Preparation of the *E* and *Z* Isomers of 9-(5,6-Dideoxy-β-D-*erythro*-hex-4-enofuranosyl)adenine[1]

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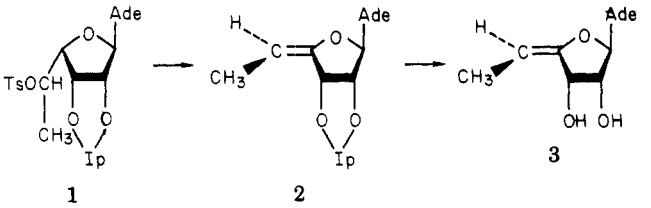
The *E* and *Z* isomers of 9-(5,6-dideoxy-β-D-*erythro*-hex-4-enofuranosyl)adenine were prepared by starting from methyl 5,6-dideoxy-5-iodo-2,3-*O*-isopropylidene-β-D-allofuranoside and methyl 5,6-dideoxy-5-iodo-2,3-*O*-isopropylidene-α-L-talofuranoside, respectively. By a series of reactions in which the isopropylidene groups were removed, the hydroxyl groups benzoylated, and the methoxyl groups replaced with acetates by acetolysis, the 1-*O*-acetyl-2,3-di-*O*-benzoyl-6-deoxy-5-iodohexofuranoses were prepared. The sugar derivatives were coupled with 6-(benzamidochloromercuri)purine by the titanium tetrachloride method. The blocked nucleosides were treated with 1,5-diazabicyclo[5.4.0]undec-5-ene in *N*,*N*-dimethylformamide and the blocking groups removed with methanolic ammonium hydroxide to obtain the desired 4′,5′-unsaturated nucleosides. As part of their structure proof, the nucleosides were converted to 2′,3′-*O*-isopropylidene derivatives and characterized by NMR spectroscopy.

A number of years ago I prepared 9-(5,6-dideoxy-2,3-*O*-isopropylidene-β-D-*erythro*-hex-4-enofuranosyl)adenine (**2**) by treatment of 9-(6-deoxy-2,3-*O*-isopropylidene-5-*O*-(*p*-toluenesulfonyl)-α-L-mannofuranosyl)adenine (**1**) with sodium benzoate or potassium *tert*-butoxide in hot *N*,*N*-dimethylformamide[2] (Scheme I). On the basis of earlier work[3] and the type of reaction conditions, the product was presumed formed by an E2 mechanism, where the proton at C-4′ and the *p*-toluenesulfonate group acquire an antiperiplanar conformation and leave in opposite directions (anti mechanism). Therefore, **2** would be expected to have the proton at C-5′ oriented cis to the ring oxygen (the *E* isomer). The similarity in the structure of **3** to those of the nucleoside antibiotic decoyinine (**4**) and 9-(5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)adenine (**5**) (Chart I), a biologically active nucleoside,[4] inspired further work to prepare **3** for biological studies. The isopropylidene group could not be removed from **2** because of the acid lability of the enol ether nucleoside. A similar problem had been encountered by McCarthy et al.[4] with 9-(2,3-*O*-isopropylidene-5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)-adenine. They were, however, able to prepare **5** by using the much more acid-labile 2,3-*O*-ethoxymethylidene group. Rather than attempt to prepare **3** and other 4′,5′-unsaturated aldofuranosyl nucleosides with acid-labile blocking groups, a plan was conceived by which alkali-labile groups could be used. This route required the synthesis of sugar derivatives suitably blocked with ester groups and a good leaving group, preferably an iodine atom, at the C-5 position. The blocked nucleosides, prepared by common coupling procedures, would then be treated with a powerful base of low nucleophilicity, such as 1,5-diazabicyclo-[5.4.0]undec-5-ene, to effect dehydrohalogenation; afterward, deblocking under basic conditions would give the unsaturated nucleosides. The advantages of this route were: (1) substitution of a good leaving group at C-5 of the sugar and manipulation of blocking groups could be accomplished without regard for the special problems involved with nucleoside chemistry, such as cyclonucleoside formation and acid lability; (2) no special blocking procedures had to be worked out for the sugar portion of the nucleosides, and the adenine ring did not have to be selectively blocked to inhibit cyclonucleoside formation during substitution and elimination reactions since it would now be blocked as part of the reaction scheme; (3) the nucleoside analogues had to be synthesized from monosaccharides and the base anyway, so that overall, fewer steps would be required to obtain the desired products. This plan was successfully demonstrated in a new synthesis of **5** and its L enantiomer[5] and of several other 4′,5′-unsaturated pentofuranosyl nucleosides.[6] The preparation of **3** and its *Z* isomer **18** has finally been achieved by this route, and this is the subject of this paper.

Scheme I



1 2 3

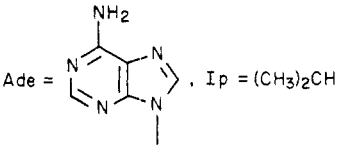
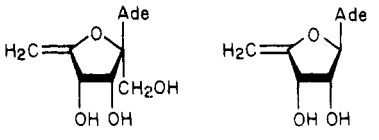


Chart I



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The syntheses of **3** and **18** are illustrated in Schemes II and III. Assuming that the elimination reaction proceeds by the anti mechanism, it is easily perceived that a 5′-iodo-D-allo nucleoside would yield the same product as a 5′-iodo-L-manno nucleoside, and similarly for the identical products expected from the 5′-iodo-L-talo and 5′-iodo-D-gulo nucleosides. The advantages of using methyl 5,6-dideoxy-5-iodo-2,3-*O*-isopropylidene-β-D-allofuranoside (**7**) and methyl 5,6-dideoxy-5-iodo-2,3-*O*-isopropylidene-α-L-talofuranoside (**13**) were that they were known compounds and conveniently prepared from methyl 6-deoxy-2,3-*O*-isopropylidene-α-L-talofuranoside (**6**) and methyl 6-deoxy-

(1) This work was supported by Grant No. CA 13802 from the National Cancer Institute, National Institutes of Health.
(2) L. M. Lerner, *J. Org. Chem.*, **37**, 477 (1972).
(3) H. Arzoumanian, E. M. Acton, and L. Goodman, *J. Am. Chem. Soc.*, **86**, 74 (1964).
(4) J. R. McCarthy, Jr., R. K. Robins, and M. J. Robins, *J. Am. Chem. Soc.*, **90**, 4993 (1968).
(5) L. M. Lerner, *Carbohydr. Res.*, **53**, 177 (1977).
(6) V. K. Srivastava and L. M. Lerner, *J. Med. Chem.*, **22**, 24 (1979).

