Anal. Calcd for $C_{10}H_{19}NO$: C, 71.00; H, 11.24; N, 8.28. Found: C, 70.88; H, 11.07; N, 8.07.

2-(2-Aminoethyl)bicyclo[2.2.2]oct-2-ene Hydrobromide (2). A 250-mL, three-necked, round-bottomed flask was equipped with a nitrogen inlet and thermometer adapter and heated at 210 °C for 8–12 h. While cooling under dry nitrogen, a condensor with a line to an oil bubbler and a magnetic stirbar were added. The flask was charged with 100 mL of dry, freshly distilled *p*-xylene and 2.1 mmol (550 mg) of triphenylphosphine (99%). With vigorous stirring, under nitrogen, 1.9 mmol (0.1 mL) of bromine was added via micropipet, and a precipitate, presumably triphenylphosphine dibromide, formed. The mixture was heated to 80 °C to drive off any unreacted bromine and then cooled to 40 °C, at which time 1.9 mmol (328 mg) of 1 was added as a solid, and heating was reinitiated. When the reaction temperature reached 70–80 °C, a catalytic amount of hydroquinone was added, the flask covered to omit light, and heating continued to 115–125 °C. The evolution of HBr was monitored by moistened pH paper, and the reaction was allowed to heat until 30 min past the point where HBr could no longer be detected (approximately 2 h). The reaction was then cooled to room temperature, and the product, as the hydrobromide salt, was isolated by suction filtration and washed with benzene. The *p*-xylene was washed three times with water, and the aqueous phases were lyophilized. A 77.8% yield of crude endo- and exocyclic olefinic isomers was obtained. The isomers could be separated by repeated recrystallization from a methanol/ether solution. Pure **2** decomposed at 229–232 °C: ^{1}H NMR δ 6.1 (2 q, 1 H), 3.1 (t, 2 H), 2.43 (m, 4 H), 1.25 (m, 8 H); ^{13}C NMR, see Table I.

Anal. Calcd for $C_{10}H_{18}NBr$: C, 51.72; H, 7.76; N, 6.03; Br, 34.48. Found: C, 51.68; H, 7.90; N, 5.94; Br, 34.56.

2-(2-Aminoethylidene)bicyclo[2.2.2]octane Hydrobromide (3). A 250-mL three-necked flask, equipped and treated as above, was charged with 2.1 mmol of triphenylphosphine (99%) and 50 mL of bis(2-ethoxyethyl) ether. Bromine (0.1 mL) was added as previously described, and the mixture was heated to 50 °C. A solution of 1.9 mmol of **1** in 50 mL of solvent was added in a dropwise fashion. The remainder of the reaction proceeded as previously described. After the mixture cooled, a majority of the solvent was removed by distillation under vacuum. Benzene was added to the residue and, if the product precipitated, it was filtered and washed with benzene. In cases where precipitation did not occur, the organic phase was extracted three times with water and the water evaporated in vacuo. A 35% yield of crude **3** resulted. Purification was accomplished by recrystallization from a methanol/ether solution. Pure **3** decomposed at 222–225 °C: ^{1}H NMR δ 5.22 (m, 1 H), 3.56 (d, 2 H), 2.27 (m, 3 H), 1.56 (m, 9 H); ^{13}C NMR, see Table I.

Anal. Calcd for $C_{10}H_{18}NBr$: C, 51.72; H, 7.76; N, 6.03; Br, 34.48. Found: C, 51.63; H, 7.78; N, 5.97; Br, 34.36.

