. Only one class of inhibitors of this biosynthetic step, the phosphoglycolipids, has been discovered; the best known member of this class is moenomycin A (**2**)[1] (Figure 2).

Moenomycin A, first reported in 1965, is a potent but fairly narrow-spectrum antibiotic that has been extensively used as a growth promotant by Hoechst under the trade name Flavomycin.[1] Comparison of the structure of this antibiotic with that of the transglycosylase substrate (**1**) invites the hypothesis that much of the structure of moenomycin might not be necessary for biological activity. In fact, recent degradative studies[2] by Welzel et al. have established that this is indeed the case: Successive removal of the sugar components has shown that monosaccharide **3** and disaccharide **4** retain much of the activity of moenomycin.



3: R = H **4**: R =

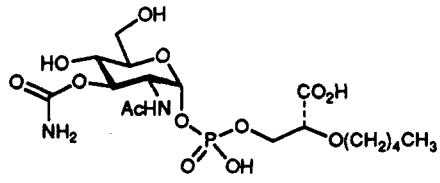
The demonstration that compounds **3** and **4** retain biological activity suggests that other small, synthetically accessible molecules could inhibit the transglycosylation step.[3] We have designed a set of potential transglycosylase inhibitors, exemplified by structures **5** and **6**, which contain features of both moenomycin A and the transglycosylase substrate. In designing these targets, we have chosen to retain most of the features of **1**, while replacing the diphosphate group of **1** with the phosphoglycerate group of

(1) Huber, G. Moenomycin and Related Phosphorus-Containing Antibiotics. In *Antibiotics*; Hahn, F. E., Ed.; Springer-Verlag: New York, 1979; Vol. 5, Part 1, p 135.

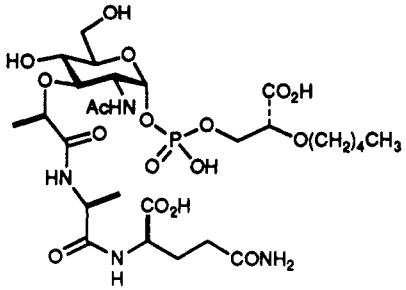
(2) (a) Welzel, P.; Kunisch, F.; Kruggel, F.; Stein, H.; Ponty, A.; Duddeck, H. *Carbohydr. Res.* **1984**, *126*, C1. (b) Welzel, P.; Kunisch, F.; Kruggel, F.; Stein, H.; Scherkenbeck, J.; Hiltmann, A.; Duddeck, H.; Muller, D.; Maggio, J. E.; Fehlhaber, H.-W.; Seibert, G.; van Heijenoort, Y.; van Heijenoort, J. *Tetrahedron* **1987**, *43*, 585.

(3) At the time we initiated this work, only one example of the synthesis of a structural analogue of moenomycin had appeared in the literature: Schubert, T.; Welzel, P. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 137. More recently, the Welzel group has reported synthesis of two disaccharide analogues of moenomycin: Hohgardt, H.; Dietrich, W.; Kuhne, H.; Muller, D.; Grzelak, D.; Welzel, P. *Tetrahedron* **1988**, *44*, 5771.

0022-3263/90/1955-4904$02.50/0



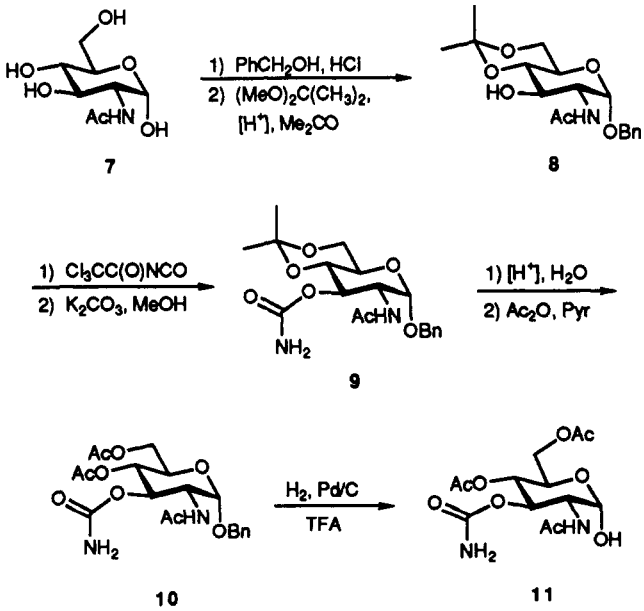
5



6

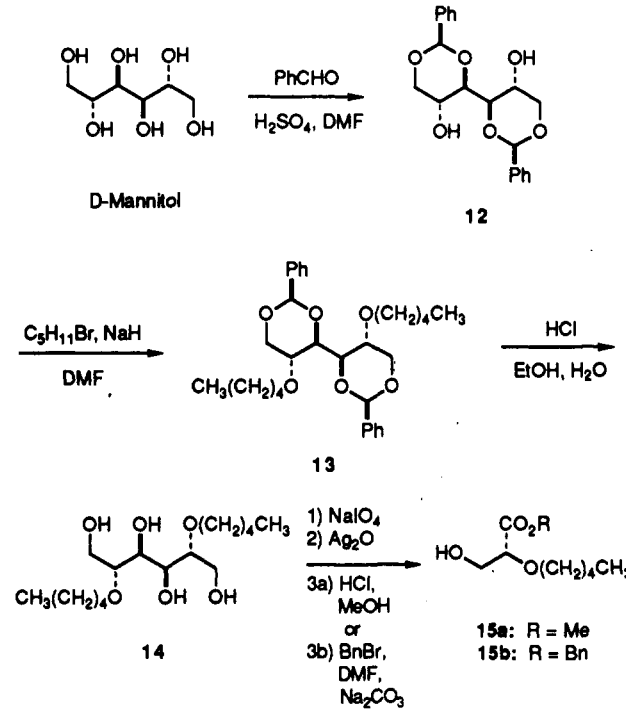
2. In structure **5**, the sugar portion is quite similar to that of **1**, with the exception that the 3-hydroxyl is substituted by the carbamoyl group of moenomycin rather than the lactoyl pentapeptide of the substrate. Structure **6** bears even closer resemblance to the transglycosylase substrate, since it incorporates a portion of the lactoyl pentapeptide. A suitable surrogate for the lipid moiety of **1** and **2** was needed; since it was difficult to estimate the structural requirements for enzyme binding in this region, we chose to synthesize a series of glycerate ethers with varying alkyl groups. The synthesis we have developed for preparation of our target compounds is illustrated with a pentyl group as the lipid surrogate in structures **5** and **6**.

The general synthetic approach to these compounds is a convergent one involving the coupling as a phosphate diester of a suitably protected sugar portion with a glycerate–lipid synthon. Synthesis of the sugar portion of target **5** proceeds from *N*-acetyl-D-glucosamine (**7**).



Following protection of the anomeric position with a benzyl group by Fischer glycosidation, the 4- and 6-hydroxyls are masked as an acetonide to give **8**.[4] The 3-hydroxyl is now free for selective functionalization; treatment with trichloroacetyl isocyanate, followed by methanolysis of the intermediate imide, affords carbamate **9**.[5] At this point the acetonide is removed and replaced with acetates, which withstand the acidic conditions required for hydrogenolysis of the benzyl glycoside. This sequence provides sugar subunit **11** in an overall yield of 41%.

The glycerate–pentyl ether is prepared according to the method of Welzel et al.[3] D-Mannitol is protected as its 1,3:4,6-bis(benzylidene) acetal **12**;[6] the remaining free alcohols are alkylated with *n*-pentyl bromide to generate **13**. Removal of the benzylidene acetals affords tetrol **14**; the vicinal diol is then cleaved with sodium periodate, the intermediate aldehyde is further oxidized to the carboxylic acid, and the acid is esterified, affording glycerate ether subunits **15a** and **15b**.



The coupling of sugar subunit **11** and glycerate ether **15a** as a phosphate diester utilizes the phosphite triester approach,[7] with phenyl chloro-*N*,*N*-diisopropylphosphoramidite (**16**) as the coupling reagent. Treatment of compound **11** in acetonitrile with reagent **16** results in clean and rapid conversion to phosphoramidite **17**. Compounds of this type are stable at neutral to basic pH and can be purified by silica gel chromatography. Exposure of phosphoramidite **17** in acetonitrile to glycerate ether **15a** in the presence of a mild acid, such as pyridinium *p*-toluenesulfonate, effects clean replacement of the diisopropylamino group; addition of *tert*-butyl hydroperoxide to the reaction mixture then oxidizes the labile tertiary phosphite to phosphate **18**. Hydrogenolysis of the phenyl phosphate ester over platinum oxide catalyst proceeds smoothly, affording phosphate diester **19**.

