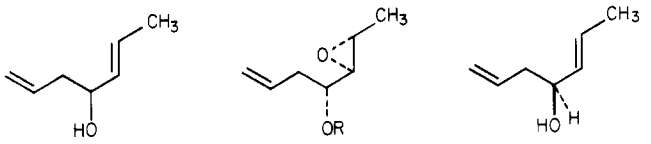
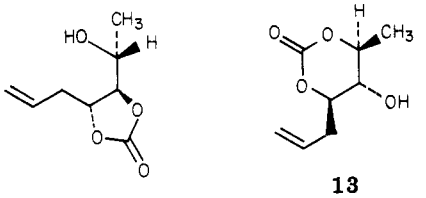


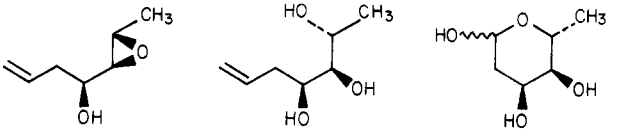
10 (+)-11, R = H (+)-12, R = $CONHC_6H_5$ (−)-10



(+)-8b 13

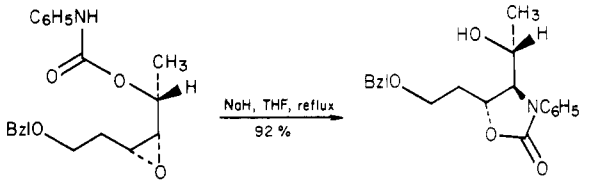
graph,[17] and distillation of the individual fractions, erythro epoxide (+)-11[12a,b] (27% yield; $[\alpha]^{25}_D$ +3.0° (*c* 0.072, CH_2Cl_2); >95% ee by Mosher analysis[18]), kinetically resolved (−)-10 (33% yield; $[\alpha]^{25}_D$ −8.9° (*c* 0.094, CH_2Cl_2); 72% ee by Mosher analysis), and recovered (−)-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

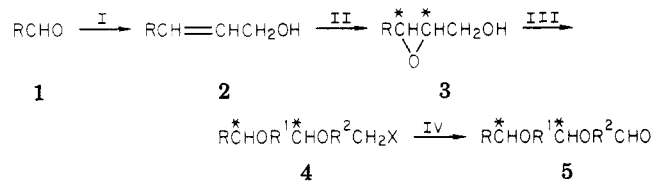
general problem of constructing the 1,3-diol system,[3] a similar retrosynthesis of the saccharides (into the 1,2- and 1,3-diols) is easily conceived. With this simple view, we have explored a *systematic, general* approach to a wide variety of saccharides and many other polyhydroxylated natural products such as palytoxin, a toxic substance of marine origin with a C-115 main-chain backbone.[4] The synthesis, in essence, consists of repetition of sequence A and/or B, both of which involve a linear two-carbon extension. The efficient execution of these transformations,

$$\mathrm{RCHO} \rightarrow \mathrm{R^*CHOH^*CHOHCHO} \qquad \text{(A)}$$

$$\mathrm{RCHO} \rightarrow \mathrm{R^*CHOHCH_2CHO} \qquad \text{(B)}$$

though superficially straightforward, has become feasible only in recent years with the advent of two highly enantioselective synthetic methodologies: asymmetric epoxidation[5] and the asymmetric aldol reaction.[3,6] Numerous advantages should accrue from this general approach.[7] We outline herein our preliminary studies on sequence A and then elaborate on sequence B in the accompanying communication.[8]

Sequence A involves four key transformations. The first



step (I) consists of the construction of an *E* or *Z* allylic alcohol (**2**; or its precursor) via a Wittig reaction. It is well-known that the use of a stabilized Wittig reagent in a nonpolar solvent leads to the *E* olefinic product.[9] The corresponding *Z* isomer, however, very often constitutes the major product if the reaction is carried out in a hydroxylic solvent such as methanol.[9] Moreover, Bestmann's reagent, $Ph_3P{=}CHCH(OEt)_2$, provides the *Z* product exclusively.[10] In the next step (II), the titanium- and vanadium-mediated epoxidations[5,11] developed in one of our laboratories, together with classical reagents such as peracids and osmium tetroxide, play a key role. While these first two steps are an obvious choice for the overall conversion of **1** to **5**, the ensuing steps, III and IV, involve both little known and new transformations of epoxy alcohols (**3**). We have now established at least three pathways through which conversion of **3** → **4** or **5** proceeds with high stereo- and regioselectivity. The synthesis of simple known sugars and sugar alcohols, chosen as models in this exploratory work, best illustrate our approach.

Tetritols. Because of the ready availability of the monobenzyl ethers, **6**[12a] and **7**,[12b] this series omits step I (Scheme I). Thus, asymmetric epoxidation of both **6** and **7** with titanium tetraisopropoxide and *tert*-butyl hydroperoxide, using (−)- and (+)-diethyl tartrate or diisopropyl tartrate (hereafter abbreviated as AE, (−)- or (+)-DET or -DIPT), proceeds satisfactorily to yield **8** and **9**, respectively.[13] The exposure of **8** to sodium benzenethiolate and sodium hydroxide in a protic solvent leads, through base-catalyzed rearrangement of the epoxy alcohol moiety,[14] to exclusive attack of benzenethiolate at the C(1) position, yielding the threo diol **10** (this new transformation is discussed latter; see **54** and **55**).[15] This product provides for protection of the two newly generated hydroxyl groups and sets the stage for a facile Pummerer rearrangement.[16] Indeed compound **10** is converted in excellent yield into **11**, which in turn is reduced to the corresponding alcohol **12**.[13] The stereochemistry and absolute configuration of **12** have been established via the corresponding tetraacetate **13**, identical with that obtained from L-threitol.