3-Bromo-2-[2-[[(*p*-methoxybenzyl)carbonyl]amino]ethyl]bicyclo[2.2.2]octane (5). The dehydrohalogenation reaction proceeded as described for the synthesis of **2**, only the protection from light and addition of hydroquinone steps were eliminated. The crude products were recrystallized from methanol/ether and dried. One gram of the mixed hydrobromides was allowed to stir in dry benzene at room temperature for 4 h with 1 mL of dry pyridine and 0.617 g of freshly distilled (*p*-methoxyphenyl)acetyl chloride, prepared in the standard manner from the acid and $SOCl_2$. The organic phase was washed consecutively with water, 10% HCl, 10% NH_4OH, and water and dried over anhydrous $MgSO_4$. The products were isolated as a medium yellow oil. A 10% aqueous neutral alumina column (2 × 40 cm) was prepared in hexane, and 400 mg of the product mixture was eluted with 250-mL aliquots of the following solvent mixtures in a nonpolar gradient: hexane/benzene, 4:1, 2:1, 1:1, 0:1; benzene/chloroform, 4:1, 2:1, 1:1, 0:1; chloroform/ether, 4:1, 3:1, 2:1, 1:1, 0:1. Fractions of 50 mL each were collected. Fractions 24–31 were combined and recrystallized twice from ether/petroleum ether to give approximately 50 mg of **5** as a white powder: mp 110–111 °C; ^{1}H NMR δ 4.17 (m, 1 H), 3.10 (t, 2 H), 3.76 (s, 3 H), 3.46 (s, 3 H), 5.43 (br, 1 H); IR (KBr) 1640, 1616, 1250, 1035 cm^{-1}; mass spectrum (ion block temperature 110–120 °C), *m/e* 379, 381 (m^+), 299 (m^+ – HBr), 82 ($H^{81}Br$), 80 ($H^{79}Br$).

Anal. Calcd for $C_{19}H_{26}NO_2Br$: C, 60.00; H, 6.84; N, 3.68; Br, 21.05. Found: C, 60.20; H, 7.00; N, 3.68; Br, 20.90.

Acknowledgment. Drs. Wallace J. Murray and Ercoli Cavalieri at the University of Nebraska Medical Center and Dr. James Henkel at the University of Connecticut are gratefully acknowledged for valuable discussion and suggestions. The mass spectra were run by Dr. Phillip Issenberg at the University of Nebraska Medical Center. V.F.R. acknowledges financial support from the American Foundation for Pharmaceutical Education and from the University of Nebraska in the forms of the Blanche Widaman and Maude Hammond Fling Fellowships.

Registry No. **1**, 80641-34-5; **2**, 80641-35-6; **3**, 80641-36-7; **5**, 80641-37-8; **6**, 53844-99-8; **7**, 53845-00-4; **8**, 4893-13-4; **9**, 18684-63-4; **10**, 5019-82-9; **11**, 80641-38-9; bicyclo[2.2.2]oct-2-ene, 931-64-6; acetonitrile, 75-05-8; (*p*-methyoxyphenyl)acetyl chloride, 4693-91-8.

Communications

Total Synthesis of Carbohydrates: Stereoselective Syntheses of 2,6-Dideoxy-D-*arabino*-hexose and 2,6-Dideoxy-D-*ribo*-hexose

Summary: Short, highly stereoselective syntheses of the title carbohydrates from allylic alcohol precursors are described. A synthesis of the racemic *arabino*-deoxyhexose is also described. These syntheses feature the highly regioselective epoxide ring opening reactions of intermediates **7**, **11**, and **12** and the asymmetric epoxidation–kinetic resolution of allylic alcohol **10**.

Sir: In connection with a synthesis of olivomycin A (**1**)[1] we require access to a number of dideoxy and branched-chain sugars.[2] Syntheses of the requisite monosaccharides starting from available hexoses have been reported, but in some cases the routes require many synthetic transformations.[2a,3] This problem is frequently encountered in syntheses which originate from carbohydrate "chiral pool" precursors.[4] On the other hand, chemical syntheses

