mol of phenylacetylene in 60 mL of anhydrous ether. The solution was saturated with HBr, and 0.03 mol of triphenylphosphine in 20 mL anhydrous ether was added. After the mixture was refluxed for 30 h, the solid material was filtered and the filtrate concentrated under reduced pressure. The residue was distilled [69 °C (2.8 torr)] to give pure α-bromostyrene in 84% yield.

General Procedure for Vinylic Phosphonate Preparation. To a 50-mL round-bottomed flask equipped with a short Vigreaux column topped with a Dean–Stark trap, a condenser, and a nitrogen inlet tube were placed 0.05 mol of the copper(I) halide complex of the trialkyl phosphite and 0.035 mol of the vinylic halide. The mixture was heated at 200 °C for 1 h, alkyl halide produced being collected in the Dean–Stark trap. After cooling to room temperature, the reaction mixture was poured into 60 mL of toluene. There was then added 5 mL of ethylenediamine dropwise with stirring. The solid material was filtered and washed with toluene, and the combined toluene portions were washed with 10 mL of 10% hydrochloric acid followed by 10 mL of water, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was chromatographed on silica gel (eluted with a hexane–ethyl acetate gradient) to separate the vinylic phosphonate and vinylic halide. The vinylic phosphonate was then vacuum distilled.

General Procedure for Halide-Exchange Reactions. To a 25-mL round-bottomed flask equipped with a condenser and nitrogen inlet tube were placed 0.02 mol of the copper(I) chloride complex of either triphenyl phosphite or triphenylphosphine and 0.018 mol of the vinylic bromide. The mixture was heated at 160–190 °C for 1.5 h. After the mixture cooled 25 mL of pentane was added. The solid material was filtered and washed with pentane; the solid material could be identified as the copper(I) bromide complex of either triphenyl phosphite or triphenylphosphine. The filtrate was concentrated under reduced pressure to give crude product which was purified by chromatography on silica gel, elution being performed with hexane.

Analysis. All IR spectra were measured by using a Perkin-Elmer 598 spectrophotometer, and NMR spectra were measured by using a Varian EM-360 instrument. Elemental analyses were performed by Guelph Chemical Laboratories and by Galbraith Laboratories.

Acknowledgment. This work has been supported by grants from the National Institutes of Health (GM 26988) and the PSC-BHE Research Award Program (RF 13354).

Registry No. (*E*)-Diethyl 2-(1-cyclohexenyl)vinylphosphonate, 78463-01-1; (*E*)-diisopropyl 2-(1-cyclohexenyl)vinylphosphonate, 78463-02-2; diethyl 1-phenylvinylphosphonate, 25944-64-3; diisopropyl 1-phenylvinylphosphonate, 79373-28-7; diethyl 2-phenylvinylphosphonate, 20408-33-7; diisopropyl 2-phenylvinylphosphonate, 78463-00-0; (*E*)-diethyl 2-phenyl-2-methylvinylphosphonate, 20408-29-1; (*Z*)-diethyl 2-phenyl-2-methylvinylphosphonate, 78462-97-2; (*E*)-diisopropyl 2-phenyl-2-methylvinylphosphonate, 78462-99-4; (*Z*)-diisopropyl 2-phenyl-2-methylvinylphosphonate, 78462-98-3; (*E*)-diethyl 2-phenyl-2-ethylvinylphosphonate, 78462-94-9; (*Z*)-diethyl 2-phenyl-2-ethylvinylphosphonate, 78462-93-8; (*E*)-diisopropyl 2-phenyl-2-ethylvinylphosphonate, 78462-96-1; (*Z*)-diisopropyl 2-phenyl-2-ethylvinylphosphonate, 78462-95-0; diethyl 2,2-diphenylvinylphosphonate, 78462-91-6; diisopropyl 2,2-diphenylvinylphosphonate, 78462-92-7; 1-chloro-2,2-diphenylethene, 4541-89-3; (*E*)-2-chlorostyrene, 4110-77-4; (*Z*)-1-chloro-2-phenylpropene, 16917-31-0; (*E*)-1-chloro-2-phenylpropene, 16917-32-1; (*Z*)-1-chloro-2-phenyl-1-butene, 78463-03-3; (*E*)-1-chloro-2-phenyl-1-butene, 64245-19-8; 1-bromo-2,2-diphenylethene, 13249-58-6; 1-chlorostyrene, 618-34-8; (*Z*)-1-bromo-2-phenyl-1-butene, 78463-05-5; (*E*)-1-bromo-2-phenyl-1-butene, 64245-20-1; (*Z*)-1-bromo-2-phenylpropene, 19647-26-8; (*E*)-1-bromo-2-phenylpropene, 16917-35-4; (*E*)-2-bromostyrene, 588-72-7; (*E*)-1-bromo-2(1-cyclohexenyl)ethene, 78463-06-6; 1-bromostyrene, 98-81-7; triisopropylphosphite–CuBr, 61918-60-3; triethylphosphite–CuBr, 72287-27-5; triethylphosphite–CuCl, 14221-63-7; triisopropylphosphite–CuCl, 39721-89-6; triphenylphosphite–CuCl, 24484-07-9; triphenylphosphine–CuCl, 22176-30-3.