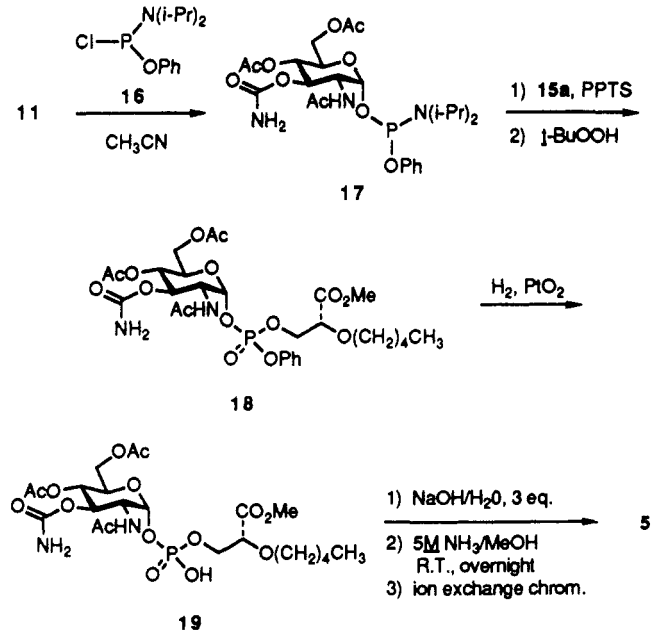
Conversion of **19** to target compound **5** required the development of a protocol for hydrolysis of the two acetates and the methyl ester in the presence of the carbamoyl

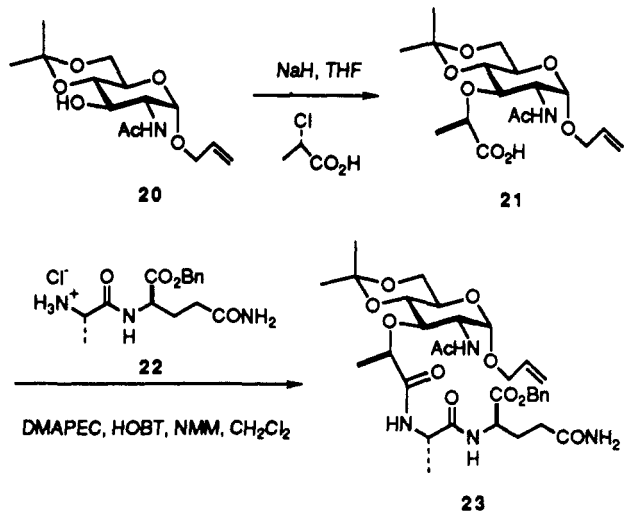
(4) Hasegawa, A.; Kaneda, Y.; Amano, M.; Kiso, M.; Azuma, I. *Agric. Biol. Chem.* **1978**, *42*, 2187.

(5) Minami, N.; Ko, S. S.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 1109, ref 21.

(6) Baggett, N.; Stribblehill, P. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1123.

(7) Westerduin, P.; Veeneman, G. H.; Marugg, J. E.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **1986**, *27*, 1211, and references therein.





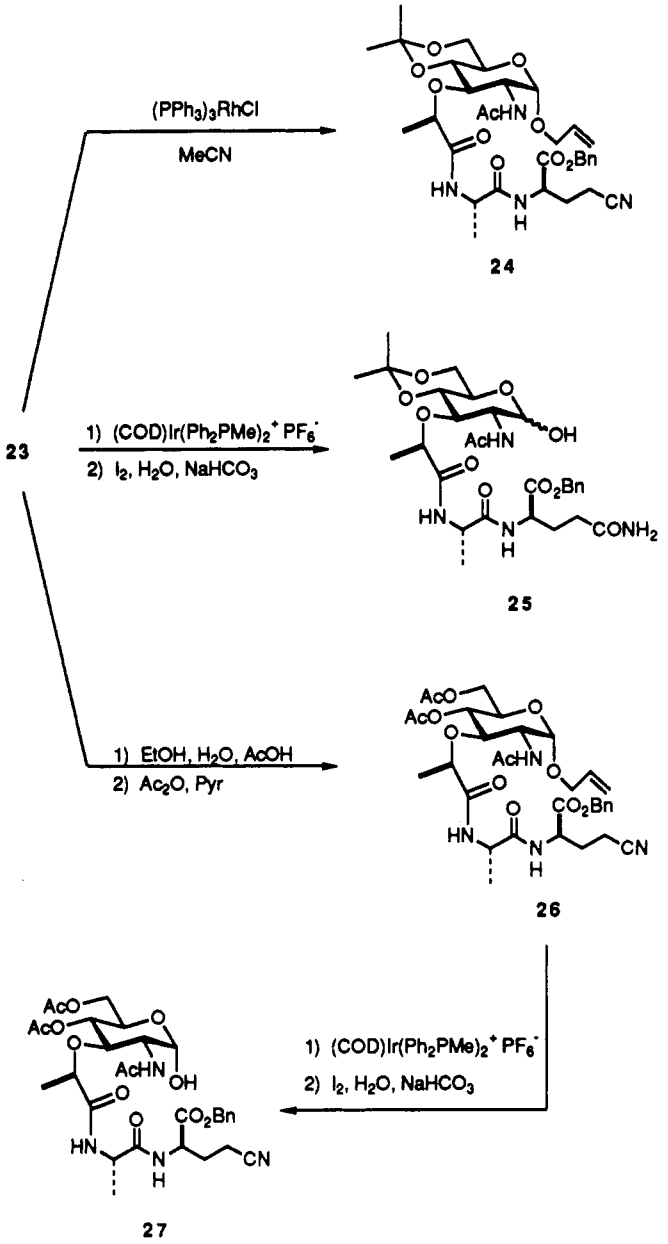
group. We observed by proton NMR studies of compound **19** in D_2O that addition of 3 equiv of sodium hydroxide results in selective cleavage of the methyl ester and primary acetate but that carbamate hydrolysis competes with cleavage of the secondary acetate upon addition of a further 1 equiv. We were pleased to find, however, that methanolic ammonia was extremely effective in causing selective cleavage of the secondary acetate in the presence of the carbamate. Thus, treatment of a solution of compound **19** in water at 0 °C with 3 equiv of aqueous sodium hydroxide solution completely removes the methyl ester and the primary acetate. A small amount of acetic acid is added (to quench any remaining hydroxide), and the solvent is removed by evaporation. The residue is taken up in methanolic ammonia solution and allowed to stand at room temperature in a sealed container overnight. This convenient two-step procedure reproducibly affords clean deprotected prototype **5**, contaminated only by sodium acetate. This contaminant can conveniently be removed on an anion-exchange resin, with use of a formic acid/water gradient to elute the pure desired material.

The approach to compound **6** is analogous to that of our first target, **5**. The allyl group was chosen for protection of the anomeric center, since it would be removable in the presence of a benzyl ester on the peptide side chain. Alkylation of allyl 4,6-*O*-isopropylidene-*N*-acetyl-D-glucosamine[8] (**20**, prepared analogously to compound **8**[4]) with (*S*)-2-chloropropionic acid affords carboxylic acid **21**. Coupling of **21** with dipeptide **22**[9] with [(dimethylamino)propyl]ethylcarbodiimide (DMAPEC)[10] gives protected nucleus **23**. Removal of the allyl protecting group at this point would provide the requisite coupling precursor. Attempted isomerization to a propenyl group with use of Wilkinson's catalyst[11] ($(PPh_3)_3RhCl$) caused dehydration of the carboxamide moiety to the nitrile[12] (**24**). Use of cyclooctadienyliridium bis(diphenylmethylphosphine) hexafluorophosphate[13] cleanly promotes the desired conversion; hydrolysis of the propenyl group with iodine/water[14] affords nucleus **25** as a 2:1 mixture of α- and β-anomers. Since we had previously observed that diacetate **11** was isolated almost exclusively as the α-anomer, we sought to prepare the diacetate relative of **25** in the hope of obtaining a more favorable α:β ratio. Removal of the acetonide of compound **23** affords a diol; unfortunately, acetylation of this diol (acetic anhydride/pyridine) proceeds with concomitant dehydration of the carboxamide moiety, affording nitrile **26**. Subjection of **26** to the isomerization/hydrolysis sequence gives subunit **27**, with an α:β anomeric ratio of 93:7.

Since nitrile **27** contains all of the desired functionality of the sugar portion of target **6**, and since the anomeric ratio of **27** is much more favorable than that of **25**, we chose to proceed with compound **27** rather than devote resources to selective acetylation of the diol obtained from acetonide **23** (Scheme I). With our carbohydrate synthon in hand, all that remained was application of the previously developed methodology for synthesis of the phosphate diester. Treatment of **27** with benzyl chloro-*N*,*N*-diisopropylphosphoramidite (**28**) in acetonitrile affords phosphoramidite **29**, which is purified by silica gel chromatography. Compound **29** is then coupled with alcohol **15b**, with tetrazole as catalyst,[7] to afford the intermediate tertiary phosphite, which is oxidized in situ with *tert*-butyl hydroperoxide to the corresponding phosphate **30**. Use of benzyl esters in both phosphoramidite reagent **28** and in glycerate **15b** greatly simplifies the deprotection sequence: The benzyl groups are removed by hydrogenolysis, following which the acetates are removed with methanolic ammonia; the final product **31** is purified by anion-exchange chromatography.