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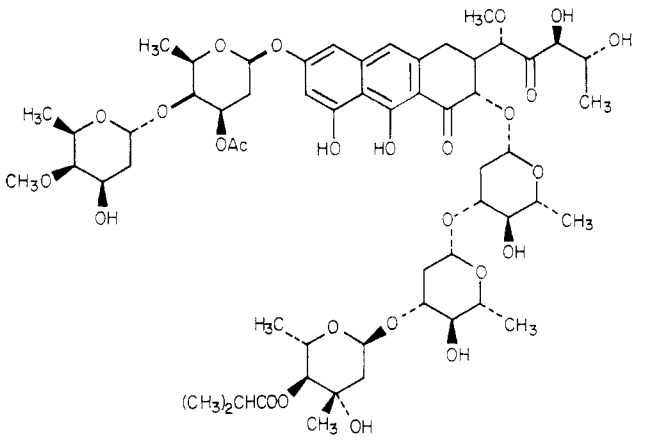
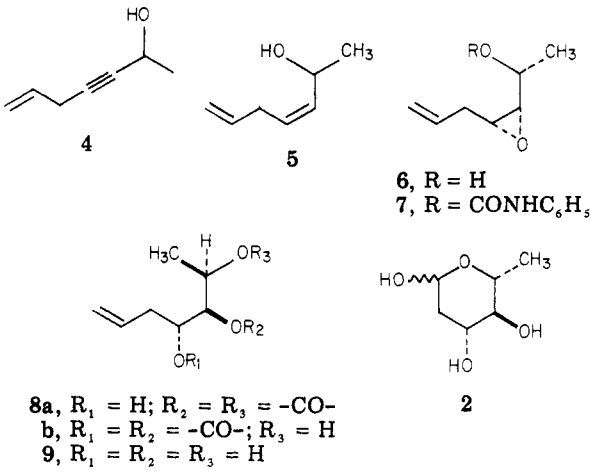


olivomycin A (1)

of these, as well as other, monosaccharides have until now suffered from a low degree or lack of stereoselectivity and generally have afforded racemic products.[5] These factors prompted us to initiate studies of carbohydrate synthesis starting from noncarbohydrate precursors.[6] We describe herein two short, highly stereoselective syntheses, one racemic and one chiral, of 2,6-dideoxy-D-*arabino*-hexose (**2**; olivose), which is a component of a number of natural products including olivomycin A (**1**)[1] and chlorothricin.[7] We also report a synthesis of 2,6-dideoxy-D-*ribo*-hexose (**3**; digitoxose, a component of the cardiac glycosides)[8] from intermediates common to the synthesis of optically active **2**. The methods developed in connection with these syntheses impinge on the general problem of stereochemical control in acyclic systems[9] and are illustrative of the approach which we intend to extend to other problems in carbohydrate chemistry.

A stereoselective synthesis of racemic a synthesis of optically active Treatment of 3-butyn-2-ol with excess allyl chloride and CuCl (0.07 equiv) in aqueous methanol maintained between pH 7.5 and 8.5 by the addition of 1 N NaOH afforded **4** in 95% yield.[10] Reduction of **4** with Zn–Cu couple in methanol (sealed tube, 120 °C) afforded cis olefin **5**, uncontaminated with the trans isomer or overreduced materials, in 67–73% yield.[11,12a,c] Epoxidation of **5** with *tert*-butyl hydroperoxide (1.1 equiv) and titanium isopropoxide (1.0 equiv) in CH_2Cl_2 at −20 °C afforded threo epoxide **6**[12a,b] with high stereoselectivity (>19:1; 80% yield).[13] Treatment of **6** with phenyl isocyanate in pyridine afforded phenylurethane **7**[12a,b] (mp 55.5–56.0 °C; 69% yield from **5**) which when treated with BF_3·Et_2O (1.1 equiv) in CH_2Cl_2 at 23 °C for 0.5 h followed by hydrolysis (1 N H_2SO_4, 23 °C, 3 h) of the intermediate iminocarbonates led to a mixture of regioisomeric carbonates **8a** and **8b** (95% yield).[12a,14,15] Treatment of this mixture with cat-



4 **5** **6**, R = H; **7**, R = $CONHC_6H_5$

8a, R_1 = H; R_2 = R_3 = -CO-
b, R_1 = R_2 = -CO-; R_3 = H
9, R_1 = R_2 = R_3 = H

2

alytic $NaOCH_3$ in CH_3OH (23 °C, 24 h) yielded a single triol, *arabino*-**9**[12a,c] (95% yield), ozonization of which (CH_3OH, −20 °C, $(CH_3)_2S$ workup) afforded racemic **2** (85% yield).

