5 Hz, 1 H), 3.42 (m, 1 H), 3.85 (dd, J = 11, 6 Hz, 1 H), 4.05 (dd, J = 10, 9 Hz, 1 H), 7.00 (s, 1 H), 7.10 (d, J = 8 Hz, 2 H), 7.24 (d, J = 8 Hz, 2 H), 7.29 (s, 1 H), 7.75 (br s, 1 H), 8.51 (br s, 1 H); CIMS (*i*-Bu) m/z 407 ($M^+ + 1$), 391 (90), 371 (40), 285 (100), 269 (75), 221 (90).

5-Acetamido-3-(bromomethyl)-6-hydroxy-1-(methanesulfonyl)-2,3-dihydroindole (17). Diazocyclohexadienone 1 (10 mg, 0.032 mmol) and $CuBr_2$ were suspended in 1 mL of DMSO, and the mixture was stirred overnight. The reaction mixture was diluted with 20% NaH_2PO_4 and extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$) and evaporated and the residue purified by flash column chromatography to yield 6.3 mg (54%) of 17. A spot that comigrated with a TLC standard of 2 was observed but could not be isolated on this small scale: ^{1}H NMR (DMSO) δ 2.14 (s, 3 H), 2.84 (s, 3 H), 3.38 (dd, J = 8, 10 Hz, 1 H), 3.58 (dd, J = 11, 4 Hz, 1 H), 3.68 (m, 1 H), 3.85 (dd, J = 11, 5 Hz, 1 H), 4.02 (dd, J = 10, 8 Hz, 1 H), 7.02 (s, 1 H), 7.73 (s, 1 H), 8.06 (s, 1 H). When 17 was treated with sodium hydride (2 equiv) in THF at 0 °C, it was cyclized to 2 in 90% yield.

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Supplementary Material Available: Proton NMR spectra for compounds **4b**, **5a**, **5b**, **7-9**, **10b**, **10c**, **12a**, **12b**, and **15-17**. Infrared spectra for compounds **4b**, **8**, and **10b** and mass spectra for compounds **4b**, **15**, and **16** (34 pages). Ordering information is given on any current masthead page.

Action of Alkali on *O*-Benzylated Aldoses: A Simple Rationalization of Some Reactions Occurring in Alkaline Media

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Treatment of some *O*-benzyl-protected aldopyranoses and aldofuranoses with sodium 2-propoxide or K_2CO_3 brought about their equilibration and the loss of the elements of benzyl alcohol, with concomitant formation of a *Z* aldehyde. The latter rearranged rapidly in solution to the corresponding *E* lactol.

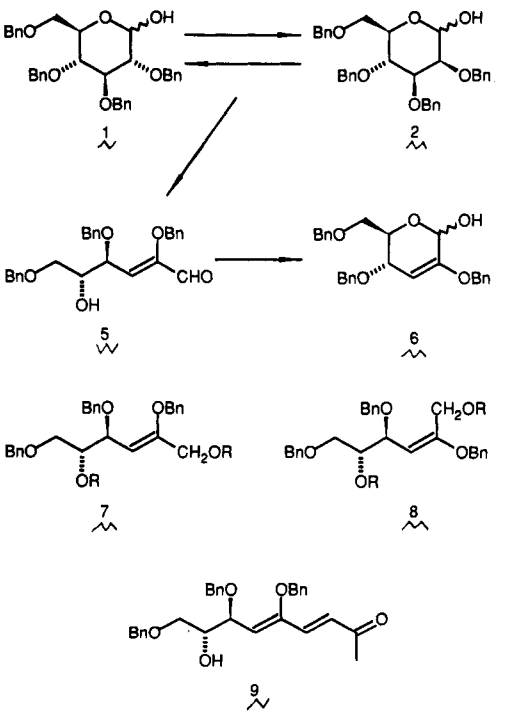
Introduction

The chemical transformations of glucose and mannose in alkaline media have been extensively studied.[1-3] In contrast, no systematic studies of the effect of alkalis or alkaline reaction conditions on their 2,3,4,6-tetra-*O*-benzyl derivatives have been made, despite the wide use of these derivatives as intermediates in a variety of reactions.[4]

A few reports[5,6] have, however, described the stereospecific elimination of benzyl alcohol from *O*-perbenzylated sugars during $NaBH_4$ reduction and the unsuccessful attempts to isolate any intermediate aldehydes produced.

In earlier works,[7] we found that the weakly basic Wittig-Horner reagent derived from diethyl (cyanomethyl)-phosphonate caused the undesired equilibration of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**1**) and 2,3,4,6-tetra-*O*-benzyl-D-mannopyranose (**2**), which was followed, in some cases,[7,8] by the elimination of benzyl alcohol. So we decided to investigate the action of both mild and strong bases on those two sugars (Scheme I) and their analogues, 2,3,5-tri-*O*-benzyl-D-arabinofuranose (**3**) and 2,3,5-tri-*O*-benzyl-D-ribofuranose (**4**) (Scheme II). Our aims were to rationalize the behavior of the *O*-benzyl-protected aldoses in these and other known reactions in alkaline media[5-10] and to obtain data that would be useful for predicting the behavior of these compounds in other possible reactions that occur in alkaline media.