Supplementary Material Available: Table IV containing C and H elemental analyses and Table V containing NMR and IR spectral data (6 pages). Ordering information is given on any current masthead page.

Reaction of Carbohydrate Halides with Magnesium. Novel C–C Coupling of Sugar Derivatives via Organometallic Intermediates[1]

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The reaction of 3-deoxy-3-*C*-(iodomethyl)-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**1c**) with sublimed magnesium in refluxing tetrahydrofuran gave dimer **2** and only traces of the 3-deoxy-3-methyl derivative **1d**. Similarly methyl 5-deoxy-5-iodo-2,3-*O*-isopropylidene-β-D-ribofuranoside (**3b**) afforded the 5–5′-coupled compound **4**, and 6-deoxy-6-iodo-1,2:3,4-di-*O*-isopropylidene-α-D-galactofuranose (**5a**) yielded the 6–6′-joined derivative **6**. 3-Deoxy-3-iodo-1,2-*O*-isopropylidene-DL-glycerol (**7b**) was also readily converted to dimer **8**. The interaction of **1c** with **3b** gave the unsymmetrical product **9** in addition to dimers **2** and **4**. Similarly, halogeno sugars **1c** and **5a** gave compound **10** along with derivatives **2** and **6**. Dimer formation was also predominant in reaction of iodide **1c** with magnesium in the presence of compounds such as benzonitrile or *N*-phthaloyl-L-phenylalanine 2-pyridyl thioester (**11a**), which otherwise effectively trap the Grignard reagents. Compound **11a** afforded smoothly the corresponding ketone **11b** after treatment with CH_3MgBr. On the other hand, 5′-deoxy-5′-iodo-2′,3′-*O*-isopropylidene-N^3-methyluridine (**3d**) gave neither dimer nor the Grignard reagent. In addition, the dimer formation from iodo derivative **1c** was inhibited in the presence of **3d**. Compound **2** resulted also from the reaction of **1c** with *n*-butyllithium in tetrahydrofuran, whereas the interaction of **1b** produced only 3-deoxy derivative **1d**. The possible reaction mechanism and the role of complexation in reactants and hypothetical transition states are discussed.

Reaction of alkyl or aryl halides with magnesium (Grignard reaction) is one of the most widely used methods of synthetic organic chemistry.[3] Applications of Grignard reagents in the carbohydrate field are also well docu-

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mented[4] but little information is available on organomagnesium compounds derived *from* a carbohydrate skeleton. It is clear that generation of such intermediates could have a considerable potential for synthesis of carbohydrates with a functionally modified sugar backbone. The latter might be useful for preparation of various analogues of carbohydrate-containing natural products, e.g., nucleosides, oligosaccharides, etc.

We have therefore explored the reactions of several representative types of properly protected carbohydrate halides with magnesium.