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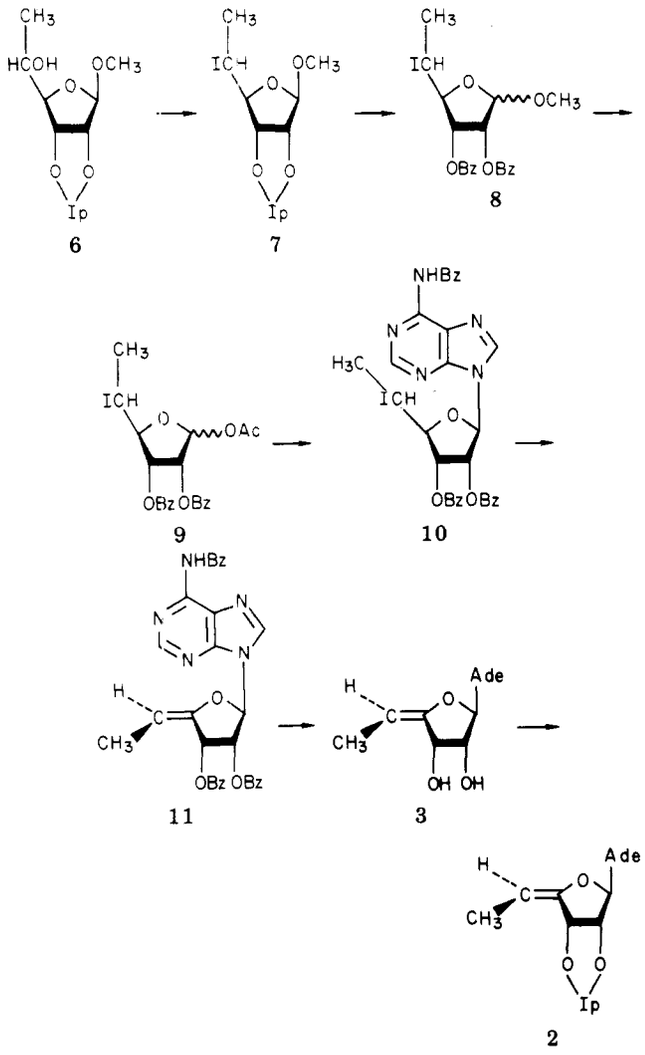
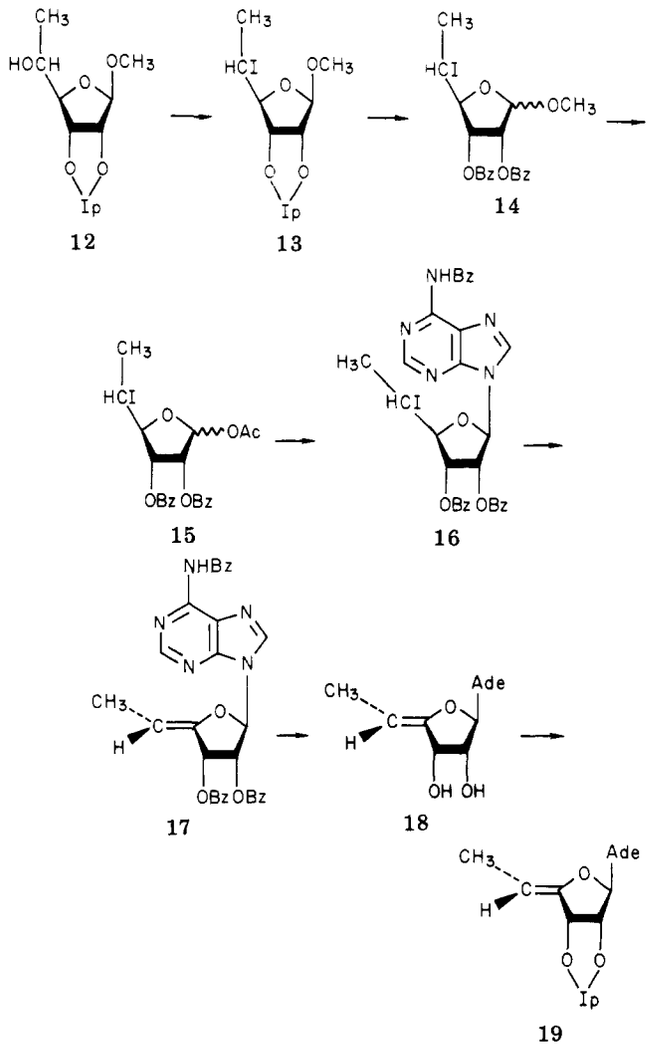
Scheme II



Scheme III



2,3-*O*-isopropylidene-β-D-allofuranoside (**12**), respectively.[7] In turn, **6** and **12** are readily prepared from 6-deoxy-L-mannose (L-rhamnose).[8] On the other hand, the corresponding 5-iodo derivatives of 6-deoxy-L-mannose and 6-deoxy-D-gulose are unknown. Moreover, previous experience has demonstrated that glycosides and nucleosides having the 6-deoxy-L-mannofuranose configuration do not easily undergo displacement reactions at C-5 and often afford unsaturated products.[2,9,10] Furthermore, a separate synthesis of a D-gulofuranoside derivative[11] needed for the preparation of **3** would be required, whereas commercially available 6-deoxy-L-mannose acts as the source for both **6** and **12**. Due to some changes in the preparation and handling of **7** and **13** as well as a lack of experimental detail in the earlier report,[7] the preparations of these compounds from **6** and **12** are described with comments in the Experimental Section.

