water, and then dried over potassium carbonate. When the mixture was filtered from the drying agent and then concentrated, a brown-yellow oil remained (1.6 g). The oil was distilled and a fraction boiling at 85–95° (0.4 mm) weighing 1.2 g was collected. This material was taken up in pentane, and on cooling in the freezer white crystals, weighing 0.9 g (24% yield), separated and were collected.

The infrared spectrum of the ketone (melt) showed a strong carbonyl peak at 5.92 μ (1690 cm^{-1}). The nmr was listed in the Discussion.

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.31; H, 10.10.

Preparation of 13.—Bromine (4.2 g, 0.025 mole) in 5 ml of acetonitrile was added dropwise to a stirred, cooled suspension of triphenylphosphine (6.8 g, 0.025 mole) in 25 ml of acetonitrile. When the ice bath had warmed to 20°, the ether **12**[7] (3.0 g, 0.025 mole) was added to the triphenyldibromophosphorane. After the reaction had stood at room temperature for 1 hr, solution occurred. The reaction mixture was placed in the freezer overnight.

The mixture was poured into ice–water and the oil was extracted with pentane. The pentane extracts were dried over sodium sulfate and then concentrated. Distillation yielded 2.0 g (30%) of material boiling at 86–89° (0.3 mm) [lit.[8] bp 103–106° (2 mm)].

An nmr spectrum (neat, values in parts per million from an external TMS standard) exhibited a doublet centered at 3.76 (4 H on the carbons bearing the bromine atom), an undefined multiplet at 2.54 (2 H), and a broad singlet at 1.84 (8 H).

Reaction of 1 with Triphenyldibromophosphorane.—In an addition funnel was placed 0.43 g (0.00236 mole) of **1** dissolved in 2 ml of acetonitrile. In a flask was placed 0.62 g (0.00236 mole) of triphenylphosphine in 2 ml of acetonitrile. The suspension was cooled in an ice bath and 9.38 g (0.00236 mole) of bromine in 3 ml of acetonitrile was added dropwise from another addition funnel. After completion of the bromine addition, the solution of **1** was added over a period of 6 min. The color of the mixture gradually changed to yellow-brown with the suspended solid still present. The mixture was stirred overnight from which a black solution resulted. The acetonitrile was removed under vacuum. Water was added to the residue and the mixture was extracted with pentane. The pentane extracts were dried over sodium sulfate and the pentane was removed under vacuum. A small amount of yellow oil was obtained. The nmr spectrum (neat, parts per million from external TMS standard) indicated that some elimination had occurred as resonances appeared at 4.7 and 5.2. A complex methyl pattern (about ten peaks) was centered at 1.0. Attempts at purification led only to the recovery of a small amount of starting material.

Registry No.—**1**, 13019-24-4; **3**, 4895-34-5; **6** (R = Ts), 13019-26-6; **7**, 13019-27-7; **8**, 13019-28-8; **9**, 13019-29-9; **13**, 13019-30-2.

Acknowledgment.—This study was supported by Research Grant GM-08241 from the U. S. Public Health Service.

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The Reduction of Free Aldonolactones by Disiamylborane

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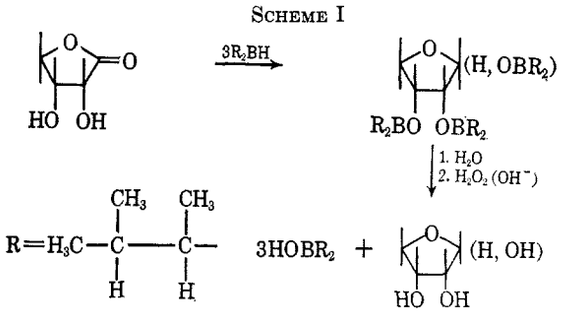
The most difficult step in the cyanohydrin synthesis of carbohydrates is the reduction of the aldonolactones to the aldose. The reagents commonly used for the reduction of lactones are sodium amalgam[1] and buffered sodium borohydride;[2] in both cases the reactions are difficult to control and unless extreme care is exercised will give poor yields.[3] In the case of erythronolactone, neither of these methods give the desired aldose.[4,5] Recently a procedure for the reduction of fully acylated lactones of aldonic acids was reported.[6] It utilized bis-3-methyl-2-butylborane (disiamylborane), a reagent developed by Brown for selective hydroboration.[7,8]

Disiamylborane is known to react with free hydroxyl groups to form the dialkylalkoxyborane derivative with the evolution of hydrogen; therefore, if a nonacylated lactone is treated with sufficient reducing agent to react with all of the hydroxyl groups as well as the carbonyl group, the reduction to the aldose should be possible. The alcoholic hydroxyls would be regenerated during the hydrolytic step giving the free sugar as a direct product (Scheme I).

