9a/b [2.31 g (78%, 10.17 mmol)]. Crystallizations with (1*S*,2*R*)-(+)- and (1*R*,2*S*)-(−)-ephedrine followed by extraction (ether/1 N HCl) gave crystalline **9a** (0.89 g, 23%, starting from aldehyde **6c**, >95% ds,[1] according to the ^{1}H NMR): mp 78–79 °C; $[\alpha]_D$ +35.5° (*c* 1.07, $CHCl_3$) [lit.[7] mp 81–82 °C; $[\alpha]^{22}_D$ +33.5° (*c* 1.0, $CHCl_3$)]; IR ($CHCl_3$) 3560–2380, 1755, 1440, 1401, 1205, 1145, 1040, 970 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.96 (d, 3 H, *J* = 6.5, $CHCH_3$); 1.67 (d, 3 H, *J* = 6.5, $CH{=}CHCH_3$), 1.81–2.06 (m, 2 H, $CHCH_2CH{=}CH$), 2.11–2.31 (m, 1 H, $CHCH_2CH{=}CH$), 2.96 (s, 3 H, NCH_3), 4.01 (d, 1 H, *J* = 5, C_4-H), 4.36 (dd, 1 H, *J* = 5, 6, C_5-H), 4.70 (br s, 1 H, COOH), 5.26–5.65 (m, 2 H, CH=CH); MS, *m/e* (relative intensity) 228 (M^+ + 1, 10), 227 (M^+, 29), 182 (20), 128 (46), 55 (92), 44 (45), 43 (36) 42 (100), 41 (54).

Mixture (ca. 1:1) of methyl (4*S*,5*R*)-3-methyl-5-[(1*R*,3*E*)-1-methyl-3-pentenyl]-1-oxo-2-oxazolidine-4-carboxylate (11a) and methyl (4*R*,5*S*)-3-methyl-5-[(1*R*,3*E*)-1-methyl-3-pentenyl]-1-oxo-2-oxazolidine-4-carboxylate (11b): R_f 0.13 (hexane/EtOAc, 7:3); ^{1}H NMR ($CDCl_3$) δ 0.95, 0.97 (d, 3 H, *J* = 6, $CHCH_3$), 1.68 (d, 3 H, *J* = 5.5, $CH{=}CHCH_3$), 1.72–2.05 (m, 2 H, $CHCH_2CH{=}CH$), 2.10–2.19 (m, 1 H, $CHCH_2CH{=}CH$), 2.91, 2.92 (s, 3 H, NCH_3), 3.83 (s, 3 H, OCH_3), 3.96, 3.97 (d, 1 H, *J* = 5, C_4-H), 4.28 (dd, 0.5 H, *J* = 5, 5.5, C_5-H), 4.35 (t, 0.5 H, *J* = 5, C_5-H), 5.26–5.62 (m, 2 H, CH=CH).

(4*S*,5*R*)-3-Methyl-5-[(3*E*)-pentenyl]-1-oxo-2-oxazolidine-4-carboxylic Acid (10a). Following the procedure described for the synthesis of 2-oxazolidinone **9a**, reaction of Cbz-Sar-OMe (**3**) (7.93 g, 33.44 mmol, 1 equiv) with (4*E*)-hexenal (**6d**) (3.07 g, 31.28 mmol, 0.93 equiv) at −78 °C gave 3.81 g of crude acids [after ^{1}H NMR, 3.10 g (47%, 92% ds[1]) of **10a/b** and 0.71 g of Cbz-Sar]. Esterification (→**12a/b**) followed by purification on a MPLC column (hexane/EtOAc, 7:3) gave 2.09 g (30%, >95% ds[1]) of pure methyl ester **12a/b** (see below for spectral data). Hydrolysis (5 mL of MeOH, 11 mL of 1 N NaOH, 1.5 h at room temperature) and two crystallizations with (1*S*,2*R*)-(+)-ephedrine (0.84 g, 5.06 mmol, 0.55 equiv) first in EtOAc/pentane at −25 °C and then in CH_2Cl_2/ether at room temperature gave diastereomerically pure **10a**·(+)-ephedrine salt (1.27 g, 11%, >95% ds[1], according to ^{1}H NMR). After extractive workup (0.5 N HCl/ether) enantiomerically pure crystalline 2-oxazolidinone **10a** (0.70 g, 11%) was isolated.[44] An analytical sample was prepared by recrystallization from ether/pentane: mp 92–93 °C; $[\alpha]_D$ +35.1° (*c* 1.14, $CHCl_3$); IR ($CHCl_3$) 3540–2360, 1755, 1436, 1400, 1229, 1203, 1145, 1040, 968 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.67 (d, 3 H, *J* = 5.5, $CH{=}CHCH_3$), 1.78–1.94 (m, 2 H, $CH_2CH_2CH{=}CH$), 2.08–2.28 (m, 2 H, $CH_2CH_2CH{=}CH$), 2.97 (s, 3 H, NCH_3), 3.94 (d, 1 H, *J* = 5.5, C_4-H), 4.50 (q, 1 H, *J* = 5.5, C_5-H), 5.30–5.64 (m, 2 H, CH=CH), 6.64 (br s, 1 H, COOH); MS, *m/e* (relative intensity) 213 (M^+, 20), 168 (37), 149 (28), 124 (28), 81 (29), 69 (66), 57 (51), 55 (87), 45 (39), 44 (88), 43 (97), 42 (82), 41 (100). Anal. Calcd for $C_{10}H_{15}NO_4$: C, 56.33; H, 7.09; N, 6.57. Found: C, 56.32; H, 7.21; N, 6.49.

Racemic *trans*-Methyl 3-Methyl-5-[(3*E*)-pentenyl]-1-oxo-2-oxazolidine-4-carboxylate (12a/b). R_f 0.10 (hexane/EtOAc, 7:3); ^{1}H NMR ($CDCl_3$) δ 1.66 (d, 3 H, *J* = 5.5, $CH{=}CHCH_3$), 1.73–1.90 (m, 2 H, $CH_2CH_2CH{=}CH$), 2.09–2.25 (m, $CH_2CH_2CH{=}CH$), 2.94 (s, 3 H, NCH_3), 3.83 (s, 3 H, OCH_3), 3.90 (d, 1 H, *J* = 5.5, C_4-H), 4.41 (q, 1 H, *J* = 5.5, C_5-H), 5.32–5.60 (m, 2 H, CH=CH).