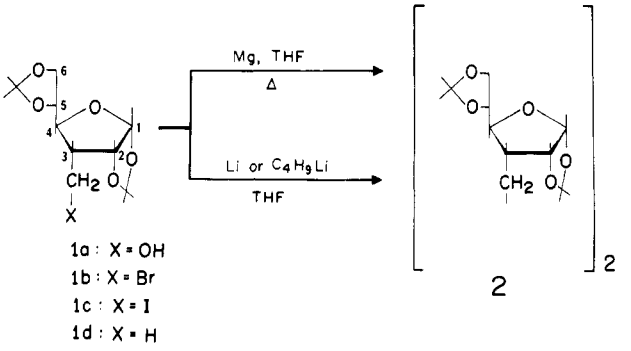
Results and Discussion

Starting Halogeno Sugars. At the outset, we selected three types of carbohydrate derivatives for study. Two of them, bromo and iodo compounds **1b** and **1c**, represent a furanose with a branched sugar skeleton, whereas derivative **3b** is a simple furanoside. The readily available iodo compound **5a** was selected as a type of a pyranose sugar. Finally, the iodoglycerol derivative **7b** does not formally belong among carbohydrates, but it is related to the simplest monosaccharides (trioses).

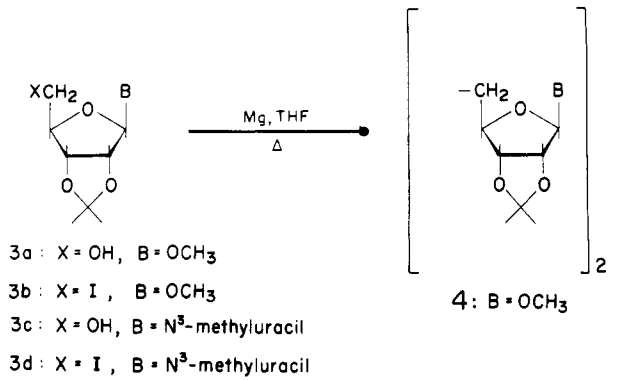
Compounds **1b** and **1c** were readily obtained from the corresponding hydroxy derivative **1a**. However, we were unable to repeat the described hydroboration–oxidation procedure[5] for preparation of **1a** from 1,2:5,6-di-*O*-isopropylidene-3-*C*-methylene-α-D-ribofuranose, which was obtained in crystalline form, on a large scale. In our hands, the reaction at room temperature for 4 h[5] gave less than 5% of product **1a**. When the recovered olefin was subjected to hydroboration–oxidation for 18 h at room temperature, the major product was 1,2-*O*-isopropylidene-3-deoxy-3-(hydroxymethyl)-α-D-allofuranose, which was identical with an authentic sample prepared by the method[6] described for the corresponding 3-deoxy-3-hydroxyethyl derivative. Reisopropylidenation with $ZnCl_2$ and acetone[7] led to the desired compound **1a** but in a low (27%) yield. We were unable to detect the 6-hemiacetal derivative claimed[5] to be a side product. The hydroxy derivative **1a** was readily obtained in 68% yield by performing the reaction with diborane at 4 °C overnight after the usual[5] work up.

For the preparation of the bromo sugar **1b** two routes were explored. Thus, the reaction of **1a** with CBr_4 and triphenylphosphine[8] gave **1b** in 60% yield, whereas the transformation effected with *N*-bromosuccinimide and triphenylphosphine[9] led to **1b** in 90% yield. The iodo derivatives **1c**, **3b**, and **7b** were obtained by the triflate exchange method.[10] The triflate intermediates were not isolated, but they were transformed in situ to the corresponding iodo compounds by the reaction with tetra-*n*-butylammonium iodide in 55–75% yield. The same procedure was applied for the preparation of the uridine derivative **3d**. Thus, 2′,3′-*O*-isopropylideneuridine was first methylated with dimethylformamide dimethyl acetal[11] to the corresponding *N*-methyl derivative **3c** in 95% yield. The latter was then converted to the 5′-iodo nucleoside **3d** in 60% yield.