SCHEME I



We would like to report the successful use of disiamylborane for the direct reduction of aldonic acid γ- and δ-lactones. The success of this reaction in the presence of free hydroxyl groups renders unnecessary the acylation and subsequent saponification to remove the blocking groups during a synthetic sequence.

D-Erythronolactone was reduced to D-erythrose by this method; to our knowledge this is the first time this lactone has been successfully reduced to the aldehyde. The reagent was also shown to reduce unacylated D-galactono-γ-lactone and D-glucono-δ-lactone to the respective aldohexoses in good yield.

Results and Discussion

The reaction conditions for the disiamylborane reductions of the unblocked lactones were investigated using D-erythronolactone, since this compound is the most difficult to reduce by other techniques and since our principal interest is with tetrose chemistry. The extent of lactone reduction to aldose was determined spectrophotometrically, using the phenol–sulfuric acid assay.[9] D-Erythronolactone was rapidly reduced to yield about 60% of theoretical tetrose which then remained unchanged over an extended period of time.

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Two parameters affecting the yield of aldotetrose were investigated; these were the ratio of reducing agent to substrate and the reaction temperature. Molar ratios of disiamylborane to tetronolactone of 3:1 or 4:1 were found to give the greatest production of aldotetrose. The highest yield of tetrose was obtained by carrying out the reaction at −10° rather than at room temperature as had been employed with the acylated lactones.[6]

The composition of the reduced reaction mixtures was investigated by gas–liquid partition chromatography (glpc) of the trimethylsilyl derivatives. After reduction of D-erythronolactone the prevalent peaks were D-erythrose and erythritol with D-erythronolactone represented by a small peak. Direct chemical analysis showed the presence of 2.4% unreacted lactone.

The reduction of D-glucono-δ-lactone and D-galactono-γ-lactone was carried out at a ratio of (10:1) disiamylborane to lactone. Yields of 60% D-glucose and 72% D-galactose, respectively, were found. Conditions for these reactions were not investigated and it is quite possible that better yields could be obtained, particularly with a smaller excess of reducing agent. Gas chromatography of these reaction mixtures showed that the major components were the expected aldose and the corresponding polyol with small amounts of unreacted lactones sometimes remaining.

It would appear that under the conditions used in this study for the disiamylborane reduction of unblocked aldonolactones the major side reaction is over-reduction to polyol. This might be due to the presence of a small amount of diborane in the disiamylborane preparation which would rapidly reduce a portion of the lactone to polyol, or to some opening of the hemiacetal ring of the aldose product giving a free aldehyde which could be reduced further by this reagent.

Experimental Section

Equipment and Methods.—Infrared spectra were taken on a Perkin-Elmer Model 421 spectrophotometer. Visible and ultraviolet spectra were taken on a Cary 15. Glpc was carried out on a Barber-Coleman Model 10 with an ionization detector. All chemicals used are reagent grade, specially purified when necessary. Melting points are uncorrected. Microanalysis was performed by Spang Microanalytical Laboratory. D-Erythronolactone (mp 103–104°) was prepared by perpropionic acid oxidation of 2,4-O-ethylidene-D-erythrose.[10] D-Galactono-γ-lactone was purchased from Pfanstiehl Laboratories and D-glucono-δ-lactone was obtained from CalBiochem. The lactone assay consisted of a modification of the hydroxamic acid procedure of Lipmann and Tuttle.[11] Tetrose and hexose assays were done by the phenol–sulfuric acid technique.[9] Disiamylborane in tetrahydrofuran was prepared by the method of Brown;[8] subsequently, commercial samples of this reagent obtained from the Ventron Corp., were employed with equal success. Paper chromatography on Whatman No. 1 paper was carried out using the following solvent systems: water–saturated *n*-butyl alcohol, pyridine–*n*-butyl alcohol–water (4:8:3), and *n*-butyl alcohol–acetic acid–water (4:1:5).