Another stereoselective epoxide opening employs attack by an intramolecular oxygen nucleophile at the C(2) center of **8**.[17,18] The phenylurethane **14** undergoes smooth ring opening with the aid of an acid catalyst, and the resulting carbonate **15** is converted to **16** with potassium hydroxide in aqueous methanol and then to the known tetraacetate

(2) For a recent review, see: Westley, J. W. *Adv. Appl. Microbiol.* **1977**, *22*, 177.

(3) For representative total syntheses using this concept, see the following: (a) 6-Deoxyerythronolide B: Masamune, S.; Hirama, M.; Mori, S.; Ali, Sk. A.; Garvey, D. S. *J. Am. Chem. Soc.* **1981**, *103*, 1568. (b) Rifamycin S: Nagaoka, H.; Rutsch, W.; Schmid, G.; Iio, H.; Kishi, Y. *Ibid.* **1980**, *102*, 7965. Also, Masamune, S.; Imperiali, B.; Garvey, D. S.; Toyoda, T., to be published.

(4) (a) Hirata, Y.; Uemura, D.; Ueda, K.; Takamo, S. *Pure Appl. Chem.* **1979**, *51*, 1875. (b) Uemura, D.; Ueda, K.; Hirata, Y.; Naoki, H.; Iwashita, T. *Tetrahedron Lett.* **1981**, *22*, 1909, 2781 and references quoted therein. (c) Scheuer, P. J.; Moore, R. E. *Science* **1971**, *172*, 495. (d) Moore, R. E.; Bartolini, G. *J. Am. Chem. Soc.* **1981**, *103*, 2491.

(5) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Rossiter, B. E.; Katsuki, T.; Sharpless, K. B. *Ibid.* **1981**, *103*, 464. (c) Martin, V. S.; Woodward, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *Ibid.* **1981**, *103*, 6237.

(6) (a) Masamune, S.; Choy, W.; Kerdesky, F.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566. (b) Evans, D. A.; McGee, L. R. *Ibid.* **1981**, *103*, 2876. (c) Evans, D. A.; Bartroli, J.; Shih, T. L. *Ibid.* **1981**, *103*, 2127. (d) Heathcock, C. H.; White, C. T. *Ibid.* **1979**, *101*, 7076, 7077.

(7) In the past most sugar syntheses have involved modification of existing sugars. Recorded total syntheses have usually been carried out in a racemic form and very often with rather unsatisfactory stereoselection. See: Jones, J. K. N.; Szarek, W. A. in "The Total Synthesis of Natural Products"; ApSimon, J., Ed.; Wiley-Interscience: New York, 1973; Vol. 1, Chapter 1.

(8) Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Viti, S. M., following paper in this issue.

(9) For recent reviews, see: (a) Cadogen, J. I. G. "Organophosphorus Reagents in Organic Synthesis"; Academic Press: New York, 1979. (b) Bestmann, H. J. *Pure Appl. Chem.* **1979**, *51*, 515. For most recent mechanistic discussions, see: (c) Vedejs, E.; Meier, G. P.; Snoble, K. A. J. *J. Am. Chem. Soc.* **1981**, *103*, 2823. (d) House, H. O.; Rasmusson, G. H. *J. Org. Chem.* **1961**, *26*, 4278. (e) Schlosser, M.; Tuong, H. B. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 633. For application of the Wittig reaction to saccharides, see: Zhdanov, Y. A.; Alexeev, V. G. *Adv. Carbohydr. Chem.* **1972**, *27*, 222.

(10) Bestmann, H. J.; Roch, K.; Ettlinger, M. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 687.

(11) Sharpless, K. B.; Verhoeven, T. R. *Aldrichim. Acta* **1979**, *12*, 63.

(12) (a) Danishefsky, S.; Regan, J. *Tetrahedron Lett.* **1981**, 3919. (b) Allylic alcohol **7** was prepared by borohydride reduction of the corresponding *E* α,β-unsaturated aldehyde (this aldehyde is also described in ref. 12a).

(13) Epoxy alcohols **8** and **9** and the acetonide **12** (Scheme I) have been prepared in both enantiomeric forms from D- or L-tartaric acid. See Hungerbühler, E.; Seebach, D. *Helv. Chim. Acta* **1981**, *64*, 687.

(14) Payne, G. B. *J. Org. Chem.* **1962**, *27*, 3819.

