(±)-Methyl 3-*O*-Acetyl-4-*O*-benzoyl-2,6-dideoxy-β-*lyxo*-hexopyranoside (25b). The alcohol **25a** (22 mg, 0.083 mmol) was acetylated with acetic anhydride (0.1 mL), triethylamine (0.2 mL), and 4-(dimethylamino)pyridine (catalytic) in dichloromethane (0.25 mL) for 12 h. Concentration of the reaction and chromatography on silica gel (ether/hexane) gave **25b** (23 mg, 90%): ^{1}H NMR (270 MHz) δ 1.29 (d, J = 6.7 Hz, 3 H), 1.97 (s, 3 H), 2.0–2.05 (m, 2 H), 3.58 (s, 3 H), 3.80 (dq, J = 6.7, 1 Hz, 1 H), 4.51 (m, 1 H), 5.09 (m, 1 H, irradiation at 5.37 gives dd, J = 11.2, 6 Hz), 5.37 (br d, J = 3.0 Hz, 1 H), 7.30–7.63 (m, 3 H), 8.13–8.16 (m, 2 H); IR ($CHCl_3$) 1714 cm^{-1}. MS, m/e 308 (0.2, M$^+$), 204 (13.2), 105 (100).

Acknowledgment. This work was supported by P.H.S. Grant CA 49002. An F.W. and E. H. Heyl Fellowship 49902. C.M. is also acknowledged. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale University, which was supported by N.S.F. Chemistry Division Grant CHE 7916210.

Registry No. 3, 54125-02-9; **4**, 91861-05-1; **7**, 91861-06-2; **8**, 90084-24-5; **9**, 91861-07-3; **10**, 91861-08-4; **11**, 91861-09-5; **13**, 91861-10-8; **14**, 91861-11-9; **15**, 91861-12-0; **16**, 91926-30-6; **17**, 91926-31-7; **18**, 24332-97-6; **19**, 24333-02-6; **20**, 91861-13-1; (*E*)-**21**, 91861-14-2; (*Z*)-**21**, 91861-15-3; (*E*)-**22**, 91861-16-4; (*Z*)-**22**, 91861-17-5; **23**, 91926-32-8; (L)-**23**, 57918-58-8; **24**, 91926-33-9; **25a**, 91861-18-6; **25b**, 91861-19-7; zinc chloride, 7646-85-7; acetaldehyde, 75-07-0; L-fucose, 2438-80-4; α-L-daunosamide hydrochloride, 32385-06-1; *N*-acetyl-α-L-daunosamide, 32385-07-2; methyl-*N*-acetyl-β-L-daunosamide, 57918-56-6; BF_3·OEt_2, 109-63-7; Eu(hfc)$_3$, 34788-82-4.

A Totally Synthetic Route to Lincosamine: Some Observations on the Diastereofacial Selectivity of Electrophilic Reactions on the Double Bonds of Various 5-(1-Alkenyl)arabinopyranosides

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Contribution from the Department of Chemistry, Yale University, New Haven, Connecticut 06511, and the Research Division, Merck Sharp and Dohme, Rahway, New Jersey 07065. *Received February 27, 1984. Revised Manuscript Received April 18, 1984*

Abstract: Under the influence of boron trifluoride etherate, crotonaldehyde reacts with 1-methoxy-3-((trimethylsilyl)-oxy)-4-(benzoyloxy)-1,3-butadiene to afford (*E*)-*cis*-2-(1-propenyl)-3-(benzoyloxy)-2,3-dihydro-4-pyrone. The latter is converted to (±)-β-methylinocosaminide with high stereochemical selectivity.

Background

There has been relatively little effort addressed to the total synthesis of saccharides.[1,2] With few exceptions, such targets have been attacked by partial synthesis, using the common sugars as matrices. The pioneering Sharpless discovery of asymmetric epoxidation[3] has awakened interest in saccharide total synthesis, since major new opportunities for the introduction and manipulation of oxygen functionality are now available. The asymmetric synthesis of the eight aldohexoses by the MIT school, via catalytically mediated enantiospecific and diastereospecific oxidation of acyclic intermediates, must be seen as a landmark accomplishment.[4]

The recently demonstrated Lewis acid catalyzed cyclocondensation of activated dienes with aldehydes provides a direct route to functionalized pyran rings.[5] Extensive functionality may be incorporated via inclusion in the diene and in the "R" group of the aldehyde.[6] Moreover, the unsaturated linkages in the pyranoids produced from the cyclocondensation reaction offer convenient access points for the introduction of hetero (or branched) functionality.[7] A potential relationship with saccharide synthesis presented itself.

The total synthesis of unusual hexoses including talose,[8a] 4-deoxymannose,[8a] chalcose,[8b] fucose,[8c] and daunosamine[8c] by cycloaddition technology was first demonstrated. Several of these targets had previously been prepared by partial synthesis, though often only after rather laborious exercises in functional group modification.

With the feasibility of this approach for the total synthesis of some of the rarer hexoses well demonstrated, its applicability to the construction of the higher monosaccharide was next investigated. The varied substitution and chirality patterns of the higher monosaccharides and their presence as substructures in a variety of physiologically active compounds[9] should serve to heighten interest in their total synthesis. In spite of such apparent inducements, all efforts at the preparation of the higher monosaccharides had hitherto involved partial synthesis via chain elongation and functional group modifications of the common

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§ Merk Sharp and Dohme.

(1) Jones, J. K. N.; Szarek, W. A. In "The Total Synthesis of Natural Products"; ApSimon, J., Ed.; Wiley-Interscience: New York, 1973; Vol. 1, pp 1–80.

(2) For a recent compilation, which describes previous approaches to carbohydrate synthesis using carbonyl functions as heterodienophiles, see: Zamosjki, A.; Banaszek, A.; Gyrienkiewicz, G. *Adv. Carbohydr. Chem. Biochem.* **1982**, *40*. 1.

(3) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.

(4) Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed, L. A., III; Sharpless, K. B.; Walker, F. J. *Science (Washington, D.C.)* **1983**, *220*, 949.

(5) Danishefsky, S.; Larson, E.; Askin, D.; Kato, N. *J. Am. Chem. Soc.*, first paper of this series of four.

(6) Danishefsky, S.; Harvey, D. F.; Quallich, G.; Uang, B.-J. *J. Org. Chem.* **1984**, *49*, 392.

(7) For a review of many transformations of unsaturated sugars, see: Ferrier, R. J. in "The Carbohydrates"; Pigman, W., Horton, D., Eds.; Academic Press: New York, **1980**; Vol. 1B, Chapter 19, pp 843–879.

(8) (a) Danishefsky, S.; Kerwin, J. F., Jr.; Kobayashi, S. *J. Am. Chem. Soc.* **1982**, *104*, 358. (b) Danishefsky, S.; Kerwin, J. F., Jr. *J. Org. Chem.* **1982**, *47*, 1597. (c) Danishefsky, S.; Maring, C. *J. Am. Chem. Soc.*, preceding paper in this issue.

(9) Representative examples. (a) Heptoses, pupurosamine: Umezawa, S. *Adv. Carbohydr. Chem. Biochem.* **1974**, *30*, 111. (b) Octoses, 3-deoxy-D-manno-2-octulosonic acid (KDO): Unger, F. M. *Ibid.* **1981**, *38*, 323. (c) Nonoses, acylneuraminic acids: Schauer, R. *Ibid.* **1982**, *40*, 132. (d) Decoses, sinefungin: Suhadolnik, R. J. "Nucleosides as Biological Probes"; Wiley: New York, 1979; p 19. (e) Undecoses, hikizimycin: Vuilhorgne, M.; Ennifar, S.; Das, B. P.; Paschal, J. W.; Nagarajan R.; Hagman, E. W.; Wenkert, E. *J. Org. Chem.* **1977**, *42*, 3289. Tunicamycin: Takatsuki, A.; Kawamura, K.; Okina, M.; Kodama, J.; Ito, T.; Tamma, G. *Agric. Biol. Chem.* **1977**, *41*, 2307.

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aldohexoses.[10] The multistep nature of these exercises and the absence of stereochemical control during these chain and functionality extensions suggested that total synthesis might well eventually prove to be a practical alternative to partial synthesis in this series. Furthermore, total synthesis could also be useful in gaining access to deep-seated molecular modifications with a view toward modifying biological activity. Accordingly, a program in the total synthesis of the higher monosaccharides was undertaken.

The first target structure in this regard was the amino octose lincosamine (**1**).[11] As its methyl thioglycoside (methyl thiolincosaminide, MTL, **2**), lincosamine is the saccharide portion of the clinically important antibiotic lincomycin (**3**).[12] The partial synthesis of **1** from galactose had been the object of extensive experimentation.[13] While yielding much in the way of interesting chemistry, none of these forays succeeded in installing the C_6 amino function and the C_7 hydroxyl group with even a modicum of control.

