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Synthesis and reactivity of nonstabilized diazo sugars

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Abstract—1,6-Anhydro-4-deoxy-4-diazo-2,3-*O*-isopropylidene-β-D-*lyxo*-hexopyranose (**4**) is a stable crystalline compound readily accessible by an improved synthetic procedure. It has been used as a model for evaluating the reactivity of the diazo group, when not stabilized by an adjacent carbonyl function, in a rigid chiral matrix. A range of carbene-type, electrophile-promoted, and 1,3-dipolar reactions were evaluated, leading to 4,4′-alkene dimers, 4-deoxy-3-enose and related derivatives, 4,4-dihalo compounds, 4-spirocyclopropane derivatives, 4-spiropyrazole structures, and by skeletal rearrangement, branched-chain anhydropentose structures having a bicyclo[2.2.2] skeleton.

Keywords: Diazo sugars; *gem*-Dihalo sugars; Dimeric sugars; Pyrazole; Spirocyclopropane; Branched-chain sugars

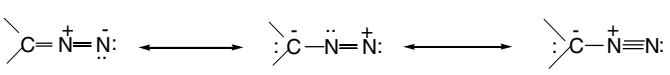
1. Introduction

Diazomethane and diazoethane have long been used for the alkylation of acidic and enolic hydroxyl groups in sugars[1,2] and for the esterification of aldonic acids.[3] A classic synthesis of 2-ketoses involves reaction of acetylated aldonyl chlorides with two moles of diazomethane to generate terminal diazoketones and thence the ketose derivatives.[4–7] The canonical forms of the diazo group (Scheme 1) indicate a high negative polarity on the carbon atom adjacent to nitrogen, and consequently derivatives having a carbonyl or ester group adjacent to the diazo function are greatly stabilized[8] by comparison with those derivatives lacking such stabilization.

Thus terminal diazo-2-ketose derivatives may be reduced to 1-deoxyketoses,[9] converted by HCl or HBr into 1-deoxy-1-haloketoses,[10] and converted into dimeric C=C linked structures with loss of nitrogen by the action of cupric oxide.[11] Such stabilized diazo derivatives are not decomposed in acetic acid solution,[12] although displacement of nitrogen occurs with stronger acids.[10]

Typical reactions of the diazo group include loss of N_2 to form transient carbenes[13] or carbenoid species in either the singlet or triplet state,[14–16] which may react intramolecularly or intermolecularly in a variety of modes.[17–27] Singlet carbenes, generally formed thermally or photochemically, tend to react indiscriminately,[28–32] whereas triplet (diradical) carbenes[33,34] show greater selectivity.[35,36] Carbenoids, formed catalytically by the action of copper salts on diazo compounds,[37–40] are of lower energy, typically reacting with unsaturated functions to form cyclopropanes,[41,42] and may display carbocation-like character.[43] Carbenes and carbenoids have been reviewed in detail.[44–47]

The diazo function can also act as a 1,3-dipole, reacting with π systems to form pyrazoles. Furthermore, it



Scheme 1.

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may be considered formally as a deprotonated diazonium ion, so that in a protic environment it is susceptible to protonation at carbon with rapid loss of N_2 to generate a 'hot' carbocation. The latter can be attacked by a nucleophile, or undergo deprotonation to form an alkene, or be stabilized by carbon-skeleton rearrangement before reacting with a nucleophile.[48,49]

Our previous studies on the reactivity of 2-deoxy-2-diazoaldonic acid ester derivatives[50]demonstrated their conversion upon thermolysis or photolysis into unsaturated or deoxygenated structures, presumably via carbene-type intermediates, as well as 1,3-dipolar cycloaddition of phenylacetylene to generate pyrazole derivatives. The action of strong base leads to chain degradation with loss of the ester group and formation of a chain-terminal acetylenic sugar, again presumably via a carbene species.[51] Subsequent work[52,53] has shown the conversion of 2-deoxy-2-diazoaldonic esters into cyclopropanes by carbenoid-type insertion into alkenes, their intramolecular reaction with alcohols to form cyclic ethers,[54] and a range of insertion reactions involving diazoester substituents.[55–57]

There is little in the literature on diazo sugars where the diazo functionality is not stabilized by an adjacent ketone or ester group. Earlier work from this laboratory[58] applied the Bamford–Stevens reaction on several 2,4,5-trichlorobenzenesulfonylhydrazones of protected sugars, affording nonstabilized diazo derivatives having the diazo group at the 2-, 3-, and 4-positions of a hexose chain. The products were highly reactive, of generally limited stability, and difficult to prepare in quantity. Nonstabilized 1-diazo sugar derivatives have been employed in 1,3-dipolar addition reactions with alkynes as a route to C-nucleoside analogues,[59,56] and recent work[61] has described other applications of diazo sugars in the generation of heterocyclic structures.

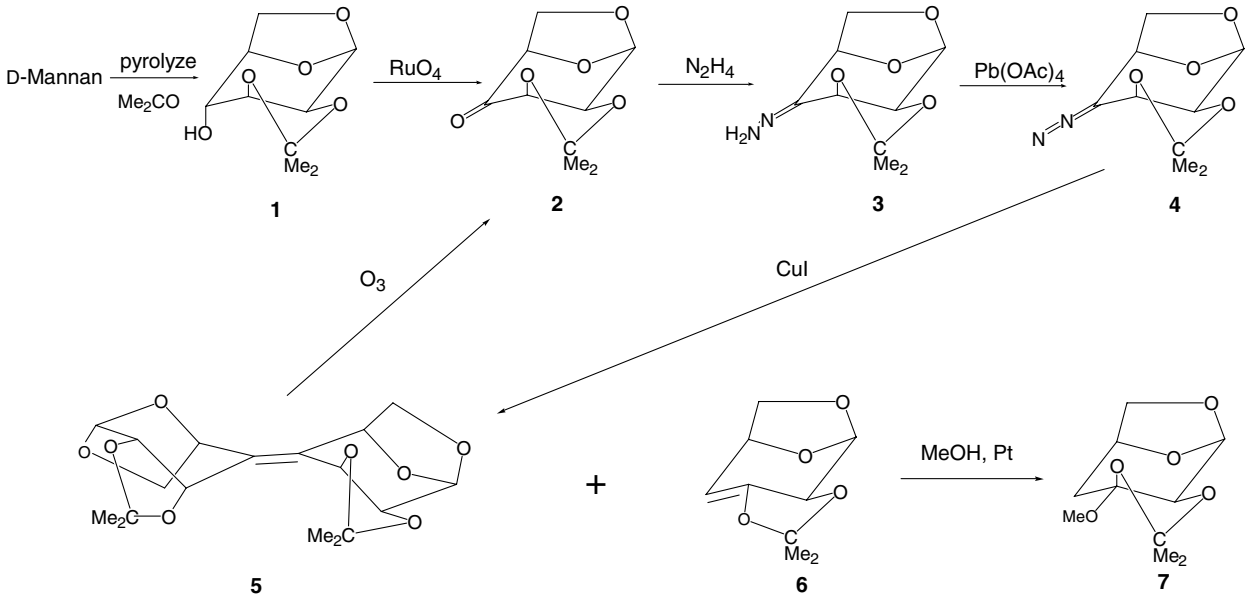
The present work[62–64] reports an improved synthesis of the 4-diazo derivative, 1,6-anhydro-4-deoxy-4-diazo-2,3-*O*-isopropylidene-β-D-*lyxo*-hexopyranose (**4**), a well-crystallized compound accessible on a larger scale without recourse to chromatography and amenable to storage for several days. This compound was used as a model to evaluate the reactivity of the nonstabilized diazo function, embedded in a rigid chiral matrix, in a variety of representative reactions of potential utility in synthetic transformations of sugars.

2. Results and discussion

2.1. Preparation of 1,6-anhydro-4-deoxy-4-diazo-2,3-*O*-isopropylidene-β-D-*lyxo*-hexopyranose (4)

The starting compound for this work, 1,6-anhydro-2,3-*O*-isopropylidene-β-D-mannopyranose (**1**) was obtained by pyrolysis of ivory-nut mannan and acetonation of the resultant crude 1,6-anhydro-β-D-mannopyranose by a revision of the procedure of Hudson and co-workers.[65] Oxidation of **1** by ruthenium tetraoxide by a minor modification of an earlier procedure[66] afforded the corresponding 4-ketone, 1,6-anhydro-2,3-*O*-isopropylidene-β-D-*lyxo*-hexopyranos-4-ulose (**2**) in 85% yield.