In summary, this paper describes the preparation of sugar–phosphate–glycerate ethers that are designed to inhibit bacterial cell wall transglycosylation. The synthesis comprises procedures for construction of suitably protected sugar units (**11** and **27**), for their derivitization as phosphate diesters (**18** and **30**), and for their ultimate protection to give final products (**5** and **31**). Although compounds **5** and **31** do not themselves exhibit antibacterial activity, the methodology described herein is general enough to allow synthesis of a wide variety of analogs; in fact, much

(8) Suami, T.; Sasai, H.; Matsuno, K.; Suzuki, N.; Fukuda, Y.; Sakanaka, O. *Tetrahedron Lett.* **1984**, *25*, 4533.
(9) Dipeptide **22** was prepared from BOC-D-glutamine by (1) alkylation of the carboxylate with benzyl bromide, (2) acid-catalyzed removal of the BOC group, (3) coupling with BOC-L-alanine with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (DMAPEC), and (4) acid-catalyzed removal of the BOC group (see the Experimental Section).
(10) Kimura, T.; Takai, M.; Masui, Y.; Morikawa, T.; Sakakibara, S. *Biopolymers* **1981**, *20*, 1823.
(11) Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1973**, *38*, 3224.
(12) Blum, J.; Fisher, A.; Greener, E. *Tetrahedron* **1973**, *29*, 1073.
(13) Oltvoort, J.; van Boeckel, C. A. A.; DeKoning, J. H.; van Boom, J. H. *Synthesis* **1981**, 305.
(14) Nashed, M. A.; Anderson, L. *J. Chem. Soc., Chem. Commun.* **1982**, 1274.



of this chemistry would be applicable to synthesis of analogues of compounds **3** and **4**, which are known inhibitors of the transglycosylase enzyme.[2]

Experimental Section[15]

Benzyl 2-acetamido-2-deoxy-4,6-*O*-isopropylidene-α-D-glucopyranoside (8) was prepared by a modification of a known procedure.[4] Thus, *N*-acetyl-α-D-glucosamine (10.0 g, 45.2 mmol) was suspended in benzyl alcohol (70 mL), and the mixture was warmed to 95 °C. A saturated solution of anhydrous HCl in 5 mL of benzyl alcohol was added. The suspended material dissolved, and the resulting solution turned dark over 20 min. The solution was filtered through glass wool into 400 mL of vigorously stirring diethyl ether. The precipitated glycoside was filtered, washed thoroughly with ether, air-dried, and used without further purification.

The crude glycoside was suspended in a mixture of acetone (200 mL) and 2,2-dimethoxypropane (80 mL). *p*-Toluenesulfonic acid monohydrate (700 mg) was added, and the mixture was stirred for 2 h at room temperature, during which time a clear, light yellow solution formed. The solvent was evaporated under reduced pressure; the residue was taken up in methylene chloride, washed (dilute sodium bicarbonate, water, brine), dried over magnesium sulfate, and filtered, and the solvent was removed with a rotary evaporator. The resulting light brown oil was purified by chromatography on 600 g of silica gel, eluting with 2.5% methanol/chloroform, to yield **8** as an amorphous solid: 10.6 g, 30.2 mmol, 67%; $[\alpha]^{23}$ +99.6° (*c* 0.895, $CHCl_3$); IR (KBr) 3411, 1662, 1544, 1074; ^1H NMR: δ 7.41–7.26 (m, 5), 5.92 (d, 1, *J* = 9.0), 4.85 (d, 1, *J* = 4.8), 4.70 (d, 1, *J* = 12), 4.44 (d, 1, *J* = 12), 4.16 (dt, 1, *J* = 10.0, 5.0), 3.83–3.61 (m, 4), 3.04–3.02 (d, 1, *J* = 3.9), 1.97 (s, 3), 1.52 (s, 3), 1.43 (s, 3); ^{13}C NMR δ 171.35, 136.80, 128.63, 128.23, 128.05, 99.84, 97.18, 74.69, 70.80, 69.81, 63.66, 62.18, 54.05, 29.04, 23.19, 19.06; mass spectrum, *m/z* 352.0 (M + 1). Anal. Calcd for $C_{18}H_{25}NO_6$: C, 61.53; H, 7.17; N, 3.99. Found: C, 61.32; H, 7.22; N, 3.93.

Benzyl 2-Acetamido-2-deoxy-3-*O*-carbamoyl-4,6-*O*-isopropylidene-α-D-glucopyranoside (9). According to the method of Kishi et al.,[5] compound **8** (3.4 g, 9.65 mmol) was dissolved in methylene chloride (100 mL) and the mixture was chilled to 0 °C. Trichloroacetyl isocyanate (1.45 mL, 2.5 g, 13.3 mmol) was added, and the mixture was stirred for 15 min. A solution of potassium carbonate (3.5 g) in 100 mL of water/methanol (1:1) was added, and the mixture was stirred at room temperature for 4 h. Saturated sodium bicarbonate solution (20 mL) was added, and the methylene chloride layer was separated and dried over magnesium sulfate. The solvent was removed with a rotary evaporator to yield **9** as an amorphous solid: 3.80 g, 9.64 mmol, 100%; $[\alpha]^{23}$ +96.2° (*c* 0.505, $CHCl_3$); IR (KBr) 3424, 3340, 1726, 1663, 1544, 1389; ^1H NMR δ 7.37–7.28 (m, 5), 5.97 (d, 1, *J* = 9.3), 4.98 (t, 1, *J* = 10.8), 4.86 (m, 3), 4.69 (d, 1, *J* = 11.7), 4.44 (d, 1, *J* = 11.7), 4.24 (dt, 1, *J* = 2.7, 9.0), 3.76 (m, 4), 1.89 (s, 3), 1.46 (s, 3), 1.37 (s, 3); ^{13}C NMR δ 170.32, 156.85, 136.73, 128.56, 128.19, 128.08, 99.83, 97.30, 71.96, 71.48, 69.84, 64.13, 62.30, 52.78, 28.99, 23.13, 18.96; HRMS for $C_{19}H_{27}N_2O_7$ (M + 1), calcd 395.1818, found 395.1833.

Benzyl 2-Acetamido-2-deoxy-3-*O*-carbamoyl-α-D-glucopyranoside. Compound **9** (265 mg, 0.670 mmol) was dissolved in ethanol (8.5 mL), water (1.5 mL), and acetic acid (1.0 mL), and the mixture was heated at reflux for 3 h under nitrogen. The solvent was removed under reduced pressure, azeotroping with several portions of toluene, to yield the title compound: 224 mg, 0.630 mmol, 94%; mp 184 °C; $[\alpha]^{23}$ +136.4° (*c* 0.153, MeOH); IR (KBr) 3441, 3313, 1694, 1657, 1555, 1051; ^1H NMR (DMSO-d_6) δ 7.77 (d, 1, *J* = 9.3), 7.37 (m, 5), 6.45 (br s, 2), 5.18 (d, 1, *J* = 6.9), 4.86 (dd, 1, *J* = 11.1, 9.2), 4.66–4.45 (m, 4), 3.92 (dt, 1, *J* = 3.6, 9.9), 3.52 (m, 4), 1.81 (s, 3); ^{13}C NMR (DMSO-d_6) δ 169.54, 157.01, 137.66, 128.22, 127.88, 127.59, 96.04, 73.32, 72.52, 68.54, 67.99, 60.45, 51.81, 22.49; mass spectrum, *m/z* 354.8 (M + 1). Anal. Calcd for $C_{16}H_{22}N_2O_7$: C, 54.23; H, 6.27; N, 7.91. Found: C, 54.30, H, 6.36, N, 7.62.