Below are detailed a series of experiments which have provided a fully synthetic route to (±)-lincosamine. All stereochemistry except that at the anomeric center is introduced with very high selectivity. The end product of the total synthesis, β-methyl lincosamide (**4**), was characterized as its pentaacetyl derivative **5**.

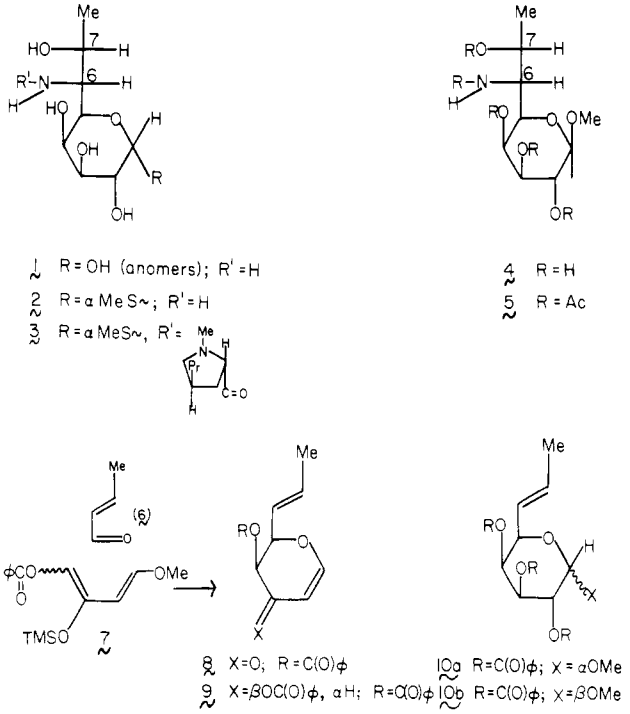
In the course of the synthesis of daunosamine, the chemistry of benzoyl diene **7** had been developed by Maring.[8c] Of particular interest for the application projected herein was the finding that a stereoisomeric mixture of dienes **7** reacted with acetaldehyde with a variety of catalysts to afford, primarily, *cis*-2-methyl-3-(benzoyloxy)-2,3-dihydropyran-4-one. Another important background finding was provided by Kerwin in his investigations of the Lewis acid catalyzed cyclocondensation of activated dienes with α,β-unsaturated aldehydes. Reaction of a variety of enals with the parent (*E*)-1-methoxy-3-((trimethylsilyl)oxy)-1,3-butadiene, mediated by $BF_3{\cdot}OEt_2$, occurred exclusively at the formyl group rather than at the olefin.[14] While the generality of this result had not been probed with other enals and other dienes, the contrast with the strictly thermal process, which occurs exclusively at the double bond,[15] was remarkable.

Results

By use of the precedents from the previous studies of Maring[8c] and Kerwin,[14] the diene mixture **7** was combined with crotonaldehyde (**6**) under the influence of $BF_3{\cdot}OEt_2$. The material obtained after reaction for 2 h at −78 °C in methylene chloride was subjected to the action of trifluoroacetic acid. There was thus obtained a 67% yield of the 2-((*E*)-1-propenyl)pyrone **8**. The cis relationship of the hydrogens at C_2 and C_3 is revealed through NMR analysis (see Experimental Section). Examination of the proton and carbon spectra of the crude reaction mixtures indicated the possible formation of ca. 10% of a C_2–C_3 trans stereoisomer, though this compound was not isolated. Reduction of the ketone in a 1,2 fashion was achieved using the conditions of Luche.[16] Benzoylation afforded the galactal derivative **9**, in 72% yield.

It should be noted that the per-acetyl equivalent of the D-antipode of **9** had been prepared as one of the components of an inseparable *E*,*Z* mixture of propenyl isomers by partial synthesis from D-galactose in eight steps.[17] A mixture of propenyl compounds was obtained by photolysis of the pure *Z* isomer, which was itself available by a Wittig methylenation of a 6-aldehydo function. Of course, through total synthesis we are operating in the racemic series. However, the simplicity of the chemistry, the quality of the stereochemical control, and the purity of the products arising from the total synthesis approach are not without advantage.

Treatment of **9** with *m*-chloroperoxybenzoic acid in anhydrous methanol followed by benzoylation afforded the methyl glycosides **10a** and **10b** in 27% and 64% isolated yields.[18] Apparently,



epoxidation had occurred strictly from the α-face. For purposes of this synthesis, only the β-anomer was carried forward though, in principle, the α compound could presumably be recycled. The challenge associated with installation of the amino and hydroxy groups at C_6 and C_7 in the proper configurational sense was now at hand.

It will be recalled that the Szarek partial synthesis of lincosamine utilized a *Z* propenyl group.[13c] Though stereoselectivity in the overall hydroxyamination process had not been achieved from this isomer, one of the steps was particularly striking. Thus, Szarek had reported that reaction of compound **11** with $KMnO_4$ afforded a single diol **12**. The configuration at C_7 in compound **12** must have corresponded to that required for lincosamine since the transformation of **12** to lincosamine was accomplished in a fashion in which the stereointegrity of the centers was not perturbed. However, similar control was not attained during the introduction of the amino function at C_6.

(10) For example: (a) Purpurosamine B: Honda, Y.; Suami, T. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2825. (b) KDO: Williams, D. T.; Perry, M. P. *Can. J. Biochem.* **1969**, *47*, 1969. (c) *N*-Acetylneuraminic acid: Benzing-Nguyen, L.; Perry, M. B. *J. Org. Chem.* **1978**, *43*, 551. (d) Sinefungin: Lyga, J. W.; Secrist, J. A., III. *Ibid.* **1983**, *48*, 1982. (e) Hikosamine: Secrist, J. A., III; Barnes, K. D. *J. Org. Chem.* **1980**, *45*, 4528. (f) Tunicamycin: Suami, T.; Sasai, H.; Matsuno, K. *Chem. Lett.* **1983**, 819.

(11) Larson, E. R.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 6715.

(12) Lincomycin is a copyrighted trademark of the Upjoin Co., Kalamazoo, MI. For an excellent review of the chemistry of lincomycin, see: Magerlein, B. J. In "Structure Activity Relationships among the Semisynthetic Antibiotics"; Pearlman, D., Ed.; Academic Press: New York, **1977**; pp 601–650.

(13) (a) Magerlein, B. J. *Tetrahedron Lett.* **1970**, 33. (b) Saeki, H.; Ohki, E. *Chem. Pharm. Bull.* **1970**, *18*, 789. (c) Howarth, G. B.; Szarek, W. A.; Jones, J. K. N. *J. Chem. Soc. C* **1970**, 2218. (d) Hems, R.; Horton, D.; Nakadate, M. *Carbohydr. Res.* **1970**, *25*, 205. (e) Atsumi, T.; Fukumaru, T.; Ogawa, T.; Matsui, M. *Agric. Biol. Chem.* **1973**, *37*, 2621. (f) David, S. M.; Fischer, J. C. *Carbohydr. Res.* **1974**, *38*, 147. (g) Woolard, G. R.; Rathbone, E. B.; Szarek, W. A.; Jones, J. K. N. *J. Chem. Soc., Perkin Trans. 1* **1976**, 950. (h) Gateu-Olesker, A.; Sepulchre, A. M.; Vass, G.; Gero, S. D. *Tetrahedron Lett.* **1977**, *33*, 393. (i) Hoppe, I.; Schollkopf, U. *Liebigs Ann. Chem.* **1980**, 1474.

(14) Danishefsky, S.; Kerwin, J. F. *J. Org. Chem.* **1982**, *47*, 3183.

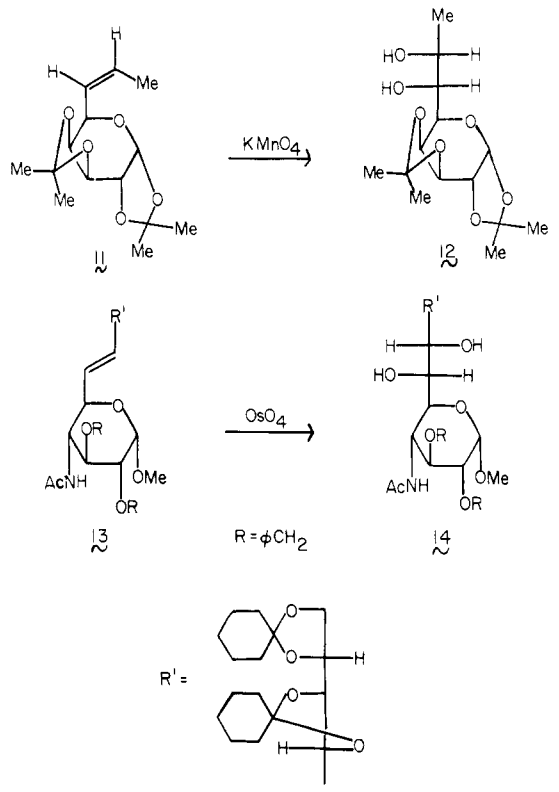
(15) Danishefsky, S.; Yan, C. F.; Singh, R. K.; Gammill, R. B.; McCurry, P. M., Jr.; Fritsch, N.; Clardy, J. *J. Am. Chem. Soc.* **1979**, *101*, 7001. Lewis acid complexation of α,β-ethylenic carbonyls has been suggested to reverse the relative magnitude of the C_2 and C_4 LUMO orbital coefficients, relative to the uncomplexed system (wherein coefficient $C_4 > C_2$) thereby enhancing reactivity at C_2 (Loupy, A.; Seyden, J. *Tetrahedron Lett.* **1978**, 2571). Such an effect may be responsible for the surprising reversal of regioreactivity observed for α,β-unsaturated aldehyde upon reaction with siloxy dienes under Lewis acid catalysis.