In our earlier work,[58] this ketone was converted into its 2,4,5-trichlorobenzenesulfonylhydrazone, the latter being deprotonated by sodium hydride in hexane, followed by pyrolysis of the sodium salt under high vacuum in a sublimation apparatus to give 1,6-anhydro-4-deoxy-4-diazo-2,3-*O*-isopropylidene-β-D-*lyxo*-



Scheme 2.

hexopyranose (**4**) as yellow needles, collected on a cold finger. While this synthesis is adequate for the preparation of small amounts of material, it has shortcomings: the overall yield is low, and scaling up the reaction to multigram quantities is difficult. Accordingly, an alternative synthesis was devised (Scheme 2).

The 4-ketone **2** was allowed to react with a large excess of hydrazine (to inhibit azine formation) in boiling methanol to give the hydrazone **3** in 95% yield. After recrystallization from 2-propanol, the hydrazone in dichloromethane solution (containing tetramethylguanidine) at −78 °C was brought into reaction with 1 M equiv of lead tetraacetate with rapid stirring for 40 min, whereupon the resultant intensely orange-colored solution afforded, after processing, 1,6-anhydro-4-deoxy-4-diazo-2,3-*O*-isopropylidene-β-D-*lyxo*-hexopyranose (**4**) as orange needles in 74% yield. The net yield by this route is more than double that of the previous procedure,[58] and the synthesis can be readily scaled up. The observed specific rotation of **4** in ether at the sodium D line is close to zero, but its ORD spectrum shows a positive Cotton effect with a maximum at 488 nm and zero at 442 nm, and a positive circular dichroism curve centered at 455 nm.[58] The compound could be stored at room temperature in a vacuum desiccator for several days, but it subsequently decomposed; consequently, for reference purposes the experimental section records X-ray powder diffraction data for this and other compounds in this work that are of limited stability.

Lead tetraacetate oxidizes the hydrazone in a two-step dehydrogenative process,[67] and tetramethylguanidine acts as an efficient trap for the acetic acid formed in the reaction, which would otherwise decompose the product. The organic base is removed quantitatively from the mixture by simple addition of dry ice to precipitate the insoluble carbonate salt for removal by filtration.

2.2. Catalytic decomposition of diazo derivative 4 in inert solvents

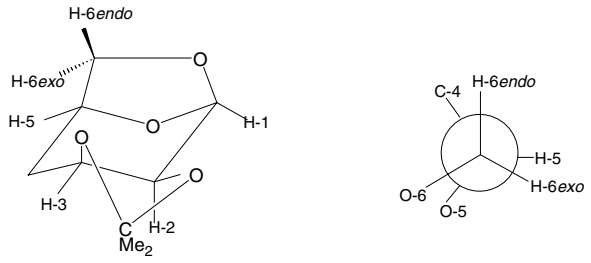
The catalytic decomposition of diazo compounds with metal salts generates reactive intermediates whose properties are closely dependent on the salt used and the solvent in which the reaction is performed. The use of copper salts generally produces a carbenoid having electrophilic character, whose mode of the reaction often involves addition to alkenes to produce cyclopropanes. When this possibility is not available, the routes of the reaction may involve formation of a dimeric alkene, or intramolecular collapse to generate an alkene; azine formation from the diazo precursor is another possibility.

A rapidly stirred solution of diazo derivative **4** in acetonitrile was treated with cuprous iodide, whereupon there was immediate reaction with evolution of gas and darkening of the solution. TLC analysis showed two products, with a major fraction having R_f 0.95 that was isolated by chromatography and recrystallized from 2-propanol as short colorless needles in 62% yield. Its mass spectrum showed a parent ion at m/z 368, clearly indicating that the product was a dimer resulting from the coupling of two molecules of **4** with concurrent loss of two molecules of nitrogen. Its IR spectrum gave no evidence of a double bond, which is not surprising for a highly symmetrical tetrasubstituted alkene, but ozonolysis at −78 °C in dichloromethane–pyridine gave a single, analytically pure product having physical constants identical to those of the glycos-4-ulose derivative **2**.

From this evidence, this product was formulated as the unsaturated dimer, 1,6;1′,6′-dianhydro-4,4′-dideoxy-2,3;2′,3′-di-*O*-isopropylidene-bi(β-D-*lyxo*-hexopyranos-4-ylidene) (**5**). In support of this assignment, the ^{1}H NMR spectrum showed the presence of only six apparent proton signals, indicating the highly symmetrical form of the molecule. It is noteworthy that H-5 and H-6*endo* show essentially zero coupling; inspection of molecular models show that the dihedral angle between these protons is approximately 90° (Scheme 3), and this is in accord with observations on many related compounds having this same bicyclo[3.2.1] skeleton.[68–70]

The dimer **5** is strongly levorotatory. The (*Z*) configuration about the double bond is depicted, but this point was not established by independent criteria. Attempts to reduce the alkene **5** by catalytic hydrogenation were unsuccessful, and the starting material was recovered quantitatively.

A simple change of solvent from acetonitrile to iodomethane markedly altered the course of the foregoing reaction. The same two products were observed by TLC, but the minor, fast-moving component was now the predominant product. It was isolated by column chromatography and recrystallized from ether–hexane in 48% yield as clear prisms. The IR spectrum showed a strong band at 1700 cm^{-1}, and the mass spectrum showed a parent ion at m/z 184. The material rapidly decolorized bromine in carbon tetrachloride. Based on these considerations, this product is formulated as the enol ether 1,6-anhydro-4-deoxy-2,3-*O*-isopropylidene-β-D-*threo*-hex-3-enopyranose (**6**). Its ^{1}H NMR spectrum again showed, as with the dimer **5**, an essentially zero



Scheme 3. Dihedral angle between H-5 and H-6*endo* in the bicyclo[3.2.1] skeleton.

coupling between H-5 and H-6*endo*, along with several long-range couplings in this strained-ring system, as observed in related systems.[68–70] Formation of an alternative 4,5-unsaturated compound was not observed nor expected, as its structure would be in violation of Bredt's rule.[71,72]

Attempted catalytic hydrogenation of **6** with platinum in methanol under 60 lb in.$^{-2}$ (414 kPa) of hydrogen gave a crystalline product in 68% yield, but this did not arise from simple hydrogenation of the double bond. Instead, mass-spectral analysis showed a parent ion having *m*/*z* 216, indicating net incorporation of a molecule of methanol into **6**. Treatment of a methanolic solution of **6** with a trace of hydrochloric acid gave the same compound, but in lower yield. The ^{1}H NMR spectrum showed the H-1 and H-2 signals as simple doublets, indicating absence of a proton at C-3, along with a high-field two-proton doublet indicative of a methylene group at C-4, and allowing formulation of the product as 1,6-anhydro-4-deoxy-2,3-*O*-isopropylidene-3-methoxy-β-D-*threo*-hexopyranos-3-ulose (**7**). The complex multiplet at δ 4.1–4.0 arises from H-5 being directly coupled to four adjacent protons. Evidently the reaction follows the course of simple addition of an alcohol (methanol) to an enol ether (**6**) under the electrophilic catalysis of platinum or a proton source. The configuration, *R* or *S*, at C-3 was not established.

Attempts to hydrolyze **7** led to decomposition and the formation of a tarry product from which no discrete products could be identified.

2.3. Catalytic decomposition of diazo derivative 4 in the presence of an alkene

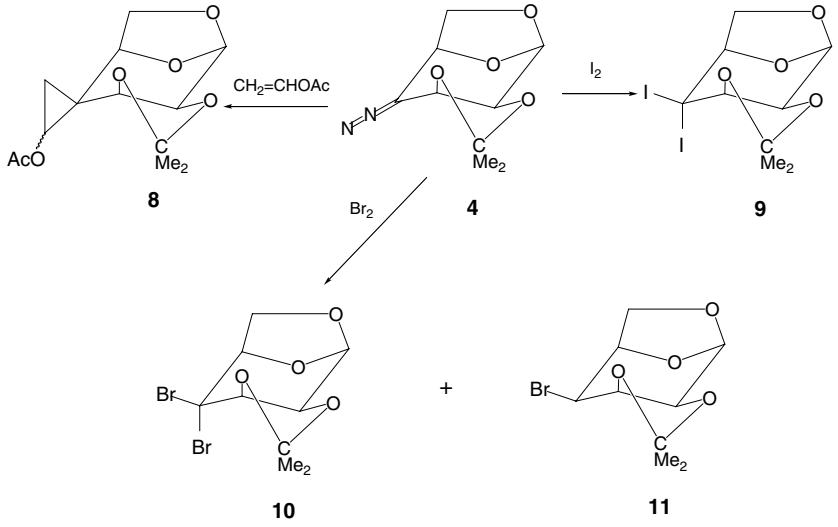
When a diazo compound is catalytically decomposed by copper salts in the presence of an alkene, the carbenoid initially formed may add to the alkene to form a cyclopropane; if the diazo precursor is nonterminal, and the resulting product is a spirocyclopropane. In the sugar field, such a product offers a potential route, via opening of the three-membered ring, to branched-chain sugars.