Scheme I



Scheme II



Scope and Limitations of the Grignard Reaction with Halogeno Sugars. The reaction of iodo sugar **1c** with sublimed magnesium in refluxing tetrahydrofuran (THF) initiated by I_2 gave a 57% yield of the dimeric product **2** (Scheme I). In addition to the starting material **1c**, very little of the deoxy compound **1d** was detected by TLC in the mixture. The latter, apparently, arose from the reaction of the Grignard intermediate with water during TLC. An authentic sample of **1d** was obtained in 66% yield by hydrogenolysis of the bromo derivative **1b** according to a method[12] described for reduction of 5′-deoxy-5′-iodocytidine which yielded a product with properties (NMR, optical rotation) identical with those described.[13] Similar results were obtained with bromo compound **1b**. Thus, stirring of **1b** with magnesium in THF for several hours led to no products when the reaction was initiated with Br_2. However, the presence of dimer **2** and traces of **1d** were clearly evident on TLC after entrainment with I_2 or when the transformation was carried out in the presence of MgI_2. Thus, it is likely that conversion to the iodo derivative **1c** is a prerequisite for dimerization. Also, when the usual Mg turnings (Baker Chemical Co.) were used in conjunction with **1b** in ether or THF, no reaction was observed. Likewise, the attempted reaction of **1b** with sublimed magnesium in toluene in the presence of triethylamine[14] was unsuccessful.

Dimer formation has been observed before in Grignard reactions, but only rarely does this route become predom-

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(2) To whom correspondence should be addressed.

(3) (a) Kharasch, M. A.; Reinmuth, O. "Grignard Reactions of Nonmetallic Substances"; Prentice-Hall: New York, 1954. (b) Wakefield, B. J. *Organomet. Chem. Rev.* **1966**, *1*, 131.

(4) Grisebach, H.; Schmid, R. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 159.

(5) Rosenthal, A.; Sprinzl, M. *Can. J. Chem.* **1969**, *47*, 4477.

(6) Rosenthal, A.; Nguyen, L. *J. Org. Chem.* **1969**, *34*, 1029.

(7) Schmidt, O. T. In "Methods in Carbohydrate Chemistry"; Academic Press: New York, 1963; Vol. II, p 320.

(8) Verheyden, J. P. H.; Moffatt, J. G. *J. Org. Chem.* **1972**, *37*, 2289.

(9) Ponpipom, M. M.; Hanessian, S. *Carbohydr. Res.* **1971**, *18*, 342.

(10) Binkley, R. W.; Ambrose, M. G.; Hehemann, D. G. *J. Org. Chem.* **1980**, *45*, 4387.

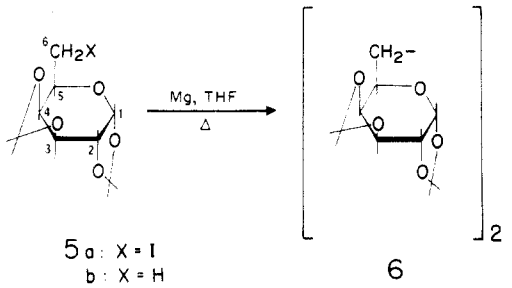
(11) Žemlička, J. *Collect. Czech. Chem. Commun.* **1970**, *35*, 3572.

(12) Verheyden, J. P. H.; Moffatt, J. G. *J. Am. Chem. Soc.* **1970**, *35*, 2868.

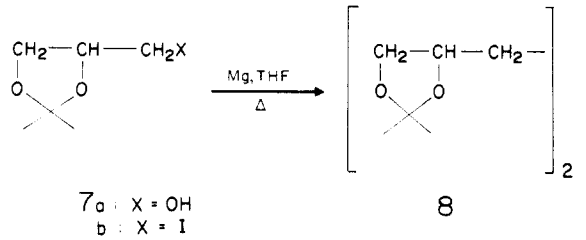
(13) Rosenthal, A.; Sprinzl, M. *Can. J. Chem.* **1969**, *47*, 3941.

(14) Ashby, E. C.; Reed, R. *J. Org. Chem.* **1966**, *31*, 971.