The isopropylidene groups of **7** and **13** were removed in refluxing methanol in the presence of a strong-acid ion-exchange resin. The hydroxyl groups were benzoylated to give **8** and **14**, and acetolysis afforded the 1-*O*-acetates **9** and **15**. The conversions of **7** to **9** and **13** to **15** were nearly quantitative and were followed by NMR spectroscopy to ensure the proper exchange of blocking groups. Condensation of 6-(benzamidochloromercuri)purine[12] with **9** and **15** by the titanium tetrachloride method,[13] followed by partial purification by column chromatography, afforded the fully protected 5′-iodo nucleosides **10** and **16**, respectively. Treatment of **10** and **16** with 1,5-diazabicyclo[5.4.0]undec-5-ene in *N*,*N*-dimethylformamide (giving **11** and **17**) and removal of the benzoyl groups under basic conditions gave the desired nucelosides **3** and **18** after purification by chromatography on an ion-exchange column.[14] Overall yields from **7** and **13** were about 20%.

Initially the nucleosides were recrystallized from ethanol; however, the crystalline forms were not well defined, and physical characterization was difficult. The NMR spectra showed that various samples of each nuceloside contained from 20 to almost 50% ethanol by comparison of the integration of the 6′-methyl group with the integration of the ethanol methyl group. Reliable elemental analyses

(7) N. K. Kochetkov, A. I. Usov, and K. S. Adamyants, *Tetrahedron*, **27**, 549 (1971); N. K. Kochetkov and A. I. Usov, *Methods Carbohydr. Chem.*, **6**, 205 (1972).

(8) (a) P. A. Levene and J. Compton, *J. Biol. Chem.*, **116**, 169 (1936); (b) E. J. Reist, L. Goodman, R. R. Spencer, and B. R. Baker, *J. Am. Chem. Soc.*, **80**, 3962 (1958); (c) E. J. Reist, L. Goodman, and B. R. Baker, *ibid.*, **80**, 5775 (1958).

(9) A short review and some further examination of this phenomenon are given in: J. S. Brimacombe, J. Minshall, and L. C. N. Tucker, *Carbohydr. Res.*, **31**, 146 (1973).

(10) Several attempts to prepare methyl 5,6-dideoxy-5-iodo-2,3-*O*-isopropylidene-β-D-gulofuranoside from methyl 6-deoxy-2,3-*O*-isopropylidene-α-L-mannofuranoside by methods described in this paper for the synthesis of **7** and **13** were discouraging.

(11) L. M. Lerner, *Carbohydr. Res.*, **44**, 116 (1975).

(12) P. Kohn. R. H. Samaritano, and L. M. Lerner, *Synth. Proced. Nucleic Acid Chem.*, **1**, 120 (1968).

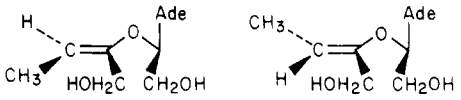
(13) B. R. Baker, R. E. Schaub, J. P. Joseph, and J. H. Williams, *J. Am. Chem. Soc.*, **77**, 12 (1955); J. Prokop and D. H. Murray, *J. Pharm. Sci.*, **54**, 359 (1965).

(14) C. A. Dekker, *J. Am. Chem. Soc.*, **87**, 4027 (1965).

could not be obtained. Crystallization from acetone provided **18** in an anhydrous, nonsolvated form. However, **3** crystallized as beautiful soft prisms, again in the form of a solvate. The amount of acetone was 0.4–0.5 mol/mol of **3** (NMR). This form did not give an adequate elemental analysis. Attempts to remove the acetone with heat under high vacuum caused some browning of the samples. If the temperature was too high (e.g., 140 °C) or the heating too long (e.g., 24 h at 110 °C), this change in appearance occurred. It was eventually found that anhydrous, nonsolvated **3** is obtained after heating the acetonate at 110 °C for 4–5 h. The nucleoside undergoes a change in physical form during the process but is still cyrstalline according to its characteristics under the polarized microscope.

The structures for **3** and **18** were supported by the elemental analyses and the IR, UV, and NMR spectra. The UV spectra had peaks at 260 nm, indicative of N-9 substitution. The NMR spectra had the correct number of proton peaks, and exchange with D_2O helped in the assignment of peaks and to clarify the spectra, although the 2′, 3′, and 5′ protons still overlapped. The splitting of the anomeric protons ($J_{1',2'}$ = 6 Hz for both **3** and **18**) was not helpful in the determination of the anomeric configuration because it is generally recognized that coupling constants for trans protons have to be less than 1 Hz in order to assign the configuration with some confidence.[15] It was expected that the configurations of the adenine rings would be trans[16] to the hydroxyl groups at C-2′, and the large negative values for the optical rotations appeared to support this assumption. It is known that the anomeric proton of a 2′,3′-*O*-isopropylidenefuranosyl nucleoside having a trans relationship to the proton at C-2′ has a dramatically lowered coupling constant compared to that of the free nucleoside.[17] The J value would collapse to <3 Hz and quite often become a singlet. The nucleosides **3** and **18** were converted to their respective isopropylidene derivatives **2** and **19**. A procedure was desired that would form the products under mild enough conditions so as to give satisfactory yields of products without degradation of the acid-labile enol ethers. The isopropylidenation procedure[18] using bis(*p*-nitrophenyl) phosphate was unsatisfactory; the unreacted nucleosides were recovered in high yields. A procedure using *p*-toluenesulfonic acid worked well enough to give the desired products in moderate yields. The formation of the isopropylidene derivatives provided evidence that the vicinal hydroxyl groups were still oriented cis to each other and that none of the reaction conditions had affected the D-*erythro* configuration. The isopropylidene derivative of **3** was identical with **2** obtained earlier[2] from **1** and demonstrated that the product of the elimination from either the D-allo isomer or the L-manno isomer is indeed the same. In fact, the finding that **2** was actually formed from either source is additional evidence that the iodination reaction of **6** to form **7** actually did occur with inversion of configuration at C-5. The NMR spectrum of **2**, as reported earlier,[19] had a sharp singlet for the anomeric proton at δ 6.40, indicating that the configuration was β. Similarly, **19** exhibited a singlet at δ 6.48. An interesting observation is that the chemical shift differences (Δδ values) for **2** (0.09 ppm) and **19** (0.11 ppm) were obtained for