(2*S*,3*R*,4*R*,6*E*)-3-Hydroxy-4-methyl-2-(methylamino)-6-octenoic Acid (2). The solution of 2-oxazolidinone **9a** [0.100 g (0.44 mmol)] in 2 mL of 2 N KOH was heated under reflux for 5 h, cooled (room temperature), acidified with Dowex H^+ (50 × 8-100) (pH <4), and heated for 5 min at 80 °C. The mixture of Dowex H^+/water was filtered through 10 mL of Dowex H^+ (1.7 × 5 cm column) and eluted with 150–200 mL of 1.5 M aqueous ammonia. The aqueous eluant was evaporated (16 Torr, 30 °C) and dried (1 Torr, room temperature, 16 h). MeBmt (**2**) was received quantitatively (0.10 g) as a white solid. In order to obtain an analytically pure sample of MeBmt (**2**), the amino acid was purified by Sephadex LH-20 chromatography (methanol)[7,8] and crystallized from ethanol/water: mp 240–241 °C (decomposition with scintering at 200–225 °C); $[\alpha]_D$ +12.0° (*c* 0.38 H_2O at pH 7 (phosphate buffer Titrisol pH 7.00 from Merck)) [lit.[7] mp 240–241 °C; $[\alpha]_D$ +13.5° (*c* 0.50, H_2O at pH 7 (phosphate buffer Titrisol pH 7.00 from Merck)); lit.[8] mp 242–243 °C; $[\alpha]_D$ +11.4° (*c* 0.50, H_2O at pH 7 (phosphate buffer Titrisol pH 7.00 from Merck))]; ^{1}H NMR (D_2O, HDO = 4.63 ppm) δ 0.74 (d, 3 H, *J* = 6.5, C_4-CH_3), 1.46 (d, 3 H, *J* = 5, C_8-H), 1.35–1.92 (m, 2 H, C_4-H, C_5-H), 2.00–2.17 (m, 1 H, C_5-H), 2.54 (s, 3 H, NCH_3), 3.44 (d, 1 H, *J* = 5.5, C_2-H), 3.58 (t, 1 H, *J* = 5.5 C_3-H), 5.18–5.47 (m, 2 H, CH=CH); ^{1}H NMR (CD_3OD, CHD_2OD = 3.30) δ 0.93 (d, 3 H, *J* = 6.5, C_5-CH_3), 1.64 (d, 3 H, *J* = 4, C_8-H), 1.60–1.96 (m, 2 H, C_4-H, C_5-H), 2.29–2.44 (m, 1 H, C_5-H), 2.67 (s, 3 H, NCH_3), 3.45 (d, 1H, *J* = 5.5, C_2-H), 3.71 (t, 1 H, *J* = 5.5, C_3-H), 5.32–5.58 (m, 2 H, CH=CH). Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.68; H, 9.52; N, 6.96. Found: C, 59.45; H, 9.46; N, 6.90.

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(44) The absolute configuration of 2-oxazolidinone **10a** was deduced by comparing to **9a**. The optical rotation for 10a was nearly idential with the optical rotation for 2-oxazolidinone **9a**.

Alkaline and Enzymatic Hydrolysis of Isobutyl 3,4-Anhydro-2,6-dideoxy-DL-hexopyranosides. Preparation of Enantiomeric Boivinopyranosides through a Highly Efficient Kinetic Resolution

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Racemic isobutyl 3,4-anhydro-2,6-dideoxy-β-*ribo*-hexopyranoside and -*lyxo*-hexopyranoside have been prepared starting from the cycloadduct between 3-buten-2-one and isobutyl vinyl ether. Alkaline hydrolysis converted the lyxo isomer exclusively into isobutyl 2,6-dideoxy-β-DL-*xylo*-hexopyranoside (isobutyl β-DL-boivinopyranoside), the ribo isomer into a 57:43 mixture of the same glycoside, and its arabino diastereomer (isobutyl β-DL-olivopyranoside). Rabbit microsomal epoxide hydrolase similarly converted the racemic lyxo epoxide into the xylo diol in a regiospecific way and exhibited a high degree of enantioselectivity: when the enzymatic reaction was stopped at 50% conversion, isobutyl β-L-boivinopyranoside and isobutyl 3,4-anhydro-2,6-dideoxy-β-D-*lyxo*-hexopyranoside were obtained, both with an enantiomeric excess of at least 96%.

Carbohydrates with nonconventional structures, such as branched chain, deoxy, and aminodeoxy sugars, are often found as components of biologically relevant compounds, such as glycoside antibiotics and cardioactive

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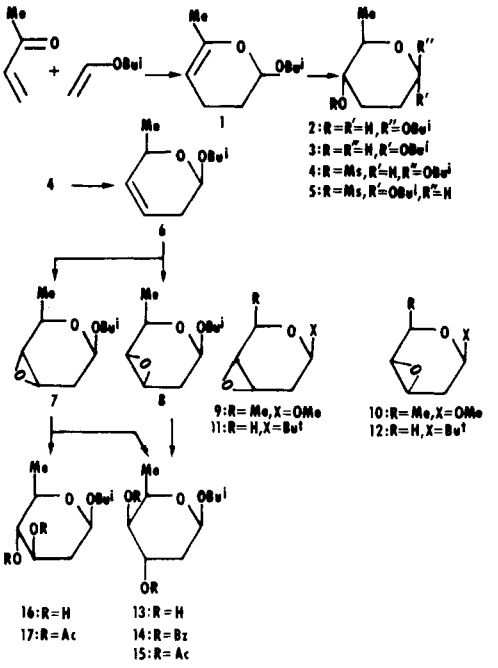
glycosides.[1] Their synthesis, a worthwhile target, can be achieved either through a usually lengthy series of transformations starting from abundant natural sugars or by often simpler totally synthetic approaches. The main disadvantage of the latter procedure is the need to generate optically active compounds, either via traditional resolution techniques or through a highly enantioselective step. Regioselective oxirane ring-opening reactions on anhydrohexopyranoses with nucleophiles are often used in such synthetic sequences.[2] Previous studies on the use of microsomial epoxide hydrolase (MEH) on simple racemic epoxytetrahydropyran derivatives had revealed that this enzymatic reaction can exhibit a high regio- and enantioselectivity.[3] In order to explore the applicability of this approach to the total synthesis of optically active deoxy sugars, we started a research program on the use of MEH in chiral syntheses of anomalous carbohydrates. As a start we investigated the steric course of the enzymatic hydrolysis of isobutyl 3,4-anhydro-2,6-dideoxy-*lyxo*-β-DL-hexopyranoside (**8**), easily obtained by total synthesis. Its conversion into the D- and L-forms of the isobutyl boivinopyranoside (**13**) is the subject of the present paper.[4]

Results

The easy preparation of isobutyl 2,3,6-trideoxy-DL-*erythro*-hexopyranoside (isobutyl amicetoside) as an 83:17 mixture of the β- and α-anomers (**2** and **3**),[5] by hydroboration–oxidation of the cycloadduct **1** of 3-buten-2-one with isobutyl vinyl ether, has been previously described.[6] The pure β-anomer **2** can be separated at this stage or, more conveniently in our synthetic sequence, separation can be carried out by preparative HPLC after conversion of the crude mixture of **2** + **3** into the mesylates **4** and **5**. The conversion of **4** into the unsaturated deoxy sugar **6** was not entirely satisfactory. The reaction was regiospecific, as expected for an anti elimination on a trans β-alkyl mesylate, but even under the best conditions (potassium *tert*-butoxide in Me_2SO), the yield did not exceed 50%, a substantial amount (ca. 40%) of **4** undergoing conversion into **2**, probably formed by attack on sulfur in a transesterification side reaction. Separation of **6** from **2** was, however, easily carried out by filtration through silica gel. When the reaction with potassium *tert*-butoxide was conducted in toluene, only transesterification was observed. Alternative methods of eliminaton on **4** (pyrolysis on soda lime, DBN in toluene, etc.) failed to produce any **6**. The structure of **6** was fully confirmed through its ^1H NMR spectrum; the anomeric proton signal at δ 4.65 is a "deceptively simple" system, an apparent triplet with splitting of ca. 6 Hz; however, the value of $J_{1,2_a} + J_{1,2_e}$ (≃12 Hz) points to an axial H-1 and consequently to a preference for the equatorial disposition of the isobutoxy group, in accordance with the fact that the alternative half-chair conformer, though more favorable from the point of view of the anomeric effect, would not be expected to compete,



owing the unfavorable interaction between axial isobutoxy and pseudoaxial methyl groups.