We planned originally to achieve an asymmetric synthesis of optically active **2** by adopting simple modifications of the previous route, in which propargyl alcohol intermediate **4** would be generated by an asymmetric reduction of the corresponding ketone.[16] This strategy, however, has been obviated by the powerful method of asymmetric epoxidation–kinetic resolution recently developed by Sharpless and co-workers.[13] Thus, treatment of racemic **10** with 1.0 equiv of Ti(O-*i*-Pr)$_4$, 1.5 equiv of (−)-diisopropyl tartrate ((−)-DIPT), and 0.4 equiv of *tert*-butyl hydroperoxide (TBHP) in CH_2Cl_2 at −20 °C afforded, after workup,[13] chromatographic separation of products by using a Waters Prep 500 liquid chromato-

(4) (a) Fraser-Reid, B.; Anderson, R. C. *Prog. Chem. Org. Nat. Prod.* **1980**, *39*, 1. (b) Hanessian, S. *Acc. Chem. Res.* **1979**, *12*, 159. (c) Fraser-Reid, B. *Ibid.* **1975**, *8*, 192. (d) See also ref 5b.

(5) (a) Jones, J. K. N.; Szarek, W. A. In "The Total Synthesis of Natural Products"; Apsimon, J., Ed.; Wiley-Interscience, 1973; Vol. I, p 1. (b) Hough, L.; Richardson, A. C. "*The Carbohydrates*"; Academic Press: New York, 1972; Vol IA, p 113. (c) Lemal, D. M.; Pacht, P. D.; Woodward, R. B. *Tetrahedron* **1962**, *18*, 1275. (d) Korte, F.; Claussen, U.; Göhring, K. *Ibid.* **1962**, *18*, 1257. (e) Grisebach, H.; Hofheinz, W.; Doerr, N. *Chem. Ber.* **1963**, *96*, 1823. (f) Fuganti, C.; Grasselli, P. *J. Chem. Soc., Chem. Commun.* **1978**, 299. (g) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1981**, *46*, 227.

(6) This is a subject of much current interest at MIT. See also the accompanying communications by Professors K. B. Sharpless and S. Masamune.

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(8) Elderfield, R. C. *Adv. Carbohydr. Chem.* **1945**, *1*, 147.

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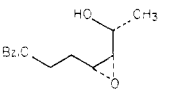
(10) Kurtz, P. *Justus Liebigs Ann. Chem.* **1962**, *658*, 6.

(11) (a) Clarke, A. J.; Crombie, L. *Chem. Ind.* **1957**, 143. (b) Crombie, L; Jenkins, P. A.; Roblin, J. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1099. (c) Bergman, R. G. *J. Am. Chem. Soc.* **1969**, *91*, 7405.

(12) (a) The spectroscopic data obtained for all new compounds was fully consistent with the assigned structures. (b) A satisfactory combustion analysis (±0.3%; C, H, and N (where appropriate)) was obtained for this compound. (c) The elemental composition of this compound was verified by a precise mass measurement.

(13) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.

(14) The conditions used for the conversion of **6** to **9** were selected during preliminary investigations involving epoxide i. Ring-opening

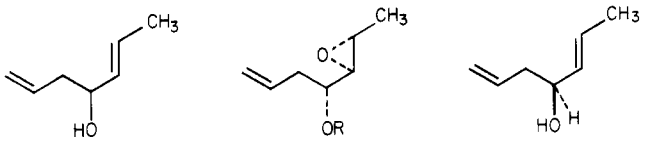


i

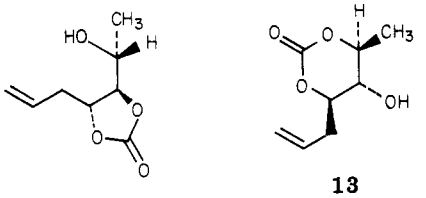
reactions of a number of derivatives (including urethanes, carbonates, and the chloral hydrate adduct) were investigated. Best results were obtained with the phenylurethane derivative, but only when BF_3·Et_2O was used to promote the reaction. The use of protic acids led in most cases to mixtures of α- and β-opened products. An account of these studies will be published separately. For another example of a phenylurethane-promoted epoxide ring opening reaction, see Corey, E. J.; Hopkins, P. B.; Munroe, J. E.; Marfat, A.; Hashimoto, S. *J. Am. Chem. Soc.* **1980**, *102*, 7986.