Reduction of D-Erythronolactone.—A 100-mg (0.85 mmole) sample of D-erythronolactone was placed in a carefully dried, 50-ml reaction flask. To this was added 2.8 ml of 1 *M* disiamylborane in tetrahydrofuran. The reagent and the reaction mixture were maintained at −10° and all manipulations were conducted in a glove box purged with dry nitrogen in order to minimize contamination by atmospheric moisture and oxygen. The reaction flask was sealed with a ground-glass stopper equipped with a vent, protected by a drying tube after which the glove box was dispensed with. Immediate hydrogen evolution occurred and the lactone slowly dissolved in the reaction solution. After 15 min the temperature was allowed to rise to room temperature and the reaction mixture was left overnight for convenience. One preparation was worked up within 2 hr of starting the reaction without alteration in yield. To the reaction flask, 1 ml of water was carefully added and the solution was refluxed for 0.5 hr. The solvent was removed by taking the solution to dryness *in vacuo* at 40°. In those cases where 6:1 or greater ratios of disiamylborane to lactone were employed some difficulty in the removal of the dialkylborinic acid was encountered and oxidation at pH 7–8 with H_2O_2 was employed to convert it to boric acid and 3-methyl-2-butanol. The latter was readily volatilized while the boric acid, which interferes with glpc of the samples, could be removed by dissolving the residue in absolute methanol and taking the solution to dryness *in vacuo* several times.

The reduction products were taken up in water and analyzed for tetrose content. The average yield of D-erythrose in five runs was 60 ± 5%. The spectrum observed in the phenol–sulfuric acid assay was that characteristic of aldotetroses and was identical with that observed with D-erythrose prepared by other procedures.[12,13] The aldose produced was indistinguishable from known D-erythrose when examined by paper chromatography.

The reduction product was further characterized as the phenylhydrazine derivative.[14] After purification the phenylosazone melted at 163–165.5° with decomposition at 166.5° (lit. mp 167°[15] and 165°[16]). *Anal.* Calcd for $C_{16}H_{18}N_4O_2$ (1 mg of phenylosazone): C, 64.40; H, 6.09. Found: C, 63.89; H, 6.20. This phenylosazone was identical in its chromatographic behavior, infrared, and ultraviolet spectra with that prepared from known D-erythrose by the same procedure.

Reduction of D-Galactono-γ-lactone.—The reduction of 73.3 mg (0.412 mmole) of D-galactono-γ-lactone was carried out as described above except that 4.5 ml of a 1 *M* disiamylborane in tetrahydrofuran solution was employed. Analysis by the phenol–sulfuric acid method showed 72% yield of hexose in the reaction mixture, relative to a D-galactose standard run simultaneously. This product was identical with known D-galactose by glpc and by paper chromatography.

Reaction of D-Glucono-δ-lactone.—A 100.2-mg (0.562 mmole) sample of D-glucono-δ-lactone was treated with 5.7 ml of 1 *M* disiamylborane in tetrahydrofuran in the same manner as described above. Analysis of the reduction product by the phenol–sulfuric acid method showed a 60% yield of hexose, relative to a D-glucose standard. This product was indistinguishable from known D-glucose by glpc and by paper chromatography.

Investigation of Products by Glpc.—Aliquots of the final reaction mixtures were taken to dryness and the trimethylsilyl derivatives of the samples were prepared according to the procedure of Sweeley.[17] These were fractionated on a 6-ft column of 10% diethylene glycol succinate on (80–100 mesh) Chromosorb W at 125° (isothermal) and 30 psi of argon giving a flow rate of 360 cc/min. Relative retention times compared to a β-methyl-D-xylopyranoside standard are given in parentheses. In the case of the D-erythronolactone reduction, the major peaks corresponded to D-erythrose (0.18, 0.25) and erythritol (0.39). A small peak was identified as D-erythronolactone (1.16). The magnitude of the erythritol peak indicated that it represented 20 to 40% of the expected product; a more precise estimation of erythritol was not possible owing to the nonlinear response of our detector system.

Investigation of the reduction of D-galactono-γ-lactone was carried out at 160° (isothermal) using the same column. The major peaks corresponded to D-galactose (2.78, 3.00, 3.78) and D-galactitol (4.11), and D-galactono-γ-lactone (5.11) was detected. The reduction products of D-glucono-δ-lactone showed major peaks corresponding to D-glucose (2.89, 5.00) and D-glucitol (4.11) as well as somewhat stronger peaks for D-glucono-δ-lactone (1.22, 1.78, 5.22) than encountered with the other lactones.

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Registry No.—Disiamylborane, 1069-54-1; D-galactono-γ-lactone, 2782-07-2; D-glucono-δ-lactone, 90-80-2; D-erythronolactone, 13016-40-5.