Chart II



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the *exo*- and *endo*-methyl peaks of the isopropylidene groups. Imbach and co-workers[20] have claimed that Δδ values are ≥0.18 ppm in Me_2SO-d_6 when the configurations are β-D. They have stressed that their observations are limited to ribofuranosyl nucleosides and that discrepancies appear when C-5′ has a substituent. This may account for the values obtained for **2** and **19**; nevertheless, it is worthwhile to collect data with other sugar analogues of nucleosides in order to ascertain the limits of application of this technique.[21] As a further corroborative experiment, the nucleosides **3** and **18** were oxidized with periodate and reduced with borohydride to give solutions of the dialcohols **20** and **21** (Chart II). The optical rotations of these solutions were positive values. It has been observed[22] that solutions of alcohols derived from nucleosides in this way acquire optical rotations having signs opposite to that of the nucleosides. Nucleosides with β-D or α-L configurations yield alcohols with positive optical rotations, a result obtained here and which is a further argument in favor of the β-D configuration.[23]

The difference in physical properties of **3** and **18**, as well as **2** and **19**, in itself supports the idea that they are geometric isomers but does not really identify which isomer is *E* and which is *Z*. The preparation of **2** from two precursors does not designate what the geometry is but only says that the same product is formed. The assumption, as stated at the beginning, is that the E2 anti elimination mechanism is operating. The NMR spectra of **2** and **19** provided evidence that the proposed geometry is correct. The peaks for H-5′ in each case are resolved as a quartet, as expected due to splitting from the neighboring methyl group. The peak centered at δ 4.96 for **2** is almost 0.2 ppm downfield from the peak at δ 4.79 for **19**. It has been shown that the proton in an enol ether that is oriented cis to the oxygen will generally appear 0.15–0.3 ppm (or even further) downfield of the one that is oriented trans to the oxygen.[24] Therefore, the structural assignments for **2** and **19**, and thus **3** and **18**, are supported.

Experimental Section

General Methods. Melting points were determined on a Kofler micro hot stage as corrected values. The crystals were observed through a microscope outfitted with polarizing lenses to determine crystallinity and changes in physical structure. Optical rotations were measured with a Perkin-Elmer 141 polarimeter. NMR spectra were recorded on a Varian T-60A spectrometer with Me_4Si as the internal reference. IR spectra were recorded on a Perkin-Elmer Model 21 spectrophotometer and UV spectra on a Beckman Model 25 spectrophotometer.

(15) L. B. Townsend, *Synth. Proced. Nucleic Acid Chem.*, **2**, 330–1 (1973).
(16) B. R. Baker, *Chem. Biol. Purines, Ciba Found. Symp.*, 120 (1957).
(17) N. J. Leonard and R. A. Laursen, *J. Am. Chem. Soc.*, **85**, 2026 (1963).
(18) N. J. Leonard and R. A. Laursen, *Biochemistry*, **4**, 354 (1965); A. Hampton, *J. Am. Chem. Soc.*, **83**, 3640 (1961).
(19) In the earlier paper,[2] the peaks at δ 5.78 and 5.37 were accidentally reported as being singlets rather than doublets.
(20) J.-L. Imbach, *Ann. N.Y. Acad. Sci.*, **255**, 177 (1975); B. Rayner, C. Tapiero, and J.-L. Imbach, *Carbohydr. Res.*, **47**, 195 (1976).
(21) For an example of where it seems to work with a hexofuranosyl nucleoside, see: L. M. Lerner, *J. Org. Chem.*, **43**, 2469 (1978). For some examples where it does not work, see: G. Mackenzie and G. Shaw, *J. Chem. Soc., Chem. Commun.*, 753 (1977).
(22) (a) L. M. Lerner, *J. Org. Chem.*, **41**, 306 (1976); (b) *ibid.*, **43**, 962 (1978).
(23) The relationship of **1** to 9-(6-deoxy-α-L-mannofuranosyl)adenine has been clearly established and serves as further proof of the anomeric configuration. See L. M. Lerner, *J. Org. Chem.*, **38**, 3704 (1973); L. M. Lerner and Y. Y. Cheng, *Carbohydr. Res.*, **14**, 297 (1970); ref 2.
(24) J. Feeney, A. Ledwith, and L. H. Sutcliffe, *J. Chem. Soc.*, 2021 (1962); Y. Wang and H. P. C. Hogenkamp, *J. Org. Chem.*, **43**, 3324 (1978); A. B. Brookes, S. Sternhell, B. K. Tidd, and W. B. Turner, *Aust. J. Chem.*, **18**, 373 (1965).

N,N-Dimethylformamide was dried by allowing the solvent to stand over molecular sieve 4A and then distilling with benzene at atmospheric pressure; a second distillation under reduced pressure and storage over molecular sieve 4A afforded the dry solvent. Moist organic solutions of compounds were dried over anhydrous magnesium sulfate. Evaporations were performed with a rotary evaporator under reduced pressure at a bath temperature of 35–40 °C, unless otherwise stated.