Scheme I[a]



[a] **a**, R = H; **b**, R = Ac.

Results and Discussion

The results (summarized in Scheme I) showed that simple bases (K_2CO_3 and sodium 2-propoxide) brought

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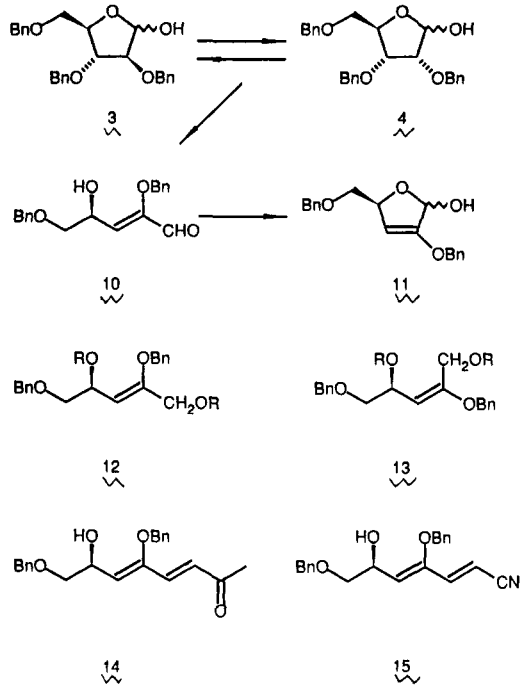
0022-3263/91/1956-3054$02.50/0

Scheme II[a]



[a] **a**, R = H; **b**, R = Ac.

about equilibration of **1** and **2** and concomitant competitive β-elimination of the 3-benzyloxy group and the C-2 hydrogen atom to yield either both the unsaturated *Z* aldehyde **5** and the *E* lactol **6** (in a 1:20 ratio by treatment with K_2CO_3) or only the *E* lactol **6** (by treatment with sodium 2-propoxide).

These results suggested that the two bases caused the formation of different elimination products by two different reaction mechanisms. The *Z* aldehyde **5**, which could be obtained by treatment of **1** and **2** with K_2CO_3 in MeOH, or better yet, by oxidation with MnO_2 of the alcohol **7a**,[5,6] was immediately and irreversibly transformed into the *E* lactol **6** simply by exposure to sodium 2-propoxide in 2-propanol at room temperature. The same isomerization could be effected, more slowly, by treatment of **5** with K_2CO_3 in MeOH at reflux. It thus became necessary to determine if compounds **5** and **6** were both formed directly from the parent sugars by an elimination reaction, or if **6** arose only by base-catalyzed isomerization of aldehyde **5**. Compounds **1** and **2** were treated with sodium 2-propoxide in the presence of $NaBH_4$. Because **1** and **2** only slowly undergo "normal" reduction by $NaBH_4$,[5] the aldehyde **5**, if formed first, should be trapped as the corresponding alcohol **7a** before the partial or total isomerization of **5** to the lactol **6** could occur.

In fact, the *Z* alcohol **7a** (characterized as the diacetate **7**[5,6]) was obtained exclusively. This result suggested that the treatment of **1** and **2** with base did initially give only the aldehyde **5**, which was then transformed into the lactol **6**. The isomerization was rapid and complete in the presence of sodium 2-propoxide and less rapid and incomplete in the presence of K_2CO_3.

Similarly, treatment of *O*-benzylated arabinofuranose **3** and ribofuranose **4** with K_2CO_3 or sodium 2-propoxide afforded the *E* lactol **11** (Scheme II). In some experiments with K_2CO_3, compound **11** was accompanied by a trace amount of the *Z* aldehyde **10** (about 1% was detected by ^1H NMR analysis of the reaction mixture).

Treatment of **3** and **4** with sodium 2-propoxide and $NaBH_4$ afforded the *Z* alcohol **12a** (characterized as the diacetate **12b**[5,6]), which was accompanied by varying amounts of tri-*O*-benzylarabinitol and tri-*O*-benzylribinitol, the products of normal reduction of **3** and **4** (see Experimental Section).

These results showed that the *O*-benzylated pyranoses **1** and **2** and the *O*-benzylated furanoses **3** and **4** reacted with bases to initially afford the homologous *Z* aldehydes **5** and **10**. The latter were subsequently transformed into the *E* lactols **6** and **11**, respectively. In the presence of $NaBH_4$, **1** and **2** underwent elimination of benzyl alcohol faster than normal reduction, and aldehyde **5** was formed and was trapped before it isomerized to **6**. In contrast, with **3** and **4**, normal reduction was faster but was accompanied by the elimination of benzyl alcohol. In fact, a considerable amount of tri-*O*-benzylpentitols was obtained along with the unsaturated alcohol **12a**. These results suggested that a similar series of reactions occurred during the reported reduction[5,6] of **1**, **2**, and **3** by $NaBH_4$ in 2-propanol. In fact, a repetition of those experiments, under slightly different reaction conditions, produced results that allowed a simple rationalization of the original observations.