Benzyl 2-Acetamido-2-deoxy-3-*O*-carbamoyl-4,6-di-*O*-acetyl-α-D-glucopyranoside (10). Benzyl 2-acetamido-2-deoxy-3-*O*-carbamoyl-α-D-glucopyranoside (869 mg, 2.45 mmol) was slurried in dry pyridine (2.0 mL) under nitrogen at room temperature. Acetic anhydride (1.50 mL, 1.62 g, 15.9 mmol) was added, and the reaction was heated at 90 °C for 2 h. The reaction was cooled, diluted with ethyl acetate, and washed with 1 N HCl, back-extracting once with fresh ethyl acetate. The organic layer was washed (1× with water, 2× with $NaHCO_3$, 2× with water, 2× with brine), dried over magnesium sulfate, and filtered; the solvent was removed with a rotary evaporator, affording pure **10**: 984 mg, 2.25 mmol, 92%; mp 179–180 °C $[\alpha]^{23}$ +113.5° (*c* 0.555, MeOH); IR (KBr) 3432, 3319, 1739, 1715, 1648, 1553, 1260; ^1H NMR δ 7.33 (m, 5), 5.81 (d, 1, *J* = 9.9), 5.08 (m, 2), 4.93 (d, 1, *J* = 3.6), 4.71 (br s, 2), 4.68 (d, 1, *J* = 12), 4.49 (d, 1, *J* = 12), 4.30 (dt, 1, *J* = 2.1, 4.2), 4.21 (dd, 1, *J* = 4.5, 12), 3.98 (m, 2), 2.07 (s, 3), 2.02 (s, 3), 1.89 (s, 3); ^{13}C NMR δ 170.70, 170.11, 169.52, 156.41, 136.54, 128.65, 128.34, 128.17, 96.74, 72.21, 70.23, 68.09, 68.04, 61.88, 52.01, 23.15, 20.74, 20.67; mass spectrum, *m/z* 438.7 (M + 1). Anal. Calcd for $C_{20}H_{26}N_2O_9$: C, 54.79; H, 5.98; N, 6.39. Found: C, 54.37; H, 6.04; N, 6.24.

2-Acetamido-2-deoxy-3-carbamoyl-4,6-di-*O*-acetyl-α-D-glucopyranose (11). Compound **10** (503 mg, 1.15 mmol) was placed in a 250-mL Parr bottle with trifluoroacetic acid (15 mL)

(15) ^1H NMR spectra were determined at 300 MHz. Unless otherwise specified, all NMR spectra were recorded in $CDCl_3$ and the chemical shifts are expressed downfield from tetramethylsilane. Data are presented in the following order: multiplicity, number of hydrogens, coupling constant in hertz. IR values are in inverse centimeters. Specific rotations, $[\alpha]$, were measured at the sodium D line.

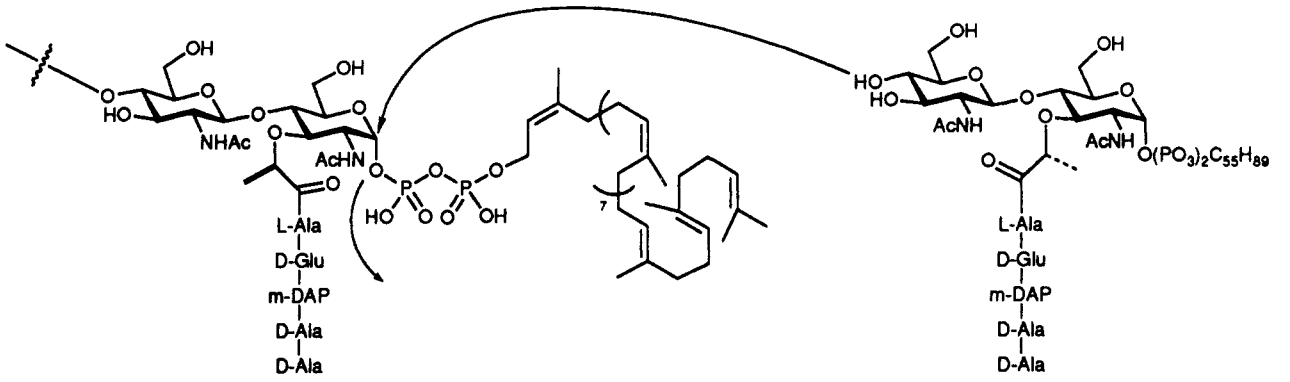


Figure 1. Transglycosylation in cell wall biosynthesis.

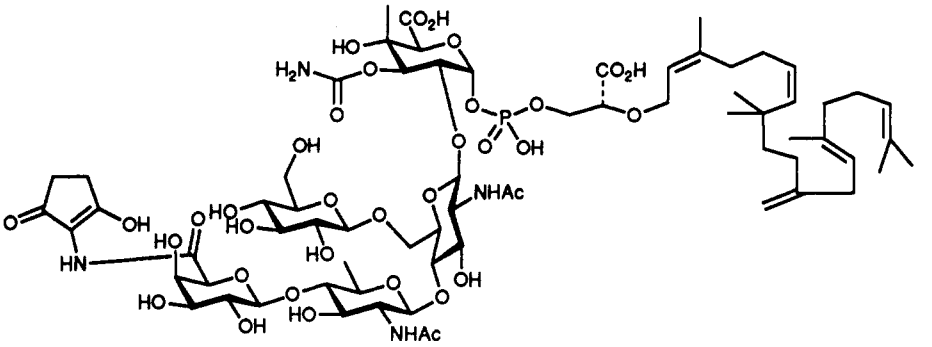
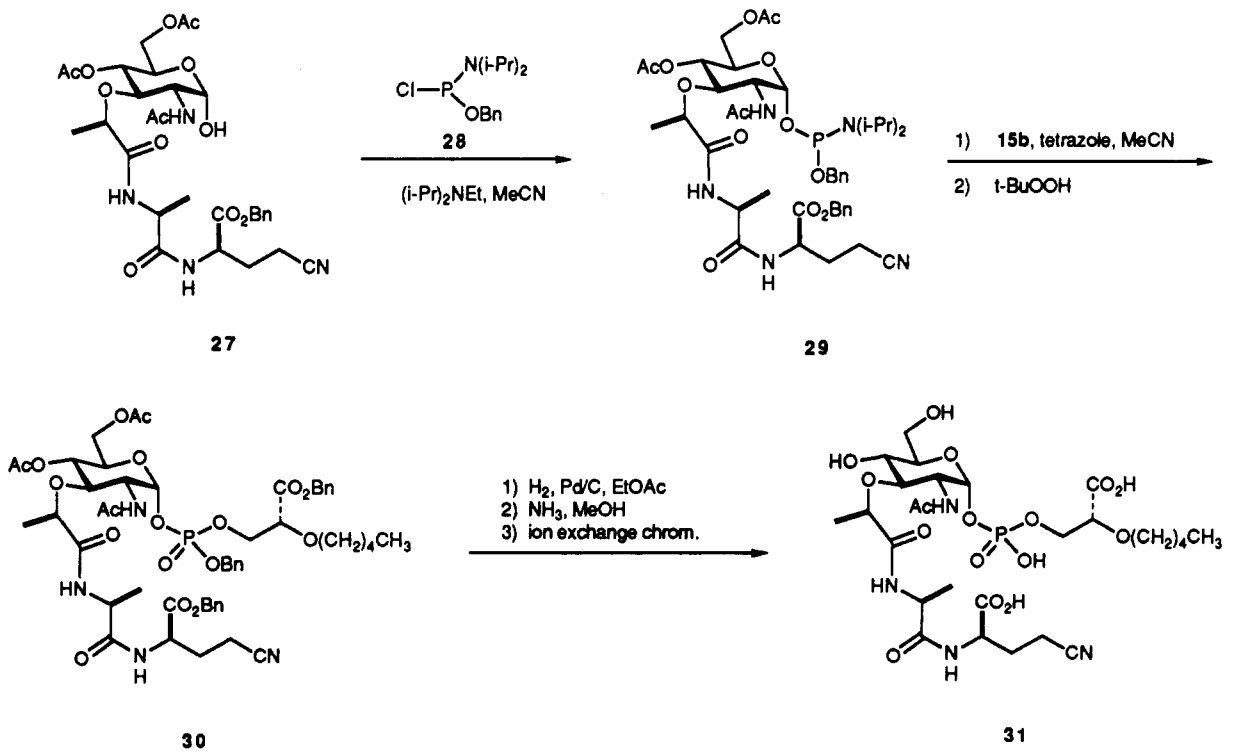


Figure 2. Moenomycin A.

Scheme I



and 10% Pd/C (78.1 mg), and the contents were shaken under 52 psi of hydrogen for 3.5 h. The mixture was filtered, and the trifluoroacetic acid was removed under reduced pressure. The residue was recrystallized from acetonitrile/ether to yield 208 mg of **11**. The mother liquor was concentrated and subjected to chromatography on silica gel (20 g), eluting with 5% MeOH/EtOAc, yielding a further 156 mg of **11**. The total yield of **10** was 364 mg (1.05 mmol, 91%); by ^{1}H NMR analysis, the α:β anomeric ratio appeared to be >9:1: mp 150 °C dec; IR (KBr) 3575, 3445, 3310, 1744, 1714, 1278; ^{1}H NMR (DMSO-d_6) δ 7.80 (d, 1, J = 9.3), 7.09 (d, 1, J = 2.7), 6.55 (br s, 1), 6.43 (br s, 1), 5.04 (dd, 1, J = 11.1, 9.8), 4.95 (d, 1, J = 3.0), 4.80 (t, 1, J = 9.6), 4.10 (m, 2), 3.97 (m, 2), 2.01 (s, 3), 1.97 (s, 3), 1.81 (s, 3); ^{13}C NMR (DMSO-d_6) δ 170.14, 169.49, 169.26, 156.10, 90.84, 69.61, 69.45, 66.60, 62.45, 51.78,

22.40, 20.57, 20.51; mass spectrum, m/z 349.2 (M + 1). Anal. Calcd for $C_{13}H_{20}N_2O_9$: C, 44.83; H, 5.79; N, 8.04. Found: C, 44.55; H, 5.63; N, 7.87.