(16) Luche, J.-L.; Gemal, A. L. *J. Am. Chem. Soc.* **1979**, *101*, 5848.

(17) Lesage, S.; Perlin, A. S. *Can. J. Chem.* **1978**, *56*, 2889.

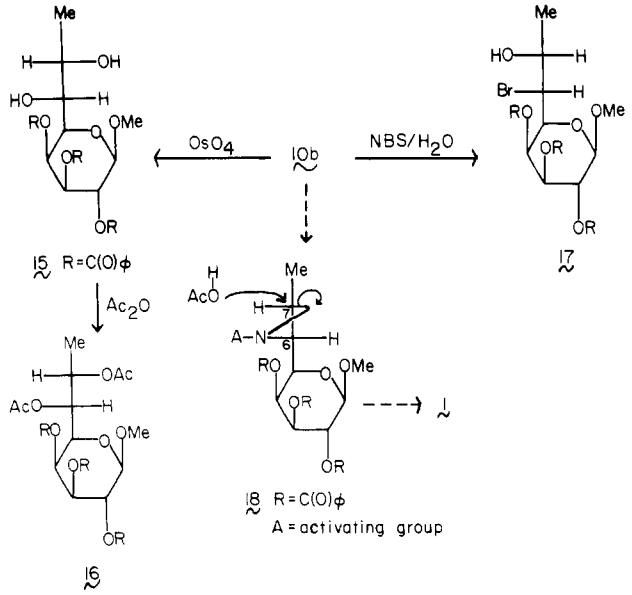
(18) Sweet, F.; Brown, R. K. *Can. J. Chem.* **1966**, *44*, 1571. For a more recent description of this method, see: Frimer, A. A. *Synthesis* **1977**, 578.

A comparable finding was registered by Secrist[10e] who reported that the reaction of compound **13** with osmium tetraoxide afforded compound **14**. It is seen that the sense of approach of $KMnO_4$



on Szerek's compound **11** and that of OsO_4 on Secrist's compound **13** were the same (vide infra).

The diastereofacial characteristics of electrophilic reactions of compound **10b** were then examined. Indeed, reaction of this anomer with catalytic osmium tetroxide in the presence of *N*-methylmorpholine *N*-oxide[19] provided an 89% yield of a single diol (**15**). Similarly, reaction of **10b** with *N*-bromosuccinimide in the presence of wet acetic acid afforded a 92% yield of a single bromohydrin (**17**). Conjectures concerning the high diastereo-



facial selectivity in these electrophilic addition reactions will be considered after the synthetic results are described. For now we only consider the structure of these addition products.

The structure advanced for **15** follows from the single-crystal X-ray diffraction analysis of its derived diacetate **16**, mp 187–188 °C. No correspondingly rigorous data could be obtained to define the configuration at C_6 and C_7 in the formal HOBr addition product **17**. The case for its assignment rested on an analogy drawn with **15**. It was assumed that the cyclic bromonium equivalent generated from the reaction of NBS–AcOH–H_2O on **10a** is produced in the same diastereofacial sense as is the osmate ester equivalent leading to **15**. *The eventual transformation of compound 17 to target system 4 by the particular sequence of steps that was employed (vide infra) serves to corroborate the correctness of this surmise.*

At the planning level it seemed that bromohydrin **17** would more readily lend itself to conversion to lincosamine than would diol **15**. For substrate **15**, inversion of the hydroxyl stereochemistry at C_7 must be coordinated with an overall retention in replacing the C_6 hydroxyl by an amino function. To reach the same goal via bromohydrin **17** would require overall hydroxyl retention at C_7 and bromide amino interchange at C_6. This latter prospectus seemed more attainable and was pursued experimentally.

Before describing how this goal was accomplished, we note that a still simpler solution was considered and examined. Given the diastereofacial characteristics of electrophilic reactions on the trans propenyl group of **10a**, it might be anticipated that direct aziridination by a nitrenium equivalent would afforded **18**. Considering the much greater accessibility of C_7 relative to C_6 for nucleophilic attack (note the regiospecific formation of bromohydrin **17**), it would be anticipated that an activated aziridine variant, **18**, would suffer solvolytic opening at C_7, thereby providing a concise solution to the problem. This hypothetical solution failed because no direct aziridination could be performed on the double bond of **10a**.[20] Accordingly, attentions turned to the conversion of the readily available bromohydrin to a functional version of **18**.

Reaction of **17** with DBN afforded epoxide **19** in 96% yield. Reaction of epoxide **19** with tetra-*n*-butylammonium azide in the presence of trimethylsilyl azide[21] afforded a high yield of azidohydrin silyl ether **20** along with a 14% yield of a compound provisionally formulated as **21** (see Experimental Section for the full proton NMR spectral data for this byproduct). Treatment of the crude **20** with trifluoroacetic acid in methanol gave the azidohydrin **22** in 78% yield from **19**. Mesylate **23** was obtained from **22** in the usual way. Reaction of the azidomesylate **23** with trimethyl phosphite followed by sodium hydride afforded the phosphorylaziridine **24** in 78% yield from **22**.[22]

Before undertaking the seemingly difficult proposition of converting the *N*-phosphoryl group to a variation of an *N*-acyl function,[23] in order to facilitate solvolysis, the possibility that the dimethylphosphoryl group might provide sufficient activation was evaluated.[24] In the event, when **24** was heated in acetic acid, there was obtained a hydroxy phosphoramideate shown by high-field NMR analysis to be compound **25** (see Experimental Section). The formation of this unexpected and unwanted product could be ascribed to neighboring group participation by the carbonyl

(19) VanRheenan, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1967**, 1973.

(20) An ideal solution would entail direct nitrene insertion into the olefinic linkage of **10b**, in the same sense as observed for the osymlative oxidation. Unfortunately, existing methods for effecting this transformation suffer from the requirement of a large excess of the olefinic participant to achieve satisfactory trapping of the reactive nitrogen species, an unsatisfactory situation when advanced synthetic intermediates are involved. Nonetheless, a number of attempts at nitrene addition to **10b** (Bottaro, J. C. *J. Chem. Soc., Commun.* **1980**, 560. Lwowski, W.; Maricich, T. J. *J. Am. Chem. Soc.* **1965**, *87*, 3630. See also ref 25, pp 68–79) were tried with no success.

(21) Omission of trimethylsilyl azide resulted in extensive acyl transfer under these conditions. Lewis acid catalyzed azide opening ($Me_3SiN_3/ZnCl_2$; Birkofer, L.; Kaiser, W. *Liebigs Ann. Chem.* **1975**, 266) cleanly afforded the undesired orthoacyl azide **21**.

(22) Cf.: Nakatsubo, F.; Fukuyama, T.; Cocuzza, A. J.; Kishi, Y. *J. Am. Chem. Soc.* **1977**, *99*, 8115.

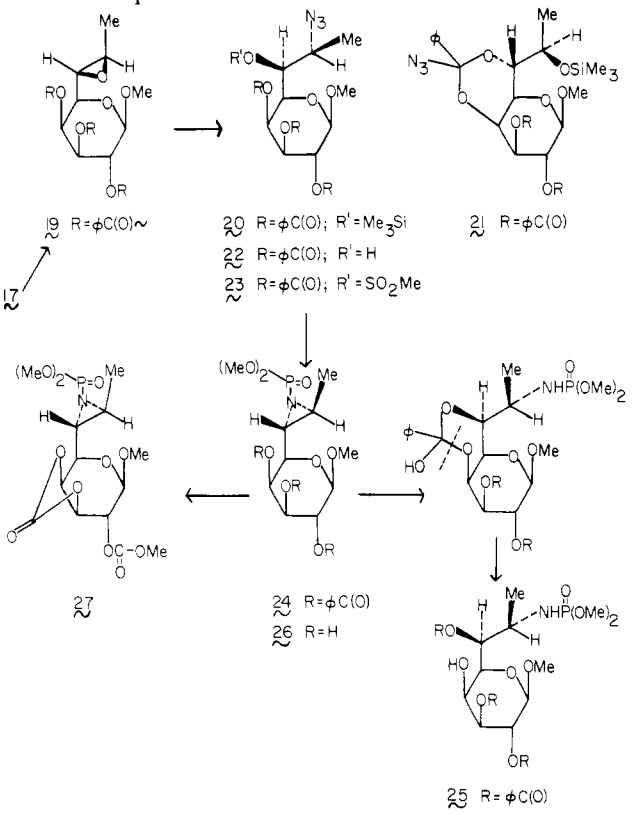
(23) For a review of the reactivity of aziridines toward SN displacement see: Dermer, O. C.; Ham, G. E. In "Ethylenimine and other Aziridines"; Academic Press: New York, 1969; pp 206–273.