Separate reductions were performed by adding **1** or **2** (or **3** or **4**) to a mixture of $NaBH_4$ and sodium 2-propoxide in 2-propanol. The monitoring of the reactions by HPLC and TLC showed that equilibration of the epimers accompanied the formation of the *Z* alcohol **7a** (or **12a**) (characterized as the diacetate **7b** or **12b**), the only unsaturated compound detected. In contrast, after $NaBH_4$ was added to a mixture of **1** or **2** (or **3** or **4**) that had been refluxed for 30 min in 2-propanol containing sodium 2-propoxide, only the *E* alcohol **8a** (or **13a**) was obtained (characterized as the diacetate **8b** or **13b**). Thus, before $NaBH_4$ was introduced into the reaction mixture, **1** or **2** (or **3** or **4**) had already been completely transformed, through the *Z* aldehyde **5** (or **10**), into the *E* lactol **6** (or **11**). Lactol **6** (or **11**) could be isolated from the reaction mixture if $NaBH_4$ was not introduced.

If, however, $NaBH_4$ was added to the mixture before the complete transformation of **1** or **2** (or **3** or **4**) into **6** (or **11**), the alcohol **8a** (or **13a**) was formed, along with a minor amount of the isomer **7a** (or **12a**), derived from the aldehyde **5** (or **10**).

The same transformations of **1** and **4** probably occurred in the recently reported aqueous K_2CO_3-catalyzed aldol condensation of these sugars with acetone[9] to afford (3*E*,5*Z*,7*S*,8*R*)-5,7,9-tris(benzyloxy)-8-hydroxynona-3,5-dien-2-one (**9**, Scheme I) and (3*E*,5*Z*,7*S*)-5,8-bis(benzyloxy)-7-hydroxyocta-3,5-dien-2-one (**14**, Scheme II) and also in the Wittig–Horner reaction of **3** with diethyl (cyanomethyl)phosphonate in the presence of excess lithium hexamethyldisilazide (LiHMDS)[10] to afford (2*E*,4*Z*,6*S*)-4,7-bis(benzyloxy)-6-hydroxyhepta-2,4-dienenitrile (**15**). In fact, the reaction of each individual component of the epimeric couples, **1** and **2** and **3** and **4**, with acetone and K_2CO_3 gave the same unsaturated compounds (**9** and **14**), regardless of the stereochemistry at C-2 of the parent compound. HPLC analysis of the reaction mixtures showed that the parent compounds underwent rapid equilibration during the first stages of the reaction.

Also, during the reactions of **1** and **2**, a trace amount of the *Z* aldehyde **5** was detected by ^1H NMR.

Similar results were obtained from the Wittig–Horner reaction of **3** or **4** with diethyl (cyanomethyl)phosphonate (1 equiv) and excess LiHMDS (2.2 equiv). In this case, although it was not possible to detect the presence of the *Z* aldehyde **10**, the formation of benzyl alcohol was observed by HPLC and TLC analysis during the reaction. Also, exposure of arabinofuranose **3** or ribofuranose **4** to

LiHMDS (1 equiv) effected equilibration of the epimers and quantitative elimination of benzyl alcohol.

A simple explanation of these transformations of **1**, **2**, **3**, and **4** is that an equilibrium between the two epimers of each pair is set up, probably via the enolates of the corresponding hydroxy aldehydes. The latter can also undergo β-elimination of the elements of benzyl alcohol to afford an unsaturated *Z* aldehyde, the geometry of whcih is determined by the conformational preferences of the enolates. Support for this view could be obtained by inspection of Dreiding models of the *E* and *Z* enolates common to **1** and **2** (or **3** and **4**). In all cases the conformations that would lead to the formation of the *Z* aldehyde by β-elimination of a benzyloxy group appeared to be sterically more favorable than those that would lead to the formation of the *E* lactol.

The equilibrations and degradations that were observed explain some unusual reactions[5-10] and, therefore, must be taken into account when predicting the results of other reactions that involve *O*-benzylated aldoses and alkaline reagents.

Experimental Section

^{1}H NMR spectra of $CDCl_3$ solutions were recorded at 500 MHz. Mass spectra were obtained with a Varian MAT 112 S spectrometer equipped with a direct inlet. Optical rotations are of $CHCl_3$ solutions (c = 1). All reactions and the progress of column chromatography (silica gel, 230–400 mesh) were constantly monitored by both TLC and HPLC. Products were purified by flash chromatography. TLC was performed with silica gel (HF_{254}) coated plates. The plates were developed with CH_2Cl_2/acetone or hexane/EtOAc and visualization was achieved by spraying the plates with 70% H_2SO_4 and then heating them to induce charring. HPLC analysis was performed with a Jasco HPLC instrument using an Uvidec 100 II UV detector operating at 208 nm. A 4 mm × 250 mm 3 μm particle size reverse-phase Lichrosorb C-18 column (Merck) was employed. An 85:15 mixture of MeOH/H_2O at a flow rate of 1 mL min^{-1} served as the eluant.

