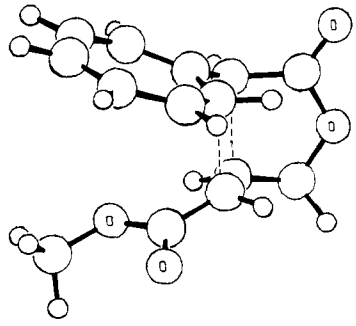
the pathway constrained to have synchronous formation of the two forming CC bonds.[10] The ester side chain was then substituted for the appropriate hydrogens in each of the four stereochemically distinct ways, and the geometry of the side chain was optimized by MNDO, keeping the heptafulvenyl and vinyl groups frozen in the geometries obtained from the model transition-state calculations. The relative energies of the terminal exo and endo ester moieties were calculated separately in the same manner. The preferred cis endo ester (cis-endo-E) transition structure, which leads to **6**, is shown below.



The relative energies of the four transition structures obtained by adding the contribution from the developing lactone side chain and the ester group are 0, +1.6, +28.9, and +37.3 kcal/mol for cis-endo-E, cis-exo-E, trans-endo-E, and trans-exo-E, respectively. Astonishingly, these calculations predict that **6** and **7** will be formed in a 7:1 ratio at 145 °C! While this perfect agreement must be considered accidental, the calculations provide at least qualitative clues to relative stabilities of isomeric transition structures. The difference in energy between cis and trans transition structures is calculated to be even larger than the difference in cis and trans fused products, because of severe angle strain required to connect the developing γ-lactone ring in a trans fashion to the [8 + 2] transition state. The cis-endo-E transition structure may be more stable than the cis-exo-E because of attractive secondary orbital interactions between the ester and tetraene orbitals. However, the MNDO calculations suggest that the CO_2CH_2 side chain can be substituted for exo hydrogens on the heptafulvene and ethylene (which gives the cis-endo-E transition state) with very little strain, while replacement of endo hydrogens with the CO_2CH_2 fragment (which gives the cis-exo-E transition state) introduces greater strain. The exo CH bonds are more nearly parallel than the endo, so the relatively small ring can be fused onto the transition state more easily in an exo fashion.

Synthetic applications of this reaction and the generality of this computational method will be described at a later date.

Acknowledgment. We are grateful to the National Science Foundation for research and equipment grants, the Swiss National Science Foundation for a Fellowship to J.M., and the National Institutes of Health (PROPHET and CMU NMR Facility).

Registry No. 1, 87306-51-2; **2**, 87306-52-3; **4**, 87306-53-4; **5**, 87306-54-5; **6**, 87306-55-6; **7**, 87334-96-1; **8**, 87306-56-7.

Supplementary Material Available: ORTEP drawing and listing of fractional atomic coordinates of **6** (4 pages). Ordering information is given on any current masthead page.

(9) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899, 4907.

(10) Although MNDO calculations predict an unsymmetrical reaction pathway and a diradical intermediate for the Diels–Alder reaction (Dewar M. S. S.; Olivella, S.; Rzepa, H. S. *J. Am. Chem. Soc.* **1978**, *100*, 5650), a C_s symmetry constraint gives a geometry very similar to the STO-3G transition structure (Townshend, R. E.; Ramunni, G.; Segal, G.; Hehre, W. J.; Salem, L. *J. Am. Chem. Soc.* **1976**, *98*, 2190). The procedure adopted here for the [8 + 2] reaction is expected to give a resonable transition structure, assuming that the reaction is concerted and approximately synchronous. For other intramolecular cycloadditions, we have had success in the use of ab initio transition-structure calculations on the parent system, followed by MM2 side chain and substituent calculations for stereochemical predictions (F. K. Brown and K. N. Houk, submitted for publication).

A Totally Synthetic Route to Lincosamine

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Received July 19, 1983

The significant physiological properties of the higher monosaccharides as well as their varied substitution and chirality patterns[1] render them attractive targets for total synthesis. Aside from providing a response to the intrinsic chemical challenge, total synthesis could allow for the achievement of molecular modifications of a nature not readily accessible by the manipulative approach of partial synthesis. Such analogues could be helpful in the important matter of sorting the interplay of chemical structure and biological function. Thus far, however, these systems have been approached via known pentoses and hexoses[2] by resorting to chain extensions and multiple adjustments of functional groups.

As part of our studies of the cyclocondensation of aldehydes with dienes,[3a,b] we have undertaken the total synthesis of several of the biologically active higher monosaccharides. Below are related a series of experiments that have resulted in a de novo stereospecific route to the aminooctose lincosamine (**2**). As its methyl thioglycoside ((methylthio)lincosaminide = MTL, **3**), lincosamine is the saccharide portion of the clinically important antibiotic lincomycin (**1**).[4] Numerous synthetic undertakings in the lincosamine series have been confined to chain extensions and modifications of D-galactose[5] with little in the way of stereocontrol of the side-chain functionality.