Epoxidation of **6** with *m*-chloroperbenzoic acid gave in good yield a mixture of the ribo and lyxo derivatives **7** and **8** in a ratio of 57:43. These compounds were easily separated by preparative HPLC or flash chromatography. We have repeatedly observed that diastereomeric epoxytetrahydropyran derivatives differ significantly in their affinity for silica and are therefore highly amenable to chromatographic separation. Since the unsaturated compound **6** is very volatile, it is advisable to avoid evaporation of the washed (H_2O) CH_2Cl_2 extract of the crude reaction product and to carry out the epoxidation directly on this solution. A slight preference for the formation of the ribo epoxide (attack anti to the pseudoequatorial methyl group) was expected owing to the sensitivity of peroxyacid oxidation to steric effects.[7] The relative configurations of **7** and **8** were confirmed on the basis of a complete analysis of their ^1H NMR spectra, which were compared with those of the corresponding methyl glycosides (**9** and **10**)[8] and those of the conformationally rigid 2-*tert*-butyl-4,5-epoxytetrahydropyrans (**11** and **12**)[9] (Table I). Both **7** and **8**, are evidently essentially in the $^0H_1$(D) conformation with equatorial methyl and isobutoxy substituents.

Hydrolysis of the lyxo epoxide **8** with aqueous sodium hydroxide was regio- and stereospecific, giving as the only product isobutyl 2,6-dideoxy-β-DL-*xylo*-hexopyranoside (isobutyl β-DL-boivinopyranoside, **13**). The homogeneity of the crude hydrolysis product was proven by GC and TLC and by the fact that only nine signals were present in its ^{13}C NMR spectrum, the signals for C-3 and C-5 being coincident at 20 MHz. Benzoylation produced a single crystalline dibenzoate **14**.

The xylo relative configuration of **13** was confirmed by the fact that the ^{13}C NMR chemical shift closely corresponded (less than 1 ppm difference) with those reported for boivinose,[10] with the exception of that for the anomeric carbon, shifted, as expected,[11] 6.1 ppm downfield. Furthermore, in the ^1H NMR spectrum of **14**, the small $J_{3,4}$

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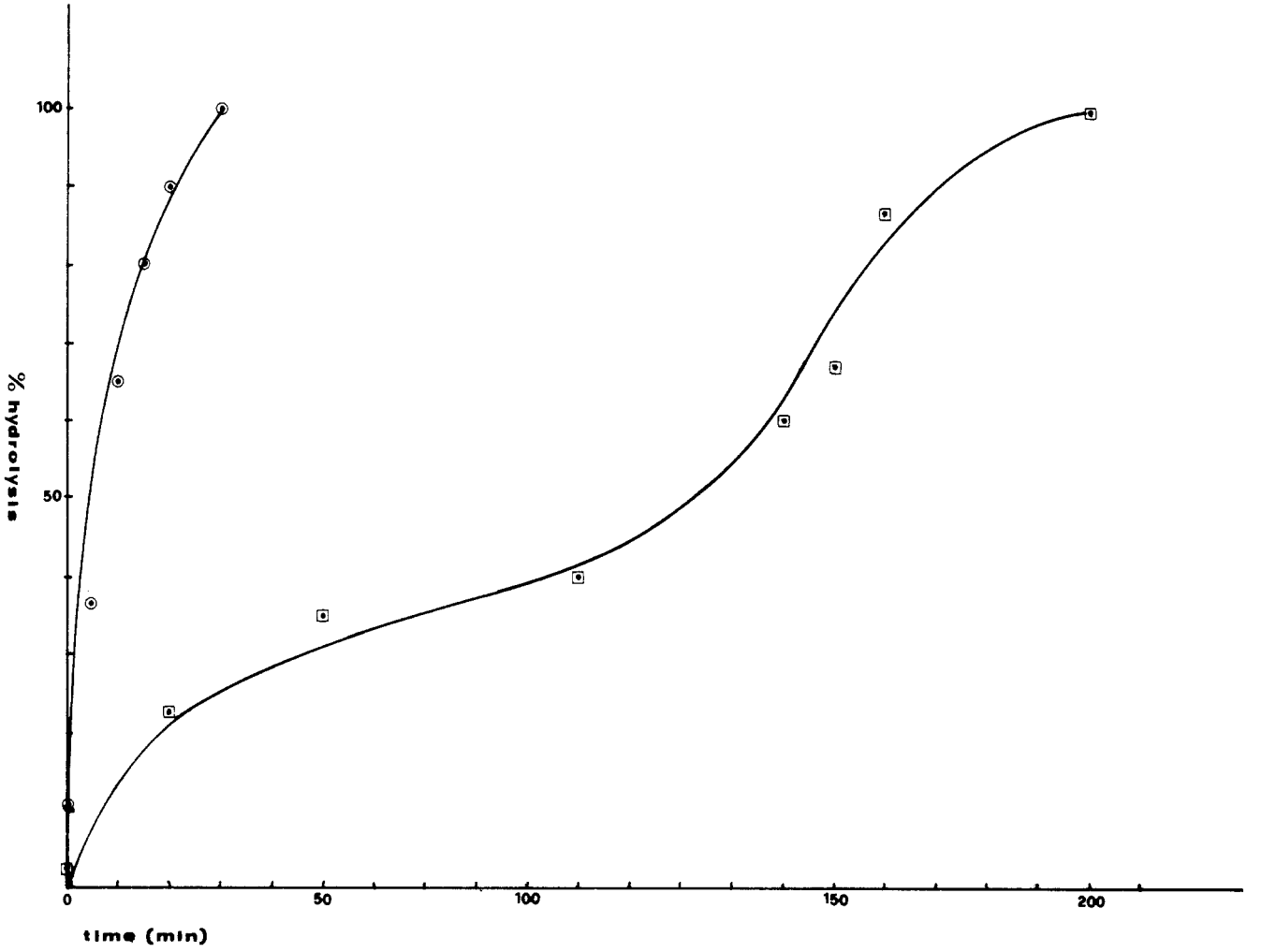

Figure 1. Enzymatic hydrolysis of DL-8: (⊙) concentration of 8 = 0.01 M; (⊡) concentration of 8 = 0.05 M.