Treatment of *O*-Benzyl-Protected Aldopyranoses 1 or 2 and Aldofuranoses 3 or 4 with K_2CO_3 in MeOH. General Procedure. A mixture of the *O*-benzyl-protected aldopyranose **1** or **2** or aldofuranose **3** or **4** (10 mmol), MeOH (30 mL), tetrahydrofuran (40 mL), H_2O (15 mL), and K_2CO_3 (14 mmol) was refluxed for 12 h (the aldopyranoses) or for 1 h (the aldofuranoses). The reaction mixture was then evaporated to dryness, and the residue was treated with H_2O. The aqueous solution was extracted with CH_2Cl_2. The extract was dried (Na_2SO_4), filtered, and concentrated to give a syrup, which was purified by flash column chromatography or recrystallization.

i. 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose (**1**; 5.4 g) afforded 2,4,6-tri-*O*-benzyl-3-deoxy-D-*erythro*-hex-2-enopyranose (**6**; 3.28 g): mp 116–119 °C (diisopropyl ether); $[\alpha]^{20}_D$ = +38.0; ^{1}H NMR δ 4.97 (1 H, d, $J_{3,4}$ = 2.1 Hz, 3-H) and 5.31 (1 H, d, $J_{1,OH}$ = 4.7 Hz, 1-H); MS 432 (M^+).

Anal. Calcd for $C_{27}H_{28}O_5$: C, 75.0; H, 6.6. Found: C, 75.3; H, 6.7.

Flash chromatography of the residue from the mother liquor afforded (2*Z*,4*S*,5*R*)-2,4,6-tris(benzyloxy)-5-hydroxyhex-2-enal (**5**; 0.160 g): an oil; $[\alpha]^{20}_D$ = −20.8; ^{1}H NMR δ 5.98 (1 H, d, $J_{3,4}$ = 9.1 Hz, 3-H) and 9.32 (1 H, s, C*H*O); MS 432 (M^+).

Anal. Calcd for $C_{27}H_{28}O_5$: C, 75.0; H, 6.6. Found: C, 75.2; H, 6.4.

ii. 2,3,4,6-Tetra-*O*-benzyl-D-mannopyranose (**2**; 5.4 g) afforded 2,4,6-tri-*O*-benzyl-4-deoxy-D-*erytro*-hex-2-enopyranose (**6**; 3.2 g): mp 116–119 °C (diisopropyl ether); $[\alpha]^{20}_D$ = 38.2. The product was identical in all respects with that described above. Flash chromatography of the residue from the mother liquor afforded (2*Z*,4*S*,5*R*)-2,4,6-tris(benzyloxy)-5-hydroxyhex-2-enal (**5**; 0.130 g): an oil; $[\alpha]^{20}_D$ = −21, identical with that described above.

Anal. Calcd for $C_{27}H_{28}O_5$: C, 75.0; H, 6.6. Found: C, 75.3; H, 6.5.

iii. 2,3,5-Tri-*O*-benzyl-D-arabinofuranose (**3**; 4.2 g) afforded a crude product containing benzyl alcohol, 2,5-di-*O*-benzyl-3-deoxy-D-*glycero*-pent-2-enofuranose (**11**), and, in some cases, a trace amount (<2%) of (2*Z*,4*S*)-2,5-bis(benzyloxy)-4-hydroxypent-2-enal (**10**), as was evident from the ^{1}H NMR spectrum of the mixture. Signals characteristic of **10** appeared at δ 9.24 (1 H, s, CHO) and 5.94 (1 H, d, J = 7.7 Hz, 3-H). After flash chromatography, the lactol **11** (2.2 g) was obtained along with a trace amount of decomposition products. Compound **11**: an oil; ^{1}H NMR δ 4.69 (1 H, d, $J_{3,4}$ = 2.0 Hz, 3-H) and 5.57 (1 H, d, $J_{1,OH}$ 11.0 Hz, 1-H); MS 312 (M^+).

Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.1; H, 6.4. Found: C, 73.5; H, 6.2.

iv. Treatment of 2,3,5-tri-*O*-benzyl-D-ribofuranose (**4**; 4.2 g) with K_2CO_3 at reflux afforded a mixture of benzyl alcohol, the furanose **11**, and a trace amount of the aldehyde **10**, as the ^{1}H NMR spectrum of the mixture showed. The mixture was purified by flash chromatography to afford the lactol **11** (2.18 g): an oil identical in all respects with that described above.

Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.1; H, 6.4. Found: C, 73.3; H, 6.3.

Reduction with $NaBH_4$ and Acetylation of the Aldehydes 5 and 10 and of the Hemiacetals 6 and 11. General Procedure. The aldehyde or lactol (2 mmol) in 2-propanol (100 mL) was treated with $NaBH_4$ (1 mmol) at room temperature for 10 min. Water and then Et_2O were added, and the two liquid layers were separated. The organic layer was washed with H_2O, dried, and evaporated to dryness. The residue was treated with 2 mL of 1:2 acetic anhydride/pyridine for 2 h to afford the tribenzyl diacetates **7b** and **8b** or the dibenzyl diacetates **10b** and **11b**.

i. Aldehyde **5** afforded (2*Z*,4*S*,5*R*)-2,4,6-tris(benzyloxy)-1,5-diacetoxyhex-2-ene (**7b**; 850 mg): an oil; $[\alpha]^{20}_D$ −0.9; ^{1}H NMR δ 4.65 (1 H, d, $J_{1a,1b}$ = 13.6 Hz, 1-Ha), 4.72 (1 H, d, $J_{1b,1a}$ = 13.6 Hz, 1-Hb), and 4.97 (1 H, d, $J_{3,4}$ = 9.2 Hz, 3-H); MS 518 (M^+). These properties were identical with those reported.[7,8]

Anal. Calcd for $C_{31}H_{34}O_7$: C, 71.8; H, 6.6. Found: C, 72.0; H, 6.8.