Silica gel (Baker no. 3404, 40–140 mesh) and alumina (Fisher no. A-540, 80–200 mesh) were utilized for column chromatography. TLC was performed on 0.25-mm layers of silica gel HF-254 (E. Merck, AG–, Darmstadt) prepared with Desaga equipment. Solvent mixtures are expressed as v/v ratios.

Methyl 5,6-Dideoxy-5-iodo-2,3-*O*-isopropylidene-β-D-allofuranoside (7). The preparation of **7** is based upon the work of Kochetkov and co-workers.[7] They gave few details; however, the present method has been scaled up with a number of alterations in procedure and handling.

A solution containing 9 g (0.041 mol) of methyl 6-deoxy-2,3-*O*-isopropylidene-α-L-talofuranoside[8c] (**6**) in 150 mL of dry benzene was slowly added dropwise, under a nitrogen atmosphere, to a suspension containing 44 g (0.097 mol) of methyltriphenoxyphosphonium iodide[25] in 75 mL of benzene. The mixture was heated in an oil bath at 80 °C and stirred. As the crystals of reagent reacted, the mixture turned dark. After 20 h, the mixture was cooled to room temperature and placed on a column 4 cm wide containing 34 cm of silicic acid and a 9-cm layer of alumina on top. The dark materials stayed in the alumina layer. Elution with benzene and collection of 100-mL fractions gave the product in fractions 3–7 (TLC determination). The fractions were combined, the benzene was evaporated, and crystallization was effected from petroleum ether (bp 35–60 °C) to give 5.398 g of product. Two additional crops were obtained from the mother liquors (1.810 g). The remaining mother liquor and fractions 8–11 from the column were rechromatographed on 100 g of silica gel to afford 0.446 g, giving a total yield of 7.654 g (56.5%) of **7**: mp 56–58 °C, $[\alpha]^{23}_{D}$ −85° (*c* 1.98, chloroform) [lit.[7] mp 57–58 °C, $[\alpha]^{20}_{D}$ −71° (*c* 3.54, chloroform)]. Compound **7** gave a positive Beilstein test for halogen. Fractions 13–21 of the original column contained 14 g of an oil, presumably diphenyl methylphosphonate.

(*E*)-9-(5,6-Dideoxy-β-D-*erythro*-hex-4-enofuranosyl)adenine (3). Amberlite IR-120 (H^+) ion-exchange resin (76 g) was equilibrated with absolute methanol and the methanol removed by decantation. This procedure was repeated five times and the resin collected by filtration. The resin was added to a solution containing 7.6 g (23.2 mmol) of **7** in 230 mL of methanol, and the mixture was heated under reflux with stirring until TLC (1:1 *n*-hexane–ethyl acetate) showed that the reaction was complete. After 5.5 h, the mixture showing two adjacent spots for products on TLC (probably the α,β anomers) was cooled to room temperature and filtered through a pad of Celite-545, and the resin and pad were washed with 200 mL of methanol. The methanol was removed by evaporation, and the dark syrup was dissolved in 60 mL of dry pyridine. The pyridine solution was chilled in an ice bath, and 11 mL of benzoyl chloride was added dropwise. The mixture was allowed to warm to room temperature, and after 15 h, the solution was chilled again, and 5 mL of methanol was slowly added. The mixture was allowed to stir at room temperature for 3 h, chilled, and diluted with 75 mL of chloroform. The mixture was placed in a separatory funnel, and the chloroform solution was washed consecutively with 200-mL portions of water, saturated sodium bicarbonate solution, and again with water, and evaporated. Three coevaporations with toluene (50–75-mL portions) removed a small amount of residual pyridine. For removal of methyl benzoate, the syrup was dissolved in 50 mL of methanol, 50 mL of water was added, and the turbid mixture was evaporated. This process was repeated four times. Finally, the syrup was dried by three evaporations of 50-mL portions of anhydrous ethanol to yield 11.31 g (98%) of a dark orange syrup (**8**), which gave a positive Beilstein test. The NMR spectrum (chloroform-*d*) showed the presence of methoxyl peak δ 3.47, benzoate peaks from δ 7.20 to 8.27, and a terminal methyl group centered at δ 2.03. A trace amount of isopropylidene group was still present, as indicated by tiny methyl proton peaks at δ 1.32 and 1.20 and by TLC.

The entire sample was dissolved in a mixture of 50 mL of glacial acetic acid and 5 mL of acetic anhydride. The solution was stirred and chilled in an ice bath while 2.2 mL of concentrated sulfuric acid was slowly added dropwise. The mixture was kept at room temperature for 18 h and poured on 150 mL of ice, and the ice was allowed to melt as the mixture was stirred. Chloroform (75 mL) was added, and stirring was continued until all the solid matter dissolved. The chloroform layer was separated, the aqueous layer was extracted further with chloroform (3 × 50 mL), and the chloroform extracts were combined, washed with 200-mL portions of water, saturated sodium bicarbonate, and water, and dried. Evaporation and three coevaporations with benzene to get rid of traces of acetic acid gave a pale, straw yellow syrup (**9**) weighing 11.78 g (99%). The NMR spectrum (chloroform-*d*) revealed that the methoxyl group was replaced by an acetyl group. Peaks at δ 1.90–2.00 for acetyl methyl overlapped with the terminal methyl peaks of the sugar centered at δ 2.03 (doublet). No traces of isopropylidene groups remained, and the benzoate groups were intact.