Photolysis of a dilute solution of **4** in neat vinyl acetate with the Pyrex-filtered light of a mercury arc led to an intractable mixture of products containing a large amount of polymerized vinyl acetate. Cooling the same solution to −78 °C and addition of cuprous bromide under rapid stirring led to disappearance of the yellow color in 2–3 min. Removal of the cuprous bromide and evaporation gave crystals that, after recrystallization from methanol, afforded short needles in 43% yield; this product was formulated (Scheme 4) as 2,3-*O*-isopropylidenespiro[1,6-anhydro-4-deoxy-β-D-*lyxo*-hexopyranose-4,1′-cyclopropan]-2′-y1 acetate (**8**). Its mass spectrum showed a parent ion at *m*/*z* 270 and strong carbonyl absorption in the infrared. The ^{1}H NMR spectrum showed an acetyl-group resonance and a high-field (δ 1.90) two-proton pattern, the part of an essentially A_2X spin system with the cyclopropyl methine proton at low field (δ 6.80) on account of deshielding by the acetoxy group.

With two new asymmetric centers in the molecule, four possible stereoisomers could, in principle, be formed, but only a single product was isolated. Conceivably steric effects might favor introduction of the acetoxy group on the *endo* side of the pyranose ring to give the (4*R*,2′*R*) isomer, but specific evidence for this stereochemical assignment was not obtained.

2.4. Reaction of diazo derivative 4 with halogens

Diazo ketones are known to react photochemically with iodine and bromine to produce *gem*-dihalo com-



Scheme 4.

pounds,[73] and an analogous reaction of **4** was investigated. It was found that **4** reacted very rapidly with iodine in dichloromethane, even in the dark, indicating that the halogen molecule itself initiated the reaction. The crystalline product isolated was identified (Scheme 4) as the 4,4-diiodo derivative **9** from its mass spectrum, which showed a molecular ion at *m*/*z* 438, corresponding to loss of N_2 and incorporation of I_2, along with its ^{1}H NMR spectrum. The compound is not stable, and it decomposed in 24 h at room temperature.

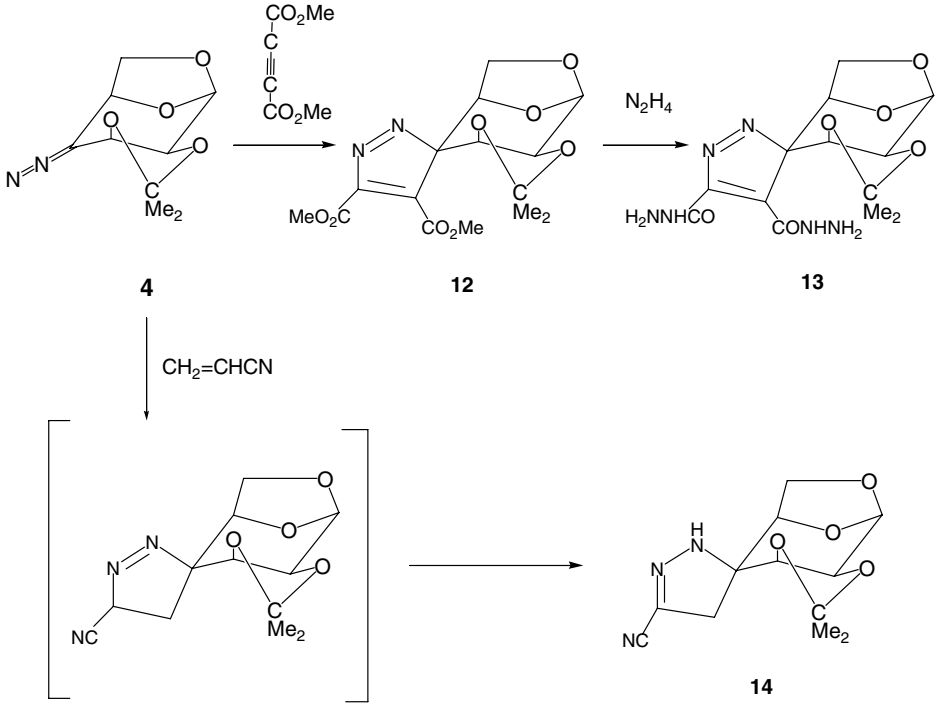
A similar reaction was observed between **4** and bromine, and a crystalline 4,4-dibromo product **10** was obtained (Scheme 4), as evidenced by a mass-spectral parent ion at *m*/*z* 344 and a ^{1}H NMR spectrum similar to that of **9**, but better resolved. The H-5,6, and 6′ signals generally appear as an ABX type of multiplet in related compounds possessing the same bicyclic structure, but taking the 4-keto compound **2** as a reference for chemical shifts, it is noteworthy that in the dibromide **10**, H-6*endo* is shifted downfield by about 0.8 ppm, whereas H-6*exo* is little affected. This may be attributed to deshielding because of the close proximity of the *exo* bromine atom in **10** to H-6*endo*.

This reaction most probably involves a mechanistic pathway analogous to the addition of halogen to alkenes, with attack by Br_2 at C-4 via Br^+ and formation of a transient diazonium ion that in a concerted manner loses N_2 and accepts Br^-. Had a C-4 carbocation been formed, there would have been a rearrangement of the molecule (see Section 2.6). Given the low ion-solvating power of the medium, an alternative mechanism via an intermediate carbene species, cannot be ruled out. A free-radical pathway is implausible, given that light is not needed for the reaction to proceed, and addition of hydroquinone (a radical trap) to the reaction medium did not diminish the yield of dibromide **10**.

A minor side-product (<5%) accompanying **10** was identified as 1,6-anhydro-4-bromo-4-deoxy-2,3-*O*-isopropylidene-β-D-talopyranose (**11**); its mass spectrum indicated it to be a monobromo derivative formed by net addition of HBr to and loss of N_2 from the diazo precursor, and its NMR spectrum was consistent with the talo configuration with equatorial bromine at C-4. As with the dibromo derivative **10**, H-6*endo* in **11** resonates at low field, attributable to deshielding by bromine, but the H-3 and H-5 signals lie upfield by ~0.8 ppm, attributable to the absence of the additional axial bromine at C-4. Formation of **11** might be rationalized on the basis of a minor pathway via triplet carbene at C-4, abstraction of an atom of bromine, and addition of hydrogen to the less-hindered side of the molecule.

2.5. 1,3-Dipolar addition of diazo derivative 4

The diazo group is highly polarized and can act as a 1,3-dipole toward unsaturated centers. For such a process, an electron-deficient alkene or alkyne should be more reactive, as positive polarity on the unsaturated center should be more attractive toward the nucleophilic diazo carbon atom. As already observed, an electron-rich alkene such as vinyl acetate is inert toward



Scheme 5.

compound **4** as a dipolarophile. The reactivity of **4** toward an electron-poor alkyne (dimethyl acetylenedicarboxylate) and an alkene (acrylonitrile) was evaluated (Scheme 5).