We hoped that methodology might be uncovered, wherein a *trans*-propenyl function, such as is found in structure **4**, could accommodate the installation of the *erythro* vicinal amino alcohol function at the appropriate carbons and in the proper stereochemical sense (relative to the pyranose chirality) required for lincosamine. Thus, a crucial element of the investigation was the study of the facial bias, if any, that would be exhibited by such a double bond toward attack by external reagents. *That such a bias has indeed been uncovered for several crucial reactions (vide infra) is a favorable augury for future prospects in this area.*

Our total synthesis starts with the cyclocondensation of crotonaldehyde[3b] with diene **5**[6] under the influence of $BF_3{\cdot}O(Et)_2$ ((i) CH_2Cl_2, −78 °C; (ii) TFA, room temperature). There is thus obtained a 67% yield of **6**.[7] Previous studies with a diene related to **5**[3a] and subsequent studies with **5**[8]itself have served to indicate

(1) Representative examples. (a) Heptoses, purpurosamine: 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.

(2) For example: (a) Purpurosamine B: Honda, Y.; Suami, T. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2825. (b) KDO: Ref 1b. (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.

(3) (a) Danishefsky, S.; Kerwin, J. F., Jr.; Kobayashi, S. *J. Am. Chem. Soc.* **1982**, *104*, 358. (b) Danishefsky, S.; Kerwin, J. F.; *J. Org. Chem.* **1982**, *47*, 3183.

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

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

(6) Prepared from 1-[(trimethylsilyl)oxy]-4-methoxy-3-buten-2-one (ref 3a) via desilylation (MeOH, room temperature), benzoylation (PhCOCl, Et_3N, DMAP/CH_2Cl_2), and silylation (TMSOTf, Et_3N/Et_2O).

(7) All isolated compounds gave satisfactory IR, ^1H NMR (270 or 500 MHz), ^{13}C NMR (cmpd **6-14**), and elemental analyses (cmpd **8-13**) or exact masses (cmpd **6**, **7**, **14**, **15**).

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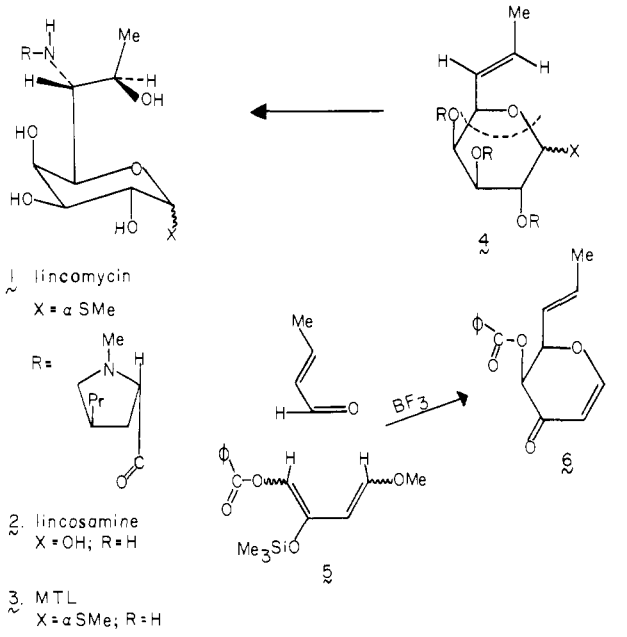
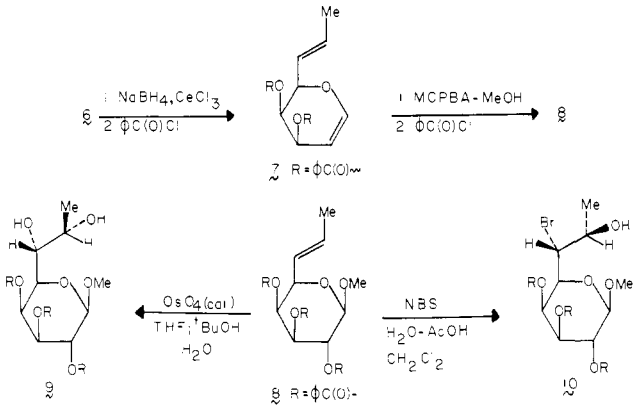
that cyclocondensation reactions of 1,2,4-trioxgenated dienes with aldehydes provide a stereoselective route to "galactosidal" congeners (cf. **6**).