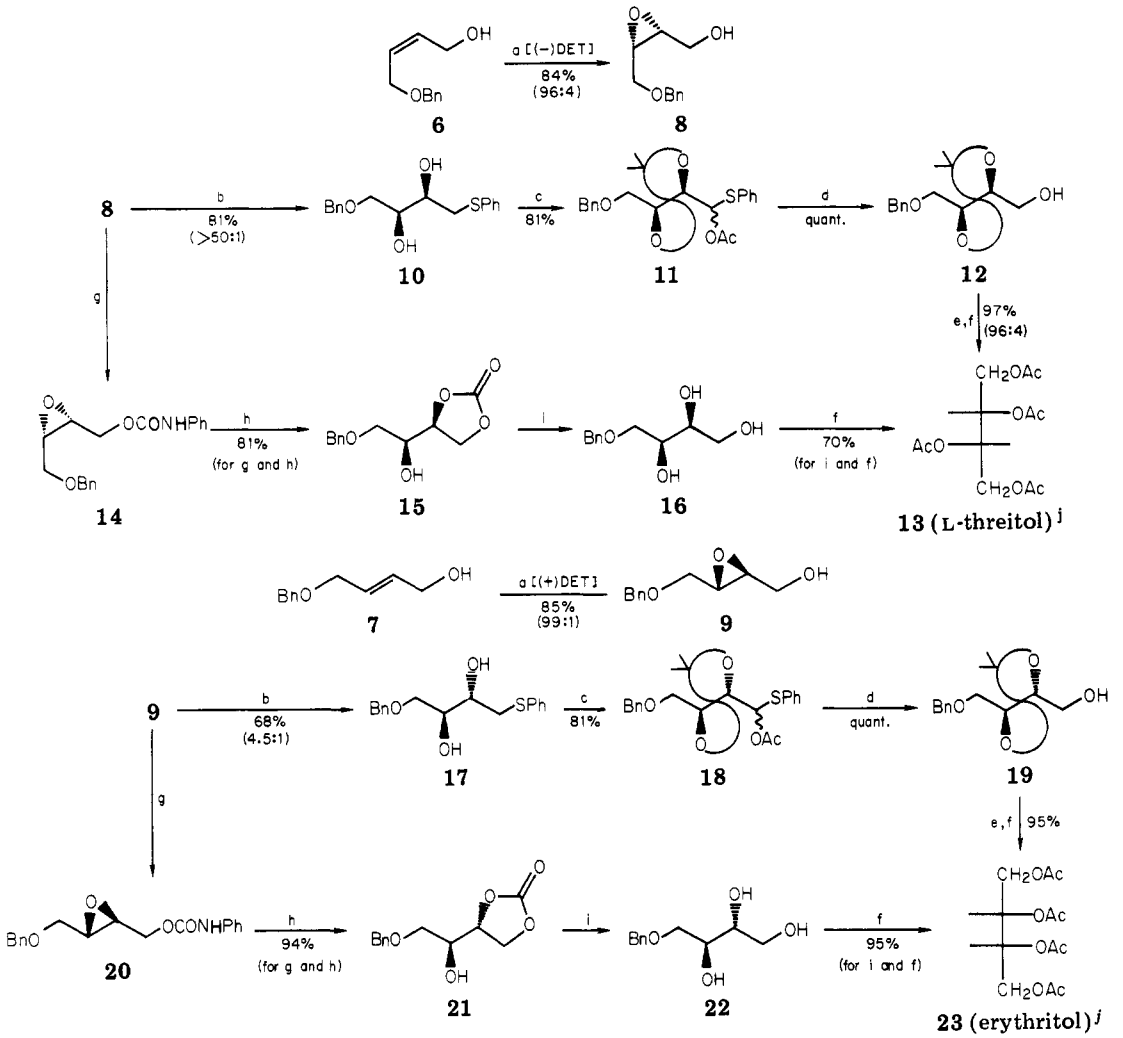
(15) Spectral data for all new compounds except for unpurified intermediates are available as supplementary material. The specific rotations $[\alpha]_D$ (°C, concentration, solvent) are as follows: **8**, +25.9 (25, 1.45, $CHCl_3$); **9**, −22.0 (24, 0.50, $CHCl_3$); **10**, +11.4 (25, 1.94, $CHCl_3$); **12**, +7.8 (25, 0.99, $CHCl_3$); **13**, −21.9 (25, 1.07, $CHCl_3$); **15**, +44.1 (25, 1.66, $CHCl_3$); **17**, +40.3 (25, 0.77, EtOH); **19**, −3.7 (26, 2.31, EtOH); **21**, −2.23 (25, 1.35, $CHCl_3$); **23**, 0.0 (23, 0.9, $CHCl_3$) meso; **24** +30.0 (21, 2.13, EtOH); **25**, +10.7 (25, 3.00, EtOH); **26**, +64.9 (21, 5.73, benzene); **27**, −16.6 (25, 2.28, EtOH); **28**, +32.4 (21.1, 1.85, EtOH); **29**, −15.8 (25, 1.99, EtOH); **30**, −2.31 (22, 1.30, EtOH); **31**, −0.42 (23, 1.92, EtOH); **32**, +13.7 (25, 1.37, EtOH); **33**, −0.63 (26, 2.35, EtOH); **34** +8.31 (24, 3.05, EtOH); **35**, +37.3 (22, 1.72, EtOH); **36**, +0.3 (23, 1.55, EtOH) meso; **37**, +37.4 (24, 1.85, EtOH); **38**, +0.2 (21, 1.82, EtOH) meso; **39**, +17.8 (25, 1.48, $CHCl_3$); **40**, −22.3 (25, 1.45, EtOH); **41**, −23.9 (25, 1.30, EtOH); **42**, +4.55 (25, 1.23, EtOH); **43**, −24.6 (25, 1.01, EtOH); **44**, −16.8 (25, 1.00, EtOH); **45**, +6.3 (25, 1.42, $CHCl_3$); **46**, −37.4 (25, 2.15, $CHCl_3$); **47**, +1.9 (25, 1.14, $CHCl_3$) **48**, −9.8 (25, 1.23, EtOH); **50**, −23.9 (25, 1.00, $CHCl_3$); **51**, −27.0 (25, 1.17, EtOH); **52**, +8.8 (24, 0.82, EtOH); **53**, 0.0 (25, 2.39, $CHCl_3$) meso.

(16) Iriuchijima, S.; Maniwa, K.; Tsuchihashi, G. *J. Am. Chem. Soc.* **1974**, *96*, 4280.