An excess of dimethyl 2-butyndioate (dimethyl acetylenedicarboxylate) in dichloromethane was added to a solution of diazo compound **4** at room temperature. Over a period of 10 min, the yellow color of the mixture faded with no evolution of gas, and TLC indicated that a single product had been formed. Following removal of volatiles there resulted a syrup that crystallized, and was recrystallized from 2-propanol to give long needles of a product identified as 2,3-*O*-isopropylidenespiro[1,6-anhydro-4-deoxy-β-D-*lyxo*-hexopyranose-4,3′-pyrazole]-4′,5′-di(methyl carboxylate) (**12**) in 76% yield. The IR spectrum of the product showed carbonyl absorptions, and its ^{1}H NMR spectrum was very well resolved and fully supportive of the assigned structure, with doublets for H-1 and H-3, a doublet of doublets for H-2, and the H-5 resonance showing coupling to the C-6 methylene protons. Notably the H-3 and H-5 signals were more deshielded than the anomeric proton, probably because of the effect of the π electron clouds on the heterocycle at C-4. Approach of the alkyne from the 'topside' of the diazo group would be subject to severe steric hindrance, and the (*R*) configuration assigned at C-4 is based on approach of the reactant from the unhindered lower face.

Treatment of a methanolic solution of **12** with an excess of anhydrous hydrazine afforded the corresponding dihydrazide **13**. Attempts to effect thermally a ring-closure reaction between the hydrazide groups were not successful; decomposition with evolution of gas was observed.

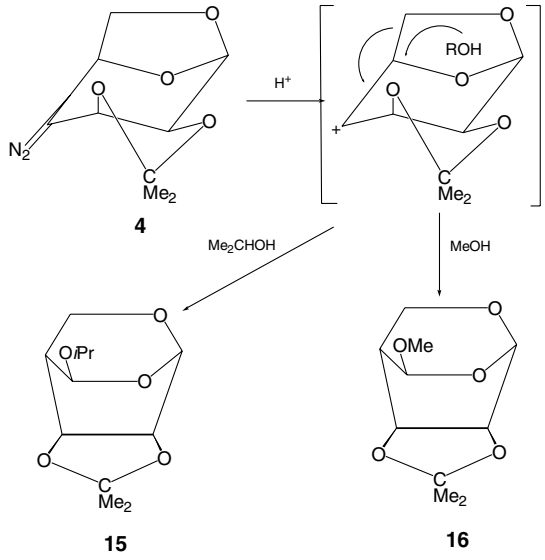
Addition of diazo derivative **4** to neat acrylonitrile failed to yield a spirocyclopropyl derivative analogous to compound **8**; the solution boiled spontaneously and **4** was decomposed. However, when a solution of **4** in dichloromethane was added to a solution of acrylonitrile in the same solvent, a controlled reaction ensued with no evolution of gas. Removal of volatiles gave a crystalline mass containing (TLC) two products, the major one of which was separated by fractional crystallization from 2-propanol and was assigned the structure (4*S*)-2′,4′-dihydro-2,3-*O*-isopropylidenespiro[1,6-anhydro-4-deoxy-β-D-*lyxo*-hexopyranose-4,3′-pyrazole]-5′-carbonitrile (**14**). Evidence for this structure is based on observed IR absorptions for NH and a conjugated CN group, along with a mass spectrum showing a parent ion at *m*/*z* 265, indicative of the net addition of acrylonitrile to **4**, the odd number being consistent with an odd number of nitrogen atoms. It would appear that initial 1,3-dipolar addition of acrylonitrile to the lower face of the diazo derivative **4** affords a 3(*H*)-dihydropyrazole, and the five-membered ring subsequently tautomerizes to the 1(*H*) form, driven by the conjugation stabilization in the C=N isomer.

The ^{1}H NMR spectrum of **14** showed a high-field AB pattern for the methylene group on the pyrazole ring plus a broadened singlet for the N–H proton, but otherwise there was very close resemblance of the spectrum to that of the 4,4-dibromo derivative **10**, emphasizing the underlying similarity of structure.

2.6. Reactions with protic substrates

Our earlier observation[50] that an α-diazo ester in 2-propanol underwent net reduction upon photolysis prompted a similar investigation on the nonstabilized diazo sugar derivative **4**. However, when a solution of **4** was prepared, and prior to irradiation, it was observed that the intense yellow color of the solution faded slowly during ~8 h at room temperature. When the color had completely disappeared, the solvent was evaporated off to give a thick syrup that crystallized spontaneously during several days. Recrystallization from 2-propanol gave fine white crystals, mp 103–104 °C, whose mass spectrum showed a parent ion of *m*/*z* 244, consistent with loss from **4** of a molecule of nitrogen and incorporation of a molecule of 2-propanol. This product was inert toward bromine in carbon tetrachloride, and its IR spectrum showed no evidence of a double bond. Its ^{1}H NMR spectrum showed resonances of not one but two protons in the 'anomeric region,' along with a high-field one-proton multiplet near δ 2.2. These results suggested that the molecule of **4** had not only lost nitrogen and incorporated a molecule of 2-propanol, but that it had also undergone internal reorganization (Scheme 6).

When the diazo derivative **4** was dissolved in methanol, a similar reaction took place, although considerably more rapidly. A crystalline product was formed, mp 92–93.5 °C, whose mass spectrum showed a parent ion at



Scheme 6.

m/*z* 216, indicating loss from **4** of a molecule of nitrogen and incorporation of a molecule of methanol. Repetition of the procedure, but with addition of a catalytic amount of mineral acid, made the reaction almost instantaneous, with visible evolution of gas and formation of the same product. The ^{1}H NMR spectrum of this product was better resolved than that of the isopropyl analogue, showing two separate one-proton doublets in the anomeric region, and all proton resonances could be readily assigned with the aid of spin-decoupling experiments.

The combination of two protons resonating in the anomeric region along with a one-proton multiplet resonating at high ($\delta \sim 2.2$) field is consistent with formation from **4** of an initial C-4 carbocation that subsequently is stabilized by a 1,2-alkyl shift to give the branched-chain anhydro sugar derivative (5*S*)-5-methyl 1,4^1-anhydro-4-deoxy-4-*C*-hydroxymethyl-2,3-*O*-isopropylidene-β-L-*ribo*-pentodialdo-1,5-pyranoside-1,6-pyranose (**16**). The driving force for this rearrangement may be attributed both to the relief of ring strain and formation of a more-stable carbocation at C-5, which subsequently captures a molecule of the solvent alcohol. The product of the preceding experiment may thus be assigned as the isopropyl congener (**15**) of compound **16**.

The bicyclo[2.2.2] ring system in **15** and **16** confers a degree of symmetry to the molecule. The large $J_{2,3}$ value (8.0 Hz) results from the near-eclipsing of H-2 and H-3. The H-5 signal falls in the 'anomeric region' because, as with H-1, it is attached to an acetal carbon atom. The H-4 resonance is at high field because it is attached to a carbon atom unsubstituted by heteroatoms, and its multiplicity results from it being coupled to four other protons.

Assignment of the configuration at C-5, the new asymmetric center in **15**, may also be made from inspection of the ^{1}H NMR spectrum. The pyranose ring in **15** is held rigidly in a boat conformation by the anhydro bridge. The H-5 resonance is not a simple doublet, but rather a doublet of doublets with spacings of 1.1 and 3.3 Hz. Irradiation of H-4 collapses the H-5 resonance to a narrow doublet, while irradiation of H-4^1,4$^{1'}$ collapses the H-5 signal to a wider doublet, indicating that H-5 is coupled not only to H-4 but also to one of the methylene protons at C-4^1. Inspection of molecular models indicates that, if H-5 is axially oriented, it is correctly aligned in a 'W' configuration with one of the C-4^1 protons to exhibit 1,3-coupling and generates the observed narrow spacing. (The same is true for the relation between H-3 and the other C-4^1 proton, and leads to an additional small splitting of the H-3 signal in addition to its coupling with H-2 and H-4.) Were H-5 to be oriented equatorially there would be no 1,3-'W' relation with one of the protons at C-4^1, and so the axial orientation of H-5 may be assigned to the two products **15** and **16**.

The stereochemical outcome at C-5 may be rationalized as possibly the result of a concerted process, with synchronous loss of N_2 from the protonated diazo parent, shift of C-6 to C-4, and equatorial attack of the alkoxy group at C-5.