(24) For an example of phosphoryl activation of aziridines toward carboxylic acid solvolysis, see: Lambert, R. F.; Thompson, G.; Kristofferson, C. E. *J. Org. Chem.* **1964**, *29*, 3116. Sonnett, P. E.; Bořkovec, A. B. *Ibid.* **1966**, *31*, 2962.

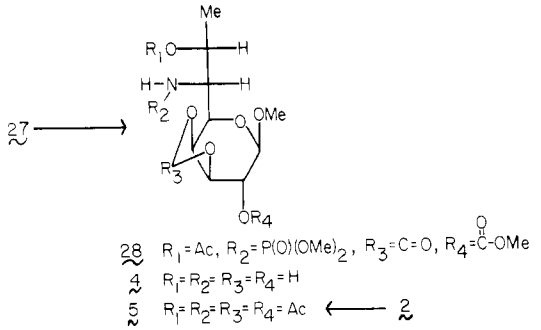
function of the 4-benzoate followed by collapse of a derived ortho benzoic acid derivative in the indicated sense.

While discouraging in its outcome, the conversion of **24** to **25** did indicate that the *N*-phosphorylaziridine linkage is sufficiently electrophilic to suffer displacement. It was reasoned that if neighboring group participation could be prevented, solvolysis in the desired sense (i.e., at C_7) could be achieved. It was further reasoned that neighboring group participation from the carbonyl oxygen of a C_4-mentioned alkoxycarbonyl group could be curtailed if such a function could be constrained in the form of a cyclic carbonate. Accordingly, the following sequence was undertaken.

Treatment of **24** with potassium carbonate in methanol afforded triol **26**. The C_3 and C_4 hydroxyl groups were engaged in the form of a cyclic carbonate upon reaction of **26** with carbonyldiimidazole. The C_2-hydroxyl apparently was converted to a mixed imidazolide, for on follow-up reaction with methanol, compound **27** was obtained in 73% yield. The setting for the fateful solvolysis reaction was now complete.



Reaction of **27** with hot glacial acetic acid afforded phosphoramidatoacetate **28** whose NMR spectrum indicated that solvolysis



had indeed taken place at C_7. Treatment of the crude solvolysis product **28** with potassium carbonate–methanol sufficed to cleave all the blocking groups.[25] The β-methyl lincosaminide (**4**) thus produced was not characterized but converted to its pentaacetyl derivative **5**. The 500-MHz NMR spectrum, the infrared spectrum, and the chromatographic properties of (±)-**5** thus obtained by total synthesis were indistinguishable from those of (+)-**5** derived from MTL (**2**) by peracetylation followed by conversion of the methyl thioglycoside to the methyl glycoside through the action of *N*-bromosuccinimide in methanol.[26] A fully synthetic route to lincosamine, which is highly stereoselective in its introduction of six contiguous nonanomeric heteroatoms (C_2–C_7), had been achieved. This is the first fully synthetic route to a higher monosaccharide.

In retrospect the two key elements of the synthesis were the cyclocondensation reaction (**7** → **8**) and the oxidation of the side-chain olefin with aqueous NBS (**10a** → **17**). The first step provided rapid access to the cis stereochemistry of the C_4 oxygen and the side chain at C_5 bearing the configurationally homogeneous *E* propenyl side chain. This type of reaction has been considered in detail in this series of papers.[8c]

The oxidation of **10a** to **17** is representative of a very important class of processes because it produces highly selective off-template[27] stereochemical definition. This kind of capability is crucial to our future plans for the construction of long chain networks of contiguous chirality. It is therefore well to consider the basis for the high stereoselectivity as well as the related osmylation of **10b** leading to **15**. As noted earlier, the findings reported herein are in good agreement with those previously reported by Szarek[13c] for the cis propenyl isomer **11** and by Secrist[10e] in the case of **13** bearing a more elaborate alkenyl side chain. The sense of asymmetric induction of all of these highly selective reactions is the same.

Rationalization of such findings are generically difficult owing to the need to clarify two uncertainties (i.e., the conformation of the reacting species and the sense of attack) with one observation (i.e., overall sense of diastereofacial induction). Well mindful of the conjectural nature of this kind of reasoning, we would advance for consideration the notion that the reactive conformation may be the one in which there is in s-cis conformational arrangement between the olefinic linkage and the C_5–O bond of the pyranose (cf. **29**).[28a,b,c] Attack of the electrophiles generated from $KMnO_4$, OsO_4, or NBS/H_2O occurs on that face of the double bond which is anti to the pyran projection. It must be emphasized that the proposal offered here does not address the question of the ground-state conformation of **10b** or of related olefins. It seeks to describe the conformation of the reacting species.[29]

We first note that this proposition accounts for the observed results. Going beyond this necessary albeit insufficient condition are some findings from the field of photoelectron spectroscopy.[30] Thus, the ionization potentials of allylic ethers are generally higher than those of the parent alkenes if the carbon–oxygen bond is gauche to the plane of the double bond (cf. **31**). By contrast, a cis orientation (cf. **30**) leads to no significant change in ionization energy relative to the parent alkene. Presumably, the π system of an olefin suffers electronic depletion during electrophilic at-

(25) Facile dephosphorylation of **28** under these conditions stands in contrast to the selective debenzoylation of **24** under similar conditions and may be attributed to anchimeric participation by the C_7 hydroxyl, unmasked in the course of the methanolysis.

(26) The procedure for conversion of α-methyl thiolincosamide was suggested by Dr. David White of the Upjohn Co.

(27) Molino, B. F.; Magdzinski, L.; Fraser-Reid, B. *Tetrahedron Lett.* **1983**, 5812.

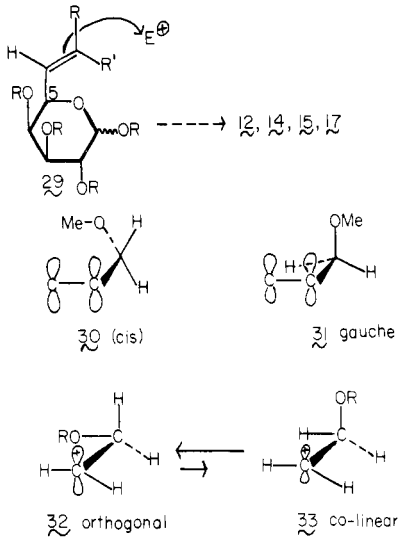
(28) For other recent observations and interpretations of the stereoselective osmylative oxidation of allyl derivatives, see: (a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**. Christ, W. J.; Cha, J. K.; Kishi, Y. *Tetrahedron Lett.* **1983**, 3947. (b) Stork, G.; Kahn, M. *Tetrahedron Lett.* **1983**, 3951. (c) The preference for the s-cis conformation over the s-trans rotamer, with respect to the transition state for an electrophilic addition, may be understood in terms of minimization of charge separations with regard to the C_5–O dipole and the incipient depletion of electron density from the π system of the side chain.

(29) While our observations regarding the selectivities seen in functionalizations of the olefin **10b** are consistent with the predictive model advanced in ref 30a, our interpretation focuses on *stereoelectronic* considerations of the transition states for these reactions. The complementary nature of this perspective vis à vis models advanced for *nucleophilic* addition to α-heterosubstituted carbonyl systems (see: Anh, N. T. *Topics Curr. Chem.* **1980**, *88*, 145) should be noted.

(30) Brown, R. S.; Marcinko, R. W.; Tse, A. *Can. J. Chem.* **1979**, *57*, 1890.

tack.[31] *Thus, to the extent that the C–O bond is oriented colinear with the π orbitals of the olefin (a situation which pertains in the gauche form* ***31****), the nucleophilicity of the double bond must be attenuated. Such stereoelectronic destabilization is absent in the cis form* ***30****.*

Further support for this hypothesis came from calculations of the effects of a 2-oxygen substituent on the stability of ethyl cation.[32] Colinearity of the C–O and π bonds (cf. **33**) incurs a



destabilization of ca 8 kcal/mol relative to an orthogonal relationship (**32**). *Insofar as cationoid character is generated in electrophilic reactions, structure* ***28*** *is favored as the reacting conformer.*

Regardless of the reasons, the excellent accessibility of such alkenylpyrans through hetero Diels–Alder reactions, coupled to their high diastereofacial selectivity toward electrophilic attack, opens up many fascinating possibilities in stereospecific synthesis. Some of these opportunities are being actively investigated in our laboratory.