Table I. Coupling Constants (Hz) for 7, 8, and Reference Compounds

compd	$J_{1,2_a}$	$J_{1,2_e}$	$J_{2_a,2_e}$	$J_{2_a,3}$	$J_{2_e,3}$	$J_{3,4}$	$J_{4,5}$
7	8.8	2.8	14.5	2.0	2.0	4.2	0.5
9	9	2.5	14.5	2	1.5	4	<1
11	11.4	2.4	14.4	2.2	2.3	4.4	0.0
8	9.0	3.8	15.0	0.3	5.6	3.9	0.8
10	9	4	16	<0.5	5	4	<1
12	11.6	3.6	13.4	0.0	6.7	3.9	0.0

and $J_{4,5}$ values proved the diaxial disposition of the two benzoyloxy groups, further confirmed by the $J_{1,2_a} + J_{1,2_e}$ values that were ~12 Hz, both for the diol **13** and its dibenzoate **14**. These compounds therefore exist mainly in the $^4C_1$(D)conformation. A high preference for the equatorial conformation ($-\Delta G° = 2.86$ kcal/mol) has recently been reported for 2-methyltetrahydropyran.[12] The syn-diaxial repulsive interaction between *i*-BuO and Me in the alternative $^1C_4$(D) conformers of **13** and **14** should cause their further significant destabilization with respect to the $^4C_1$(D) ones, making the latter the main contributors to the conformational equilibria, in spite of the unfavorable features of an equatorial anomeric group and of diaxial 3,4-substituents.

The alkaline hydrolysis of the ribo epoxide **7** was not stereospecific, a mixture of the xylo diol **13** and of the arabino diastereomer **16** (isobutyl DL-β-olivopyranoside) being formed in a ratio of 57:43. The latter was easily obtained pure owing to the fact that, in contrast with all other compounds described in this paper, it had a pronounced tendency to crystallize. Its structure and $^4C_1$(D), all equatorial conformation was proven by the ^{1}H NMR spectrum of its diacetate **17** in which the coupling constants between protons H-3/H-4, H-4/H-5, and H-1/H-2_a were all large (over 9 Hz).

The lyxo epoxide **8** was also subjected to enzymatic hydrolysis by using microsomal fractions from rabbits as a source of MEH. Racemic **8** proved to be a very good substrate for MEH and was transformed completely and exclusively into the racemic diol **13** at 100% conversion. When the evolution of the reaction was followed by withdrawing samples at given intervals and analyzing by GC, the biphasic curve shown in the Figure 1 was obtained. After a rapid start the reaction rate slows down when nearing 50% conversion and then an increase in reaction rate is observed. Runs conducted on a larger scale were stopped around 50% conversion, and the product diol **13** and the unconverted epoxide **8** were extracted and separated by partition between solvents. Both were optically

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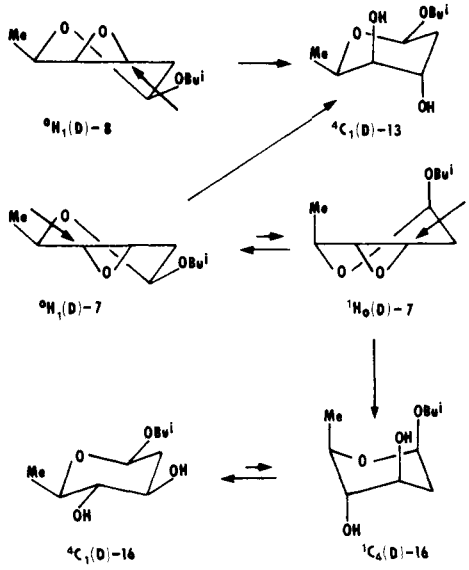
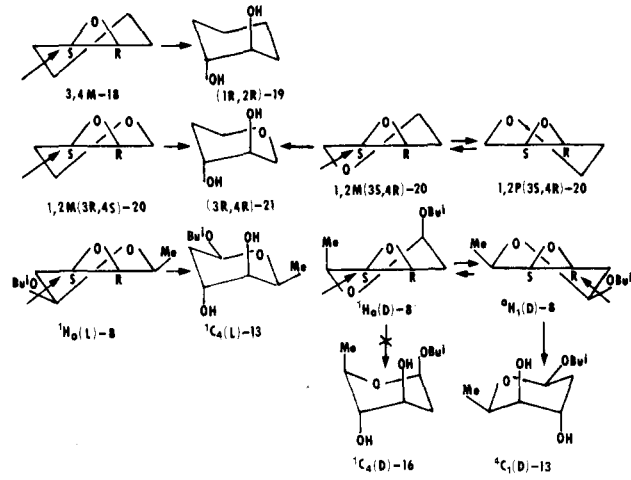
Scheme I



Scheme II



active, the former being dextrorotatory and the latter levorotatory. Although isobutyl β-boivinopyranoside has not been previously reported, analogy with methyl β-boivinopyranoside points to the fact that the dextrorotatory enantiomer belongs to the L-series,[13] since it is known that in simple alkyl glycosides molar rotations are similar and are independent of the type of alkyl group. Analogously, the fact that L-10 is dextrorotatory[8] proves that (−)-8 belongs to the D-series. MEH therefore exhibits an enantioselectivity favoring attack on the L-enantiomer of racemic 8.

In order to ascertain the optical purities of 8 and 13 obtained in the partial enzymatic hydrolysis, use was made of the chiral shift reagent Eu(hfc)$_3$. In the case of the racemic epoxide 8, addition of the reagent produced a splitting of the doublet for the methyl group at C-5 into two doublets of equal area, whereas for the levorotatory 8 recovered from the enzymatic incubation only the lower field doublet appeared after addition of Eu(hfc)$_3$, no trace of the other one being visible. Similarly the diacetyl derivative 15, obtained from the diol 13 extracted after 50% enzymatic conversion of racemic 8, showed in its NMR spectrum, in the presence of Eu(hfc)$_3$, only the lower field one of the two C-5-Me doublets that were present in the spectrum of (±)-15. Spectra taken on D-8 and L-15 to which 2% of the corresponding racemates had been added clearly revealed respectively the presence of L-8 and D-15. It can therefore be reliably asserted that the enantiomeric excess of the enzymatically produced D-8 and L-13 were at least 96%, an exceptionally good result for a kinetic resolution.

Discussion

The results of the alkaline hydrolysis of the epoxides 7 and 8 are in agreement with those previously reported[8] for the ring opening of the analogous methyl glycosides 9 and 10 with other types of nucleophiles (amines, N_3^-, MeO^-). Also in these cases the lyxo epoxide 10 was opened in a regiospecific manner to produce the xylo adducts. Such a reaction course is justified by the high preference for diaxial opening of oxirane rings and by the fact that attack by OH^- occurs on the more stable conformer D-8-$^0H_1$ at the relatively unhindered C-3 that is less subject to the unfavorable inductive effect by the tetrahydropyran ring oxygen[14] (Scheme I).

On the other hand, diaxial opening of 7 in its more stable $^0H_1$(D) conformation to give 13 would involve nucleophilic attack at C-4 that is hindered both by the pseudoequatorial methyl group and by the inductive effect of the tetrahydropyran ring oxygen. Alternative attack at C-3 to give 16 therefore becomes competitive, even though this involves an apparently rather unfavorable situation: conformation $^1H_0$(D) with syn-diaxial Me and *i*-BuO and approach of the nucleophile on the syn side with respect to these substituents. A certain degree of twisting of the tetrahydropyran ring during attack by the nucleophile on the oxirane ring may decrease its unfavorable interactions with the substituents. That opening of the epoxide ring in 7 is definitely more difficult than in 8, is also proven by the fact that the rate of reaction with OH^- is about 6 times lower in the former than in the latter case. Also in the case of reaction of the glycoside 9 (methyl analogue of 7) with other nucleophiles, mixtures of xylo and arabino products had been obtained in ratios ranging from 80:20 for ammonia to 25:75 for dimethylamine.[8] Apparently there is some relationship between size of the nucleophile and percentage of formation of the arabino product, that increases in the order $NH_3 < MeNH_2 < Me_2NH$ for neutral nucleophiles and $N_3^- < OH^- < MeOH^-$ for charged ones, a fact that could imply a higher sensitivity to steric effects of the $^0H_1$(D) epoxide → $^4C_1$(D) product pathway with respect to the $^1H_0$(D) epoxide → $^1C_4$(D) product one.