1,3:4,6-Di-*O*-benzylidene-2,5-di-*O*-pentyl-D-mannitol (13). Compound 12[6] (5 g, 14 mmol) was dissolved in dry DMF (70 mL). NaH (1 g, 42 mmol) was added in portions, followed by 1-bromopentane (4.64 g, 31 mmol). The mixture was heated at 70 °C for 3 h, cooled, diluted with ether, and filtered. The filtrate was washed (3× with 1 N HCl, 1× with brine) and concentrated to yield 13 as an oil: 6.95 g, 100%; IR ($CHCl_3$) 2950, 1680, 1110; ^1H NMR δ 7.48 (m, 4), 7.34 (m, 6), 5.48 (s, 2), 4.22 (m, 2), 3.95 (m, 2), 3.86 (m, 2), 3.60 (m, 4), 3.45 (m, 2), 1.55 (m, 4), 1.30 (m, 8), 0.86 (m, 6); HRMS for $C_{30}H_{43}O_6$ (M + 1), calcd 499.3059, found 499.3032.

2,5-Di-*O*-pentyl-D-mannitol (14). Compound 13 (1 g, 2.01 mmol) was dissolved in ethanol (25 mL). Water (5.5 mL) and 12 N HCl (1.8 mL) were added, and the reaction was heated at reflux for 18 h. The mixture was cooled, and barium carbonate was added until the mixture was neutral. The solvent was removed under reduced pressure, and the residue was triturated with hot ethyl acetate. The ethyl acetate was concentrated, and the residue was taken up in hot carbon tetrachloride. A white precipitate settled upon cooling, which was filtered and dried under high vacuum to yield 14: 494 mg, 76.5%; mp 68 °C; IR (KBr) 3500–3300, 2950, 1120; ^1H NMR δ 3.87 (m, 2), 3.76 (m, 4), 3.59 (m, 2), 3.46 (m, 4), 1.55 (m, 4), 1.30 (m, 8), 0.85 (m, 6); HRMS for $C_{16}H_{35}O_6$ (M + 1), calcd 323.2434, found 323.2430.

(*R*)-Methyl 3-Hydroxy-2-(pentyloxy)propionate (15a). Compound 14 (250 mg, 0.78 mmol) was dissolved in 9:1 THF/water (4 mL) at room temperature. $NaIO_4$ (183 mg, 0.85 mmol) was added, and the mixture was heated at 50 °C for 1 h. The precipitated white solid was removed by filtration, the filtrate was added to silver oxide (720 mg, 3.1 mmol), and the mixture was stirred for 18 h at room temperature. The reaction mixture was filtered through a Nylon 66 Autovial filter (0.45 gauge), and the solvent was removed with a rotary evaporator to yield the crude carboxylic acid as a dark residue that was used without further purification: ^1H NMR δ 3.97 (m, 1), 3.85 (m, 2), 3.65 (m, 1), 3.45 (m, 1), 1.59 (m, 2), 1.30 (m, 4), 0.85 (m, 3).

The crude carboxylic acid (0.78 mmol) was taken up in methanol (5 mL), 12 N HCl (0.3 mL) was added, and the mixture was heated at 50 °C for 18 h. The solvent was removed under reduced pressure. The residue was triturated with three successive portions of ether, which were combined and evaporated to yield **15a** as a light yellow oil: 135.6 mg, 46%; IR ($CHCl_3$) 3580, 2950, 1755, 1135; ^1H NMR δ 3.95 (m, 1), 3.80 (m, 2), 3.72 (s, 3), 3.65 (m, 1), 3.35 (m, 1), 1.59 (m, 2), 1.30 (m, 4), 0.85 (m, 3); ^{13}C NMR δ 171.29, 79.55, 71.31, 63.24, 51.97, 29.20, 28.00, 22.36, 13.90; HRMS for $C_9H_{19}O_4$ (M + 1), calcd 191.1283, found 191.1293.

(*R*)-Benzyl 3-Hydroxy-2-(pentyloxy)propionate (15b). The crude carboxylic acid obtained from 14 (18 mmol, see preparation for **15a**) was taken up in dry DMF (91 mL). Sodium bicarbonate (4.61 g, 55 mmol) was added, followed by benzyl bromide (9.41 g, 55 mmol). The mixture was heated with stirring at 70 °C for 15 h; it was cooled to room temperature and was poured into vigorously stirring ether. The resulting solution was washed (water, 0.1 N HCl, brine), and the solvent was removed with a rotary evaporator. The crude residue was purified by chromatography on 350 g of silica gel, eluting with 80:20 hexane/ethyl acetate. It was then repurified by chromatography on 250 g of silica gel, eluting with 9:1 hexane/ethyl acetate, to yield **15b** as a clear oil: 1.89 g, 24.4%; ^1H NMR: δ 7.33 (m, 5), 5.21 (d, 1, J = 12), 5.15 (d, 1, J = 12), 3.97 (m, 1), 3.79 (m, 2), 3.67 (m, 1), 3.39 (m, 1), 2.57 (br s, 1), 1.59 (m, 2), 1.30 (m, 4), 0.85 (br t, 3, J = 6.6); ^{13}C NMR δ 170.64, 135.34, 128.48, 128.27, 128.08, 79.66, 71.25, 66.60, 63.25, 29.19, 27.97, 22.33, 13.88; IR (neat) 3440 (br), 2958, 2935, 2870, 1745, 1125; HRMS for $C_{15}H_{23}O_4$ (M + 1), calcd 267.1596, found 267.1583.

Chloro(*N*,*N*-diisopropylamino)(phenyloxy)phosphine (16). A dry 250-mL three-neck flask was charged with dry ether (30 mL) and phenyl phosphorodichloridate (6.87 mL, 9.75 g, 0.05 mol), and the contents were chilled to −15 °C under dry nitrogen. A solution of diisopropylamine (freshly distilled from calcium hydride; 14 mL, 10.11 g, 0.1 mol) in dry ether (10 mL) was added dropwise from an addition funnel over 20 min. The cooling bath was removed, and the slurry was allowed to stir for 2 h at room temperature. The precipitated diisopropylamine hydrochloride was removed by filtration, and the cake was washed with dry ether. The ether was removed by distillation, and the residue was transfered to a short-path distillation apparatus and distilled twice at 1 mm of pressure to yield **16** (4.42 g, 17 mmol, 34%), which was used without further purification: ^1H NMR δ 7.35 (m, 5), 3.83 (m, 2), 1.45 (m, 12).

2-Acetamido-2-deoxy-3-*O*-carbamoyl-4,6-di-*O*-acetyl-α-D-glucopyranos-1-yl (2′*R*)-2′-Carbomethoxy-2′-(pentyloxy)-eth-1′-yl Phenyl Phosphate (18). Compound 16 (471 mg, 1.82 mmol) was dissolved in dry acetonitrile (5 mL) under nitrogen at room temperature. To this solution was added compound 11 (506 mg, 1.453 mmol), followed by diisopropylethylamine (freshly distilled from calcium hydride; 371 mg, 2.87 mmol). The mixture was stirred for 40 min, during which time all reagents dissolved. The solvent was removed with a rotary evaporator, and the residue was taken up in methylene chloride, washed (saturated $NaHCO_3$, 2× with saturated NaCl), dried over sodium sulfate, and filtered. The solvent was removed with a rotary evaporator, and the crude product was used immediately without further purification. The ^1H NMR of this material showed two diastereomers (at phosphorus), with the anomeric protons of the sugar appearing as double doublets at δ 5.3 in deuteriochloroform.