Experimental[33] Section

Preparation of Dihydropyrone 8. Diene mixture **7** was prepared as previously described.[8c] To a cold (0 °C) suspension of (*E*)-1-(benzoyloxy)-4-methoxybut-3-en-2-one (3.5 g, 16 mmol) in dry Et_2O (35 mL) was added Et_3N (3.0 mL, 22 mmol) followed by dropwise addition of trimethylsilyl triflate (3.8 mL, 19 mmol) with vigorous stirring. After 20 min, pentane (50 mL) was added and the supernatant was removed by decantation, washed rapidly with cold saturated $NaHCO_3$ solution (50 mL) and brine, dried (Na_2SO_4), and concentrated to given dienes **7** as a mixture of stereoisomers (4.1 g, 90%). The crude diene mixture was dissolved in dry CH_2Cl_2 (100 mL) under N_2 and cooled to −78 °C, and 2-propenal (2.2 mL, 28 mmol) was added, followed by dropwise addition of boron trifluoride etherate (1.7 mL, 14 mmol). After 2 h at −78 °C, saturated $NaHCO_3$ solution (30 mL) was added, the mixture warmed to 25 °C and separated, and the aqueous layer extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and evaporated, and the residue was redissolved in CH_2Cl_2 (50 mL). Trifluoroacetic acid (2 mL) was added and after stirring 0.5 h at 25 °C, the solution was diluted with CH_2Cl_2 (50 mL), washed with saturated $NaHCO_3$ (2 × 25 mL) and brine, dried (Na_2SO_4), filtered, and evaporated. The oily residue, purified by flash chromatography (65% Et_2O/hexane), gave 2.4 g (67%) of the desired product **8** as an oil: ^1H NMR (500 MHz) δ 8.07–7.45 (m, 5 H), 7.40 (d, J = 6 Hz, 1 H), 5.97 (dqd, J = 16, 6, 1 Hz, 1 H), 5.75 (d, J = 5 Hz, 1 H), 5.71 (ddq, J = 16, 6, 2 Hz, 1 H), 5.52 (d, J = 6 Hz, 1 H), 5.10 (ddd, J = 6, 5, 1 Hz, 1 H), 1.75 (ddd, J = 6, 2, 1 Hz, 3 H); ^{13}C NMR (22.5 MHz) δ 186.0, 164.7, 162.2, 133.6, 133.2, 129.7, 128.8, 128.2, 121.7, 105.1, 80.6, 70.7, 17.7; IR ($CHCl_3$) 1725, 1685, 1600 cm^{-1}; HRMS calcd for $C_{15}H_{14}O_4$ 258.0892, found 258.0906.

Preparation of Glycal Dibenzoate 9. To a cold (−78 °C) solution of **8** (2.3 g, 8.8 mmol) and $CeCl_3 \cdot 7H_2O$ (4.0 g, 10.8 mmol) in MeOH (50 mL) was added 0.5 M $NaBH_4$ in EtOH (22 mL, 11 mmol) via syringe pump over 20 min. After stirring at −78 °C for 0.5 h, the mixture was warmed to 0 °C and excess hydride quenched by addition of acetone (10 mL). The mixture was diluted with EtOAc (500 mL) and washed with saturated $NaHCO_3$ solution (5 × 50 mL). The combined washes were back extracted with EtOAc (100 mL), then the combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and evaporated. The glassy residue was dissolved in dry CH_2Cl_2 (50 mL), along with 4-(dimethylamino)pyridine (50 mg), and cooled to 0 °C. Triethylamine (2.5 mL, 18 mmol) was added followed by benzoyl chloride (1.8 mL, 15 mmol) and the mixture stirred at 0 °C for 0.5 h and then at 25 °C for an additional 1.5 h. Saturated $NaHCO_3$ solution (20 mL) was added, stirring was continued for a further 0.5 h, then the mixture was separated, and the aqueous layer was extracted with CH_2Cl_2 (25 mL). The combined organic layers were washed with aqueous 1 N HCl (25 mL), saturated $NaHCO_3$ solution (25 mL) and brine, dried (Na_2SO_4), filtered, and evaporated to give a viscous oil, which was purified by flash chromatography (35% Et_2O/hexane) to give 2.3 g (72%) of the compound **9** as the more polar diastereomer: ^1H NMR (500 MHz) δ 8.05–7.20 (m, 10 H), 6.65 (dd, J = 6, 2 Hz, 1 H), 5.97 (ddd, J = 5, 3, 2 Hz, 1 H), 5.95 (dqd, J = 16, 7, 1 Hz, 1 H), 5.73 (dd, J = 5, 2 Hz, 1 H), 5.68 (ddq, J = 15, 6, 2 Hz, 1 H), 4.89 (ddd, J = 6, 3, 2 Hz, 1 H), 4.71 (d, J = 6 Hz, 1 H), 1.73 (dd, J = 7, 2 Hz, 1 H); IR ($CHCl_3$) 1720, 1640 cm^{-1}; HRMS calcd for $C_{15}H_{14}O_3$ ($M^+ - PhCO_2H$) 242.0943, found 242.0948. Anal. Calcd for $C_{22}H_{20}O_5$: C, 72.51; H, 5.53. Found: C, 72.49; H, 5.55.

Preparation of Tribenzoate Methyl Glycosides 10a and 10b. To a cold (0 °C) solution of the glycal dibenzoate **9** (2.1 g, 5.8 mmol) in MeOH (60 mL) was added solid *m*-chloroperbenzoic acid (85%, 1.2 g, 6.0 mmol) and the solution stirred at 5 °C for 12 h then 25 °C for 6 h. Dimethyl sulfide (3 mL) was added and stirring continued for a further 0.5 h; then the mixture was concentrated and the residue dissolved in EtOAc (75 mL), washed with 10% $NaHSO_3$ solution (2 × 15 mL), saturated $NaHCO_3$ solution (2 × 50 mL), and brine, dried (Na_2SO_4) filtered, and evaporated. The crude product was dissolved in CH_2Cl_2 (50 mL) along with 4-(dimethylamino)pyridine (50 mg) and cooled to 0 °C, and triethylamine (1.3 mL, 10 mmol) was added followed by benzoyl chloride (0.65 mL, 7.0 mmol). After stirring at 0 °C for 0.5 h then 25 °C for 2 h, saturated $NaHCO_3$ (25 mL) was added and the mixture separated. The aqueous layer was extracted with CH_2Cl_2 (50 mL) and the combined organic layers then washed with aqueous 1 N HCl (20 mL), saturated $NaHCO_3$ solution (20 mL), and brine, dried (Na_2SO_4), filtered, and evaporated. Separation of the oily residue by flash chromatography (40% Et_2O/hexane) gave, in order of elution, the α-methyl glycoside **10a** (800 mg, 27%) and the β-methyl glycoside **10b** (1.9 g, 64%).

β-Anomer **10b**: mp 201–202 °C (EtOAc/hexane); ^1H NMR (500 MHz) δ 8.2–7.1 (m, 15 H), 5.94 (dqd, J = 15, 7, 1 Hz, 1 H), 5.79 (dd, J = 4, 1 Hz, 1 H), 5.75 (dd, J = 10, 8 Hz, 1 H), 5.59 (dd, J = 10, 4 Hz, 1 H), 5.55 (ddq, J = 15, 6, 1 Hz, 1 H), 4.73 (d, J = 8 Hz, 1 H), 4.40 (dd, J = 6, 1 Hz, 1 H), 3.61 (s, 3 H), 1.67 (dd, J = 7, 1 Hz, 3 H); ^{13}C NMR (22.5 MHz) δ 165.7, 165.6, 165.3, 133.2, 133.1, 130.5, 129.8, 129.6, 128.8, 128.4, 128.1, 124.8, 102.1, 74.2, 72.0, 70.8, 69.7, 56.9, 17.7; IR ($CHCl_3$) 1720 cm^{-1}. Anal. Calcd for $C_{30}H_{28}O_8$: C, 96.75, H, 5.46. Found: C, 69.49; H, 5.55.

α-Anomer **10a**: ^1H NMR (90 MHz) δ 8.2–7.1 (m, 15 H), 6.1–5.5 (m, 5 H), 5.24 (d, 3 Hz, 1 H), 4.65 (d, 5 Hz, 1 H), 3.46 (s, 3 H), 1.64 (d, J = 7 Hz, 3 H); ^{13}C NMR (22.5 MHz) δ 165.9, 165.5, 165.4, 133.1, 132.8, 130.7, 129.6, 129.4, 129.1, 128.4, 128.2, 128.0, 124.9, 97.5, 71.6, 69.5, 69.2, 68.4, 55.4, 17.7; IR ($CHCl_3$) 1720 cm^{-1}.