2.7. Nomenclature

Compounds **15** and **16** present challenges in naming by standard carbohydrate nomenclature,[74] but the branched-chain sugar names given here have the advantage of retaining recognizable stereochemistry in relation to their precursors. Alternatively they can be named by standard organic nomenclature[75] as (1*R*,2*S*,6*S*,7*R*,9*R*)-4,4-dimethyl-9-methoxy-3,5,8,11-tetraoxa[5.2.3.0^{2,6}]-undecane (**16**) and its 9-(2-propoxy) analogue **15**. The names assigned to the spiro derivatives **8**, **12**, and **14** use the recommendations[74] in 2-Carb-35.3 in conjunction with general principles of organic nomenclature.[75]

2.8. Summary conclusions

The reactions described here demonstrate, using the nonstabilized 4-diazo sugar derivative **4**, preparative procedures for making spiro cyclopropanes from electron-rich alkenes, spiro pyrazoles from electron-poor alkenes, *gem*-dihalo and C=C dimeric structures, and products of skeletal rearrangement upon protonation. These reactions have potential in the application to a variety of structural targets in the sugar field. The improved preparative procedure described here for the 4-diazo derivative **4** should similarly be applicable with the 2-diazo and 3-diazo hexose derivatives reported earlier,[58] extending the general scope of these reactions in the sugar field.

3. Experimental

3.1. General methods

Evaporations were performed under diminished pressure with a Büchi 'Rotavapor' rotary evaporator at 40 °C or less unless otherwise stated. Melting points were determined on a Thomas–Hoover 'Unimelt' melting point apparatus and are uncorrected. TLC was performed with 0.25-mm layer precoated aluminum plates (E. Merck, Darmstadt, Germany), or with glass plates coated with a 0.25-mm layer of silica gel (Silica gel G, E. Merck, Darmstadt, Germany), activated by heating to 105 °C before use, using $(NH_4)_2SO_4$ as an indicator. Unless otherwise stated, the developing solvent for both thin-layer and column chromatography was 3:1 CH_2Cl_2–diethyl ether (v/v). Column chromatography was performed with Silica gel 7734 (E. Merck) as adsorbent. The ratio of silica gel to compound was 100:1 (w/w).

IR spectra were recorded with a Perkin–Elmer Model 137 'Infracord' infrared spectrophotometer; samples were examined as pellets in KBr. Specific rotations were measured in a 1-dm tube with a Perkin–Elmer Model 141 photoelectric polarimeter. ^{1}H NMR spectra were recorded at 100 MHz with a Varian HA-100 spectrometer equipped with accessories for spin decoupling; coupling constants are all first order, and chemical shifts are relative to Me_4Si ($\delta = 0.00$). Unless otherwise stated, spectra were measured at 30 °C in $CDCl_3$ solution. Mass spectra were obtained with an AEI-MS-9 double-focusing, high-resolution mass spectrometer at an ionization potential of 70 eV and an accelerating potential of 8 kV. X-ray powder diffraction data gave interplanar spacings in Ångstroms for Cu Kα radiation (camera diameter = 114.59 mm). Relative intensities were estimated visually: m, moderate; s; strong; w, weak; v, very. The strongest lines are numbered (1, strongest), and double numbers indicate approximately equal intensities.

3.2. Preparation of 1,6-anhydro-2,3-*O*-isopropylidene-β-D-mannopyranose (1)

Crude D-mannan (ground ivory nut, Pfanstiehl, 500 g) was pyrolyzed in a modification of the procedure of Hudson and co-workers[65] in 100-g portions under aspirator vacuum with a large bushy flame from a Meker burner in a Pyrex flask, with the degree of heating maintained below the softening point of the glass. The brown, opaque pyrolyzate was filtered through a 12″ column of activated charcoal in a 3″ chromatography column, and the clear, colorless filtrate was evaporated under diminished pressure at 50 °C to a thin, light-yellow syrup. Acetone (1 L) was gradually added to the syrup with stirring, and the mixture was kept for 4 h. The acetone solution was decanted from a solid, opaque residue into a 2-L flask. Anhyd $CuSO_4$ (250 g) and 2,2-dimethoxypropane (100 mL) were added, and the mixture was gently boiled under reflux for 6 h. At the end of that time, the $CuSO_4$ was removed by filtration, and evaporation of solvent resulted in a solid mass of **1**. Recrystallization from 2-propanol gave the pure product as thick needles with a yield of 25 g (5% by weight of D-mannan); mp 159–160 °C (lit.[65] mp 161–162 °C).

3.3. Preparation of 1,6-anhydro-2,3-*O*-isopropylidene-β-D-*lyxo*-hexopyranos-4-ulose (2)

The glycos-4-ulose **2** was prepared by a minor modification of the method of Horton and Jewell.[66] Ruthenium dioxide hydrate (5 g, soluble form, 50% Ru, Englehard Industries) was suspended in 100 mL of water, and the mixture was cooled in an ice bath. Gradual addition of 5% aq NaOCl (Clorox) to the rapidly stirred mixture resulted in complete oxidation of the dioxide to RuO_4 in 10 min. The yellow, flocculent mixture was poured into a 1-L separatory funnel and extracted (3 × 150 mL) with CCl_4. The combined extracts were added directly to a rapidly stirred solution of **1** (10 g, 50 mmol) in 250 mL of CH_2Cl_2. The solution immediately turned black and opaque. After 10 min, 2-propanol (5 mL) was added to decompose any excess RuO_4. Filtration resulted in a clear solution with nearly quantitative recovery of RuO_2. Evaporation of the solvent gave the glycos-4-ulose **2** as a fine, white powder: yield 8.4 g (85%); mp 81–82.5 °C (lit.[66] mp 82.5–83 °C). The product was used in the next step without further purification.

3.4. 1,6-Anhydro-2,3-*O*-isopropylidene-β-D-*lyxo*-hexopyranos-4-ulose hydrazone (3)

A solution of ketone **2** (20 g, 0.1 mol) in MeOH (200 mL) was boiled under reflux for 1 h with 95% hydrazine (50 mL, 1 mol), excess hydrazine being used to avoid azine formation. TLC indicated complete disappearance of the starting material at this time. Solvent and unreacted hydrazine were evaporated off to give a thick syrup that crystallized upon addition of diethyl ether. Trituration with ether and drying in vacuo gave the crude hydrazone in essentially quantitative yield. Recrystallization from 2-propanol gave the pure hydrazone **3** (16.7 g, 78%) in two crops. Purification of the hydrazone was accompanied by some decomposition; mp 124–125.5 °C; $[\alpha]_D^{21}$ −49 (*c* 1.0, $CHCl_3$); R_f 0.42; IR ν_{max} 3460 (NH), 1620 (C=N), 1380 cm^{-1} (CMe_2); ^{1}H NMR δ 5.47 (d, 1H, $J_{1,2}$ 2.5 Hz, H-1), 4.92 (d, 1H, $J_{5,6exo}$ 6.2 Hz, H-5), 4.20 (dd, 1H, H-2), 3.72–3.92 (m, 2H, H-6,6′), 1.46 and 1.31 (s, 3H, CMe_2); X-ray powder diffraction data: 7.82 vw, 7.09 m, 5.62 vs (1), 5.23 vs (2), 4.54 s, 3.97 s, 3.81 s (3), 3.45 w, 3.34 w, 3.24 w, 3.07 m, 2.96 w, 2.87 vw, 2.74 w, 2.63 w. Anal. Calcd for $C_9H_{14}N_2O_4$: C, 50.47; H, 6.5; N, 13.08. Found: C, 50.50; H, 6.77; N, 13.05.

3.5. Preparation of 1,6-anhydro-4-deoxy-4-diazo-2,3-*O*-isopropylidene-β-D-*lyxo*-hexopyranose[58] (4)

A solution of hydrazone **3** (10 g, 47 mmol) in CH_2Cl_2 (250 mL) was cooled in a dry ice–2-propanol bath to −78 °C. Tetramethylguanidine (25 mL) was added[60] to keep the solution basic. With rapid stirring, 23 g (1.05 equiv) of $Pb(OAc)_4$ was added neat. The solution immediately turned bright yellow. Every few minutes, a drop of the solution was placed on moistened filter paper to test for unreacted $Pb(OAc)_4$, a positive reaction being indicated by formation of a brown spot of PbO_2. After 40 min, the reaction was negative, and the clear yellow solution was poured into a separatory funnel containing 300 mL of cold, 10% NaOH. After thorough shaking, the lower, yellow organic layer was drained from the

cloudy, white, aqueous layer through a cone of $MgSO_4$ into a 1-L erlenmeyer flask, and small chunks of dry ice were added during 30 min to precipitate excess tetramethylguanidine as its insoluble carbonate salt. Filtration of the solution and evaporation at room temperature gave **4** as fine, light-yellow crystals: yield 7.3 g (74%); mp 108 °C (dec). Physical constants were in agreement with those recorded earlier[58] for this compound prepared by the Bamford–Stevens method. The material could be crystallized from ether or an ether–hexane mixture to afford large, yellow-orange needles, but at the cost of considerable loss to decomposition.