A sample of crude 17 (1.45 mmol) was dissolved in dry acetonitrile (5 mL) at room temperature under nitrogen. To this solution was added a solution of compound **15a** (393 mg, 2.07 mmol) in dry acetonitrile (1 mL), followed by pyridinium tosylate (557 mg, 2.22 mmol). The reaction was stirred at room temperature for 1 h, and *tert*-butyl hydroperoxide (3 M in trimethylpentane, 1.0 mL) was added. The reaction was stirred an additional 30 min and diluted with methylene chloride, washed (1 M phosphoric acid, saturated sodium bicarbonate, water, brine), dried (sodium sulfate), and filtered. The solvent was removed with a rotary evaporator, and the product was purified by flash chromatography on silica gel (10 g), eluting with ethyl acetate, to give 18 (234.8 mg, 0.35 mmol, 24% from 11) as a mixture of phosphate diastereomers: IR (KBr) 3292–3465, 1751, 1676, 1242; ^1H NMR δ 7.2 (m, 5), 6.91 and 6.40 (d, 1), 5.75 (m, 1), 5.06 (m, 4), 4.45–3.90 (m, 7), 3.71 and 3.69 (s, 3), 3.57–3.32 (m, 2), 2.00–1.78 (3 s, 9), 1.50 (m, 2), 1.20 (m, 4), 0.82 (m, 3); ^{13}C NMR δ 170.85, 170.50, 169.94, 169.73, 169.28, 169.21, 156.39, 156.28, 129.72, 125.43, 119.99, 119.84, 97.07, 96.96, 77.61, 77.52, 71.41, 71.16, 71.01, 70.67, 69.89, 68.04, 67.97, 67.73, 67.66, 67.50, 67.23, 61.28, 61.11, 52.40, 52.24, 51.93, 51.82, 51.59, 51.48, 29.07, 28.97, 27.84, 22.61, 22.25, 20.47, 20.40, 13.85.

2-Acetamido-2-deoxy-3-*O*-carbamoyl-4,6-di-*O*-acetyl-α-D-glucopyranos-1-yl (2′*R*)-2′-Carbomethoxy-2′-(pentyloxy)-eth-1′-yl Phosphate (19). Compound 18 (218 mg, 0.322 mmol) was dissolved in ethyl acetate (4.5 mL), placed in a Parr bottle with PtO_2 (48.5 mg), and shaken under 48 psi of hydrogen for 3 h. The catalyst was removed by filtration, and the solvent was removed under reduced pressure to give 19 (184 mg, 0.307 mmol, 95%) as a white solid: mp 70–75 °C; $[\alpha]^{23}$ +66.7° (c 0.384, $CHCl_3$); IR (KBr) 3461–3302, 1751, 1666, 1240; ^1H NMR δ 7.97 (br s, 1), 7.73 (d, 1, J = 9.0), 5.60 (m, 1), 5.40 (br s, 2), 5.13 (m, 2), 4.39 (m, 1), 4.15 (m, 7), 3.74 (s, 3), 3.54 (m, 1), 3.45 (m, 1), 2.04 (s, 3), 2.01 (s, 3), 1.99 (s, 3), 1.55 (m, 2), 1.25 (m, 4), 0.85 (m, 3); ^{13}C NMR δ 172.75, 170.74, 170.54, 169.43, 156.63, 95.44, 95.37, 77.94, 77.82, 71.39, 70.80, 69.53, 67.71, 66.73, 61.44, 52.37, 52.08, 29.02, 27.84, 22.34, 22.17, 20.61, 13.93; HRMS for $C_{22}H_{37}N_2O_{15}PNa$, calcd 623.1829, found 623.1824.

2-Acetamido-2-deoxy-3-*O*-carbamoyl-α-D-glucopyranos-1-yl (2′*R*)-2′-Carboxy-2′-(pentyloxy)eth-1′-yl Phosphate (5). Compound 19 (66 mg, 0.11 mmol) was dissolved in 1:1 methanol/water (3.6 mL), and the solution was chilled in an ice bath. To this was added 0.8 M NaOH solution (0.14 mL, 0.11 mmol), and the mixture was stirred for 15 min. A second 1 equiv of NaOH was added, and the mixture was stirred 30 min. A third 1 equiv of NaOH was added, and the mixture was stirred for 1 h. The reaction was quenched with one drop of acetic acid, and the solvent was removed with a rotary evaporator. ^1H NMR analysis showed removal of the methyl ester, the primary acetyl group, and a significant portion of the secondary acetyl group. The material was taken up in 5 M NH_4OH/MeOH and was left at room temperature for 15 h to complete cleavage of the secondary acetyl. The solvent was removed under reduced pressure. Amberlite

AG1-X8 anion-exchange resin (formate form, 850 mg) was packed into a small column and washed with water. Crude **5** was loaded onto the resin in water. The resin was washed with 10 column volumes of water, and **5** was then eluted with 5% aqueous formic acid. The solvent was removed under reduced pressure, and the product was dried under high vacuum to yield purified **5** (19.4 mg, 0.039 mmol, 35%) as a glassy solid: ^{1}H NMR (D_2O) δ 5.41 (m, 1), 4.87 (t, 1, J = 10), 4.48 (m, 1), 4.29 (m, 1), 4.15 (m, 3), 3.90 (m, 1), 3.65 (m, 4), 2.00 (s, 3), 1.59 (m, 2), 1.30 (m, 4), 0.85 (m, 3); HRMS (FAB) for $C_{17}H_{31}N_2O_{13}PNa$, calcd 525.1461, found 525.1450.

Allyl 2-Acetamido-2-deoxy-4,6-*O*-isopropylidene-α-D-glucopyranoside (20).[8] *N*-Acetyl-α-D-glucosamine (20 g, 90.5 mmol) was heated at reflux in dry allyl alcohol (200 mL) under nitrogen. Boron trifluoride etherate (2.5 mL) was added, and heating was continued for 4 h, during which time the starting material dissolved. Dry allyl alcohol saturated with anhydrous hydrogen chloride (10 mL) was added, and the reaction was heated at reflux for an additional 1 h. The cooled solution was filtered through glass wool into vigorously stirring ether (1100 mL) and was allowed to stand overnight. An oily yellow solid separated. The ether was decanted; the precipitate was washed with more ether and air-dried. Acetone (300 mL) and 2,2-dimethoxypropane (100 mL) were added, followed by *p*-toluenesulfonic acid monohydrate (920 mg). The mixture was stirred at room temperature for 3 h, during which time the starting material dissolved. The solvent was removed with a rotary evaporator, and the residue was taken up in ethyl acetate, washed (saturated $NaHCO_3$, water, brine), dried (magnesium sulfate), filtered, and concentrated to a glassy solid. The product was purified by column chromatography on silica gel (450 g), eluting with 2.5% methanol/chloroform, to yield **20** (11.3 g, 37.5 mmol, 41%) as an amorphous solid: mp 39–41 °C; $[\alpha]^{23}$ +72.9° (c 0.133, $CHCl_3$); IR (KBr) 3500–3278, 1642, 1570, 1122, 1043; ^{1}H NMR δ 6.14 (d, 1, J = 9), 5.84 (m, 1), 5.21 (m, 2), 4.77 (d, 1, J = 3.6), 4.08 (m, 1), 4.15 (dd, 1, J = 6, 12), 3.95 (dd, 1, J = 6, 12), 3.69 (m, 6), 1.97 (s, 3), 1.46 (s, 3), 1.37 (s, 3); ^{13}C NMR (DMSO-d_6) δ 169.49, 134.47, 116.78, 99.01, 96.89, 74.76, 67.61, 67.47, 63.61, 61.64, 54.23, 22.57, 19.17; HRMS for $C_{14}H_{24}NO_6$ (M + 1), calcd 302.1503, found 302.1490.

2-*N*-Acetyl-1-α-*O*-allyl-4,6-*O*-isopropylidenemuramic acid (21) was prepared by a modification of a known procedure.[4] Thus, sodium hydride (1.43 g of a 50% dispersion in oil, 29.9 mmol) was placed in a 50-mL round-bottom flask, washed with three portions of hexane, and suspended in dry THF (5 mL). A solution of compound **20** (2.55 g, 8.47 mmol) in dry THF (18 mL) was added dropwise over 10 min with stirring under nitrogen. To this mixture was added dropwise over 10 min a solution of (*S*)-(−)-2-chloropropionic acid (0.622 mL, 735.2 mg, 6.78 mmol) in dry THF (15 mL). The mixture was heated at reflux for 18 h, cooled, quenched with ethanol, diluted with water, and washed with ether. The aqueous layer was acidified with 1 M phosphoric acid and extracted with three portions of methylene chloride. The organic solution was extracted with dilute sodium bicarbonate solution, which was reacidifed with 1 M phosphoric acid and reextracted with ethyl acetate. The ethyl acetate solution was washed with brine, dried over magnesium sulfate, filtered, and concentrated with a rotary evaporator to yield **21** as an amorphous solid: 2.1 g, 5.6 mmol, 83%; mp 62–67 °C; $[\alpha]^{23}$ +115.4° (c 0.108, $CHCl_3$); IR (KBr) 3500–2800, 1717, 1623, 1558, 1121; ^{1}H NMR (DMSO-d_6) δ 7.82 (d, 1, J = 6), 5.86 (m, 1), 5.29 (dd, 1, J = 17, 1.35), 5.16 (dd, 1, J = 10.8, 1.5), 4.94 (d, 1, J = 3.3), 4.23 (q, 1, J = 6.9), 4.12 (dd, 1, J = 6, 12), 3.88 (dd, 1, J = 6, 12), 3.71 (m, 4), 3.48 (m, 2), 1.83 (s, 3), 1.46 (s, 3), 1.37 (s, 3), 1.26 (d, 3); ^{13}C NMR (DMSO-d_6) δ 175.60, 169.40, 134.42, 116.89, 99.00, 96.43, 75.29, 74.97, 74.81, 67.62, 63.64, 61.58, 53.39, 29.06, 22.65, 19.20, 18.67; HRMS for $C_{17}H_{28}NO_8$ (M + 1), calcd 374.1815, found 374.1792.