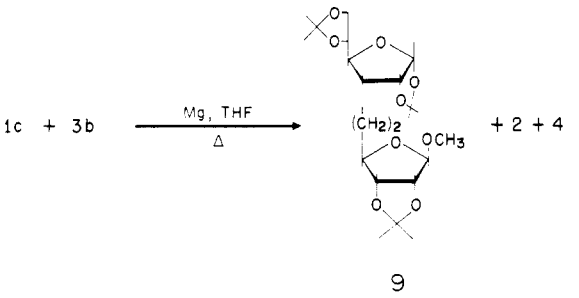
Scheme III



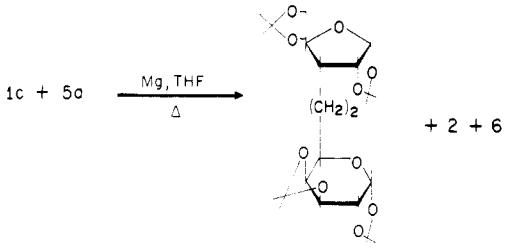
Scheme IV



Scheme V



Scheme VI

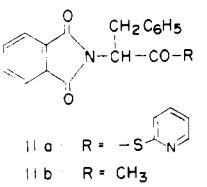


inant except in cases of stabilized radicals[15] or induced couplings[16] in the presence of transition-metal ions (Co^{2+}). Experiments with additional carbohydrate derivatives have shown that dimer formation is the rule rather than the exception in the sugar series. Thus, iodoribofuranoside[10] **3b** gave, after refluxing with sublimed magnesium in THF for 5 h, the corresponding dimer **4** (Scheme II) in 68% yield. By contrast, the corresponding reaction of nucleoside derivative **3d** did not afford any Grignard reagent or dimer. Significantly, when sugar derivative **1c** was coupled in the presence of **3d**, no dimer **2** was observed. It is generally agreed[17] that Grignard reactions involve radical intermediates, and, on this basis, our observation is readily explained: the nucleoside **3d** probably acted as a scavenger of free radicals, thus inhibiting the reaction of **1c**.

Dimer formation is not limited to the furanose series. Thus, iodo galactose derivative **5a**, when refluxed with magnesium in THF for 6 h, afforded the dimer **6** (Scheme III), albeit in lower (31%) yield. In addition, a 4% yield of deoxy compound **5b** was obtained and a significant portion of unreacted **5a** was recovered. Compound **5b** proved to be identical with an authentic sample prepared by hydrogenolysis of **5a** in 41% yield and exhibited properties (NMR,[18] optical rotation[19]) indistinguishable from those of the previously described material. Iodo derivative[20] **7b** was the simplest model investigated; it contains only one isopropylidene group and a single center of asymmetry. However, the formation of a dimer (**8**, Scheme IV) was predominant also in this case (70% yield). Thus, compound **8** was readily obtained in two simple steps from commercially available solvent (Solketal) in almost 40% overall yield. It is of interest to note that our method constitutes a new approach to 1,2,5,6-hexanetetrol whose acetal derivatives similar to **8** are used as plasticizers.[21] The parent compound itself is available only by difficult or multistep procedures from less readily accessible starting materials.[22-25]

We have also examined the possibility of formation of unsymmetric dimers by the reaction of an equimolar mixture of two different iodo derivatives with magnesium in THF. Thus, the two furanose derivatives **1c** and **3b** smoothly afforded the mixed dimer **9** in 53% yield (Scheme V). Symmetric dimers **2** and **4** were also present in the reaction mixture. Statistically, the formation of mixed dimer **9** should be favored, with the ratio of products **2**, **4**, and **9** being 1:1:2. Consequently, a 50% yield of **9** is to be expected which is in good agreement with the observed value. The reaction is also applicable to the synthesis of mixed dimers of furanoses and pyranoses. Thus, the refluxing of an equimolar mixture of **1c** and **5a** with magnesium in THF for 8 h gave the unsymmetrical derivative **10** in 51% yield (Scheme VI), which is again in good agreement with the value determined on statistical grounds. When a similar coupling reaction was attempted with bromofuranose **1b** and iodide **5a**, the symmetric dimer derived from **1b** was virtually absent, and the unsymmetric derivative **10** was obtained in 8% yield. This, again, indicates that iodides are more reactive in the coupling reaction with magnesium than bromides, a trend observed earlier for similar exchange reactions with simple alkyl groups.[15,26]

It appears that dimerization of carbohydrate moieties is the favored transformation even in the presence of Grignard reagent trapping substances. On the one hand, the very reactive[27] thioester **11a** smoothly gave with



CH_3MgBr in THF the expected ketone **11b** in 76% yield. However, when the reaction of iodo derivative **1c** with magnesium in THF was run in the presence of **11a**, dimer