3.6. 1,6;1′,6′-Dianhydro-4,4′-dideoxy-2,3;2′,3′-di-*O*-isopropylidene-bi(β-D-*lyxo*-hexopyranos-4-ylidene) (5)

A solution of diazo derivative **7** (0.8 g, 3.8 mmol) in MeCN (150 mL) was treated with CuI (100 mg) with rapid stirring at room temperature. The mixture darkened immediately with rapid evolution of gas and then turned light green. The MeCN was evaporated, CH_2Cl_2 (100 mL) was added, and the flask was shaken to dissolve the products. The CuI was removed by filtration, and the CH_2Cl_2 was evaporated off to give a thick syrup, shown by TLC to contain two components having R_f 0.55 and 0.90. The major, slower-moving product **5** was isolated by column chromatography as short, fine needles: yield 0.44 g (64%); mp 215–217 °C; $[\alpha]_D^{20}$ −256 (*c* 1.0, $CHCl_3$); IR(KBr) ν_{max} 1380 cm^{-1}; *m*/*z* 368 (M^+), 353 ($M-CH_3$); ^1H NMR δ 5.40 (d, 1H, $J_{1,2}$ 2.2 Hz, H-1), 5.19 (m, 1H, $J_{5,6exo}$ 5.3, $J_{5,6endo}$ 1.6, $J_{3,5}$ 0.8 Hz, H-5), 4.97 (dd, 1H, H-3), 4.13 (dd, 1H, $J_{2,3}$ 6.2 Hz, H-2), 4.03 (q, $J_{6,6'}$ 7.9 Hz, H-6), 3.84 (q, 1H, H-6′), 1.54 and 1.33 (s, 3H, CMe_2); X-ray powder diffraction data: 10.90 vw, 8.79 w, 7.70 m (3), 7.17 vw, 5.23 s (2), 4.75 s (1), 4.38 w, 4.04 vw, 3.64 vw. Anal. Calcd for $C_{18}H_{24}O_8$: C, 58.69; H, 6.52. Found: C, 58.88; H, 6.32.

Ozonolysis of the dimer **5** (100 mg, 0.2 mmol) in 30 mL of a 2:1 (v:v) CH_2Cl_2–pyridine mixture at −78 °C gave a single analytically pure product, identical to the glycos-4-ulose **2**; yield 88 mg (81%).

The dimer **5** (200 mg) was dissolved in MeOH (150 mL) containing 100 mg of platinum oxide, and the mixture was shaken under 60 lb $in.^{-2}$ (414 kPa) of H_2 for 24 h. Filtration from the catalyst and evaporation of the solution resulted in quantitative recovery of **5**.

3.7. 1,6-Anhydro-4-deoxy-2,3-*O*-isopropylidene-β-D-*threo*-hex-3-enopyranose (6)

A solution of diazo derivative **4** (0.6 g, 2.8 mmol) in MeI (100 mL) was treated at room temperature with cuprous iodide (200 mg) with rapid stirring. The solution immediately lost its yellow color with evolution of gas. Filtration from the copper salt and evaporation gave a thick syrup that crystallized after addition of a small amount of 2-propanol and scratching. The 3-alkene **6** was separated from a small amount of the dimer **5** by column chromatography to give clear prisms: yield 0.27 g (42%); mp 50–52 °C; $[\alpha]_D^{22}$ −60 (*c*, 1.0, $CHCl_3$); IR (KBr) ν_{max} 1700 (enol ether), 1370 cm^{-1} (CMe_2); *m*/*z* 184 (M^+), 169 (M^+-CH_3); ^1H NMR (acetone-d_6) δ 5.67 (d, 1H, $J_{1,2}$ 2.2 Hz, H-1), 4.83 (dd, 1H, $J_{4,5}$ 3.2, $J_{5,6}$ 3.1 Hz, H-5), 4.74 (dd, 1H, $J_{2,4}$ 1.8 Hz, H-4), 4.62 (m, 1H, H-2), 3.86 (d, 1H, $J_{6,6'}$ 7.6 Hz, H-6*endo*), 3.74 (dd, H-6*exo*), 1.42 (s, 6H, CMe_2); X-ray powder diffraction data: 8.38 m, 7.05 vw, 6.37 vs (1), 5.15 s, 4.75 vs (2), 4.57 s (3), 4.41 m, 4.18 m, 3.97 m, 3.70 vw, 3.55 w, 3.42 m, 3.23 m, 2.35 m. Anal. Calcd for $C_9H_{12}O_4$: C, 58.74; H, 6.54, Found: C, 58.83; H, 6.35.

The material immediately decolorized Br_2 in CCl_4.

3.8. 1,6-Anhydro-4-deoxy-2,3-*O*-isopropylidene-3-methoxy-β-D-*threo*-hexopyranos-3-ulose (7)

The enol ether **6** (200 mg, 1.1 mmo1) was dissolved in MeOH (200 mL), PtO_2 (100 mg) was added, and the mixture was shaken at 25 °C under 60 lb $in.^{-2}$ pressure of H_2 for 16 h. At the end of that time, TLC indicated that the starting material had disappeared. Filtration to remove Pt and evaporation of the MeOH gave a syrup that gradually crystallized. Recrystallization from 2-propanol gave the product as clear crystals: yield 147 mg (68%); mp 120–122 °C; $[\alpha]_D^{23}$ −44 (*c* 0.5, $CHCl_3$); IR (KBr) ν_{max} 1370 cm^{-1} (CMe_2); *m*/*z* 216 (M^+), 201 (M^+-CH_3); ^1H NMR (C_6D_6): δ 5.31 (d, 1H, $J_{1,2}$ 3.0 Hz, H-1), 4.02 (d, 1H, m, 1H, H-2 and H-5), 3.67 (dd, 1H, $J_{5,6endo}$ 0.7, $J_{6,6'}$ 6.7 Hz, H-6*endo*), 3.38 (dd, 1H, $J_{5,6exo}$ 6.2 Hz, H-6*exo*), 3.00 (s, 3H, OMe), 1.81 (d, 2H, $J_{4,5}$ 3.7 Hz, H-4, 4′), 1.60 and 1.48 (s, 3H, CMe_2); X-ray powder diffraction data: 7.28 s (2), 6.06 w, 5.64 m, 5.38 vs (1), 5.03 m, 4.75 m, 4.35 s (3), 3.96 w, 3.78 w, 3.51 vw, 3.32 w, 3.02 w, 2.96 w, 2.62 m. Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.56; H, 7.40. Found: C, 55.83; H, 7.17.

3.9. 2,3-*O*-Isopropylidenespiro[1,6-anhydro-4-deoxy-β-D-*lyxo*-hexopyranose-4,1′-cyclopropan]-2′-y1 acetate (8)

Irradiation of a solution of diazo derivative **4** (400 mg, 1.9 mmol) in neat vinyl acetate with Pyrex-filtered light of a medium-pressure mercury arc gave an intractable mixture of several products, including polymerized vinyl acetate. However, when an identical, rapidly stirred solution was treated at room temperature with CuBr (150 mg), a simpler mixture resulted; the reaction proceeding rapidly with evolution of gas. Removal of CuBr by filtration and evaporation of the filtrate gave a thick syrup, column chromatography of which afforded the spirocyclopropane derivative **8** in modest yield (66 mg,

13%), together with significant quantities of other products.

In a more-satisfactory procedure, an identical vinyl acetate solution of **4** was first cooled to −78 °C in a dry ice–acetone bath. Addition of the same amount of CuBr with rapid stirring brought about a slow reaction, which required about 10 min for completion. The mixture was filtered, and the filtrate was evaporated to a thick syrup. Addition of a small amount of 2-propanol and by scratching the inside of the flask for a few minutes brought about the crystallization of **8**. Recrystallization from 2-propanol gave pure **8** as fine needles: yield 214 mg (42%); mp 89–91 °C; $[\alpha]_D^{20}$ −101 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max} 1740 (OAc), 1370 cm^{-1} (CMe_2); *m/z* 270 (M^+), 255 (M^+-CH_3); ^1H NMR δ 6.81 (app t, 1H, $J_{A,X}$ 7.0 Hz, cyclopropyl CH), 5.55 (d, 1H, $J_{1,2}$ 3.0 Hz, H-1), 4.50 (dd, 1H, $J_{2,3}$ 5.9 Hz, H-2), 4.11 (d, 1H, H-3), 4.05–3.80 (m, 3H, H-5,6,6′), 2.17 (s, 3H, $COCH_3$), 1.88 (m, 2H, AB portion of ABX system, cyclopropyl CH_2), 1.55 and 1.30 (s, 3H, CMe_2); X-ray powder diffraction data: 10.21 vw, 6.44 w, 5.95 m (3), 4.42 m (2), 3.62 m (1), 3.27 vw, 2.96 vw, 2.86 w. Anal. Calcd for $C_{13}H_{18}O_6$: C, 57.78; H, 6.67. Found: C, 57.51; H, 6.89.