The results obtained in the case of the enzymatic hydrolysis of racemic 8 are of particular interest. The same regiospecificity in the alkaline- and MEH-promoted hydrolysis was expected, owing to the well-established fact that the enzymatic reaction involves a base-catalyzed mechanism,[15] but the observed enantioselectivity was remarkably high. The regio- and stereoselectivity of MEH has been extensively investigated, particularly for systems in which the oxirane ring is fused to a six-membered ring,[3,16] which usually are fair to good substrates. Optically active diols of variable optical purity are often obtained from meso epoxides (such as cyclohexene oxide[17] and

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cis-stilbene oxide[18]) usually with a preference for attack at the *S* oxirane carbon to give the *R,R* diols. Racemic epoxides may undergo some degree of kinetic resolution during the enzymatic hydrolysis, the *R,R* enantiomer of the diol being usually formed preferentially, with recovery of optically active epoxide. Apparently there is a preference for epoxycyclohexane and its derivatives to open diaxially in the 3,4*M* conformation as shown for the parent compound **18** that gives the *R,R* diol **19** with an ee of 70% (Scheme II).[16a,17] A similar situation holds for the structural analogue 3,4-epoxytetrahydropyran (**20**).[3a] In this case both enantiomers are converted entirely into the 3*R*,4*R* diol **21** in a reaction involving the diaxial opening of the 1,2*M* conformers (analogues of the 3,4*M* conformers of epoxycyclohexane), attack by water occurring at C-4 in the 3*R*,4*S* enantiomer and at C-3 in the 3*S*,4*R* enantiomer.

The enzymatic hydrolysis of racemic **8** follows only in part these lines. The L-enantiomer, reacts in the $^1H_0$(L) conformation, the same that is present in 1,2*M*-(3*R*,4*S*)-**20**. In order to behave as its analogue (3*S*,4*R*)-**20**, D-**8** should react in the less favorable $^1H_0$(D) conformation and produce D-**16**. Instead it reacts in the $^0H_1$(D) conformation corresponding to 1,2*P*-(3*S*,4*R*)-**20** and therefore gives D-**13**. This is well explained by the fact that whereas the conformational inversion between the 1,2*M* and 1,2*P* conformers of **20** involves a low barrier between states of similar energy (conformer 1,2*M* is actually more stable than 1,2*P* by about 0.8 kcal/mol in $CDCl_3$),[9] the barrier between $^0H_1$(D)- and $^1H_0$(D)-**8** is certainly much higher. Reaction in the diequatorial conformation $^0H_1$(D) therefore becomes the preferred course, even if it involves the 1,2*P*-type conformer and attack by water at the *R* carbon. A further feature of these enzymatic reactions involving substituted epoxycyclohexanes and -tetrahydropyrans is that the MEH-active site preferentially accommodates the enantiomer in which the alkyl substituent is situated on the right side of the oxirane ring when the molecule is viewed with the epoxide oxygen on the top side such as shown in Scheme II, probably in correspondance with a large lipophilic cavity in the active site.[3,16] It follows that L-**8** is ideally structured for working as a substrate for MEH since both the conformation and the orientation of the methyl group are the right ones, and this explains the high preference for the hydrolysis of this enantiomer when (±)-**8** is used as the substrate. Another interesting point is that D-**8**, although much less suited to fit into the enzyme active site acts as a good substrate too, when L-**8** is absent, as shown by Figure 1. This means that L-**8** probably has a much lower K_m than D-**8** so that the former acts as a competitive inhibitor for the latter. On the other hand D-**8** probably has the higher V_{max}, so that when all the L-enantiomer has reacted, it is rapidly hydrolyzed. A similar behavior has been reported and in part substantiated by K_m and V_{max} measurements for other substrates, such as the oxides of *trans*-3,4-dimethylcyclohexene,[16c] styrene,[19] and *p*-nitrostyrene.[20]

One further observation is that L- and D-**8** as well as (±)-**20** are much better substrates for MEH than cyclohexene oxide.[16a] Apparently the tetrahydropyran ring oxygen, as well as the anomeric alkoxy group do not hinder but rather assist MEH-promoted hydrolysis. This could be an interesting feature favoring the use of MEH in the total synthesis of deoxy sugars. Although our experiments have so far been carried out at most on the millimolar scale, preliminary experiments show that scale-up to the 10^{-2} molar and probably higher scale should pose no problems. On the other hand the enzyme containing material (microsomes, or even the S-9 fraction) is easily obtainable anywhere and has the great advantage not to require the addition of cofactors. Finally, by this method racemic **8** can be converted into D-**8** and into both enantiomers of isobutyl boivinoside (**13**), in practically optically pure state, since D-**8** can be hydrolyzed, both chemically and enzymatically, to D-**13**.

This study is being extended to the enzymatic hydrolysis of (±)-**7** and to the α-anomers of the isobutyl 3,4-anhydro-2,6-dideoxy-*lyxo*-hexopyranoside and -*ribo*-hexopyranoside.

Experimental Section

Melting points (uncorrected) were taken on a Kofler block. NMR spectra were recorded with Varian EM-360 and CFT-20 spectrometers on $CDCl_3$ solutions (Me_4Si internal standard). GC analyses were run on a DANI 3800 and on a Perkin-Elmer Sigma 3B chromatograph, both equipped with flame ionization detectors, under the following conditions: (A) 2-m glass column, 10% Carbowax 20M on 80–100 mesh silanized Chromosorb W, N_2 flow 25 mL/min, programmed temperature 150 °C (2 min) to 200 °C, 7 deg/min, relative retention times for **6**, **7**, **8**, **3**, and **2** were 1.00:2.43:3.11:3.51:4.06; (B) 20 m × 0.8 mm capillary column, SE 52, N_2 flow 3 mL/min, 170 °C, relative retention times of **8**, **7**, **13**, and **16** were 1.00:1.11:1.69:1.83. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. Analytical TLC was carried out on silica plates (Merck, PSC Fertigplatten Kieselgel 60 F_{254}), components being located by spraying with 10% ethanolic phosphomolybdic acid and heating. Silica gel (Merck, Kieselgel 60, 70–230 mesh) was used for column chromatography. Preparative HPLc was performed on a Waters 500A instrument with Prepack 500-Silica cartridges. $MgSO_4$ was used as the drying agent. Petroleum ether indicates the fraction bp 40–60 °C.

2-Isobutoxy-6-methyl-2,3-dihydro-4*H*-pyran (1). This product was obtained in 73% yield by the previously described method.[6]

Isobutyl 2,3,6-Trideoxy-β-DL-*erythro*-hexopyranoside (2) and -α-DL-*erythro*-hexopyranoside (3). The 83:17 mixture of **2** and **3**, obtained in 59% yield as previously described,[6] was separated by preparative HPLC (petroleum ether/AcOEt, 7:3).