Preparation of Diol 15. To a mixture of *N*-methylmorphiline *N*-oxide hydrate (150 mg, 1.10 mmol) and H_2O (15 μL) in THF/*t*-BuOH (1:2, 1.5 mL) was added a 10 wt % solution of osmium tetroxide (125 μL, 0.050 mmol) followed by a solution of the tribenzoate methyl glycoside (**10b**) (515 mg, 1.00 mmol) in THF (2.5 mL), and the mixture was stirred at 25 °C for 1.5 h. Florisil (100 mg) and solid $NaHSO_3$ (50 mg) were added, followed by H_2O (300 μL). After it was stirred at 25 °C for 15 min, the mixture was filtered through Celite and the filter pad washed with CH_2Cl_2 (2 × 10 mL). The combined filtrates were washed with brine, dried (Na_2SO_4), filtered, and evaporated. Flash chromatography of the residue (70% EtOAc/hexane) gave the diol **15** (500 mg, 89%): mp 189–190 °C (Et_2O); ^1H NMR (500 MHz) δ 8.2–7.2 (m, 15 H), 5.94 (d, J = 3 Hz, 1 H), 5.88 (dd, J = 8, 11 Hz, 1 H), 5.63 (dd, J = 3, 11 Hz, 1 H), 4.78 (d, J = 8 Hz, 1 H), 4.13 (q, J = Hz, 1 H), 4.05 (d, J = 9 Hz, 1 H), 3.60 (s, 3 H), 3.46 (br d, J = 9 Hz, 1 H), 2.1 (br s, 2 H), 1.32 (d, J = 6 Hz, 3 H); IR ($CHCl_3$) 3600–3300, 1720 cm^{-1}.

(31) While the mechanism of osmylative oxidation of olefins is not clearly defined (see: Schroder, M. *Chem. Rev.* **1980**, *80*, 187), it does show the sensitivity of an electrophilic addition, with regard to the effect of variation of olefin nucleophilicity (see: Henbest, H. B.; Jackson, W. R.; Robb,B. C. G. *J. Chem. Soc. B* **1966**, 803).

(32) Radom. L.; Pople, J. A.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1972**, *94*, 5935.

(33) Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

Anal. Calcd for $C_{30}H_{30}O_{10}$: C, 65.44; H, 5.49. Found: C, 65.19; H, 5.65.

Preparation of Diacetate 16. To a solution of the diol **15** (22 mg) in CH_2Cl_2 (2 mL) was added 4-(dimethylamino)pyridine (2 mg), Et_3N (100 μL), and acetic anhydride (100 μL). After stirring at 25 °C for 2.5 h, the mixture was diluted with CH_2Cl_2 (5 mL) and saturated $NaHCO_3$ solution (2 mL) and separated and the aqueous layer extracted with CH_2Cl_2 (2 × 10 ML). The combined organic layers were washed with saturated $NaHCO_3$ solution (2 mL) and brine (5 mL), dried (Na_2SO_4), filtered, and evaporated. Flash chromatography of the residue (65% Et_2O/hexane) gave the diacetate **16** (23 mg, 92%). Vapor diffusion crystallization (pentane/EtOAc, −20 °C) gave the crystal for the X-ray diffraction study: mp 187–188 °C; ^1H NMR (90 MHz) δ 8.1–7.1 (m, 15 H), 5.81 (d, J = 3 Hz, 1 H), 5.75–5.10 (m, 4 H), 4.56 (d, J = 8 Hz, 1 H), 3.95 (d, J = 10 Hz, 1 H), 3.53 (s, 3 H), 2.13 (s, 3 H), 2.04 (s, 3 H), 1.15 (d, J = 7 Hz, 3 H); IR ($CHCl_3$) 1730 (br) cm^{-1}.

Preparation of Bromohydrin 17. To a solution of the olefin **10b** (800 mg, 1.6 mmol) in a mixture of CH_2Cl_2 (7 mL), acetic acid (7 mL), and H_2O (0.3 mL) was added *N*-bromosuccinimide (300 mg, 1.7 mmol) and the solution stirred at 25 °C for 5 h with exclusion of light. EtOAc (75 mL) was added, and the mixture was washed with saturated $NaHSO_3$ solution (5 mL), H_2O (4 × 15 mL), saturated $NaHCO_3$ solution (3 × 15 mL), and brine, dried (Na_2SO_4), filtered, and evaporated. Crystallization from EtOAc/hexane gave 480 mg of the bromohydrin **17**. Flash chromatography of the mother liquors afforded an additional 400 mg (92% total yield): mp 206–207 °C dec (benzene/EtOAc); ^1H NMR (500 MHz) δ 8.2–7.3 (m, 15 H), 5.74 (dd, J = 6, 3 Hz, 1 H), 5.72 (dd, J = 8, 10 Hz, 1 H), 5.32 (dd, J = 10, 3 Hz, 1 H), 4.65 (d, J = 8 Hz, 1 H), 4.58 ("quintet", J = 7 Hz, 1 H; q, J = 7 Hz on D_2O exchange), 4.44 (dd, J = 6, 3 Hz, 1 H), 4.30 (d, J = 3 Hz, 1 H), 3.54 (s, 3 H), 2.33 (d, J = 7 Hz, 1 H, D_2O exchange), 1.81 (d, J = 7 Hz); IR ($CHCl_3$) 3600–3500, 1720 cm^{-1}. Anal. Calcd for $C_{30}H_{29}BrO_9$: C, 58.73; H, 4.76; Br, 13.03. Found: C, 58.48; H, 4.85; Br, 12.70.

Formation of Epoxide 19. To a suspension of the bromohydrin **17** (610 mg, 1.0 mmol) in dry benzene (15 mL) was added 1,5-diazabicyclo-[4.3.0]non-5-ene (0.5 mL, 4.0 mmol) at 25 °C under N_2. After 1 h, the mixture was diluted with EtOAc (30 mL) and washed with 1 N HCl (10 mL) and the aqueous layer back extracted with EtOAc (20 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (5 mL) and brine, dried (Na_2SO_4), filtered, and evaporated to give a crystalline solid, which was purified by flash chromatography (80% Et_2O/hexane) to yield compound **19** (510 mg, 96%): mp 198–199 °C (benzene/hexane); ^1H NMR (500 MHz) δ 8.1–7.2 (m, 15 H), 5.90 (dd, J = 3.5, 1 Hz), 5.81 (dd, J = 10.5, 8 Hz, 1 H), 5.51 (dd, J = 10.5, 3.5 Hz, 1 H), 4.69 (d, J = 8 Hz, 1 H), 3.63 (s, 3 H), 3.60 (dd, J = 6, 1 Hz, 1 H), 3.05 (qd, J = 5, 2 Hz, 1 H), 2.96 (dd, J = 6, 2 Hz, 1 H), 1.28 (d, J = 5 Hz, 3 H); ^{13}C NMR (22.5 MHz) δ 165.5, 165.1, 133.4, 133.1, 129.8, 129.5, 129.2, 128.7, 128.5, 128.1, 102.0, 75.1, 71.5, 69.6, 69.5, 57.8, 57.1, 51.3, 16.8; IR ($CHCl_3$) 1720 cm^{-1}. Anal. Calcd for $C_{30}H_{28}O_9$: C, 67.66; H, 5.30. Found: C, 67.43; H, 5.38.

Azidolysis of Epoxide 19. Isolation of Compounds 21 and 22. A solution of the epoxide **19** (490 mg, 0.92 mmol), tetra-*n*-butylammonium azide (1.05 g, 3.7 mmol), and azidotrimethylsilane (1.2 mL, 10 mmol) in dry toluene (10 mL) was heated to 90 °C under N_2 for 10 h, then cooled, diluted with EtOAc (75 mL), washed with H_2O (5 × 15 mL) and brine, dried (Na_2SO_4), filtered, and evaporated. The residue was dissolved in CH_2Cl_2/MeOH (5:1, 10 mL) and trifluoroacetic acid (0.5 mL) added. After 1 h, the mixture was diluted with CH_2Cl_2 (40 mL) and washed with saturated $NaHCO_3$ solution (5 mL) and brine, dried (Na_2SO_4), filtered, and evaporated. Flash chromatography (65% Et_2O/hexane) of the residue afforded 410 mg (78%) of the azidohydrin **22**: mp 157–158 °C (benzene/hexane); ^1H NMR (500 MHz) δ 8.1–7.2 (m, 15 H), 5.92 (d, J = 3.5 Hz, 1 H), 5.81 (dd, J = 10.5, 8 Hz, 1 H), 5.58 (dd, J = 10.5, 3.5 Hz, 1 H), 4.81 (d, J = 8 Hz, 1 H), 4.06 (d, J = 3.5 Hz, 1 H), 3.77 ("t"d, J = 7, 3.5 Hz, 1 H), 3.63 (s, 3 H), 3.60 ("quintet", J = 7 Hz, 1 H), 2.49 (d, J = 7 Hz, 1 H, D_2O exchange), 1.39 (d, J = 7 Hz, 3 H); ^{13}C NMR (22.5 MHz) δ 165.4, 165.2, 133.4, 133.2, 129.8, 129.6, 129.1, 129.0, 128.5, 128.2, 102.5, 73.6, 71.8, 71.7, 69.5, 58.1, 57.3, 14.7; IR ($CHCl_3$) 3600–3500, 2080, 1720 cm^{-1}. Anal. Calcd for $C_{30}H_{29}N_3O_9$: C, 62.60; H, 5.08; N, 7.30. Found: C, 62.43; H, 5.28; N, 7.05. Earlier fractions gave the orthoacyl azide **21**[34] (85 mg, 14%): mp 156–158 °C (hexane); ^1H NMR (500 MHz) δ 8.1–7.3 (m, 15 H), 5.79 (dd, J = 7.9, 10.6 Hz, 1 H), 5.67 (dd, J = 4.0, 8.4 Hz, 1 H), 5.23 (dd, J = 2.8, 10.6 Hz, 1 H), 4.56 (d, J = 7.9 Hz, 1 H), 4.45 (d, J = 2.7 Hz, 1 H), 3.83 (d, J = 8.5 Hz, 1 H), 3.78 (qd, J = 6.7, 4.1 Hz, 1 H), 3.23 (s, 3 H), 1.50 (d, J = 6.7 Hz, 3 H), 0.04 (s, 9 H); IR ($CHCl_3$) 2080, 1725, 1260 cm^{-1}. Anal. Calcd for $C_{33}H_{37}SiN_3O_9$: C, 61.19; H, 5.76; N, 6.49; Si, 4.33. Found: C, 61.36; H, 5.91; N, 6.54; Si, 4.22.