(15) Reference 3a, p 131.
(16) Reference 3a, p 1056.
(17) Schaart, B. J.; Blomberg, C.; Akkerman, O. S.; Bickelhaupt, F. *Can. J. Chem.* **1980**, *58*, 932 and references therein.
(18) Cone, C.; Hough, L. *Carbohydr. Res.* **1965**, *1*, 1.
(19) Freudenberg, K.; Raschig, K. *Ber.* **1927**, *60*, 1633.
(20) Jung, M. E.; Shaw, T. J. *J. Am. Chem. Soc.* **1980**, *102*, 6304.
(21) U.S. Patent 3 232 907, 1966; *Chem. Abstr.* **1966**, *64*, P11234*b*.
(22) Gorin, P. A. J.; Perlin, A. S. *Can. J. Chem.* **1958**, *36*, 661.
(23) Belgian Patent 626 582, 1963; *Chem. Abstr.* **1964**, *60*, P9250*a*.
(24) Brettle, R.; Latham, D. W. *J. Chem. Soc. C* **1968**, 906.
(25) Deane, C. C.; Inch, T. D. *J. Chem. Soc. D* **1969**, 813.
(26) Zakharkin, L. I.; Okhlobystin, O. Y.; Bilevitch, K. A. *J. Organomet. Chem.* **1964**, *2*, 309.
(27) Almquist, R. G.; Chao, W. R.; Ellis, M. E.; Johnson, H. L. *J. Med. Chem.* **1980**, *23*, 1392.

Table I. NMR Constants ($CDCl_3$) and Optical Rotations ($[\alpha]^t_D$ ($CHCl_3$)) of Starting Materials and Reaction Products

compd[a]	chemical shifts, δ (no. of protons, multiplicity) H_1	H_2	H_3	H_4	H_5	H_6	CCH_3	$J_{1,2}$, Hz	$[\alpha]^t_D$, deg[b]	c
1b	5.78 (d, 1)	4.78 (t, 1)	2.38 (m, 1)	3.98, 3.62[c] (2 m, 6)			1.53, 1.40, 1.36, 1.34 (4 s, 12)	3.4	+95.0[d]	1
1c	5.74 (d, 1)	4.72 (t, 1)	2.30 (m, 1)	3.26 (q[e])	3.98, 3.54[c] (2 m, 6)		1.52, 1.40, 1.34 (3 s, 12)	3.4	+119.6	0.5
2[f]	5.74 (d, 2)	4.76 (d, 2)	1.83[g] (m, 6)	3.92[h] (m, 10)			1.44, 1.36, 1.29 (3 s, 24)	3.7	+87.2	0.25
3b	5.05 (s, 1)	4.77[i] (d, 1)	4.62[i] (d, 1)	4.45 (q, 1)	3.22[j] (m, 2)		1.48, 1.33 (2 s, 6)	0	−67.3[k]	1
3c[l]	5.57 (s, 1)	5.01 (t, 2)		4.31, 3.90[m] (q + m, 3)			1.59, 1.36 (2 s, 6)	2.4		
3d[n]	5.66 (d, 1)	5.02[o] (dd, 1)	4.80[p] (dd, 1)	4.24 (m, 1)	3.42[q] (m, 2)		1.57, 1.36 (2 s, 6)	2.2		
4	4.94 (s, 2)	4.55 (q, 4)		4.25[h] (t, 2)	1.65[h] (m, 4)		1.47, 1.31 (2 s, 12)	0	−53.2	1.14
6	5.51 (d, 2)	4.23[r] (m, 4)	4.57 (dd, 2)		3.74 (t, 2)	1.76 (m, 4)	1.50, 1.45, 1.33, 1.31 (4 s, 24)	5.1	−66.1	0.8
8[s]	4.03, 3.52 (2 m, 6)		1.64 (m, 4)		*t*	*t*	1.40, 1.35 (2 s, 12)			
9[u] A	5.74 (d, 1)	4.59[v] (m, 3)	1.80[w] (m, 5)				1.48, 1.41, 1.34, 1.32 (4 s, 18)	3.7	+30.9	0.6
R	4.95 (s, 1)			3.99[x] (m, 5)				0		
10[y] F	5.73 (d, 1)	4.64[z] (t, 2)	1.74[δ] (m, 5)		4.32-3.75[β] (cluster of m, 7)		1.51, 1.49, 1.47, 1.41, 1.35, 1.31 (6 s, 24)	3.7		
P	5.54 (d, 1)		4.59[γ] (dd)					5.1	+3.4	2