(17) This approach was brought to our attention by Professor William R. Roush. See Roush, W. R.; Brown, R. J., Preceding paper in this issue.

(18) (a) Corey, E. J.; Hopkins, P. B.; Munroe, J. E.; Marfat, A.; Hashimoto, S. *J. Am. Chem. Soc.* **1980**, *102*, 7986. (b) Buchanan, J. G.; Sable, H. Z. In "Selective Organic Transformations"; Thyogarajan, B. S., Ed.; Wiley: New York, 1972; Vol. 2, p 1 and reference cited therein. (c) Pauls, H. W.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1980**, *102*, 3956.

Scheme I. Tetritols[a]



[a] Bn = $PhCH_2$. The percentage and ratio shown in each step indicate the isolated yield of the major product and its ratio to the combined yield of all other stereo- and regioisomers. The product ratios are determined by ^1H NMR spectroscopy (250 or 270 MHz) and/or HPLC analysis. The enantiomer ratios are based on ^1HNMR analysis with $Eu(hfbc)_3$, the Mosher ester method (Dale, J. A.; Dull, G. L.; Mosher, H. S., *J. Org. Chem.* **1969**, *34*, 2543), and/or optical rotation. (a) Ti(O-*i*-Pr)$_4$, TBHP, (+)- or (-)-DET (or -DIPT) (CH_2Cl_2), -20 °C, 24 h. (b) NaOH, PhSH (dioxane, H_2O), 65 °C, 3 h. (c) i, $Me_2C(OMe)_2$, H^+; ii, *m*-CPBA (CH_2Cl_2), -20 °C, 1 h; iii, Ac_2O, NaOAc, reflux, 6 h. (d) LAH (ether), 0 °C, 1 h. (e) MeOH, H^+, 70 °C, 1 h. (f) i, H_2, Pd/C (acidic MeOH), 25 °C, 6 h; ii, Ac_2O, C_5H_5N. (g) PhNCO, $(Et)_3N$ (CH_2Cl_2), 25 °C, 24 h. (h) 5% $HClO_4$ (CH_3CN), 25 °C, 24 h. (i) NaOH (aqueous MeOH), 25 °C, 24 h. (j) See "Rodd's Chemistry of Carbon Compounds"; Coffey, S., Ed.; Elsevier: New York, 1976; Vol. 1G.

13. Every step proceeds in excellent yield.

The above two modes of epoxide ring opening also apply to **9** with equal success: **9** is transformed through two sets of intermediates **17–19** and **20–22** to the final tetraacetate product **23**, which has been identified as the meso isomer by comparison with the tetraacetate prepared from erythritol.

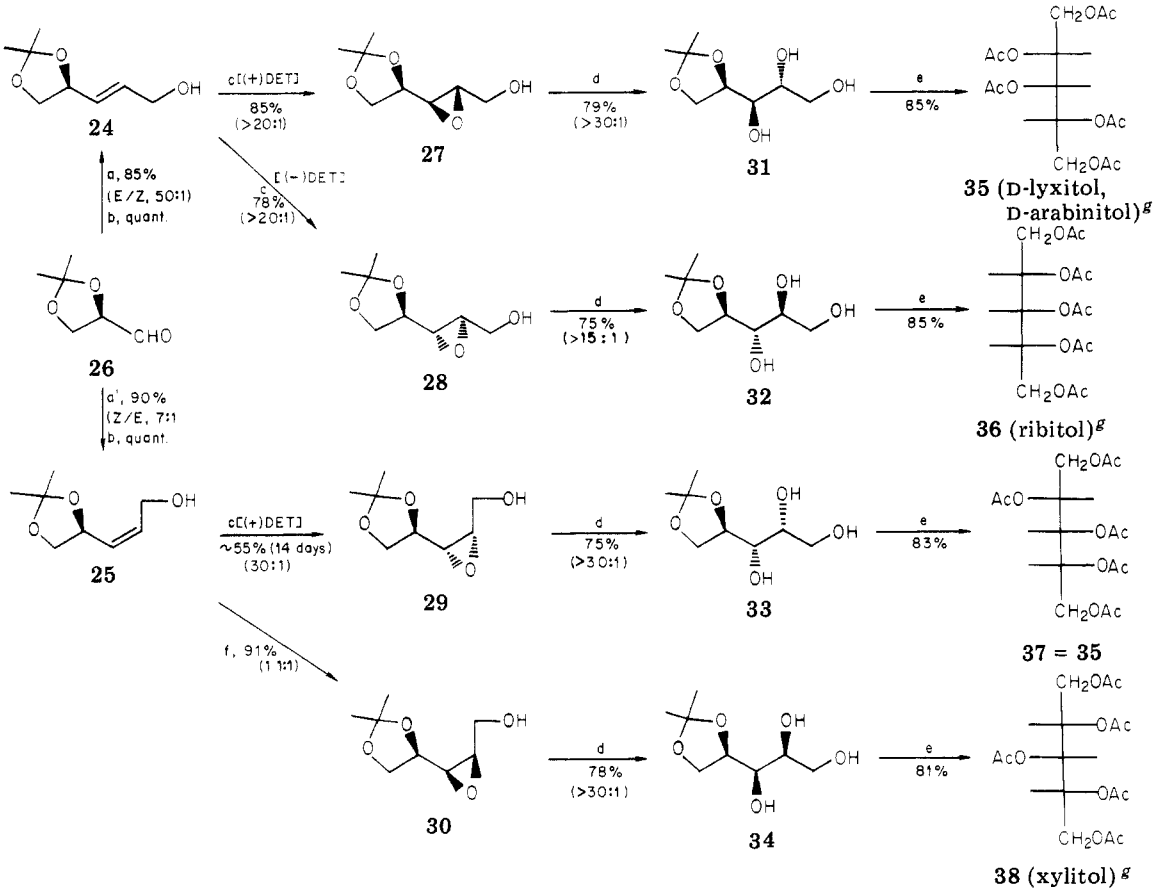
Pentitols. Both the *E* and *Z* allylic alcohols (**24** and **25**) are prepared stereoselectively (vide supra) from the known D-glyceraldehyde acetonide **26**.[19,20] While asymmetric epoxidation of **24** proceeds in the normal fashion with both (+)- and (-)-DET to afford **27** and **28**, respectively, the rate of epoxidation of the *Z* allylic alcohol is very slow. Thus the AE reaction of **25** with (+)-DET reaches only 55% completion in 14 days at -20 °C.[21] However, excellent stereoselection is attained, favoring the formation of **29** in a 30:1 ratio. With (-)-DET, the reaction is too slow to be practical. The remaining epoxy alcohol isomer **30** (not available via the AE route) is prepared by *m*-chloroperoxybenzoic acid epoxidation of **25** which yields **29** and **30** in about equal amounts. Epoxy alcohol **30** is isolated by chromatography on silica gel where it separates easily from isomer **29**. The four epoxy alcohols (**27–30**) in Scheme II are selectively opened to the four possible D-pentitol monoacetonides (**31** → **34**) by yet a third variation on the stereo- and regioselective epoxide ring opening theme. In this instance hydroxide is the nucleophile (cf.