Formation of Azido Mesylate 23. To a cold (0 °C) solution of the azidohydrin **22** (250 mg, 0.43 mmol) in CH_2Cl_2 (5 mL) was added Et_3N (140 μL, 1 mmol) followed by dropwise addition of methanesulfonyl chloride (50 μL, 0.65 mmol). After 2 h, further portion of methanesulfonyl chloride (20 μL, 0.25 mmol) was added and stirring at 0 °C continued for a further 1 h. H_2O (0.5 mL) was then added, and after 0.5 h at 0 °C, the mixture was diluted with CH_2Cl_2 (20 mL) and washed with 1 N HCl (2 mL), and the combined aqueous layers were extracted with CH_2Cl_2 (10 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (2 mL) and brine, dried (Na_2SO_4), filtered, and evaporated. Flash chromatography (80% Et_2O/hexane) of the residue afforded mesylate **23** (260 mg, 90%): mp 174–175 °C (benzene/hexane); ^1H NMR (500 MHz) δ 8.1–7.2 (m, 15 H), 5.82 (dd, J = 4, 0.8 Hz, 1 H), 5.79 (dd, J = 10, 8 Hz, 1 H), 5.54 (dd, J = 10, 4 Hz, 1 H), 4.93 (dd, J = 8.7, 2.5 Hz, 1 H), 4.74 (d, J = 8 Hz, 1 H), 4.01 (dd, J = 8.7, 0.8 Hz, 1 H), 3.89 (qd, J = 6.7, 2.6 Hz, 1 H), 3.65 (s, 3 H), 3.18 (s, 3 H), 1.42 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (22.5 MHz) δ 165.6, 165.4, 165.0, 133.4, 133.3, 133.1, 129.9, 129.5, 129.0, 128.6, 128.1, 102.2, 81.0, 72.2, 71.7, 69.1, 67.5, 57.3, 55.9, 39.0, 13.5; IR ($CHCl_3$) 2090, 1720, 1360 cm^{-1}. Anal. Calcd for $C_{31}H_{31}N_3SO_{11}$: C, 56.96; H, 4.78; N, 6.43. Found: C, 56.89; H, 4.87; N, 6.24.

Formation of Phosphorylaziridine 24. To a solution of the azido mesylate **23** (200 mg, 0.30 mmol) in dry benzene (3 mL) at 25 °C under N_2 was added trimethyl phosphite (140 μL, 1.2 mmol). After 20 h, the mixture was concentrated and the volatiles removed in vacuo (0.1 mmHg, 2 h). The residue was added as a THF (5 mL) solution to a suspension of oil-free sodium hydride (60 mg, 2.5 mmol) in dry THF (1 mL) at 25 °C under N_2. After 3 h the mixture was quenched with acetic acid (0.5 mL), diluted with EtOAc (25 mL), washed with saturated $NaHCO_3$ solution (2 × 5 mL) and brine, dried (Na_2SO_4), filtered, evaporated, and then dried in vacuo (0.1 mmHg, 8 h). The residue was resubjected to treatment with sodium hydride as above, and after a 0.5-h reaction time, worked up as before. Flash chromatography (100% EtOAc) of the residue afforded 165 mg (87%) of the phosphorylaziridine **24**: mp 221–222 °C (EtOAc/benzene); ^1H NMR (500 Mhz) δ 8.1–7.2 (m, 15 H), 5.90 (dd, J = 3.4, 1 Hz, 1 H), 5.74 (dd, J = 10.4, 8 Hz, 1 H), 5.54 (dd, J = 10.4, 3.4 Hz, 1 H), 4.68 (d, J = 8 Hz, 1 H), 3.81 (dd, J = 6, 1 Hz, 1 H), 3.79 (d, J = 11 Hz, 3 H), 3.60 (s, 3 H), 3.57 (d, J = 11 Hz, 3 H), 2.80–2.76 (m, 1 H), 2.71 (ddd, J = 15, 6, 3 Hz, 1 H), 1.38 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (22.5 MHz) δ 165.2, 165.0, 133.2, 132.9, 129.4, 129.0, 128.6, 128.3, 128.1, 128.0, 102.0, 73.6, 73.4, 71.5, 69.3, 69.0, 56.9, 53.7, 53.5, 53.2, 42.2, 41.9, 38.8, 38.5, 15.2, 15.0; IR ($CHCl_3$) 1720, 1050 cm^{-1}. Anal. Calcd for $C_{32}H_{34}NPO_{11}$: C, 60.09; H, 5.36; N, 2.19; P. 4.84. Found: C, 59.86; H, 5.33; N, 2.08; P. 4.88.

Acetolysis of Tribenzoate Phosphorylaziridine 24. Formation of Hydroxy Phosphoramidate Tribenzoate 25. A solution of the tribenzoate aziridine **24** (32 mg, 0.05 mmol) in glacial acetic acid (0.5 mL) was warmed to 75 °C. After 2 h, the volatiles were evaporated and the residue was purified by flash chromatography (100% EtOAC) to give the C_7 phosphoramide **25** (27 mg, 77%): mp 201–202 °C (EtOAc/hexane); ^1H NMR (500 MHz) δ 8.2–7.3 (m, 15 H), 5.76 (dd, J = 10.5, 8 Hz, 1 H), 5.59 (dd, J = 6.8, 4 Hz, 1 H), 5.31 (dd, J = 10.3, 3.3 Hz, 1 H), 4.61 (d, J = 8 Hz, 1 H), 4.43 (dd, J = 6.0, 3.2 Hz, 1 H), 3.92 (d, J = 6.4 Hz, 1 H), 3.78 (m, 1 H), 3.76 (d, J = 11.5 Hz, 3 H), 3.71 (d, J = 11.2 Hz, 3 H), 3.40 (d, J = 6, 1 H, D_2O exchange), 3.37 (s, 3 H), 3.15 ("t", J = 10.6 Hz, 1 H), 1.32 (d, J = 6.8 Hz, 3 H); IR ($CHCl_3$) 3400–3200, 1720 cm^{-1}. Anal. Calcd for $C_{32}H_{36}NPO_{12}$: C, 58.44; H, 5.52; N, 2.13. Found: C, 58.26; H, 5.54; N, 2.13.

Preparation of Dicarbonate 27. The phosphorylaziridine **24** (67 mg, 0.10 mmol) was dissolved in saturated methanolic K_2CO_3 (1 mL) and stirred at 40 °C for 15 min then 25 °C for 1 h. MeOH-washed Amberlite IRC-84 (weak acid ion exchange resin) was added until the mixture was neutral. The resin was removed by filtration and washed with MeOH (4 × 5 mL), and the combined filtrates were evaporated and azeotroped with $CHCl_3$ (3 × 5 mL). After drying in vacuo (0.1 mmHg, 12 h) the presumed triol **26** was suspended in dry THF (1 mL), and carbonyl diimidazole (50 mg, 0.3 mmol) was added and the mixture stirred at 25 °C for 1 h; then a further portion of carbonyl diimidazole (20 mg, 0.13 mmol) was added and the mixture warmed to gentle reflux for a further 0.5 h. The mixture was cooled and MeOH (200 μL) added: then the mixture was stirred at 25 °C for 0.5 h then 60 °C for 1 h. The mixture was concentrated and the residue purified by flash chromatography (1% MeOH/$CHCl_3$) to give 29 mg (72%) of dicarbonate **27**. ^1H

(34) The formulation of compound **21** in terms of the ortho acid structure shown is based on analysis of its high proton NMR spectrum. In particular, the coupling constant of 2.7 Hz for the C_4 proton, which is typical throughout this series, indicates that no inversion has occurred at the center. Furthermore, examination of the "aromatic" region of the NMR spectrum indicates that one of the phenyl groups lacks the sharply differentiated ortho parameter protons generally associated with benzoyl groups. While structure **21** accommodates all these data, the possibility that the compound is in fact the C_4 β-azide with the benzoate transposed to C_6 cannot rigorously be excluded.