In one case, the product was isolated without acetylation to afford (2*Z*,4*S*,5*R*)-2,4,6-tris(benzyloxy)hex-2-ene-1,5-diol (**7a**) (600 mg) after flash chromatography (which destroyed some of the product): an oil; $[\alpha]^{20}_D$ = −0.9; ^{1}H NMR δ 4.20 (1 H, d, $J_{1a,1b}$ = 13.7 Hz, 1-Ha), 4.23 (1 H, d, $J_{1b,1a}$ = 13.7 Hz, 1-Hb), and 4.87 (1 H, d, $J_{3,4}$ = 9.5 Hz, 3-H); MS 434 (M^+).

Anal. Calcd for $C_{27}H_{30}O_5$: C, 74.6; H, 7.0. Found: C, 74.3; H, 6.8.

ii. Lactol **6** afforded (2*E*,4*S*,5*R*)-2,4,6-tris(benzyloxy)-1,5-diacetoxyhex-2-ene (**8b**; 840 mg): an oil; $[\alpha]^{20}_D$ +15; ^{1}H NMR δ 4.53 (1 H, d, $J_{1a,1b}$ = 13.0 Hz, 1-Ha), 4.68 (1 H, d, $J_{3,4}$ = 9.6 Hz, 3-H), and 4.70 (1 H, d, $J_{1b,1a}$ = 13.0 Hz, 1-Hb); MS 518 (M^+). These characteristics were identical with those reported.[8]

Anal. Calcd for $C_{31}H_{34}O_7$: C, 71.8; H, 6.6. Found: C, 72.0; H, 6.4.

In one case, the product was isolated without acetylation to afford, after flash chromatography, which destroyed some of the product, (2*E*,4*S*,5*R*)-2,4,6-tris(benzyloxy)hex-2-ene-1,5-diol (**8a**) (600 mg): an oil; ^{1}H NMR δ 4.31 (1 H, d, $J_{1a,1b}$ = 11.5 Hz, 1-Ha), 4.49 (1 H, d, $J_{1b,1a}$ = 11.5 Hz, 1-Hb), and 4.77 (1 H, d, $J_{3,4}$ = 9.5 Hz, 3-H); MS 434 (M^+).

Anal. Calcd for $C_{27}H_{30}O_5$: C, 74.6; H, 7.0. Found: C, 74.8; H, 6.8.

iii. Aldehyde **10** afforded (2*Z*,4*S*)-2,5-bis(benzyloxy)-1,4-diacetoxypent-2-ene (**12b**; 620 mg): an oil; ^{1}H NMR δ 4.57 (1 H, d, $J_{1a,1b}$ = 13.5 Hz, 1-Ha), 4.65 (1 H, d, $J_{1b,1a}$ = 13.5 Hz, 1-Hb), and 4.97 (1 H, d, $J_{3,4}$ = 8.5 Hz, 3-H); MS 398 (M^+).

Anal. Calcd for $C_{23}H_{26}O_6$: C, 69.3; H, 6.6. Found: C, 69.5; H, 6.8.

In one case, the reduction product was isolated without acetylation to afford, after flash chromatography, which destroyed some of the product, (2*Z*,4*S*)-2,5-bis(benzyloxy)pent-2-ene-1,4-diol (**12a**) (360 mg): an oil; ^{1}H NMR δ 4.15 (2 H, AB, $J_{1a,1b}$ = 13.0 Hz, 1-H_2) and 4.87 (1 H, d, $J_{3,4}$ = 8.0 Hz, 3-H); MS 314 (M^+).

Anal. Calcd for $C_{19}H_{22}O_4$: C, 72.6; H, 7.0. Found: C, 72.8; H, 7.3.

iv. Lactol **11** afforded (2*E*,4*S*)-2,5-bis(benzyloxy)-1,4-diacetoxypent-2-ene (**13b**; 620 mg): ^{1}H NMR δ 4.65 (1 H, d, $J_{1a,1b}$ = 12.6 Hz, 1-Ha), 4.77 (1 H, d, $J_{3,4}$ = 9.1 Hz, 3-H), and 4.94 (1 H, d, $J_{1b,1a}$ = 12.6 Hz, 1-Hb); MS 398 (M^+).

Anal. Calcd for $C_{23}H_{26}O_6$: C, 69.3; H, 6.6. Found: C, 69.7; H, 6.7.

In one experiment, the product was isolated without acetylation to afford, after flash chromatography, which destroyed some of the product, (2*E*,4*S*)-2,5-bis(benzoyloxy)pent-2-ene-1,4-diol (**13a**) (380 mg): an oil; ^{1}H NMR δ 4.20 (1 H, d, $J_{1a,1b}$ = 13.0 Hz, 1-Ha), 4.27 (1 H, d, $J_{1b,1a}$ = 13.0 Hz, 1-Hb), and 4.66 (1 H, d, $J_{3,4}$ = 7.0 Hz, 3-H); MS 314 (M^+).