L-Alanyl-D-glutamine Benzyl Ester (22). BOC-D-glutamine (Sigma; 2.01 g, 8.17 mmol) was dissolved in dry DMF (12 mL) under nitrogen. $NaHCO_3$ (1.77 g, 21.1 mmol) was added, followed by benzyl bromide (4.31 g, 25.2 mmol), and the mixture was heated at 60 °C for 18 h. The reaction was cooled, diluted with water, and extracted with ethyl acetate. The organic layer was washed (2× with water, 1× with brine), dried over magnesium sulfate, and filtered, and the solvent was removed with a rotary evaporator. The resulting solid was triturated with ether, filtered, and dried in a vacuum oven at 45 °C, yielding 2.35 g of BOC-D-glutamine benzyl ester (6.99 mmol, 85.6%), which was used without further purification.

The benzyl ester (403.1 mg, 1.2 mmol) was stirred in dioxane (2 mL) and chilled in an ice bath. To this was added 1.0 mL of ice-cold dioxane saturated with dry hydrogen chloride, and the mixture was stirred for 15 min. The solvent and excess hydrogen chloride were removed under reduced pressure, and the crude amino ester was slurried in methylene chloride (8 mL). *N*-Methylmorpholine (0.5 mL, 460 mg, 4.55 mmol) was added, and the suspension was chilled in an ice bath. BOC-L-alanine (250.6 mg, 1.33 mmol) was added, followed by hydroxybenzotriazole (171 mg, 1.26 mmol) and [(dimethylamino)propyl]ethylcarbodiimide hydrochloride (240 mg, 1.25 mmol). The reaction was allowed to warm to room temperature and was stirred for 19 h. The mixture was diluted with methylene chloride, washed (1 M H_3PO_4, saturated $NaHCO_3$, brine), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica (20 g), eluting with 2% methanol/chloroform, to yield the protected dipeptide: 316.7 mg, 0.78 mmol, 65%; ^{1}H NMR δ 7.31 (m, 5), 7.04 (m, 1), 6.22 (br s, 1), 5.67 (br s, 1), 5.15 (d, 1, J = 12), 5.14 (br s, 1), 5.09 (d, 1, J = 12), 4.58 (m, 1), 4.14 (m, 1), 2.22 (m, 2), 1.95 (m, 2), 1.40 (s, 9), 1.32 (d, 3, J = 6.9); ^{13}C NMR δ 174.45, 173.03, 171.59, 155.97, 128.61, 128.48, 128.30, 80.77, 67.30, 51.62, 50.57, 31.40, 28.27, 27.85, 18.22; IR (KBr) 3380, 3320, 1725, 1680, 1650. Anal. Calcd for $C_{20}H_{29}N_3O_6$: C, 58.95; H, 7.01; N, 10.31. Found: C, 58.72; H, 7.17; N, 10.09.

The dipeptide was taken up in 3 mL of dioxane, and the mixture was chilled to 10 °C. Ice-cold dioxane saturated with anhydrous hydrogen chloride (5 mL) was added. The reaction was allowed to warm to room temperature and was stirred for 1 h. The solvent and excess hydrogen chloride were evaporated under reduced pressure to yield **22**, which was used without further purification: ^{1}H NMR (MeOH-d_4) δ 7.38 (m, 5), 5.21 (d, 1, J = 12.6), 5.16 (d, 1, J = 12.6), 4.51 (dd, 1, J = 9.3, 4.2), 4.05 (q, 1, J = 6.9), 2.43 (t, 2, J = 8.1), 2.24 (m, 1), 2.07 (m, 1), 1.55 (d, 3, J = 6.9); ^{13}C NMR (MeOH-d_4) δ 178.43, 172.37, 171.29, 136.98, 129.57, 129.33, 68.22, 53.54, 50.24, 32.02, 28.00, 17.79.

2-*N*-Acetyl-1-α-*O*-allyl-4,6-*O*-isopropylidenemuramyl-L-alanyl-D-glutamine Benzyl Ester (23). Compounds **21** (1.86 g, 5.00 mmol) and **22** (2.18 g, 5.70 mmol) were suspended in dry methylene chloride (70 mL) and were chilled in an ice bath. Hydroxybenzotriazole (865 mg, 6.26 mmol) and *N*-methylmorpholine (2.56 mL, 2.36 g, 23.3 mmol) were added, followed by [(diisopropylamino)ethyl]carbodiimide hydrochloride (1.21 g, 6.3 mmol). The reaction was allowed to warm to room temperature and was stirred for 18 h. The mixture was diluted with methylene chloride, washed (1 M phosphoric acid, water, saturated $NaHCO_3$, water, brine), dried over magnesium sulfate, filtered, and concentrated with a rotary evaporator. The residue was purified by column chromatography on silica gel (150 g), eluting with 3% methanol/chloroform, to yield **23** as an amorphous solid: 2.2 g, 3.32 mmol, 66%; mp 46–50 °C; $[\alpha]^{23}$ +52.5° (c 0.144, $CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 8.43 (d, 1, J = 7), 8.07 (d, 1, J = 7), 7.46 (d, 1, J = 7), 7.33 (m, 5), 7.21 (br s, 1), 6.75 (br s, 1), 5.84 (m, 1), 5.30 (dd, 1, J = 15.2), 5.13 (dd, 1, J = 8, 2), 5.09 (s, 2), 4.78 (d, 1, J = 2), 4.30 (m, 2), 4.10 (m, 2), 3.90 (m, 2), 3.70 (m, 3), 3.52 (m, 3), 2.10 (m, 2), 1.95 (m, 1), 1.90 (m, 1), 1.88 (s, 3), 1.45 (s, 3), 1.30 (s, 3), 1.22 (d, 6); HRMS (FAB) for $C_{32}H_{47}N_4O_{11}$ (M + 1), calcd 663.3241, found 663.3229.

(2*R*)-Benzyl 2-[*N*-(2′-*N*-Acetyl-1′-α-*O*-allyl-4′,6′-*O*-acetylmuramyl-L-alanyl)amino]-4-cyanobutanoate (26). Compound **23** (415.2 mg, 0.627 mmol) was dissolved in a mixture of ethanol (3.5 mL), water (0.9 mL), and acetic acid (0.45 mL), and the resultant mixture was heated at reflux for 6 h. The solvent was evaporated, azeotroping with toluene. The residue was taken up in dry pyridine (1.2 mL) and acetic anhydride (0.7 mL) and was heated at 80 °C for 18 h. The mixture was cooled, diluted with ethyl acetate, washed (1 M phosphoric acid, saturated $NaHCO_3$, brine), dried over magnesium sulfate, filtered, and concentrated to an orange oily solid. This was purified by column chromatography on silica gel (20 g), eluting with 2% methanol/chloroform, to yield **26** (244 mg, 0.345 mmol, 55%) as an amorphous solid: mp 53–55 °C; $[\alpha]^{23}$ +40.8° (c 0.121, $CHCl_3$); IR (KBr) 3386–3294, 2244, 1745, 1658, 1373; ^{1}H NMR δ 7.34 (m, 5), 7.00 (d, 1, J = 7.5), 6.93 (d, 1, J = 6), 5.88 (m, 1), 5.80 (d, 1,

J = 9.9), 5.25 (m, 2), 5.16 (s, 2), 5.03 (t, 1, J = 10.2), 4.80 (d, 1, J = 3.6), 4.62 (m, 1), 4.40 (dd, 1, J = 10, 3), 4.13 (m, 7), 3.63 (t, 1, J = 9.3), 2.33 (m, 3), 2.08 (s, 3), 2.06 (s, 3), 2.05 (m, 1), 1.94 (s, 3), 1.44 (d, J = 7.2, 3), 1.32 (d, 3, J = 6.6); HRMS for $C_{33}H_{45}N_4O_{12}$ (M + 1), calcd 689.3046, found 689.3086.