(19) Baer, E. *Biochem. Prep.* **1952**, *2*, 31.

(20) The reaction of **26** with Ph_3PCHCO_2Et in MeOH provides in 95% yield the ethyl esters corresponding to **24** and **25** in 1:7 and 1:3 ratios at 0 °C and room temperature, respectively. In toluene with $(EtO)_2POCHCOOEt$ at 25 °C the ratio changes to 40:1 in favor of the *E* isomer (85% yield), and with $Ph_3PCHCHO$ in toluene at 0 °C the aldehyde corresponding to **24** is the exclusive product (80% yield). Use of Bestmann's reagent (ref 10) followed by acid hydrolysis (0.04 M TsOH in 12% aqueous acetone at 0 °C, 30 min) provided the aldehyde corresponding to **25** in 60–70% yield with an *E*/*Z* ratio of 1:17. These experiments were performed by T. Sakai, S. Murakami, and C. H. Behrens of these laboratories.

(21) Alternatively, *Z* allylic alcohol **25** was selectively epoxidized with TBHP and vanadium catalysis[10] [$VO(OEt)_3$ was found to be superior to $VO(acac)_2$ as a source of the catalyst]. The ratio of epoxy alcohol products **29** and **30** was only about 5:1, but the reaction was much faster (overnight at 25 °C) and the overall yield was better.

Scheme II. Pentitols[a]



[a] (a) Ph_3P=CHCHO (toluene), 0 °C, 39 h. (a') i, Ph_3P=CHCH(OEt)$_2$ (THF), 0 °C, 2 h; ii, TsOH (aqueous acetone), −10 → 0 °C, 30 min. (b) DIBAL (CH_2Cl_2), 0 °C, 4 h. (c) Ti(O-*i*-Pr)$_4$, (+)- or (−)-DET, TBHP (CH_2Cl_2), −20 °C, 15 h. (d) 0.5 N NaOH (H_2O/Me_3COH, 5:1), 70 °C, 15 h. (e) i, Dowex 50X8-200 resin (H_2O), 25 °C, 3 h; ii, Ac_2O, H_2SO_4 (trace). (f) *m*-CPBA (CH_2Cl_2), 0 °C, 10 h. (g) See "Rodd's Chemistry of Carbon Compounds"; Coffey, S., Ed.; Elsevier: New York, 1976; Vol. 1F.

benzenethiolate in Scheme I) which selectively attacks the equilibrating epoxy alcohol isomers at C(1) to yield essentially a single triol in each case. The stereochemistry of **31–34** has been established by correlation with the authentic pentaacetates (**35–38**) in the usual manner.

Hexitols. Some of the problems involved in this series have not yet been fully resolved, but good routes to four of the eight possible stereoisomers have been established (Scheme III). Treatment of tetrose derivative **11** (Scheme I) with methanolic potassium carbonate most conveniently provides an appropriate starting aldehyde **39**, which is transformed into the *E* allylic alcohol **40** or the *Z* allylic alcohol **47**. Conversions of **40** to triols **43** and **44** through **41** and **42** proceed in exactly the same manner as in the pentose series, and **43** and **44** are correlated with L-gulitol and L-talitol, respectively. The *Z* allylic alcohol **47** is epoxidized with some selectivity, using *tert*-butyl hydroperoxide and vanadium catalysis to afford epoxy alcohol **48**,[22] which readily undergoes the base-catalyzed rearrangement-opening process to give triol **49** (correlated with L-iditol).

As an alternative to the epoxidation-based routes, the Wittig–osmylation sequence[23] has been examined, for cis hydroxylation of an *E* olefin brings about the same outcome as trans opening of a *Z* epoxide (e.g., **8** → **10** or **29** → **33**). Thus, catalytic osmylation[24] of the unsaturated ester **51**[25] proceeds to yield, with an 8 (galacto):1 (ido) stereoselection, diol **52** of the galacto configuration.