Anal. Calcd for $C_{19}H_{22}O_4$: C, 72.6; H, 7.0. Found: C, 72.4; H, 6.9.

Oxidation of the Diols 7a and 12a with MnO_2. The diol (500 mg), dissolved in hexane/THF (10 mL, 1:1), was shaken with MnO_2 (300 mg) at room temperature for 12 h. The mixture was then filtered through a pad of Celite. The filtrate was evaporated to dryness, and the residue was extracted with EtOAc. The residue that was obtained after flash chromatography afforded the *Z* aldehyde.

i. Diol **7a** afforded the hydroxy aldehyde **5** (375 mg), an oil, $[\alpha]^{20}_D$ = −20.6, identical in all respects (^{1}H NMR, MS, IR spectra) with that described above.

Anal. Calcd for $C_{27}H_{28}O_5$: C, 75.0; H, 6.6. Found: C, 74.9; H, 6.4.

ii. Diol **12a** afforded the hydroxy aldehyde **10** (360 mg): an oil; $[\alpha]^{20}_D$ = +3.8; ^{1}H NMR δ 5.94 (1 H, d, $J_{3,4}$ = 7.7 Hz, 3-H) and 9.24 (1 H, s, C*H*O); MS 312 (M^+).

Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.1; H, 6.4. Found: C, 73.4; H, 6.3.

Treatment of *O*-Benzyl-Protected Aldopyranoses and Aldofuranoses with Sodium 2-Propoxide in 2-Propanol. General Procedure. A solution of the *O*-Benzyl-protected aldopyranose or aldofuranose (10 mmol) in 2-propanol (100 mL) was treated with sodium 2-propoxide (6 mmol) room temperature for 24 h, or at reflux for 30 min. Under these conditions, compounds **1**, **2**, **3**, and **4** afforded only mixtures containing benzyl alcohol and the homologous lactols **6** and **11**. In all cases, the lactol was isolated by flash chromatography in a yield of from 70 to 75%. It showed the same physicochemical properties reported above.

Treatment of *O*-Benzyl-Protected Aldopyranoses 1 and 2 and Aldofuranoses 3 and 4 with a Mixture of $NaBH_4$ and Sodium 2-Propoxide and Subsequent Acetylation. General Procedure. The O-benzylated sugar (10 mmol), suspended in 2-propanol (30 mL), was added to a mixture of $NaBH_4$ (100 mmol) and sodium 2-propoxide (6 mmol) in 2-propanol (70 mL). The mixture was stirred for 28–30 h and then acetone (2 mL) was added. The mixture was poured into cold H_2O and extracted with dichloromethane. The organic layer was dried and concentrated to afford a residue, which was directly acetylated with 9 mL of 1:2 acetic anhydride/pyridine. The usual workup afforded the *Z* diacetate.

i. 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose (**1**), after flash chromatography of the crude product, afforded first 1,5-di-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-glucitrol (17 mg), an oil, identical with an authentic sample, and then (2*Z*,4*S*,5*R*)-2,4,6-tris(benzyloxy)-1,5-diacetoxyhex-2-ene (**7b**; 5.0 g): an oil, $[\alpha]^{20}_D$ = −1, identical with that described above.

Anal. Calcd for $C_{31}H_{34}O_7$: C, 71.8; H, 6.6. Found: C, 72.1; H, 6.7.

ii. 2,3,4,6-Tetra-*O*-benzyl-D-mannopyranose (**2**), after flash chromatography of the crude product, afforded first 1,5-di-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-mannitol (15 mg): an oil, identical with an authentic sample.[7]

Further elution afforded (2*Z*,4*S*,5*R*)-2,4,6-tris(benzyloxy)-1,5-diacetoxyhex-2-ene (**7b**; 5.0 g): an oil, $[\alpha]^{20}_D$ = −1, identical with that described above.

Anal. Calcd for $C_{31}H_{34}O_7$: C, 71.8; H, 6.6. Found: C, 71.7; H, 6.6.

iii. 2,3,5-Tri-*O*-benzyl-D-arabinofuranose (**3**), after flash chromatography of the crude product, afforded first a mixture (1.26 g) of 1,4-di-*O*-acetyl-2,3,5-tri-*O*-benzyl-D-arabinitol and 1,4-di-*O*-acetyl-2,3,5-tri-*O*-benzyl-D-ribinitol (in a 6:1 ratio, as determined by ^{1}H NMR and HPLC analysis) and then (2*Z*,4*S*)-2,5-bis(benzyloxy)-1,4-diacetoxypent-2-ene (**12b**; 2.4 g), which was identical in all respects with that obtained above.

Anal. Calcd for $C_{23}H_{26}O_6$: C, 69.3; H, 6.6. Found: C, 69.2; H, 6.8.

iv. 2,3,5-Tri-*O*-benzyl-D-ribofuranose (**4**), after flash chromatography of the crude product, afforded first 1,4-di-*O*-acetyl-2,3,5-tri-*O*-benzyl-D-ribinitol (2.5 g) containing some 1,4-di-*O*-acetyl-2,3,5-tri-*O*-benzyl-D-arabinitol (6%, by ^{1}H NMR and HPLC analysis) and then (2*Z*,4*S*)-2,5-bis(benzyloxy)-1,4-diacetoxypent-2-ene (**12b**; 0.8 g), identical with that described above.