(15) Control experiments established that the acyl-transfer reaction occurs in the presence of BF_3·Et_2O at the stage of the iminocarbonates. All attempts to suppress the acyl-transfer reaction in order to obtain exclusively **8a** have failed.

(16) (a) Brinkmeyer, R. S.; Kapoor, V. M. *J. Am. Chem. Soc.* **1977**, *99*, 8339. (b) Cohen, N.; Lopresti, R. J.; Neukom, C.; Saucey, G. *J. Org. Chem.* **1980**, *45*, 582. (c) Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 867. (d) Vigneron, J.-P.; Bloy, V. *Tetrahedron Lett.* **1980**, *21*, 1735. (e) Nishizawa, M.; Yamada, M.; Noyori, R. *Ibid.* **1981**, *22*, 247.



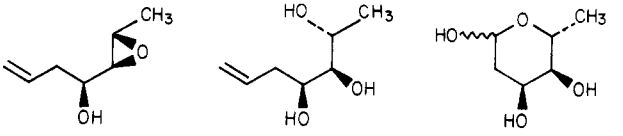
10 (+)-11, R = H (+)-12, R = $CONHC_6H_5$ (−)-10



(+)-8b 13

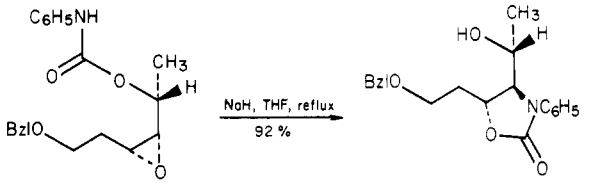
graph,[17] and distillation of the individual fractions, erythro epoxide (+)-11[12a,b] (27% yield; $[\alpha]^{25}_D$ +3.0° (*c* 0.072, CH_2Cl_2); >95% ee by Mosher analysis[18]), kinetically resolved (−)-10 (33% yield; $[\alpha]^{25}_D$ −8.9° (*c* 0.094, CH_2Cl_2); 72% ee by Mosher analysis), and recovered (−)-DIPT. Treatment of (+)-11 with phenyl isocyanate in pyridine afforded urethane 12[12a,b] (89% yield; mp 57.0–57.5 °C; $[\alpha]^{25}_D$ +24.1° (*c* 0.011, CH_2Cl_2), which when treated sequentially with $BF_3{\cdot}Et_2O$ (0.95 equiv) in *diethyl ether* at 0 °C for 1 h followed by 1 N H_2SO_4 (3 h, 23 °C) yielded a 10:1 mixture of arabino carbonate (+)-8b and ribo carbonate 13.[19] Separation of this mixture by silica gel chromatography afforded (+)-8b[12a,b] ($[\alpha]^{25}_D$ +59.3° (*c* 0.088, CH_2Cl_2); 80% yield from 12), which was then transformed into (+)-2 by using the two-step procedure described previously.[20] This synthesis of 2 proceeds in six steps starting from crotonaldehyde and allyl bromide and is well suited for the preparaton of the (−)-enantiomer.[13] By comparison, the shortest synthesis of (+)-2 starting from D-glucose proceeds in eight steps;[3a] the (−)-enantiomer is available in five steps starting from L-rhamnose.[3c]

A crucial aspect of both of these syntheses of 2 is the intramolecular delivery of an oxygen nucleophile to the α-position of the epoxy urethane intermediates 7 and 12.[14,21] In the absence of overriding steric or stereoelectronic factors, epoxy allylic alcohols undergo ring-opening reactions at the β-position.[21a] The latter mode of reactivity is illustrated by an expeditious synthesis of 2,6-dideoxy-D-*ribo*-hexose (3; digitoxose). Thus, acidic hydrolysis of (−)-11 (prepared by epoxidation of kinetically resolved (−)-10 (72% ee) with $Ti(O\text{-}i\text{-}Pr)_4$, TBHP (0.8 equiv), and (+)-diethyl tartrate, CH_2Cl_2, −20 °C; 75% yield; 95% ee by Mosher analysis) in aqueous Me_2SO (3:1 Me_2SO/1 N H_2SO_4) afforded ribo triol 14[12a,c] (mp 54–55 °C; $[\alpha]^{25}_D$ −19.3° (*c* 0.052, acetone) in 84% yield. Ozonization (O_3, CH_3OH, −20 °C; $(CH_3)_2S$ workup; 79% yield) of (−)-14 so obtained then completed the present five-step synthesis