The three epoxide-opening methods outlined above require brief comment. The benzenethiolate–Pummerer rearrangement–hydrolysis series (i.e., **8** → **10** → **11** → **39**) represents by far the most efficient route to complete sequence A for further chain elongation. The hydroxide ion best serves to secure a triol, but it (triol) is an unattractive intermediate[26] for the repetition of the sequence. The urethane route (**8** → **15**, **9** → **21** in Scheme I) is useful for the preparation of a protected α-hydroxy aldehyde which, for instance, can be obtained by successive treatment of **15** with *tert*-butyldimethylsilyl chloride, diisobutylaluminum hydride, and sodium metaperiodate.[18a] The epoxy alcohol moiety is proving to be an extremely versatile synthetic intermediate. In the present work the known facile base-catalyzed equilibration[14] of 2,3- and

(22) It should be noted that this is a change, albeit a felicitous one, in the stereoselectivity observed for vanadium catalysis in the pentose series (cf. footnote 21 above). This type of selectivity (i.e., major isomer is the one analogous to **48**) in vanadium-catalyzed epoxidation of related *Z* allylic alcohols increases to about 8:1 in the heptose series for the *Z* allylic alcohol derived (as in g of Scheme III) from the (2,3), (4,5)-diacetonide of D-arabinose (Martin, V. S., unpublished results).

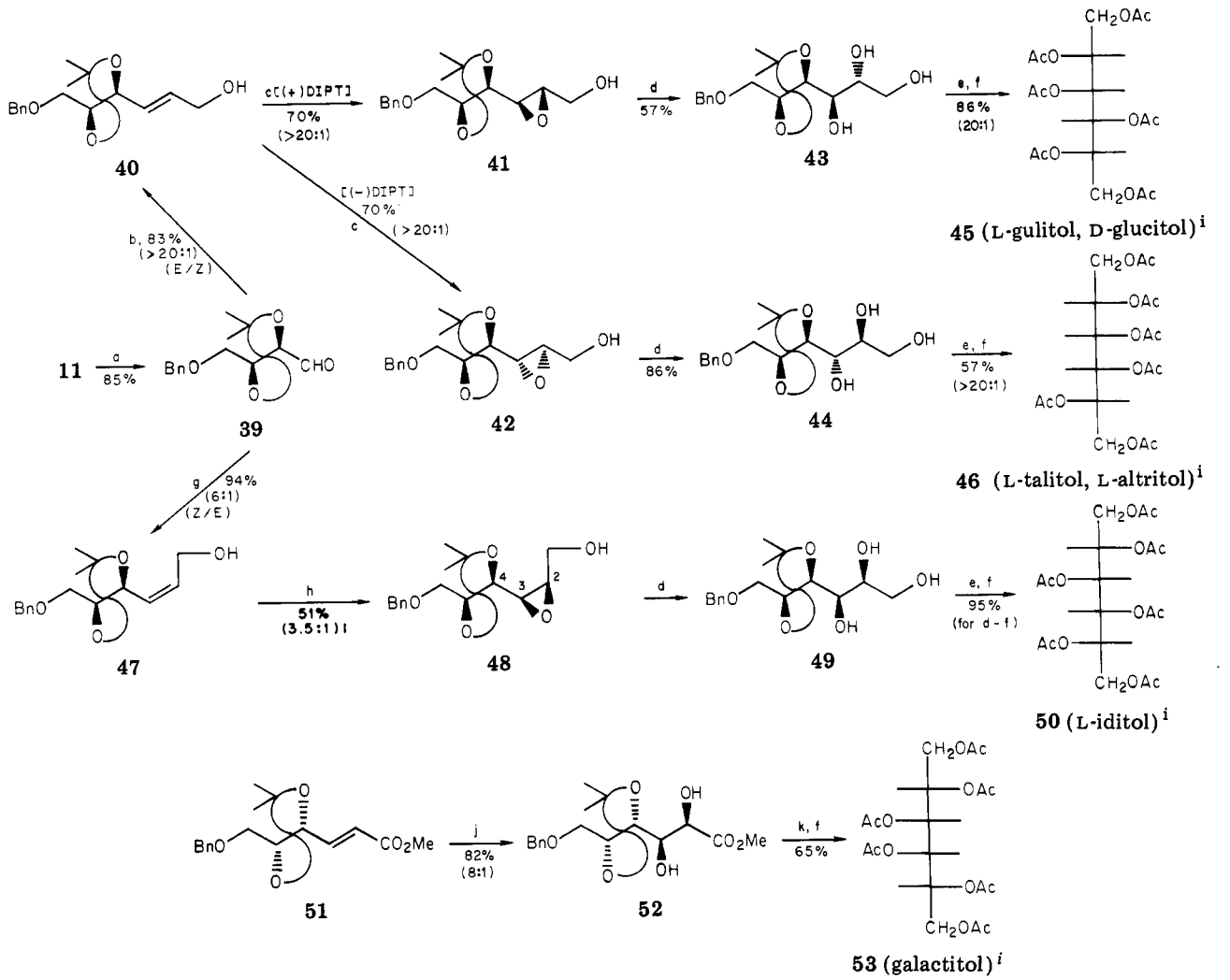
(23) This route for two-carbon homologation of carbohydrates is not new. However, only modest stereoselectivities (<2:1) have been observed previously: (a) Kochetkov, N. K.; Dimitriev, B. A. *Tetrahedron* **1965**, *21*, 803. (b) Kochetkov, N. K.; Dimitriev, B. A. *Methods Carbohydr. Chem.* **1972**, *6*, 150 and references cited therein.

(24) Akashi, K.; Palermo, R. E.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 2063.