Anal. Calcd for $C_{23}H_{26}O_6$: C, 69.3; H, 6.6. Found: C, 69.1; H, 6.7.

Aldol Reaction of *O*-Benzyl-Protected Aldopyranoses 1 and 2 and Aldofuranoses 3 and 4 with Acetone. General Procedure. The reaction was performed under essentially the same conditions as those reported earlier for **1** and **4**.[9] A mixture of the reducing sugar (1 mmol), acetone (40 mL), H_2O (5 mL), and K_2CO_3 (1.4 mmol) was refluxed, with magnetic stirring, for 12 h. The cooled mixture was then evaporated to dryness. The residue was treated with H_2O, and the aqueous solution was extracted with $CHCl_3$ (3 × 20 mL). The combined extracts were dried (Na_2SO_4) and filtered, and the solvent was evaporated to give a syrup, which was purified by flash column chromatography (hexane/EtOAc, 3:2).

i. 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose (**1**), after flash chromatography of the crude product, afforded (3*E*,5*Z*,7*S*,8*R*)-5,7,9-tris(benzyloxy)-8-hydroxynona-3,5-dien-2-one (**9**; 300 mg): an oil; IR (Nujol) 3440 and 1668 cm^{-1}; UV (MeOH) λ_{max} 276 nm (ϵ = 18900); ^{1}H NMR δ 2.31 (3 H, s, 1-CH$_3$), 5.56 (1 H, d, $J_{6,7}$ = 9.8 Hz, 6-H), 6.41 (1 H, d, $J_{3,4}$ = 15.4 Hz, 3-H), and 6.98 (1 H, d, $J_{4,3}$ = 15.4 Hz, 4-H); MS 472 (M^+). All these characteristics were identical with those reported.[9]

Anal. Calcd for $C_{30}H_{32}O_5$; C, 76.2; H, 6.8. Found: C, 76.3; H, 6.6.

ii. 2,3,4,6-Tetra-*O*-benzyl-D-mannopyranose (**2**), after flash chromatography of the crude product, afforded (3*E*,5*Z*,7*S*,8*R*)-5,7,9-tris(benzyloxy)-8-hydroxynona-3,5-dien-2-one (**9**; 310 mg): an oil; IR (Nujol) 3440 and 1668 cm^{-1}; UV (MeOH) λ_{max} 276 nm (ϵ = 18800); the spectra (IR, UV, ^{1}H NMR, MS) were identical with those described above.

Anal. Calcd for $C_{30}H_{32}O_5$: C, 76.2; H, 6.8. Found: C, 76.0; H, 6.0.

iii. 2,3,5-Tri-*O*-benzyl-D-arabinofuranose (**3**), after flash chromatography of the crude product, afforded (3*E*,5*Z*,7*S*)-5,8-bis(benzyloxy)-7-hydroxyocta-3,5-dien-2-one (**14**; 235 mg): an oil; IR (Nujol) 3420 and 1670 cm^{-1}; UV (MeOH) λ_{max} 275 nm (ϵ = 16800); ^{1}H NMR δ 2.28 (3 H, s, 1-CH$_3$), 5.50 (1 H, d, $J_{6,7}$ = 8.4 Hz, 6-H), 6.38 (1 H, d, $J_{3,4}$ = 16.1 Hz, 3-H), and 6.88 (1 H, d, $J_{4,3}$ = 16.1 Hz, 4-H); MS 352 (M^+). All these properties were identical with those reported for the compound obtained from 2,3,5-tri-*O*-benzyl-D-ribofuranose (**4**).[9]

Anal. Calcd for $C_{22}H_{24}O_4$: C, 75.0; H, 6.9. Found: C, 74.8; H, 6.6.

iv. 2,3,5-Tri-*O*-benzyl-D-ribofuranose (**4**) afforded (3*E*,5*Z*,7*S*)-5,8-bis(benzyloxy)-7-hydroxyocta-3,5-dien-2-one (**14**; 240 mg): an oil, identical in all respects with that reported above.

Wittig Reaction of *O*-Benzyl-Protected Aldofuranoses 3 and 4 with Diethyl (Cyanomethyl)phosphonate. General Procedure. The reaction was performed in the presence of excess lithium hexamethyldisilazide (LiHMDS) under the same conditions as those reported earlier for **3**.[10] To a solution of the *O*-benzyl-protected aldofuranose (45 mmol) and diethyl (cyanomethyl)phosphonate (45 mmol) in THF (175 mL) was added LiHMDS (100 mL of a 1M solution) at 0 °C. After 4.5 h of stirring at room temperature, additional phosphonate (45 mmol) was added. HPLC monitoring of the reaction showed formation of benzyl alcohol, which paralleled the formation of the Wittig compound **15**.

i. 2,3,5-Tri-*O*-benzyl-D-arabinofuranose (**3**) afforded, after purification, (2*E*,4*Z*,6*S*)-4,7-bis(benzyloxy)-6-hydroxyhepta-2,4-dienenitrile (**15**; 5.19 g): an oil; $[\alpha]^{20}_D$ +32; UV (MeOH) λ_{max} 262 nm (ϵ = 10200). The physical properties were identical in all respects with those reported.[10]

ii. 2,3,5-Tri-*O*-benzyl-D-ribofuranose (**4**) afforded compound **15** (5.3 g): an oil; $[\alpha]^{20}_D$ +31, identical with that reported above.