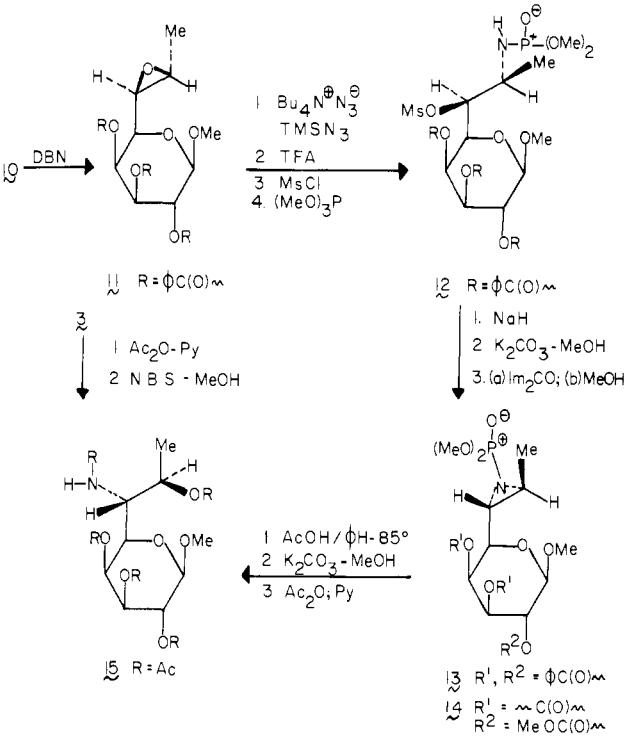


A Luche-type reduction of **6**[9] followed by benzoylation afforded the fully synthetic galactal analogue **7**[7,10] in 71% yield. Reaction of **7** with *m*-chloroperbenzoic acid in methanol[11] followed by benzoylation provided (64%) the methyl β-galactoside **8**[7,12,13] (mp 201–202 °C). The stage was now set to investigate the diastereotopic consequences of electrophilic attack on the *trans*-propenyl function. Fortunately, two key reactions occur with very high facial selectivity. Compound **8** undergoes smooth vicinal hydroxylation[14,15] to afford the *threo* diol **9**[7] (mp 189–190 °C) in



89% yield as the only observed product. Similarly, reaction of **8** with aqueous *N*-bromosuccinimide provided (92%) cleanly the bromohydrin **10**[7] (mp 206–207 °C dec). *The stereospecific access to the octoses bearing six contiguous centers of heteroatom chirality, which is available by this new chemistry, is a central element of our synthetic plans for many of the higher monosaccharides.*

For the lincosamine objective, bromohydrin **10** was converted (96%) to epoxide **11**[7] (mp 198–199 °C). Azidolysis of the epoxide was smoothly achieved with tetra-*n*-butylammonium azide in the presence of trimethylsilyl azide. The azidohydrin obtained upon desilylation (TFA/MeOH) was converted to the *N*-(dimethylphosphoryl)aziridine **13**[7] (61% from **11**) as shown.[16] To attain regiochemical control[17] over the solvolytic opening of the aziridine, it was necessary to modify the protective arrangement on the pyranose ring. This modification was accomplished by debenzoylation followed by reaction of the 2,3,4-triol with carbonyldiimidazole.[18] This provided the 3,4-cyclic carbonate while the C_2 oxygen emerged as the mixed imidazolide. Methanolysis of this product produced compound **14**[7] (71% from **13**). The *N*-phosphorylaziridine linkage undergoes acetolysis[19] with strict regiochemical control by the action of acetic acid in benzene (85 °C). Deprotection of all the blocking groups was accomplished through prolonged treatment with potassium carbonate in methanol. Peracetylation of the resultant (±)-β-methyllincosaminide[12] afforded compound **15**[7] (mp 255–257 °C). The infrared and NMR (500 MHz) spectra and chromatographic properties of fully synthetic **15**, thus prepared, were identical with those of **15** derived from (methylthio)lincosaminide (**3**).[20] A versatile, fully synthetic route to lincosamine has thus been achieved.



Acknowledgment. An American Cancer Society Postdoctoral Fellowship (PF2020) to Eric R. Larson is gratefully acknowledged. Additional support from Public Health Service Grant HL49784 was forthcoming. The authors thank Dr. David White of the Upjohn Co. for a generous sample of α-(methylthio)lincosaminide. NMR spectra were obtained through the auspices of the Northwest Regional N.S.F./N.M.R. Facility at Yale University, which was supported by N.S.F. Chemistry Division Grant CHE 7916210.

(8) Unpublished results of C. Maring of these laboratories.
(9) Luche, J.-L.; Gemal, A. L. *J. Am. Chem. soc.* **1979**, *101*, 5848. Slow addition of ethanolic $NaBH_4$ to a cold (−78 °C) methanolic solution of **6** and $CeCl_3 \cdot 7H_2O$ with careful maintenance of the reaction temperature was required to achieve the observed stereoselectivity.
(10) The C-3 epimer of **7** is obtained in 10% yield.
(11) Sweet, F.; Brown, R. K. *Can. J. Chem.* **1966**, *44*, 1571.
(12) For convenience, only a single enantiomer of the racemate is shown.
(13) The corresponding α-glycoside is obtained in 25% yield.
(14) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1967**, 1973.
(15) The stereochemistry of **9** was determined by chemical methods, which will be described in the full report of this work.
(16) Cf.: Nakatsubo, F.; Fukuyama, T.; Cocuzza, A. J.; Kishi, Y. *J. Am. Chem. Soc.* **1977**, *99*, 8115.
(17) Acetolysis of **12** took an undesired course, which will be described in the full report of this work.
(18) Kutney, J. P.; Ratcliffe, A. H. *Synth. Commun.* **1975**, *5*, 47.
(19) Cf.: Lambert, R. F.; Thompson, G.; Kristofferson, C. E. *J. Org. Chem.* **1964**, *29*, 3116.
(20) The procedure used to convert MTL (**3**) to **15** was suggested by Dr. David White of the Upjohn Co.