(25) Prepared from the enantiomer of aldehyde **39** by Wittig homologation (trimethylphosphonoacetate, NaH, toluene, 25 °C).

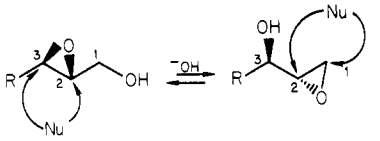
(26) At least four steps are required to convert the triol to a protected aldehyde ready for the next homologation sequence.

Scheme III. Hexitols[a]



[a] (a) K_2CO_3 (MeOH), 22 °C, 4 h. (b) i, $(MeO)_2POCH_2CO_2Me$, NaH (C_6H_6), 22 °C, 30 min; ii, LAH, $AlCl_3$ (Et_2O), 0 °C, 30 min. (c) Ti (O-*i*-Pr)$_4$ (+)- or (−)-DIPT, TBHP (CH_2Cl_2), −20 °C, 36 h. (d) 0.5 N NaOH (H_2O/$(Me)_3COH$, 5:1), 70 °C, 24 h. (e) H_2, Pd/C, Dowex 50X8-200 (MeOH/H_2O, 7:3), 22 °C, 26 h. (f) Ac_2O (C_5H_5N), 22 °C, 16 h. (g) i, Ph_3P=CHCOOMe (MeOH), 0 °C, 2 h; ii, LAH, $AlCl_3$ (Et_2O), 0 °C, 30 min. (h) $VO(OEt)_3$, TBHP (CH_2Cl_2), 0 °C, 36 h. (i) see "Rodd's Chemistry of Carbon Compounds"; Coffey, S., Ed.; Elsevier: New York, 1976; Vol. 1F. (j) OsO_4 (cat.), TBHP, Et_4NOAc (acetone), 22 °C, 48 h. (k) i, $Me_2C(OMe)_2$, $POCl_3$ (CH_2Cl_2), 22 °C, 3 h; ii, LAH (Et_2O), 22 °C, 30 min; iii, H_2, Pd/C (EtOH), 22 °C, 16 h; iv, Dowex 50X8-200 (MeOH/H_2O, 9:1), 22 °C, 16 h. (l) The major isomer was isolated by chromatography.

1,2-epoxy alcohols (i.e., **54** and **55**) has been exploited to draw out a subtle mode of reactivity. Epoxides **54** and



54 **55**

55 both possess two potential sites for nucleophilic attack. It is now evident that in this carbohydrate context (i.e., R bears an α-ethereal substituent), carbon-1 of isomer **55** is by far the most reactive electrophilic site for a range of nucleophiles, including the thiolate and hydroxide ions.[27] Furthermore, we and others are finding that under proper conditions it is also possible with epoxy alcohols such as **54** (or related derivatives) to direct nucleophiles selectively to either C(2)[8,17,18,28] or C(3).[29] With these developments and its easy access in either enantiomeric form, the epoxy alcohol unit promises to be one of the most useful functional groups in syntheses where stereochemical control (both relative and absolute) is essential.

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(27) Lee, A. W. M.; Masamune, S. ; Sharpless, K. B.; Walker, F. J., unpublished results involving extension to carbon, nitrogen, and hydride nucleophiles will be reported elsewhere.

(28) Behrens, C. H.; Lee, A. W. M.; Ma, P.; Masamune, S.; Sharpless, K. B., unpublished results.

(29) Takatani, M.; Sharpless, K. B., unpublished results.

Note Added in Proof: The difficulties associated with epoxidation of *Z*-allylic alcohols in the present work are not avoided by utilizing only *E*-allylic alcohols. In this way one obtains the erythro diol relationship by DIBAL reduction of, for example, 18 to the corresponding erythro aldehyde. Whereas, treatment of 18 with K_2CO_3 in MeOH leads, via epimerization, to an almost quantitative yield of the corresponding threo aldehyde. The epimerization process is general, and we have used it in highly selective syntheses of all four pentoses and all eight hexoses.

Supplementary Material Available: A listing of spectral data (9 pages). Ordering information is given on any current masthead page.

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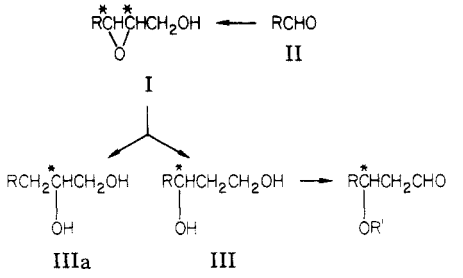
Synthesis of Saccharides and Related Polyhydroxylated Natural Products. 2. Simple Deoxyalditols

Summary: Asymmetric epoxidation of allylic alcohols followed by selective hydride reduction provides a new route to chiral 1,3-diols and 1,3,5-triols; one of the 1,3,5-triols (**21**) is also synthesized from D-glucose.