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A Three-Step Synthesis of Fichtelite from Abietic Acid

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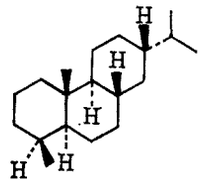
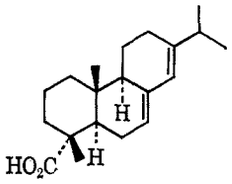
In connection with the proof of the course of a polyolefinic cyclization,[1] we had occasion to develop a convenient synthetic source of authentic fichtelite (I).[2] The following scheme is a somewhat condensed version of one of the approaches described by Burgstahler and Marx.[3]

For the first step of our synthesis we employed the known conversion of abietic acid (II), by reduction of the diamylamine salt with lithium in ammonia, into



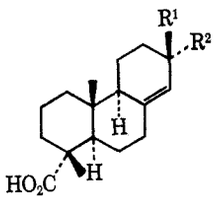
I



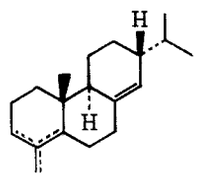
II

$\Delta^{8(14)}$-dihydroabietic acid [III, R^1 = H; R^2 = $CH(CH_3)_2$].[3,4] Four recrystallizations of the crude product afforded, in 24% yield, material, mp 197–198°, $[\alpha]^{26}D$ −24°, which is of only moderate purity.[3]

The second step involved decarboxylation of the dihydro acid by the pyridine–copper salt catalyzed[5] reaction with lead tetraacetate to give, in 76% yield, the diene mixture IV. This type of decarboxylative elimination reaction has been used before in the resin acid series and has been shown to give mainly the isomer with an exocyclic bond.[3,6] It is noteworthy that in our hands the Kochi decarboxylation procedure,[5] when applied to the known[3,7a] tetrahydroabietic acid, mp 182°, that is obtained on hydrogenation of III [R^1 = H, R^2 = $CH(CH_3)_2$], afforded the monoolefinic mixture (8,14-dihydro IV) in 76% yield.



III



IV

The third step amounted simply to catalytic hydrogenation of the diene mixture over platinum oxide in acetic acid. It seemed probable that the stereochemical course of this reaction would be predictable on the basis of the known propensity of such systems with an 8,14-olefinic bond to undergo β hydrogenation[3,7] and of such systems containing an olefinic bond involving C-4 to undergo α hydrogenation.[3] This expectation was realized in that the vapor phase chromatogram of the hydrogenation product showed only two peaks, in the ratio 3:7. The substance corresponding to the latter (major) peak, on separation by preparative vapor phase chromatography, crystallized in the collection tube. This material on a single recrystallization from methanol, melted at 45.8–46.1°, $[\alpha]^{26}D$ +19°. A mixture of this product with a sample of natural fichtelite[8] (I), mp 45.8–46.1°, $[\alpha]^{26}D$ +19°, melted at 45.8–46.1°. The infrared spectrum, as well as the nmr spectrum and gas chromatographic behavior of the synthetic material, was identical with that of the natural product.

For a somewhat simplified preparation of fichtelite in higher over-all yields, it was found that the total crude dihydroabietic acid of the first step could be employed. The hydrogenation product of the third step was shown by gas chromatographic analysis to contain 50% fichtelite. From this mixture it was possible to isolate fichtelite either by preparative gas chromatography or simply by repeated recrystallization from ether–methanol.

Experimental Section[9]

$\Delta^{8(14)}$-Dihydroabietic Acid [III, R^1 = H; R^2 = $CH(CH_3)_2$].—The following is essentially the procedure described by Kennedy.[4b] To a mixture of 400 ml of anhydrous ether and 400 ml of liquid ammonia (distilled from sodium) was added 40.0 g of the diamylamine salt of abietic acid ($[\alpha]^{25}D$ −60°).[10] The resulting light

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(8) We wish to thank Professor R. E. Ireland for providing us with a sample of natural fichtelite which originally came from Professor O. Jeger, whom we also thank.

(9) Melting points were taken on a Kofler hot-stage microscope unless otherwise indicated. Liquid film specimens were used for the infrared spectra which were determined on Perkin-Elmer 137 and 237B spectrophotometers. Nmr spectra were determined on a Varian A-60 spectrometer. Rotations were determined on 1% solutions in 95% ethanol with a Zeiss circle polarimeter 0.01. Analytical gas chromatographies were carried out on an Aerograph Hy-Fi (A-600) gas chromatograph equipped with a hydrogen flame detector; columns employed were 0.125 in. × 7.5 ft 5% SE-30 silicon rubber on 60–80 Chromosorb W, and 0.125 in. × 7.5 ft 15% Carbowax on 80–100 Chromosorb W. Preparative gas chromatographies were performed on an Aerograph Autoprep (A-700); columns employed were 0.375 in. × 20 ft 20% SE-30 silicon rubber on 60–80 Chromosorb W, and 0.375 in. × 20 ft 20% Carbowax on 45–60 Chromosorb W.

(10) This material was obtained by purification of technical abietic acid (Matheson Coleman and Bell) by the method of G. C. Harris and T. F. Sanderson, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p 1.