2: R_f 0.28; ^{1}H NMR (60 MHz) δ 1.30 (3 H, d, J = 6 Hz, H-6), 4.47 (1 H, dd, spl 9, 3 Hz, H-1).[21]

3: R_f 0.33; ^{1}H NMR (60 MHz) δ 1.25 (3 H, d, J = 6 Hz, H-6), 4.75 (1 H, m, $W_{1/2}$ = 4.5 Hz, H-1).

Isobutyl 2,3,6-Trideoxy-4-*O*-(methylsulfonyl)-β-DL-*erythro*-hexopyranoside (4) and -α-DL-*erythro*-hexopyranoside (5). The mixture of the mesylates **4** and **5**, obtained in 90% yield as previously described,[22] was completely separated by preparative HPLC (CH_2Cl_2/AcOEt, 98.5:1.5).

4: R_f 0.18; ^{1}H NMR (60 MHz) δ 0.90 (6 H, d, J = 6.5 Hz, OCH_2CHMe_2), 1.33 (3 H, d, J = 6.5 Hz, H-6), 3.06 (3 H, s, SO_2Me), 4.50 (1 H, dd, spl 9, 3 Hz, H-1); ^{13}C NMR δ 101.2 (C-1), 80.0 (C-4), 75.7 (OCH_2CHMe_2), 72.5 (C-5), 38.4 (SO_2Me), 29.9 (C-2), 28.4 (C-3), 28.2 (OCH_2CHMe_2), 19.1 and 19.0 (OCH_2CHMe_2), 17.9 (C-6).

Anal. Calcd for $C_{11}H_{22}O_5S$: C, 49.6; H, 8.3. Found: C, 50.1; H, 7.9.

5: R_f 0.28; ^{1}H NMR (60 MHz) δ 0.91 (6 H, d, J = 6.5 Hz, OCH_2CHMe_2), 1.26 (3 H, d, J = 6 Hz, H-6), 3.06 (3 H, s, SO_2Me), 4.78 (1 H, m, $W_{1/2}$ = 4.5 Hz, H-1); ^{13}C NMR δ 95.7 (C-1), 80.8 (C-4), 73.7 (OCH_2CHMe_2), 65.7 (C-5), 38.6 (SO_2Me), 29.2 (C-2), 28.1 (OCH_2CHMe_2), 25.4 (C-3), 19.2 and 19.1 (OCH_2CHMe_2), 17.7 (C-6).

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Anal. Calcd for $C_{11}H_{22}O_5S$: C, 49.6; H, 8.3. Found: C, 49.3; H, 8.0.

Isobutyl 2,3,4,6-Tetradeoxy-β-DL-*glycero*-hex-3-enopyranoside (6). A solution of **4** (5.9 g, 22 mmol) in dry Me_2SO (50 mL) was treated with *t*-BuOK (6.2 g, 55 mmol) and stirred until the starting material had completely reacted (TLC, 12 h). The mixture was diluted with water (50 mL) and extracted with petroleum ether (6 × 100 mL). The combined extracts were washed with H_2O and dried, and the bulk of the solvent was cautiously evaporated through a Vigreux column. The pale yellow oily residue contained (GC, conditions A) **6** and **2** in a 3:2 ratio that were separated by chromatography through a short column (silica gel, 70 g; petroleum ether/AcOEt, 9:1), to give 1.8 g of **6** (48% yield; single peak in GC and single spot in TLC, *Rf* 0.32; petroleum ether/AcOEt, 24:1). Pure **2** (0.86 g) was recovered with petroleum ether/AcOEt (7:3). **6** was obtained as an oil: ^1H NMR (60 MHz) δ 0.90 (6 H, d, *J* = 6.5 Hz, OCH_2CHMe_2), 1.23 (3 H, d, *J* = 6.5 Hz, H-6), 1.53–2.40 (3 H, m, H-2_e + H-2_a + OCH_2CHMe_2), 3.20 and 3.77 (2 H, 2 dd, spl 10, 7 Hz, OCH_2CHMe_2), 4.33 (1 H, dq, spl 6, 4 Hz, H-5), 4.65 (1 H, dd, spl 6, 6 Hz, H-1), 5.65 (2 H, m, H-3 + H-4). Attempts at distillation under reduced pressure (18 mm) of **6** were unsuccessful because of decomposition of the product with loss of isobutyl alcohol.

Isobutyl 3,4-Anhydro-2,6-dideoxy-β-DL-*ribo*-hexopyranoside (7) and -*lyxo*-hexopyranoside (8). A solution of **6** (1.6 g, 9.4 mmol) in 50 mL of dry CH_2Cl_2 was treated at 0 °C with commercial 85% *m*-chloroperbenzoic acid (2.4 g, 11.8 mmol), stirred 1 h at 0 °C, and then left 70 h at 5 °C. The precipitate was filtered off, and the filtrate was washed with 10% aqueous $NaHSO_3$ (50 mL) and then was saturated aqueous $NaHCO_3$ (3 × 50 mL) and dried and the solvent distilled through a Vigreux column to give 1.6 g of a liquid consisting (GC, conditions A) of **7** and **8** in a 57:43 ratio. Distillation of the crude residue gave 1.2 g (68% yield) of pure **7** + **8**, bp 120–125 °C (20 mm).

Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.5; H, 9.7. Found: C, 64.9; H, 9.9. Preparative HPLC (hexane/AcOEt, 9:1) of the **7** (R_f 0.21) and **8** (R_f 0.33) mixture allowed a complete separation of the components as colorless oils.

Double resonance experiments and/or change of solvent from $CDCl_3$ to C_6D_6 allowed analyses of the NMR spectra of **7** and **8** as first-order systems, where possible, or with the aid of a computer program. ^1H NMR (80 MHz, $CDCl_3$) diagnostic *J* couplings are only given in Table I.

7: δ 0.88 and 0.89 (6 H, 2 d, *J* = 6.3 Hz, OCH_2CHMe_2), 1.41 (3 H, d, *J* = 6.9 Hz, H-6), 1.73 (1 H, m, OCH_2CHMe_2), 1.81 (1 H, m, H-2_a), 2.25 (1 H, m, H-2_e), 2.97 (1 H, m, H-4), 3.11 and 3.59 (2 H, 2 dd, *J* = 9.4, 7.0, 6.5 Hz, OCH_2CHMe_2), 3.39 (1 H, m, H-3), 4.03 (1 H, dq, H-5), 4.46 (1 H, dd, H-1).

8: δ 0.89 and 0.89 (6 H, 2 d, *J* = 6.3 Hz, OCH_2CHMe_2), 1.39 (3 H, d, *J* = 6.5 Hz, H-6), 1.76 (1 H, m, OCH_2CHMe_2), 1.97 (1 H, m, H-2_a), 2.01 (1 H, m, H-2_e), 2.90 (1 H, m, H-4), 3.09 and 3.62 (2 H, 2 dd, *J* = 9.3, 6.8, 6.6 Hz, OCH_2CHMe_2), 3.26 (1 H, m, H-3), 3.96 (1 H, dq, H-5), 4.37 (1 H, dd, H-1).