NMR (90 MHz) δ 5.1-4.6 (m, 4 H), 4.02 (s, 3 H), 3.83, 3.72 (2 s, 3 H), 3.54 (m, 1 H), 3.43 (s, 3 H), 2.91-2.48 (m, 2 H), 1.49 (d, 3 H); IR ($CHCl_3$) 1810, 1760 cm^{-1}; MS, *m/e* 411 (4%, M^+), 396 (35%), 380 (10%), 336 (10%), 120 (100%); HRMS calcd for $C_{14}H_{22}NPO_{11}$ 411.0930, found 411.0942.

Acetolysis of Phosphorylaziridine 27. Preparation of Racemic Triacetate 5. A solution of the dicarbonate aziridine **27** (41 mg, 0.1 mmol) in acetic acid (1 mL) was heated at 50 °C for 12 h then 90 °C for an additional 4 h, cooled, and evaporated. The residue presumed to contain compound **28** (vide infra) was dissolved in MeOH (2 mL), K_2CO_3 (100 mg) was added, and the mixture was heated to 60 °C for 12 h, cooled, and evaporated. The residue, presumed to contain (±)-**4**, was suspended in pyridine (1 mL), and acetic anhydride (1 mL) was added; then the mixture was stirred for 12 h at 25 °C, evaporated, and partitioned between EtOAc (20 mL) and 1 N HCl solution (5 mL). The layers were separated, the aqueous layer was back extracted with EtOAc (10 mL), and the organic layers were combined, washed with saturated $NaHCO_3$ solution (2 mL) and brine, dried (Na_2SO_4), filtered, and evaporated. The residue was chromatographed (100% EtOAc) to give the fully synthetic pentaacetate **15** (20 mg, 45%): mp 243-245 °C (EtOAc/hexane); ^1H NMR (500 MHz) δ 5.56 (d, *J* = 10 Hz, 1 H), 5.37 (d, *J* = 3 Hz, 1 H), 5.22 (dd, *J* = 8.5, 10 Hz, 1 H), 5.10 (dq, *J* = 3, 7 Hz, 1 H), 4.98 (dd, *J* = 3, 10 Hz, 1 H), 4.57 (d"t", *J* = 3, 10 Hz, 1 H), 4.37 (d, *J* = 8 Hz, 1 H), 3.65 d, *J* = 9.5 Hz, 1 H), 3.53 (s, 3 H), 2.15, 2.08, 2.07, 1.98, 1.93 (5 s, 5 × 3 H), 1.33 (d, *J* = 7 Hz, 3 H); IR ($CHCl_3$) 3400, 2950, 1740, 1710 sh, 1680, 1360, 1240, 1060 cm^{-1}. Anal. Calcd for $C_{19}H_{29}NO_{11}$: C, 51.00; H, 6.53; N, 3.13. Found: C, 51.28; H, 6.66; N, 2.97. HRMS calcd for $M^+ - CH_3CO_2(CH_3)CH\cdot$ 360.1294, found 360.1293.

Flash chromatography (2.5% MeOH/$CHCl_3$) of the crude product from the acetic acid solvolysis above gave the phosphoramide **28** as the major mobile component: ^1H NMR (500 MHz) δ 5.27 (qd, *J* = 7, 3.5 Hz, 1 H), 5.13 (dd, *J* = 8, 1 Hz, 1 H), 4.89 ("t", *J* = 3.5 Hz, 1 H), 4.82 (dd, *J* = 8, 3.5 Hz, 1 H), 4.77 (d, *J* = 3.5 Hz, 1 H), 3.87 (s, 3 H), 3.77 (d, *J* = 15 Hz, 6 H), 2.09 (s, 3 H), 1.32 (d, *J* = 7 Hz, 3 H); IR ($CHCl_3$) 1810, 1755, 1735 cm^{-1}.

Conversion of Methyl Thiolincosaminide Pentaacetate (2) to Authentic D-Triacetate (+)-5. To a cold (0 °C) solution of pentacetyl MTL (230 mg, 0.50 mmol) in MeOH (3 mL) was added *N*-bromosuccinimide (90 mg, 0.50 mmol) in MeOH (2 mL) dropwise. After 1 h, the mixture was concentrated and the residue chromatographed to give the β-methyl glycoside **5** (105 mg, 47%): mp 255-257 °C (EtOAC/hexane); $[\alpha]^{20}_D$ +41° (c 1.03, $CHCl_3$); ^1H NMR (500 MHz) δ 5.61 (br d, *J* = 9 Hz, 1 H), 5.37 (d, *J* = 3 Hz, 1 H), 5.22 (dd, *J* = 8.5, 10 Hz, 1 H), 5.10 (dq, *J* = 3, 7.5 Hz, 1 H), 4.98 (dd, *J* = 3, 10 Hz, 1 H), 4.57 (d"t", *J* = 3, 9 Hz, 1 H), 4.37 (d, *J* = 8 Hz, 1 H), 3.65 (d, *J* = 9 Hz, 1 H), 3.53 (s, 3 H), 2.15, 2.08, 2.06, 1.99, 1.93 (5s, 5 × 3 H), 1.33 (d, *J* = 7.5 Hz, 3 H); IR ($CHCl_3$) 3410, 3350, 2950, 1740, 1675, 1360, 1240, 1060 cm^{-1}. Anal. Calcd for $C_{19}H_{29}NO_{11}$: C, 51.00; H, 6.53; N, 3.13. Found: C, 50.99; H, 6.55; N, 3.10. HRMS calcd for $M^+ - CH_3CO_2(CH_3)CH\cdot$ 360.1294, found 360.1307.

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Registry No. (±)-**2**, 13038-00-1; **4**, 87462-03-1; (±)-**4**, 92077-23-1; **5**, 87462-04-2; (±)-**5**, 92077-21-9; (*Z,E*)-**7**, 92054-25-6; (*E,E*)-**7**, 92011-04-6; **8**, 87461-95-8; **9**, 87461-96-9; **10a**, 92011-05-7; **10b**, 87461-97-0; **15**, 87461-98-1; **16**, 92011-06-8; **17**, 87461-99-2; **19**, 87462-00-8; **20**, 92011-11-5; **21**, 92011-07-9; **22**, 92011-08-0; **23**, 92011-09-1; **24**, 87462-01-9; **25**, 92054-26-7; **26**, 92011-12-6; **27**, 87462-02-0; **28**, 92011-10-4; lincosamine, 92077-22-0; (*E*)-1-methoxy-4-(benzyloxy)but-1-en-3-one, 92011-03-5; 2-butenal, 4170-30-3; boron trifluoride etherate, 109-63-7; trimethyl phosphite, 121-45-9.

Supplementary Material Available: Table I (fractional coordinates and temperature factors), Table II (bond distances in angstroms), Table III (bond angles in degrees), and ORTEP drawing for **16** and crystal data for (7 pages). Ordering information is given on any current masthead page.

Total Synthesis of (±)-3-Deoxy-D-*manno*-2-octulopyranosate (KDO)

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Abstract: Cyclocondensation of 2-(phenylseleno)propionaldehyde with 1-(α-furyl)-1-methoxy-3-[(trimethylsilyl)oxy]-4-(benzoyloxy)-1,3-butadiene under the influence of boron trifluoride produces a predominance (2.4:1) of *cis-/trans*-3-(benzoyloxy)-6-(α-furyl)-2-[(1-phenylseleno)ethyl]-2,3-dihydro-4*H*-pyran-4-one (**13**). This is converted to (±)-3-deoxy-D-*manno*-2-octulopyranosonate ((±)-KDO) in nine steps.

Unique polysaccharides have been uncovered during studies of the biochemistry of microorganisms. These polysaccharides are characteristic of the classification of the microbe.[1,2] For instance, the teichoic acids (polymers of glycerol or ribotol phosphate) are isolated from the cell walls and membranes of Gram-positive bacteria. While the analogy is far from exact, the lipopolysaccharides (LPS), also known as endotoxins, play a similar role in Gram-negative bacteria. The external section is responsible for the antigenic specificity of the LPS. The interior carbohydrate section, known as the core region, is comprised of galactose, glucose, glucosamine, *N*-acetylglucosamine, and L-glycero-D-*manno*-heptose residues. The lipid section, known as lipid A, is joined to the core region through ketosidic bonds to an eight-carbon sugar residue which has been identified as 3-deoxy-D-*manno*-2-octulopyranosate (KDO).[3,4] The KDO "section" of LPS ap-

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