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B. Marini Bettolo on the occasion of his 75th birthday.

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Supplementary Material Available: Complete list of assigned signals in the ^1H NMR spectra recorded at 500 MHz of compounds 5–14 (6 pages). Ordering information is given on any current masthead page.

Substituted Oxazoles: Syntheses via Lithio Intermediates

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Reactions of 2-α-, 2-, 4-, and 5-lithiooxazoles are used to prepare various substituted derivatives. Previously unrecognized time dependence for the reaction of a 2-lithiooxazole with benzaldehyde is described, and a rationale for this behavior is offered. Competitive reactions occur when the readily available 2,5-diphenyloxazole is treated with *n*-butyllithium. Deprotonation of the ortho position of the 2-phenyl group and addition of *n*-butyl to the 2-position of the oxazole compete with the desired 4-lithiation. The use of *sec*-butyllithium/catalytic lithium tetramethylpiperidide allows preferential formation of 4-lithio-2,5-diphenyloxazole. This intermediate has been converted to the 4-bromo, -methyl, -hydroxybenzyl, -benzoyl, and -trialkylsilyl derivatives. Lithiation of 2,4-diphenyloxazole and subsequent trimethylsilylation occur readily at the 5-position. Deprotonation of 2-alkyloxazoles occurs at the α-carbon in preference to ring sites. Further reaction of an α-phenyl-2-oxazolemethanol methoxymethyl ether with base and acetyl chloride leads to an acyloin derivative. Chromic acid oxidation is used to prepare both 2- and 4-benzoyloxazoles. The formation of a 2-ethoxyoxazole from the 2-oxazolone vis Meerwein salt chemistry is described.

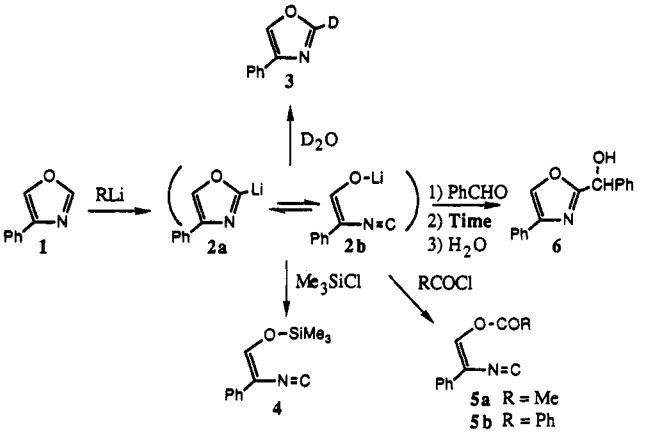
The reaction of oxazoles with benzyne provides a novel approach to the study of substituent effects on both Diels–Alder and (nonreverse) retro-Diels–Alder processes, in addition to affording a mild neutral method for the synthesis of isobenzofurans (IBFs).[1] The present paper describes the syntheses of several oxazoles needed for such studies, with emphases on new precedures and unusual findings.

Considerable effort has been devoted to the development of methods of synthesis of substituted oxazoles, but many specific examples remain difficult to prepare. Among several reviews of oxazole chemistry, that of Turchi is the most recent (1986), and it provides easy access to tabular information dealing with substituent patterns and related synthetic methods.[2]

We were especially interested in the use of metalated oxazoles to introduce substituents. The three C–H groups in oxazole itself differ considerably in acidity. It is generally believed that the 2-H is the most acidic, and a $pK_a = 20 \pm 2$ for this site has been suggested.[1b] This relatively high acidity prevents the use of base-induced methods for generating benzyne in the presence of these materials. Thus 4-phenyloxazole (1) (Scheme I) fails to give benzyne adduct when treated with PhCl/LTMP or with *o*-dibromobenzene/RLi. Instead, deprotonation occurs, as shown by quenching with D_2O to give the deuterated derivative **3**. The formation of **3** might be due to simple deuteration of the 2-lithiooxazole **2a**, but a more circuitous mechanism may be involved, analogous to the reaction with benzaldehyde discussed below.

A similar deprotonation problem arises in attempts to use LTMP induced benzyne methods with IBF ($pK_a \leq 33$) and even furan ($pK_a = 36$), but can be circumvented in these heterocycles by trimethylsilylation of the acidic sites. However, efforts to prepare 2-(trimethylsilyl)-4-phenyloxazole appear to result instead in the formation of the ring-opened isonitrile **4**; this material could not be isolated in pure form, but the structure is inferred from spectral evidence (^1H NMR 9:1 singlets at 0.22 and 6.95 ppm) and from the observation that very facile hydrolysis returns the starting oxazole. These attempts included mixing the intermediate organolithium species with Me_3SiCl at various temperatures, as well as treatment of a mixture of **1** and Me_3SiCl at −78 °C with LTMP. Distillation of crude **4** from a catalytic amount of KOH was also explored. This procedure has been reported[4] to yield the 2-$SiMe_3$ derivative from the analogous ring-opened *O*-$SiMe_3$ derivative

Scheme I



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