A more efficient preparation of epoxides **7** and **8** minimizing losses due to the volatility of **6** avoided its isolation. The reaction mixture, obtained from 20 mmol of **4** with *t*-BuOK in Me_2SO as above, was diluted with ice–water (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were washed with water (3 × 100 mL), dried, filtered, then directly subjected to epoxidation with *m*-chloroperbenzoic acid, and treated as described above. The components of the crude reaction product, constituted (GC, conditions A) of **7**, **8**, and **2** in the ratio of 34:26:40, were separated by preparative HPLC. The pure epoxides **7** and **8** were thus obtained in 22% and 20% overall yields from **4**.

Alkaline Hydrolysis of 7 and 8. A mixture of **8** (0.60 g, 3.2 mmol) and aqueous 1 N NaOH (3 mL) was sealed in a glass vial and shaken for 20 h at 95 °C. The reaction mixture was neutralized with CH_3COOH, evaporated and the residue extracted repeatedly with $CHCl_3$. The combined organic extracts were evaporated to give an oily residue, (0.48 g, 73% yield). GC analysis (conditions B) showed that the crude reaction product was pure **13**.

The same reaction conducted on the epoxide **7** gave a crude reaction product constituted (GC, conditions B) by **13** and **16** in the ratio of 57:43.

When a 61:39 mixture of **7** and **8** was heated in 1 N NaOH at 95 °C and the reaction was stopped after 3 h, GC analysis of the crude reaction product showed a ratio of **7**, **8**, and **13** + **16** of 42:4:54. If one considers these as pseudo-first-order reactions and applies the equation $k^8/k^7 = \ln(c_0^8/c^8)/\ln(c_0^7/c^7)$, where c_0 and *c* are the initial and final concentration and the superscripts 7 and 8 refer to epoxides **7** and **8**, one gets that the latter reacts about 6 times faster than the former.

Isobutyl 2,6-Dideoxy-β-DL-*xylo*-hexopyranoside (13). The alkaline hydrolysis reaction product of **8** was subjected to Kugelrohr distillation [195 °C (0.01 mm)] to yield pure **13** as colorless oil: R_f 0.24 (hexane/AcOEt, 1:4); ^1H NMR (80 MHz) δ 0.90 (6 H, 2 d, *J* = 6.5 Hz, OCH_2CHMe_2), 1.27 (3 H, d, *J* = 6.7 Hz, H-6), 1.60–2.03 (3 H, m, H-2_a + H-2_e + OCH_2CHMe_2), 3.17 and 3.68 (2 H, 2 dd, spl 9.5, 7.0 Hz, OCH_2CHMe_2), 3.87–4.20 (3 H, m, H-3 + H-4 + H-5), 4.73 (1 H, dd, spl 5, 7 Hz, H-1); ^{13}C NMR δ 98.7 (C-1), 75.9 (OCH_2CHMe_2), 70.6 (C-4), 68.8 (C-3 + C-5), 33.7 (C-2), 28.3 (OCH_2CHMe_2), 19.2 and 19.1 (OCH_2CHMe_2), 16.2 (C-6).

Anal. Calcd for $C_{10}H_{20}O_4$: C, 58.8; H, 9.9. Found: C, 58.6; H, 10.0.

Isobutyl 3,4-Di-*O*-benzoyl-2,6-dideoxy-β-DL-*xylo*-hexopyranoside (14). A solution of **13** (0.24 g, 1.17 mmol) and benzoyl chloride (0.35 mL, 2.9 mmol) in anhydrous pyridine (7 mL) was heated with stirring at 65 °C for 12 h. The usual workup gave **14** as a white solid (0.45 g, 93% yield), which was recrystallized from hexane: mp 102 °C; ^1H NMR (80 MHz) δ 0.94 and 0.93 (6 H, 2 d, *J* = 6.5 Hz, OCH_2CHMe_2), 1.32 (3 H, d, *J* = 6.5 Hz, H-6), 1.92 (1 H, m, OCH_2CHMe_2), 2.05–2.23 (2 H, m, H-2_a + H-2_e), 3.22 and 3.82 (2 H, 2 dd, spl 9.4, 7.2 Hz, OCH_2CHMe_2), 4.26 (1 H, dq, spl 6.6, 1.6 Hz, H-5), 4.87 (1 H, dd, spl 6.3, 5.6 Hz, H-1), 5.11 (1 H, dd, spl 3.3, 1.6, H-4), 5.47 (1 H, m, $W_{1/2}$ = 10.5 Hz, H-3), 7.55 and 8.16 (10 H, m, phenyl protons).

Anal. Calcd for $C_{24}H_{28}O_6$: C, 69.9; H, 6.8. Found: C, 69.7; H, 6.7.

Isobutyl 3,4-Di-*O*-acetyl-2,6-dideoxy-β-DL-*xylo*-hexopyranoside (15). Acetylation of **13** was carried out with Ac_2O in pyridine (15 h at room temperature, followed by the usual workup): ^1H NMR (80 MHz) δ 0.89 and 0.91 (6 H, 2 d, *J* = 6.5 Hz, OCH_2CHMe_2), 1.20 (3 H, d, *J* = 6.5 Hz, H-6), 1.83–1.95 (2 H, m, H-2_a + H-2_e), 2.10 and 2.12 (6 H, 2 s, AcO), 3.14 and 3.74 (2 H, 2 dd, spl 9.0, 7.0 Hz, OCH_2CHMe_2), 3.98 (1 H, dq, spl 6.5, 1.5 Hz, H-5), 4.52–4.74 (2 H, m, H-1 + H-4), 5.05 (1 H, m, $W_{1/2}$ = 10.5 Hz, H-3).

Isobutyl 2,6-Dideoxy-β-DL-*arabino*-hexopyranoside (16). Treatment with hexane of the crude alkaline hydrolysis reaction product of **7** give solid **16** that recrystallized from hexane as white platelets: mp 134–136 °C; R_f 0.28 (hexane/AcOEt, 1:4); ^1H NMR (80 MHz) δ 0.92 (6 H, 2 d, *J* = 6.5 Hz, OCH_2CHMe_2), 1.33 (3 H, d, *J* = 6.5 Hz, H-6), 4.48 (1 H, dd, *J* = 10.0, 1.5 Hz, H-1).

Anal. Calcd for $C_{10}H_{20}O_4$: C, 58.8; H, 9.9. Found: C, 59.0; H, 10.0.

Isobutyl 3,4-Di-*O*-acetyl-2,6-dideoxy-β-DL-*arabino*-hexopyranoside (17). Acetylation of **16** was carried out with Ac_2O in pyridine (15 h at room temperature, followed by the usual workup): ^1H NMR (80 MHz) δ 0.89 (6 H, 2 d, *J* = 6.5 Hz, OCH_2CHMe_2), 1.22 (3 H, d, *J* = 6.2 Hz, H-6), 1.80 (1 H, m, H-2_a), 2.01 and 2.04 (6 H, 2 s, AcO), 2.29 (1 H, m, H-2_e), 3.17 and 3.66 (2 H, 2 dd, spl 9.4, 6.6 Hz, OCH_2CHMe_2), 3.45 (1 H, dq, spl 6.3, 9.2 Hz, H-5), 4.50 (1 H, dd, spl 9.6, 2.2 Hz, H-1), 4.72 (1 H, m, $W_{1/2}$ = 18.5 Hz, H-4), 4.99 (1 H, m, $W_{1/2}$ = 24.5 Hz, H-3).