The compound was unstable at room temperature; pure material left in a tightly capped bottle for several h acquired a strong odor of AcOH, and it decomposed over a period of a few weeks at 0 °C.

3.10. 1,6-Anhydro-4-deoxy-4,4-diiodo-2,3-*O*-isopropylidene-β-D-*lyxo*-hexopyranose (9)

A solution of iodine (~0.2 M) in CH_2Cl_2 was slowly added with rapid stirring to a solution of diazo derivative **4** (0.5 g, 2.4 mmol) in CH_2Cl_2 (150 mL) at room temperature. Initially the violet color of iodine was immediately discharged. Addition was terminated when the violet color persisted. The excess of I_2 was removed by treatment with activated charcoal. Filtration of the mixture and evaporation of the filtrate gave a yellow syrup that crystallized upon the addition of a small amount of 2-propanol and by scratching the inside of the flask. Recrystallization from 2-propanol gave fine, colorless crystals of **9**: yield 0.56 g (53%); mp 203 °C (dec); $[\alpha]_D^{22}$ −46 (*c* 0.2, $CHCl_3$); IR (KBr) 1380 cm^{-1} (CMe_2); *m/z* 438 (M^+-CH_3), 311 (M^+-I); ^1H NMR δ 5.54 (dd, 1H, $J_{1,2}$ 2.4, $J_{1,3}$ 1.0 Hz, H-1), 4.83 (m, 1H, $J_{2,3}$ 4.2, $J_{3,5}$ 1.8 Hz, H-3), 4.77 (m, 1H, $J_{5,6endo}$ 1.0, $J_{5,6exo}$ 5.4 Hz, H-5), 4.50 (dd, $J_{6,6'}$ 8.0 Hz, H-6*endo*), 4.42 (dd, 1H, H-2), 3.54 (dd, 1H, H-6*exo*), 1.54 and 1.33 (s, 3H, CMe_2); X-ray powder diffraction data: 6.80 vs (2), 5.80 m, 5.55 m, 5.34 vs (1), 4.98 w, 4.73 m, 4.50 s (3), 4.33 m, 4.07 w, 3.70 m. Anal. Calcd for $C_9H_{12}I_2O_4$: C, 24.61; H, 2.74; I, 57.91. Found: C, 24.84; H, 2.84; I, 58.03.

Compound **9** was unstable at room temperature for extended periods: a closed sample kept for 24 h at 25 °C turned yellow and had the odor of iodine. It decomposed in CH_2Cl_2 solution during 8–12 h, and the solution turned violet.

3.11. 1,6-Anhydro-4,4-dibromo-4-deoxy-2,3-*O*-isopropylidene-β-D-*lyxo*-hexopyranose (10)

A solution of bromine (~0.4 M) in CH_2Cl_2 was slowly added with rapid stirring to a solution of **4** (0.5 g, 2.4 mmol) in CH_2Cl_2 (150 mL) at room temperature. The red color of the bromine was immediately discharged. Addition of Br_2 was stopped when a red color persisted in the solution, and solvent and excess of bromine were evaporated to give a thin, yellow syrup that spontaneously crystallized over several hours. Recrystallization from 2-propanol gave the pure product **10** as fine needles: yield 0.52 g (63%); mp 102.5–104 °C; $[\alpha]_D^{21}$ −53 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max} 1370 cm^{-1} (CMe_2); *m/z* 344 (M^+), 329 (327, 329, 331 in 1:2:2:1 ratio, M^+-CH_3); ^1H NMR δ 5.44 (dd, 1H, $J_{1,2}$ 2.5, $J_{1,3}$ 1.0 Hz, H-1), 4.33 (dd, 1H, $J_{2,3}$ 5.0 Hz, H-2), 4.80 (ddd, 1H, $J_{3,5}$ 1.5 Hz, H-3), 4.75 (ddd, 1H, $J_{5,6exo}$ 6.0, $J_{5,6endo}$ 1.0 Hz, H-5), 4.49 (dd, 1H, $J_{6,6'}$ 8.0 Hz, H-6*exo*), 3.75 (dd, 1H, H-6*endo*), 1.60 and 1.40 (s, 3H, CMe_2); X-ray powder diffraction data: 9.08 vs, 6.01 vs (3), 5.67 w, 2.46 w, 4.77 vs, 4.17 vs (2), 3.95 w, 3.55 vs (1), 2.73 s. Anal. Calcd for $C_9H_{12}Br_2O_4$: C, 31.40; H, 3.49; Br, 46.51. Found: C, 31.45; H, 3.32; Br, 46.60.

3.12. 1,6-Anhydro-4-bromo-4-deoxy-2,3-*O*-isopropylidene-β-D-talopyranose (11)

TLC examination of the mother liquors of the reaction that led to **10** revealed a slower-moving spot (R_f 0.30), and this component was separated by column chromatography to afford flat prisms (55 mg, less than 5%) of a product identified as **11**: mp 91–92 °C; $[\alpha]_D^{20}$ −20 (*c* 1.0, $CHCl_3$); *m/z* 264, 266 (M^+), 249, 251 (M^+-CH_3), 126 ($M^+-Br-AcO$); ^1H NMR (C_6D_6) δ 5.23 (dd, 1H, $J_{1,2}$ 2.5, $J_{1,3}$ 0.7 Hz, H-1), 4.40 (dd, 1H, $J_{6,6'}$ 7.8, $J_{5,6endo}$ 1.1 Hz, H-6*endo*), 4.04 (m, 1H, $J_{2,3}$ 5.3, $J_{3,4}$ 5.1 Hz, H-3), 3.94 (m, 1H, $J_{4,5}$ 5.3, $J_{5,6exo}$ 5.4 Hz, H-5), 3.74 (m, 1H, $J_{4,6}$ 1.2 Hz, H-4), 3.60 (dd, 1H, H-2), 3.42 (m, 1H, H-6*exo*), 1.57 and 1.15 (s, 3H, CMe_2); X-ray powder diffraction data: 10.6 m, 8.79 s, 7.37 vs (3), 5.75 vs (1), 5.09 w, 4.78 vs (2), 4.60 m, 4.22 m, 3.94, 3.59 s, 2.75 m, 2.65 vw, 2.55 w, 2.01 vw. Anal. Calcd for $C_9H_{13}BrO_4$: C, 40.75; H, 4.91; Br, 30.15. Found: C, 40.78; H, 4.94; Br, 30.41.

3.13. 2,3-*O*-Isopropylidenespiro[1,6-anhydro-4-deoxy-β-D-*lyxo*-hexopyranose-4,3′-pyrazole]-4′,5′-di(methyl carboxylate) (12)

Dimethyl acetylenedicarboxylate (1.0 g, 7 mmol) in CH_2Cl_2 (10 mL) was added to a stirred solution of **4**

(0.8 g, 3.8 mmol) in the same solvent (100 mL) at room temperature. Over a 10-min period, the yellow color of the diazo compound faded with no visible evolution of gas, and TLC indicated that a single product had formed. The solvent was evaporated off, and the excess of dimethoxycarbonylacetylene was removed by repeated evaporation with 2-propanol, giving a thick, slightly colored syrup that crystallized spontaneously upon being kept for several days; subsequent preparations crystallized immediately upon removal of the solvent. Recrystallization from 2-propanol gave the product as long, silky needles: yield 1.02 g (76%); mp 158.5–159 °C; $[\alpha]_D^{21}$ −70 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max} 1750 and 1730 (CO_2Me), 1370 cm^{-1} (CMe_2); *m*/*z* 354 (M^+), 339 (M^+-CH_3), 323 (M^+-CH_3O); ^1H NMR δ 6.30 (d, 1H, $J_{2,3}$ 5.8 Hz, H-3), 6.03 (dd, 1H, H-5), 5.66 (d, 1H, $J_{1,2}$ 3.0 Hz, H-1), 4.39 (dd, 1H, H-2), 4.26–4.08 (m, 2H, H-6,6′), 3.92 and 3.85 (s, 3H, OMe), 1.58 and 1.48 (s, 3H, CMe_2); X-ray powder diffraction data: 12.10 m, 7.92 vs (1), 7.49 s, 6.12 m, 5.75 w, 4.79 vs (2), 4.41 s, 4.30 m, 4.12 m, 3.99 s (3), 3.72 m, 3.60 m, 3.45 s, 3.28 m, 3.08 m, 2.93 s, 2.84 w, 2.37 w, 2.23 w, 2.05 vw. Anal. Calcd for $C_{15}H_{18}N_2O_8$: C, 50.85; H, 5.08; N, 7.91. Found: C, 50.58; H, 5.17; N, 7.61.