The entire sugar derivative **9** (22.5 mmol) was dissolved in 500 mL of 1,2-dichloroethane and added to a mixture containing 13 g (27.4 mmol) of 6-(benzamidochloromercuri)purine and 13 g of Celite-545 suspended in 220 mL of the same solvent. A portion (150 mL) of the solvent was distilled to remove traces of moisture. To this hot mixture was added 3.3 mL (30 mmol) of titanium tetrachloride in 170 mL of 1,2-dichloroethane, and the stirred mixture was heated under reflux for 23 h. The mixture was allowed to cool to room temperature and was stirred with 400 mL of saturated sodium bicarbonate solution for 2 h. The mixture was filtered through a Celite pad and the pad washed with 250 mL of hot 1,2-dichloroethane. The organic solvent was separated and evaporated, and the residue was dissolved in 150 mL of chloroform, washed with 30% aqueous potassium iodide solution (2 × 150 mL) and saturated sodium chloride (200 mL), and dried. Evaporation afforded 13.52 g of a foam. The foam was dissolved in a minimal amount of benzene and placed on top of a column (37 × 4 cm) of silica gel. The column was eluted with 5:1 benzene–ethyl acetate, and 300-mL fractions were collected. Fractions 1–4 gave 1.7 g of sugar derivatives. Fractions 6–9 yielded 7.5 g of a foam, which gave a positive Beilstein test; UV max (methanol) 279 nm.

The foam was dissolved in 65 mL of *N,N*-dimethylformamide, and a solution of 1,5-diazabicyclo[5.4.0]undec-5-ene (3.27 g) in 20 mL of the same solvent was added. After 48 h, the solvent was evaporated under high vacuum (oil pump, bath temperature 38 °C). The residue was dissolved in 135 mL of methanol, and 135 mL of concentrated ammonium hydroxide was slowly added to the stirring solution. After 24 h, the solvents were evaporated to afford a light brown syrup. The syrup was dissolved in a minimal amount of water and placed on top of a column (38 × 1.8 cm) of Bio-Rad AG1-X2 (OH^-, 200–400 mesh) ion-exchange resin that had been poured out in water. The column was eluted with water, and 22-mL fractions were collected. The solvent was changed to 20% aqueous methanol at tube number 150 and to 40% aqueous methanol at tube number 375. The peaks were located by UV absorption. A peak in tubes 2–15 proved to be benzamide,[5] and these fractions were discarded. A large peak (tubes 129–410) was collected, and evaporation of the solvents gave 1.6 g of a white, crystalline mass. The product was recrystallized from acetone, initially at room temperature, and then in a refrigerator to give clusters of prismatic crystals, 1.17 g of **3** (19% overall yield from **7**). The nucleoside softened around 90 °C, formed a viscous melt near 110 °C, and completely melted at 122 °C. It recrystallized between 135–140 °C and partially melted again between 185–195 °C with needlelike projections radiating out of the melt. Some decomposition also began with complete melting accompanied by decomposition at 199–201 °C. The NMR spectrum showed an acetone peak at δ 1.98 and integration revealed that the crystals were a solvate containing nearly 0.5 mol of acetone/mol of nucleoside. An accurate elemental analysis of the solvate was not obtained. After a series of experiments it was found that the acetone could be completely removed by heating the sample in an Abderhalden drying pistol at 110 °C (boiling toluene) under high vacuum for 4–5 h. The crystalline shape changes during this process; the crystals are no longer well-defined,

(25) J. P. H. Verheyden and J. G. Moffatt, *J. Org. Chem.*, **35**, 2319 (1970).

but they do exhibit crystallinity as demonstrated by the passage of polarized light. When the temperature of the crystals is raised rapidly (5°/min or faster), they melt at 100–110 °C, resolidify slowly, and melt at 160–165 °C with sublimation throughout the heating process. When the temperature is raised slowly (1–2°/min), the sample undergoes a physical transformation from one solid form to another at 107–115 °C, and sublimation begins and continues to the melting point at 180–183 °C, with some decomposition: $[\alpha]^{24}_D$ −88.5° (c 0.61, methanol); UV max (water) 260 nm (ε 13 330), min (water) 230 nm (ε 1910); IR (KBr) 843 (olefin CH), 1685 cm^{-1} (enol ether); NMR (Me_2SO-d_6) δ 8.40, 8.18 (both s, 1 proton each, H-8, H-2), 7.30 (br s, 2, NH_2), 6.12 (d, 1, $J_{1',2'}$ = 6 Hz, H-1'), 5.58, 5.42 (both d, 1 proton each, 2'-OH, 3'-OH), 5.15–4.61 (complex m, 3, H-2', H-3', H-5'), 1.60 (d, 3, 6'-CH_3). Addition of D_2O caused the peaks at δ 7.30, 5.58, and 5.42 to disappear and clarified the δ 5.15–4.61 region somewhat.

Anal. Calcd for $C_{11}H_{13}N_5O_3$: C, 50.18; H, 4.98; N, 26.60. Found: C, 50.33; H, 4.83; N, 26.54.

(*E*)-9-(5,6-Dideoxy-2,3-*O*-isopropylidene-β-D-*erythro*-hex-4-enofuranosyl)adenine (2). A mixture of 0.64 g of *p*-toluenesulfonic acid monohydrate, 3 mL of 2,2-dimethoxypropane, and 30 mL of dry acetone was stirred for 15 min. To this solution was added 100 mg (0.38 mmol) of **3**. The nucleoside dissolved in a few minutes. After being stirred for 4 h at room temperature, the solution was poured into a mixture of sodium bicarbonate (1.5 g) in 10 mL of water and stirred 15 min, and the solids were removed by filtration (suction). The filter was washed well with acetone, and the filtrate was evaporated. The residue was triturated with 50 mL of chloroform and filtered (gravity), and the filter was washed with 25 mL of chloroform. Evaporation gave a gum which was dissolved in warm methanol (7–8 mL), filtered to remove some insoluble material, and concentrated by boiling on a steam bath to 2–3 mL. When the solution was allowed to stand, crystallization slowly occurred. A total of 53 mg of product (46%) was obtained in two crops. The melting point, mixture melting point, and IR and NMR spectra established that **2** was identical with the compound prepared earlier by elimination of *p*-toluenesulfonic acid from **1**:[2] IR (KBr) 838 (olefin CH), 1678 cm^{-1} (enol ether); NMR (Me_2SO-d_6) δ 8.22, 8.17 (both s, 1 proton each, H-8, H-2), 7.32 (br s, 2, NH_2), 6.40 (s, 1, H-1'), 5.78 (d, 1, H-3'),[19] 5.37 (d, 1, H-2'),[19] 4.96 (q, 1, H-5'), 1.66 (d, 3, 6'-CH_3), 1.47, 1.38 (both s, 3 protons each, *gem*-dimethyl).