Microsomal Preparations. Liver microsomes, prepared from phenobarbital-pretreated male New Zealand white rabbits as previously described,[16a] were suspended in 0.01 M Tris–HCl buffer (pH 9.0) to a protein concentration of ca. 15 mg/mL and stored at −40 °C.

Enzymatic Hydrolysis. A typical experiment was carried out with the following procedure: to the racemic epoxide **8** (0.12 g) dissolved in 0.2 mL of MeCN was added the microsomal suspension (12 mL, 15 mg of protein/mL), and the mixture was incubated under shaking at 37 °C. After the times reported in the Figure 1, samples were withdrawn and cooled at 0 °C, and the percentages of conversion were determined on the basis of the ratios of diol to epoxide observed by direct injection of the incubation mixture into the GC column. GC analysis showed that only the diaxial diol **13** was formed in all cases. Each value is the average of at least three determinations, corrected by using

a calibration curve obtained with standard solutions of the pure reference compounds in 0.01 M Tris-HCl buffer (pH 9.0) and MeCN (2%). The curve for an analytical experiment carried out with a 0.01 M concentration of the racemic epoxide 8 is also shown in Figure 1. The preparative incubations were stopped after ca. 50% conversion (GC). The unreacted epoxide 8 was immediately extracted from the cooled incubation mixture with hexane (3 × 20 mL) with vigorous shaking for 5 min. This treatment transferred all epoxide into the organic phase, while the diol 13 remained in the aqueous phase. The organic phase was dried, evaporated under atmospheric pressure, and subjected to Kugelrohr distillation [70 °C (0.5 mm)] to yield the pure epoxide 8, $[\alpha]^{30}_D$ −68° (c 2.0, $CHCl_3$).

The aqueous phase remaining after the extraction of 8 was concentrated to dryness under reduced pressure and then extracted with hot AcOEt (3 × 20 mL). The organic phase was dried, evaporated and subjected to Kugelrohr distillation [110 °C (0.5 mm)] to give pure diol 13, $[\alpha]^{30}_D$ +53° (c 3.0, $CHCl_3$). Both unreacted epoxide 8 and produced diol 13 were obtained in ca. 70% yield, with respect to the racemic starting material. Blank experiments carried out with pure racemic epoxide 8 and boiled microsomes showed that no spontaneous hydrolysis occurred even at the longest incubation times.

Determination of Enantiomeric Excess of 8. In the ^1H NMR spectrum of the racemic epoxide 8 (4.1 mg, $CDCl_3$), after addition of tris[3-((heptafluoropropyl)hydroxymethylene)-(+)-camphorato]europium(III) [Eu(hfc)$_3$] (7.4 mg) the doublet of Me at C-5 was shifted and split into two doublets at δ 2.65 and 2.89. A 1000-Hz spectral width for 8192 data points was used, as the better compromise between folding and digitalization. Both the integral and height values of the signals were evaluated on several spectra of the same experiment. Very good agreement was obtained from the mean values of the two methods, the latter being preferred for ease of evaluation. The maximum error was never higher than 2%.

The spectrum of the epoxide 8 [5.2 mg + 9.4 mg of Eu(hfc)$_3$] recovered from enzymatic hydrolysis after 50% conversion, showed only the doublet at δ 2.89. In order to evaluate the sensitivity of the determination of ee, 25 μL of a solution of racemic 8 (4.3 mg) and Eu(hfc)$_3$ (8.0 mg) in $CDCl_3$ (1.0 mL) was added to the same sample. This corresponded to the addition of 1% of L-8 and produced no clearly detectable signal for L-8 in the spectrum. However a second addition of 25 μL of the same solution produced a signal three times more intense than the noise. This provided sure evidence for an ee of at least 96% of the epoxide 8 recovered from the partial enzymatic hydrolysis.

Determination of Enantiomeric Excess of 13. The same procedure as for 8 was applied to the diacetyl derivative 15 obtained from 13 as described above. The addition of Eu(hfc)$_3$ (32.5 mg for 5.0 mg of racemic 15) shifted and split the doublet of Me-5 into two doublets at δ 3.81 and 3.54. The spectrum of 15 obtained from the 50% conversion enzymatic product showed only the doublet at δ 3.81. A sensitivity control by addition of racemic 15 showed again an ee of at least 96%.

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A Novel Two-Step Conversion of 3′,5′-Di-*O*-tosylthymidine to 5′-Amino-5′-deoxythymidine Analogues with Inversion of the 3′-Hydroxyl Group

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The reaction of 3′,5′-di-*O*-tosylthymidine (**1a**) with methylamine at 35 °C gave a 75% yield of 2,5′-(methylimino)-1-(2-deoxy-β-D-*threo*-pentofuranosyl)thymine (**4a**). A similar reaction of **1a** with ammonia in Me_2SO at 78 °C gave a 41% yield of 2,5′-imino-1-(2-deoxy-β-D-*threo*-pentofuranosyl)thymine (**4b**). Hydrolysis of **4a** and **4b** in 1 N sodium hydroxide gave 1-[2,5-dideoxy-5-(methylamino)-β-D-*threo*-pentofuranosyl]thymine (**5a**) and the corresponding 5-amino analogue **5b**. Proposed intermediates in the conversion of **1a** to **4a** and **4b** are 2,3′-anhydro-1-[2-deoxy-5-*O*-(*p*-tolylsulfonyl)-β-D-*threo*-pentofuranosyl]thymine (**2a**) and the aminopyrimidine nucleosides **3a** (R = Me, H).

In the course of preparing analogues of 5′-(bromoacetamido)-5′-deoxythymidine (BAT), a compound with demonstrated anticancer activity,[1-6] a quantity of 5′-deoxy-5′-methylaminothymidine was required as an intermediate. This amine has been prepared[2] in near-quantitative yield by reaction of 5′-*O*-tosylthymidine with methylamine at 35 °C. When this reaction was carried out with 3′,5′-di-*O*-tosylthymidine (**1a**) present as a contaminant, the previously unreported 2,5′-iminonucleoside[7] **4a** was isolated as a byproduct (Scheme I). It was subsequently determined that **4a** could be obtained in 75% yield starting with

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(7) The *Chemical Abstracts* names for **4a** and **4b** for the 1967–1971 index period and the preferred names in accord with the IUPAC rules of organic nomenclature are, respectively, as follows: (6*R*,8*R*,9*R*)-6,7,8,9,10,11-hexahydro-8-hydroxy-3,11-dimethyl-6,9-epoxy-2*H*-pyrimido[1,2-*a*][1,3]diazocin-2-one and (6*R*,8*R*,9*R*)-6,7,8,9,10,11-hexahydro-8-hydroxy-3-methyl-6,9-epoxy-2*H*-pyrimido[1,2-*a*][1,3]diazocin-2-one. The current *Chemical Abstracts* names for **4a** and **4b** are as follows: [6*R*-(6α,8α,9α)]-6,7,8,9,10,11-hexahydro-8-hydroxy-3,11-dimethyl-6,9-epoxy-2*H*-pyrimido[1,2-*a*][1,3]diazocin-2-one and [6*R*-(6α,8α,9α)]-6,7,8,9,10,11-hexahydro-8-hydroxy-3-methyl-6,9-epoxy-2*H*-pyrimido[1,2-*a*][1,3]diazocin-2-one.

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