(−)-11 (−)-14 (+)-3

of (+)-3.[22] Application of neighboring group assistance[14,21] to overcome the preferred mode of reactivity of epoxy allylic alcohols well. to be a useful strategy not only for delivery of oxygen nucleophiles to the α-position but nitrogen nucleophiles as well:



15 16

Extension of these methods and strategies to the synthesis of other deoxy and amino sugars are in progress and will be reported upon in due course.

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(17) This separation was performed by using a single silica gel cartridge and 30:70 EtOAc–hexane as eluant. Allylic alcohol 10 elutes first (t_R 12 min, 100 mL/min) followed by DIPT (t_R 18 min) and epoxide 11 (t_R 23 min).

(18) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(19) The ratio of arabino (8b) to ribo (13) carbonates was 4:1 when the ring-opening reaction of 12 was performed in CH_2Cl_2.

(20) Synthetic (+)-2 (oil; $[\alpha]^{25}_D$ +19.6 ± 0.5° (*c* 0.029, H_2O, 22-h equilibration)) was identical in all respects with an authentic sample prepared by degradation of D-glucose[3a,b] (oil; $[\alpha]^{25}_D$ +19.5 ● 2° (*c* 0.016, H_2O, 23-h equilibration)). A value of $[\alpha]^{25}_D$ −18.2 ± 2° (*c* 0.986, H_2O) has been reported for the (−)-enantiomer (ref 3c).

(21) (a) Buchanan, J. G.; Sable, H. Z. *Sel. Org. Transform.* **1972**, *2*, 1 and references cited therein. (b) Urethanes are well-known to participate in neighboring group assisted reactions: Capon, B. *Q. Rev. Chem. Soc.* **1964**, *18*, 45. Pauls, H. W.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1980**, *102*, 3956.

(22) (a) Synthetic digitoxose ((+)-3; mp 102–103 °C (uncorrected; crystallized from EtOAc and dried over P_2O_5); $[\alpha]^{25}_D$ +48.8 ● 2° (*c* 0.013, H_2O, 36-h equilibration)) was identical in all respects with a sample obtained from Aldrich Chemical Co. (mp 105–106 °C; $[\alpha]^{25}_D$ +47.3 ± 1.5° (*c* 0.013, H_2O)). The following data have previously been reported for natural digitoxose: mp 110 °C, $[\alpha]^{20}_D$ +46.3° (ref 8); mp 108–110 °C, $[\alpha]^{19}_D$ +50.2 ± 2° (*c* 1.65, H_2O, 1 h) (Bollinger, H. R.; Ulrich, P. *Helv. Chim. Acta* **1952**, *35*, 93); and mp 105–108 °C, $[\alpha]^{22}_D$ +47.8° (*c* 1, H_2O, 1 h) (Horton, D.; Cheung, T.-K.; Weckerle, W. *Methods Carbohydr. Chem.* **1980**, *8*, 195. (b) The present synthesis would be shortened by one step if (−)-11 were produced directly by asymmetric epoxidation of racemic 10 by using (+)-DIPT as the chiral auxiliary.

(23) (a) Roger and Georges Firmenich Career Development Assistant Professor of Natural Products Chemistry. (b) NCI Trainee (Grant No. T32-CA-09258).

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Synthesis of Saccharides and Related Polyhydroxylated Natural Products. 1. Simple Alditols

Summary: A new approach to sugar synthesis is demonstrated through syntheses of tetritols, pentitols, and hexitols; titanium-catalyzed asymmetric epoxidation and a new selective opening reaction of 2,3-epoxy alcohols play essential roles.

Sir: The structures of monosaccharides represent in a formal sense a linear combination of the 1,2- and/or 1,3-diol units. Thus, in the manner that the synthesis of macrolide[1] and ionophore[2] antibiotics is reduced to a single,

(1) For a recent review of the chemistry and biochemistry of macrolide antibiotics, see: Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585.

0022-3263/82/1947-1373$01.25/0