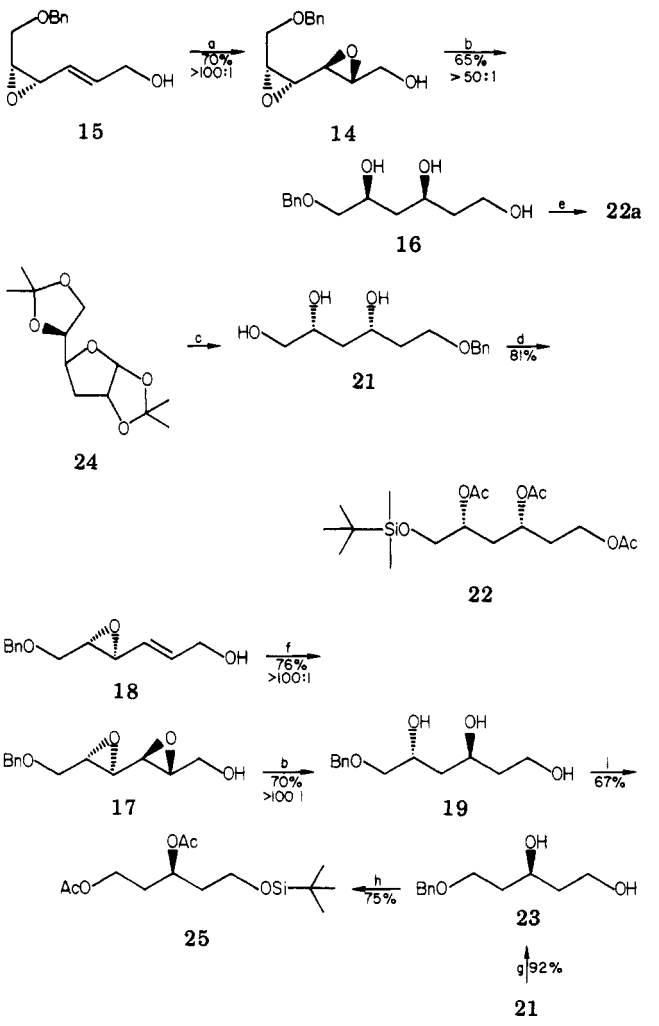
Sir: The preceding communication describes the selective synthesis of most, if not all, of the four possible stereoisomeric epoxy alcohols (I) from a variety of aldehydes RCHO (II).[1] Of many useful transformations that these versatile synthetic intermediates (I) may undergo, reductive ring opening attracts special attention. It (reduction) should provide two regioisomeric diols (III and IIIa), the ratio of which would change with three variables: the R group and stereochemistry of the epoxide in I and the reductant used in the reaction. We have found that the reduction of I, where the R group carries an ethereal substituent (or substituents) α and/or β to the epoxide, leads to the (nearly) exclusive formation of III with sodium bis(methoxyethoxy)aluminum hydride (Red-al) under normal conditions. This finding, although seemingly trivial, bears synthetic significance and indeed constitutes an essential step of sequence B, one of the two fundamental two-carbon extension sequences described earlier.[1]



(B)

(1) Katskuki, T.; Lee, A. W. M.; Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Tuddenham, D.; Walker, F. J., preceding paper in this issue.

Scheme I



[a] (a) $Ti(OPr)_4$, (−)-DET, TBHP (CCl_4), −20 °C, 3 h. (b) Red-al (THF), 22 °C, 3 h. (c) i, 0.8% H_2SO_4 (MeOH), 22 °C, 15 h, 86%; ii, $(C_3H_3N_2)_2C(=S)$ (THF), reflux, 5 h; iii, $(Me_2O)_3P$, 110 °C, 10 h; iv, disiamylborane (THF), NaOH, H_2O_2, 50%; v, NaH, $PhCH_2Br$ (DMF), 50 °C, 5 h, 87%; vi, Dowex 50W-X8 resin (H_2O), 50 °C, 2 h, 100%; vii, $NaBH_4$ (EtOH), 22 °C, 2 h, 100%. (d) i, TBDMS-Cl, DMAP (CH_2Cl_2), 22 °C, 5 h; ii, H_2, 5% Pd/C (MeOH), 22 °C, 8 h; iii, Ac_2O, C_5H_5N, 60 °C, 5 h. (e) i, Ac_2O, C_5H_5N, 60 °C, 5 h; ii, H_2, 5% Pd/C (MeOH), 22 °C, 12 h; iii, TBDMS-Cl, DMAP (CH_2Cl_2), 22 °C, 5 h. (f) $Ti(OPr)_4$, (+)-DET, TBHP (CH_2Cl_2), −20 °C, 18 h. (g) i, $NaIO_4$ (H_2O), 22 °C; ii, $NaBH_4$ (EtOH), 27 °C, 10 h. (h) i, TBDMS-Cl, DMAP (CH_2Cl_2), 22 °C, 5 h; ii, H_2, 5% Pd/C (MeOH), 22 °C, 8 h; iii, Ac_2O, C_5H_5N, 60 °C, 5 h. (i) i, TBDMS-Cl, DMAP (CH_2Cl_2), 22 °C, 5 h; ii, H_2, 5% Pd/C (MeOH), 22 °C, 8 h; iii, $NaIO_4$ (H_2O), 22 °C; iv, $NaBH_4$ (EtOH), 22 °C, 10 h; v, Ac_2O, C_5H_5N, 60 °C, 5 h.

Table I summarizes preliminary results. While lithium aluminum hydride (reagent L) or Red-al (reagent R) reduction of **1** (where R in I is *n*-alkyl) yields the 1,2-diol (**2**) and 1,3-diol (**2a**) in nearly equal amounts, some regioselection is already evident in the reaction of **3** and **4** (entries 2, 3), favoring the formation of 1,3-diols (**5** and **6**). This trend culminates with the epoxy alcohols **7**–**10** (entries 4–7), which are oxygenated at the positions α or α and β to the epoxide, where the use of Red-al leads to the (almost) exclusive formation of the 1,3-diols **11**–**13**. The absolute configuration has been correlated with that of (*R*)-(+)-malic acid,[2] and compound **12** has been converted to its tetraacetate **12a**, identical with that derived from 2-deoxy-D-*erythro*-pentose via sodium borohydride re-

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