(2*R*)-Benzyl 2-[*N*-(2′-*N*-Acetyl-4′,6′-di-*O*-acetylmuramyl-L-alanyl)amino]-4-cyanobutanoate (27). (1,5-Cyclooctadiene)bis(methyldiphenylphosphine)iridium hexafluorophosphate (200 mg) was shaken in dry THF (50 mL) in a Parr bottle under 20 psi of hydrogen for 15 min. The solution was evacuated and purged five times with nitrogen and was added to a flask containing compound **26** (1.23 g, 1.74 mmol). The reaction was heated at reflux for 6 h. The solvent was removed under reduced pressure, and the residue was taken up in methylene chloride, washed (saturated $NaHCO_3$, brine), dried over sodium sulfate, filtered, and concentrated with a rotary evaporator. The residue was taken up in THF (40 mL) and chilled in an ice bath. A solution of $NaHCO_3$ (445.5 mg, 5.3 mmol) in water (15 mL) was added, followed by a solution of iodine (1.06 g, 4.2 mmol) in THF (10 mL). The ice bath was removed, and the solution was stirred for 10 min. Water and ethyl acetate were added, the mixture was chilled in ice and stirred vigorously, and solid sodium bisulfite was added until the iodine color disappeared. The mixture was transferred to a separatory funnel, the aqueous layer was separated, and the organic layer was washed (dilute $NaHSO_3$, saturated $NaHCO_3$, brine), dried over magnesium sulfate, filtered, and concentrated with a rotary evaporator. The residue was purified by column chromatography on silica gel (40 g), eluting with 5% methanol/chloroform, to yield **27** (665 mg, 1.0 mmol, 59%) as an amorphous solid: mp 80–83 °C; ^{1}H NMR analysis of the product indicated that the ratio of anomers was >9:1 (α:β); $[\alpha]^{23}$ +40° (c 0.413, MeOH); IR (KBr) 3382–3342, 2250, 1748, 1663, 1231; ^{1}H NMR (DMSO-d_6, α anomer) δ 8.52 (d, 1, J = 7.8), 8.09 (d, 1, J = 8.1), 7.53 (d, 1, J = 7.2), 7.34 (m, 5), 6.99 (d, 1, J = 0.9), 5.12 (s, 2), 5.01 (t, 1, J = 3.6), 4.80 (t, 1, J = 9.3), 4.36 (m, 1), 4.25 (t, 1, J = 7.2), 4.18 (q, 1, J = 6.6), 4.05 (m, 3), 3.85 (m, 1), 3.66 (t, 1, J = 9.9), 2.07 (s, 3), 2.05 (m, 1), 2.00 (s, 3), 1.76 (s, 3), 1.22 (d, 3, J = 6.6), 1.14 (d, 3, J = 6.6); ^{13}C NMR (DMSO-d_6) 171.78, 170.68, 170.19, 169.45, 169.40, 135.71, 128.45, 127.88, 119.77, 90.64, 76.80, 76.29, 70.28, 66.75, 66.35, 62.58, 53.64, 50.86, 48.13, 26.64, 22.62, 20.70, 20.63, 18.61, 18.44, 13.31; HRMS (FAB) for $C_{30}H_{41}N_4O_{12}$ (M + 1), calcd 649.2731, found 649.2718.

(Benzyloxy)(*N*,*N*-diisopropylamino)chlorophosphine (28). Phosphorus trichloride (61.2 mL, 96.4 g, 0.7 mol, freshly distilled) was dissolved in dry acetonitrile (32 mL) in a dry 500-mL two-neck flask under dry nitrogen. A solution of dry benzyl alcohol (10.4 mL, 10.8 g, 0.1 mol) in dry acetonitrile (40 mL) was added dropwise over 10 min. The reaction was stirred for 20 min at room temperature, and the solvent and excess phosphorus trichloride were removed by vacuum distillation into a dry ice trap. The residue was heated at 60 °C under vacuum for 1 h. ^{1}H NMR analysis indicated that the monobenzylated product constituted about 80% of the mixture [δ 7.35 (m, 5 H), 5.22 (d, 2, J = 9)]. The crude material was dissolved in dry ether (30 mL) and the resultant solution chilled in an ice bath. A solution of dry, freshly distilled diisopropylamine (23 mL, 16.6 g, 0.164 mol) in ether (20 mL) was added dropwise with vigorous stirring. The mixture was allowed to warm to room temperature and was stirred for 14 h. The precipitated diisopropylamine hydrochloride was removed by filtration, and the ether was distilled into a dry ice trap under reduced pressure. The residue was heated at 30 °C under vacuum for 2 h and was filtered through glass wool. ^{1}H NMR showed the material to be 75–80% **28**: δ 7.35 (m, 5), 4.91 (m, 2), 3.84 (m, 2), 1.27 (m, 12). The product was used without further purification.

(2*R*,2″*R*)-Benzyl 2-[*N*-[2′-*N*-Acetyl-1′-α-*O*-[[2″-carbobenzoxy-2″-(pentyloxy)ethoxy](benzyloxy)phosphoryl]-4′,6′-di-*O*-acetylmuramyl-L-alanyl]amino]-4-cyanobutanoate (30). Compound **27** (451 mg, 0.68 mmol) was added to a solution of compound **28** (300 mg, est. 1.1 mmol) in dry acetonitrile (1 mL). Dry, freshly distilled diisopropylethylamine (0.3 mL, 223 mg, 1.72 mmol) was added, and the reaction was stirred for 1 h at room temperature, during which time the starting material dissolved. Most of the acetonitrile was removed under reduced pressure, and the residue was taken up in methylene chloride, washed (2× with saturated $NaHCO_3$, 1× with brine), dried over sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (20 g), eluting with ethyl acetate/hexane (75:25) to yield **29** (161 mg, 0.179 mmol, 26.2%) as a mixture of diastereomers.

Compound **29** (89.1 mg, 0.099 mmol) and compound **15b** (50 mg, 0.21 mmol) were dissolved in dry acetonitrile (0.5 mL) under nitrogen. 1*H*-Tetrazole (10.1 mg) was added, and the mixture was stirred at room temperature for 1.25 h. *tert*-Butyl hydroperoxide (3 M in trimethylpentane; 0.08 mL, 0.24 mmol) was added, and stirring was continued for 2 h. The reaction was diluted with methylene chloride, washed (1 M phosphoric acid, dilute sodium bicarbonate, brine), dried over sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (5 g), eluting with 1.5% methanol/chloroform, to yield **30** (43.9 mg, 0.042 mmol, 42%) as a mixture of diastereomers (at phosphorus). The ^{1}H NMR spectrum of this mixture displayed resonances for the anomeric protons of the two diastereomers at δ 5.63 and 5.60. HRMS (FAB) for $C_{52}H_{67}N_4O_{18}PNa$, calcd 1089.4077, found 1089.4007.

(2*R*,2″*R*)-2-[*N*-[2′-*N*-Acetyl-1′-α-*O*-[[2″-carboxy-2″-(pentyloxy)ethoxy]hydroxyphosphoryl]muramyl-L-alanyl]-amino]-4-cyanobutanoate (31). Compound **30** (43.9 mg, 0.042 mmol) was dissolved in ethyl acetate (1.2 mL), and the resultant mixture was placed in a Parr bottle with 10% Pd/C (10.6 mg) and shaken under 40 psi of hydrogen for 2.5 h at room temperature. The catalyst was removed by filtration and washed with ethyl acetate and methanol, and the solvent was removed with a rotary evaporator to yield the triply debenzylated species in quantitative yield. ^{1}H NMR analysis showed a multiplet at δ 5.78 for the anomeric proton, and no benzyl groups. The material was dissolved in saturated methanolic ammonia (1 mL), and the solution was allowed to stand for 18 h at room temperature. The solvent was evaporated, and the product was purified by ion-exchange chromatography (anion-exchange resin AG1-X8, 100–200 mesh, formate form), eluting with 25% formic acid in methanol, to yield **31** (15.4 mg, 0.021 mmol, 50%) as a glassy solid: ^{1}H NMR (D_2O) δ 5.36 (m, 1), 4.49 (m, 1), 4.28 (m, 3), 4.10 (m, 3), 3.82 (m, 3), 3.60 (m, 4), 2.57 (m, 2), 2.27 (m, 1), 2.04 (m, 1), 1.97 (s, 3), 1.59 (m, 2), 1.41 (d, 3, J = 6), 1.36 (d, 3, J = 6), 1.26 (m, 4), 0.85 (m, 3); ^{13}C NMR (D_2O) δ 176.50, 175.71, 174.93, 174.83, 121.15, 94.97, 94.92, 80.50, 78.68, 78.59, 73.55, 72.00, 68.95, 66.40, 60.91, 54.16, 54.10, 52.51, 50.33, 29.08, 28.13, 27.18, 22.77, 22.56, 19.52, 19.42, 17.39, 14.31; HRMS (FAB) for $C_{27}H_{45}N_4O_{16}PNa$, calcd 735.2459, found 735.2516.

Supplementary Material Available: NMR spectra for compounds **5**, **9**, **13**, **14**, **15a**, **15b**, **18–23**, **26**, **27**, **30**, and **31** (27 pages). Ordering information is given on any current masthead page.