Methyl 5,6-Dideoxy-5-iodo-2,3-*O*-isopropylidene-α-L-talofuranoside (13). The reaction of methyl 6-deoxy-2,3-*O*-isopropylidene-β-D-allofuranoside[8a,b] (**12**; 15 g, 0.069 mol) with methyltriphenoxyphosphonium iodide[25] (68 g, 0.15 mol) was carried out as described for **6** in a total of 375 mL of benzene. After 18 h the cooled mixture was chromatographed by using benzene on a column (45 × 4 cm) of alumina, and 300-mL fractions were collected. The first fraction contained 8.9 g of syrup, which crystallized from 8 mL of methanol in a deepfreeze. Fractions 2–5 contained additional product and an oil (total 22 g). This mixture was chromatographed on a column (43 × 4 cm) of silica gel with benzene as the eluant and 100-mL fractions were collected. Fractions 3–11 were combined and yielded another 7.09 g of syrup, which also crystallized from methanol in the deepfreeze and was combined with the previous crystals. It is best to work entirely in the cold when handling this substance and to remove the mother liquor from the crystals with a pipet than to filter them. Recrystallization is carried out by addition of fresh methanol and the process repeated if required. For the next reaction, the methanol was removed with a pipet, benzene added, and the flask subjected to evaporation to a constant weight of gum, 12.23 g (54%). If crystals from methanol are to be removed for characterization, this can be accomplished by using a supercooled suction funnel (dry ice–acetone temperature) and filter and continuing to chill the crystals and all surfaces that come into contact with them. The crystalline samples should be stored in a desiccator and placed in a freezer. If this is not done, the crystals become soft and sticky and consequently are very difficult to handle. In a separate, small-scale preparation, crystals obtained in this manner had mp 32–33 °C and $[\alpha]^{23}_D$ +10° (c 1.80, chloroform) and gave a positive Beilstein test; [lit.[7] mp 35 °C, $[\alpha]^{20}_D$ +17.5° (c 2.45, chloroform)].

(*Z*)-9-(5,6-Dideoxy-β-D-*erythro*-hex-4-enofuranosyl)adenine (18). Methyl 5,6-dideoxy-5-iodo-2,3-*O*-isopropylidene-α-L-talofuranoside (**13**; 12.2 g, 37.2 mmol) was treated with 120 g of Amberlite IR-120 (H^+) in 375 mL of methanol as described above for the D-allo isomer, except that the time of reflux was 4 h. The syrup obtained after evaporation of the methanol was benzoylated (17.5 mL of benzoyl chloride) in pyridine (95 mL) and worked up as described for the D-allo form. A dark syrup (**14**; 19.26 g, ca. 104% yield) was obtained. The NMR spectrum (chloroform-*d*) showed the expected peaks, a trace amount of isopropylidene remaining, and the methoxyl group as a mixture of β and α anomers (β/α = 4/1). Acetolysis was carried out in 88 mL of 10:1 acetic acid–acetic anhydride containing 3.8 mL of concentrated sulfuric acid. After workup, 19.67 g of a thick, pale yellow syrup (**15**) was obtained. The NMR spectrum (chloroform-*d*) showed that the methoxyl group had been replaced by an acetyl group. The entire sample (37.2 mmol) was reacted with 21.8 g (46 mmol) of 6-(benzamidochloromercuri)purine[12] in a refluxing mixture also containing 21.8 g of Celite-545, 5.4 mL (48 mmol) of titanium tetrachloride, and 1200 mL of 1,2-dichloroethane as described for the preparation of the *E* isomer. After a similar workup, 20.31 g of stiff foam was obtained which was dissolved in a minimum amount of benzene and chromatographed on a column (45 × 4 cm) of silica gel. Elution of the column with 900 mL of 5:1 benzene–ethyl acetate gave 4.7 g of sugar derivatives. The column was eluted with 700 mL of 3:1 benzene–ethyl acetate, and this fraction was discarded. Elution with 2:1 benzene–ethyl acetate (1500 mL) gave 11.46 g of a foam (**16**), which gave a positive Beilstein test; UV max (methanol) 279 nm.

The foam was dissolved in 100 mL of dry *N*,*N*-dimethylformamide, and 5 g of 1,5-diazabicyclo[5.4.0]undec-5-ene in 30 mL of the same solvent was added. After the mixture was allowed to stand at room temperature for 48 h, the solvent was evaporated (oil pump, bath temperature 28 °C), and the residue was dissolved in 200 mL of methanol and treated with 200 mL of concentrated ammonium hydroxide. The mixture was stirred at room temperature for 24 h and evaporated to dryness. The residue was dissolved in a minimal amount of water and applied to a column (47 × 2 cm) of Bio-Rad AG1-X2 (OH^-, 200–400 mesh) ion-exchange resin. Fractions containing 22 mL were collected. Water was the first eluant until tube number 411, and 20% aqueous methanol was the second eluant until tube number 472, whereupon 40% aqueous methanol was used. Tubes 4–60 contained benzamide.[5] The nucleoside was slowly eluted in tubes 64–529. Evaporation of the solvents left a white crystalline mass. Recrystallization from acetone afforded 1.99 g of **1**, in several crops (20% yield from **13**): mp 190–192 °C with decomposition and a soft, wet appearance becoming noticeable at ca. 175 °C; $[\alpha]^{24}_D$ −45.7° (c 0.707, methanol); UV max (water) 260 nm (ε 13 325), min (water) 230 nm (ε 1585); IR 844 (olefin CH), 1695 cm^{-1} (enol ether); NMR (Me_2SO-d_6) δ 8.42, 8.22 (both s, 1 proton each, H-8, H-2), 7.35 (br s, 2, NH_2), 6.22 (d, 1, $J_{1',2'}$ = 6 Hz, H-1'), 5.62, 5.38 (both d, 2, 2'-OH, 3'-OH), 5.08–4.42 (complex m, 3, H-2', H-3', and H-5'), 1.48 (d, 3, 6'-CH_3). Addition of D_2O causes the disappearance of the peaks at δ 7.35, 5.62, and 5.38.