3.13.1. Hydrazide derivative of 12. A solution of **12** (0.6 g, 1.7 mmol) in MeOH (50 mL) was stirred for 1 h at room temperature with 95% hydrazine (0.3 mL, 10 mmol). Solvent and excess hydrazine were evaporated off to give a thick syrup that crystallized spontaneously. Recrystallization from 2-propanol gave the product, 2,3-*O*-isopropylidenespiro[1,6-anhydro-4-deoxy-β-D-*lyxo*-hexopyranose-4,3′-pyrazole]-4′,5′-di(carboxhydrazide) (**13**): yield 0.52 g (87%); mp 222 °C (dec); $[\alpha]_D^{22}$ −51 (*c* 1.0, $CHCl_3$); *m*/*z* 354 (M^+), 339 (M^+-CH_3), 323 (M^+-NHNH_2).

3.14. 2′,4′-Dihydro-2,3-*O*-isopropylidenespiro[1,6-anhydro-4-deoxy-β-D-*lyxo*-hexopyranose-4,3′-pyrazole]-5′-carbonitirile (14)

To a stirred solution of **4** (0.6 g, 2.8 mmol) in CH_2Cl_2 (50 mL) was added a solution of acrylonitrile (1.0 mL, 2.0 mmol, in 10 mL of CH_2Cl_2) at room temperature. The yellow color of the diazo compound faded over a period of 8 min, and evaporation of solvent and unreacted acrylonitrile gave a white solid, shown by TLC to contain two components, R_f 0.70 and 0.58. The faster migrating, major component was separated from the minor one by fractional crystallization from 2-propanol and was isolated as fine, short needles: yield 0.42 g (58%); mp 231 °C (dec); $[\alpha]_D^{23}$ −406 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max} 3330 (NH), 2210 (CN, conj.), 1370 cm^{-1} (CMe_2); *m*/*z* 265 (M^+), 251 (M^+-CH_3); ^1H NMR (acetone-d_6): δ 5.22 (d, 1H, $J_{1,2}$ 2.8 Hz, H-1), 4.43 (m, 1H, $J_{5,6exo}$ 5.2 Hz, H-5), 4.36 (dd, 1H, $J_{2,3}$ 5.8, $J_{3,5}$ 1.4 Hz, H-3), 4.22 (app d, 1H, $J_{6,6'}$ 8.0 Hz, H-6*endo*), 4.08 (dd, 1H, H-2), 3.65 (dd, 1H, H-6*exo*), 3.14 (dd, 2H, *J* 17.2 Hz, CH_2 of pyrazole ring), 1.49 and 1.26 (s, 3H, CMe_2); X-ray powder diffraction data: 9.20 vs (2), 7.25 vs (1), 6.08 in, 5.75 s, 4.90 vs (3), 4.45 m, 4.35 w, 4.16 s, 3.82 m, 3.65 m, 3.47 w, 3.12 m, 3.01 vw, 2.76 m. Anal. Calcd for $C_{12}H_{15}N_3O_4$: C, 56.25; H, 5.86; N, 16.40. Found: C, 56.09; H, 5.83; N, 16.22.

The mother liquors contained the minor component, which was not characterized, along with additional **14**.

3.15. (5*S*)-5-Isopropyl 1,4[1]-anhydro-4-deoxy-4-*C*-hydroxymethyl-2,3-*O*-isopropylidene-β-L-*ribo*-pentodialdo-1,6-pyranose-1,5-pyranoside [(1*R*,2*S*,6*S*,7*R*,9*R*)-4,4-dimethyl-9-(2-propoxy)-3,5,8,11-tetraoxa[5.2.3.0^{2,6}]-undecane] (15)

To a solution of 0.7 g (3.3 mmol) of compound **4** in anhyd 2-propanol (50 mL) was added one drop of acidic 2-propanol (prepared by adding 1 drop of concentrated HCl to 20 mL of 2-propanol). An immediate reaction occurred with evolution of gas and instantaneous discharge of the yellow color of the diazo compound. The mixture was immediately made neutral by the addition of anhyd Na_2CO_3 (2.0 g), filtered, and the filtrate was evaporated to a thick syrup that slowly crystallized. Recrystallization from 2-propanol gave **15** as fine, white crystals, yield 0.35 g (41%); mp 103–104 °C; $[\alpha]_D$ −46 (*c* 0.5, $CHCl_3$); IR (KBr) ν_{max} 1370 cm^{-1} (CMe_2): *m*/*z* 244 (M^+), 229 (M^+-CH_3); ^1H NMR δ 5.03 (m, 2H, $J_{1,2}$ 2.5 Hz, H-1,5), 4.43 (dd, 1H, $J_{2,3}$ 8.2, $J_{3,4}$ 3.0 Hz, H-3), 4.18 (dd, 1H, H-2), 4.03 (m, 2H, H-4[1],4[1′]), 4.03 (septet, 1H, CH of *i*-Pr), 2.16 (m, 1H, H-4), 1.62 and 1.43 (s, 3H, CMe_2), 1.32 and 1.21 (two s, 3H each, *J* 6.0 Hz, nonequivalent Me of *i*-Pr); X-ray powder diffraction data: 17.31 m (2), 8.62 vw, 7.89 w, 6.20 vw, 5.74 w, 5.45 vw, 4.81 m (3), 4.20 s (1). Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.02; H, 8.20. Found: C, 59.03; H, 8.12.

3.16. (5*S*)-5-Methyl 1,4[1]-anhydro-4-deoxy-4-*C*-hydroxymethyl-2,3-*O*-isopropylidene-β-L-*ribo*-pentodialdo-1,6-pyranose-1,5-pyranoside [(1*R*,2*S*,6*S*,7*R*,9*R*)-4,4-dimethyl-9-methoxy-3,5,8,11-tetraoxa[5.2.3.0^{2,6}]undecane] (16)

To a solution of 0.6 g (2.8 mmol) of **4** in MeOH (50 mL) was added one drop of acidic MeOH (prepared by adding one drop of concentrated HCl to 20 mL of MeOH), The reaction was immediate, with evolution of gas and loss of the yellow color. The solution was made neutral by addition of anhyd Na_2CO_3 (2.0 g). Filtration and evaporation of solvent gave a thick syrup that crystallized slowly. Recrystallization from 2-propanol gave **16** as fine, white crystals: yield 0.30 g (50%); mp 92–93.5 °C; $[\alpha]_D^{20}$ +18 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max} 1380 cm^{-1} (CMe_2); *m*/*z* 216 (M^+), 201 (M^+-CH_3); ^1H

NMR δ 5.04 (d, 1H, $J_{1,2}$ 2.5 Hz, H-1), 4.81 (dd, 1H, $J_{4,5}$ 3.2, $J^{1}_{4,5}$ 1.1 Hz, H-5), 4.40 (dd, 1H, $J_{2,3}$ 8.0, $J_{3,4}$ 3.6 Hz, H-3), 4.18 (dd, 1H, H-2), 4.10 (m, 2H, H-4^{1},$4^{1'}$), 3.53 (s, 3H, OMe), 2.21 (m, 1H, H-4), 1.60 and 1.41 (s, 3H, CMe_2); X-ray powder diffraction data: 15.72 w, 8.41 m (3), 7.79 m, 5.95 w, 5.36 s (2), 4.20 m, 3.77 s (1), 3.54 vw, 2.78 w. Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.56; H, 7.41. Found: C, 55.75; H, 7.28.

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