Anal. Calcd for $C_{11}H_{13}N_5O_3$: C, 50.18; H, 4.98; N, 26.60. Found: C, 50.40; H, 5.18; N, 26.24.

(*Z*)-9-(5,6-Dideoxy-2,3-*O*-isopropylidene-β-D-*erythro*-hex-4-enofuranosyl)adenine (19). The preparation of **19** was carried out exactly as described for **2**, except that 125 mg (0.48 mmol) of **18** was used. The product was very soluble in methanol. Crystallization was therefore effected from ethanol in a refrigerator to give 56 mg (39% yield) of feathery needles in two crops: mp 185–187 °C with droplets forming on the cover slip above 164 °C; IR 840 (olefin CH), 1700 cm^{-1} (enol ether); NMR (Me_2SO-d_6) δ 8.27, 8.20 (both s, 1 proton each, H-8, H-2), 7.37 (br s, 2, NH_2), 6.48 (br s, 1, H-1'), 5.55, 5.37 (both d, 2, H-3', H-2'), 4.79 (q, 1, H-5'), 1.53, 1.42 [d with center at δ 1.48 overlapping with 1.48, 1.37 both s (9 protons, 6'-CH_3 and *gem*-dimethyl)].

Anal. Calcd for $C_{14}H_{17}N_5O_3$: C, 55.47; H, 5.65; N, 23.09. Found: C, 55.52; H, 5.67; N, 23.02.

Polarimetric Studies. The procedures for periodate oxidation, borohydride reduction, and determination of optical rotation have been reported.[22a,26] Both dialcohol solutions had $[\alpha]^{25}_D$ +18°.

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Hydrometalation. 3. Hydroalumination of Alkenes and Dienes Catalyzed by Transition Metal Halides

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Bis(dialkylamino)alanes, $HAl(NR_2)_2$, react with alkenes and dienes in the presence of a catalytic amount of Cp_2TiCl_2 to provide high yields of hydrometalation product. 1-Octene reacts with $HAl[N(i\text{-}Pr)_2]_2$ in benzene at 40 °C in the presence of 5 mol % Cp_2TiCl_2 in 10 min to form $n\text{-}C_8H_{17}Al[N(i\text{-}Pr)_2]_2$ in 93% yield. The formation of the hydrometalation product was determined by quenching the reaction mixtures with D_2O or iodine. The hydrometalation products react with benzaldehyde and benzophenone to form tertiary amines in high yield.

Considerable current interest in organic synthesis is centered around the use of transition metal hydrides for the hydrometalation of alkenes and dienes. For example, recent reports show that stoichiometric amounts of transition metal hydrides can reduce unsaturated organic compounds. Conjugated C=C or C=N bonds[1-6] have been reduced, and organic halides have been reductively dehalogenated by $[HFe(CO_4)]^-$ and by several derivatives of "CuH".[8-11] In protic media,[12] the same transformations can be accomplished by $[HFe_3(CO)_{11}]^-$. Wailes and Schwartz have reported independently that hydrozirconation of alkenes[13-15] and alkynes[16,17] also involves a hydrometalation intermediate.

The hydrozirconation of alkenes proceeds through the placement of the zirconium moiety at the sterically least hindered position of the alkene. The authors argue that the formation of the product involves either the regiospecific addition of Zr–H to a terminal alkene or Zr–H addition to an internal alkene followed by rapid rearrangement via Zr–H elimination–readdition to place the metal in the least hindered position. Transition metal hydrides are also catalysts for reactions of unsaturated hydrocarbons, e.g., hydroformylation, hydrogenation, hydrosilation, and isomerization.[18]

Recently, the reduction of alkenes and alkynes by the reagent $LiAlH_4$–transition metal halide was reported.[19,20] Although one might assume that this reaction proceeds through a hydrometalation intermediate, deuterolysis of the reaction mixture shows that only titanium catalysts are effective in the formation of such intermediates. We have found that other first row transition metal compounds (e.g., $NiCl_2$ and $CoCl_2$) are effective in catalyzing the formation of reduction products although no evidence for a stable transition metal intermediate has been found.

Our research has centered around an investigation of the hydrometalation of alkenes and dienes, using less expensive and more readily available hydrometalation systems than have been available so far. The importance of forming the hydrometalation intermediate rather than the reduction product (alkane or alkene) lies in the formation of an organometallic compound that can be easily functionalized. Although hydroboration proceeds readily between an olefin and diborane in THF in the absence of a catalyst, the C–B bond is relatively stable and not nearly as susceptible to functionalization as C–Mg or C–Al compounds. In addition, diborane is expensive, toxic, and explodes on contact with air. Although it has been reported that MgH_2 and AlH_3 do not hydrometalate alkenes or alkynes readily compared to B_2H_6, we have found that the reaction does take place readily and in high yield when certain transition metal halide catalysts are present.

During our investigations, we discovered an excellent hydrometalation system which consists of a bis(dialkylamino)alane ($HAl(NR_2)_2$) as the hydrometalating agent, in the presence of a catalytic amount of transition metal halide (particularly bis(cyclopentadienyl)titanium dichloride, Cp_2TiCl_2). Since $HAl(NR_2)_2$[21] compounds can be prepared by the reaction of aluminum metal, hydrogen, and dialkylamine in a one-step reaction in quantitative

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