[a] Satisfactory analytical data (C, H, N, and halogen where appropriate, ± .3%) were obtained for all new compounds. [b] Measured at 22 °C unless stated otherwise. [c] Includes 3-CH_2. [d] Measured at 28 °C. [e] For integration see H_5 and H_6. [f] Measured in CD_3COCD_3. [g] Overlapped with 3-CH_2. [h] Poorly resolved. [i] These values differ from those reported.[10] $J_{2,3} = J_{3,2} = 5.9$ Hz. [j] Partially overlapped with δ 3.37 (s, 3, OCH_3). [k] The literature[40] gives −68.6°. [l] δ 7.36 (d, 1, H_6, uracil), 5.78 (d, 1, H_5, uracil), $J_{6,5} = J_{5,6} = 8.1$ Hz. The δ values for H_6, $H_{1'}$ and $J_{1',2'}$ differ from those reported.[41] [m] δ 3.32 (s, 3, NCH_3). [n] δ 7.31 (d, 1, H_6, uracil), 5.79 (d, 1, H_5, uracil). For $J_{6,5}$ and $J_{5,6}$ see *l*. [o] $J_{2,1} = 2.2$ Hz. [p] $J_{2,3} = J_{3,2} = 6.6$ Hz; $J_{3,4} = 3.7$ Hz. [q] Partially overlapped with δ 3.31 (s, 3, NCH_3). [r] Overlapped with H_4. [s] Noncarbohydrate nomenclature and numbering; see the Experimental Section. [t] See $H_1 + H_2$. [u] A = allofuranose, R = ribofuranose portion. [v] Overlapped with $H_2 + H_3$ (R). [w] Overlapped with 3-CH_2 (A) and H_5 (R). [x] Overlapped with $H_4 + H_5 + H_6$ (A), δ 3.37 (s, 3, OCH_3). [y] F = furanose, P = pyranose portion. [z] Partially overlapped with H_3 (P). [α] Overlapped with 3-CH_2 (F) and H_6 (P). [β] $H_4 + H_5 + H_6$ (F) and $H_2 + H_4 + H_5$ (P). [γ] Overlapped with H_2 (F).

2 was practically the only product containing a carbohydrate moiety, and the expected keto derivative was absent. A similar result was obtained when thioester **11a** had been replaced by benzonitrile.

In view of the accumulated evidence[26,28] for a mechanistic link between the Grignard and other organometallic reagents, we have examined the reaction of halides **1b** and **1c** with lithium metal and *n*-butyllithium. Thus, the only product obtained from the interaction of **1b** with *n*-butyllithium in low yield was the deoxy compound **1d**. No dimer **2** was found, and attempts to trap the organolithium intermediate by the reaction with lithium *N*-phthaloyl-L-phenylalaninate[29] were not successful. By contrast, the reaction of iodo derivative **1c** with *n*-butyllithium gave only a small amount of **1d**, and dimer **2** was the major product. Similar results were obtained when *n*-butyllithium was replaced by lithium metal; only a significant portion of **1c** remained unchanged. As in the case of the reaction effected by magnesium, the coupling reactivity decreases from iodide to bromide. The cleavage of the furanose ring was observed in neither case. By contrast, 6-bromo-6-deoxy perbenzylated pyranosides[30] suffered extensive ring cleavage during reaction with *n*-butyllithium, and a degradation of compound **7b** was also noted under similar conditions.[20]

Structure of Coupling Products. The NMR and mass spectra provided the necessary confirmation of the structures of the carbohydrate dimers. The relevant data are summarized in Table I and II. In the case of symmetric dimers **2**, **4**, **6**, and **8**, marked upfield shifts (Table I) of the resonances at the carbon atoms, where the covalent C–C linkage was formed, relative to those in starting halogeno derivatives were of particular diagnostic value. NMR spectra of dimers **2**, **4**, and **6** indicate a perfect symmetry of the molecule.

These assignments were corroborated by mass spectroscopy. The mass spectra of all isopropylidene derivatives in this study, as expected,[31] failed to exhibit molecular ion peaks (Table II) but invariably showed the presence of the diagnostic[10,31] M − 15 ion derived by cleavage of the methyl radical from the isopropylidene group in a significant abundance. The exception was dimer **4** which gave only traces of M − 15. The appearance of other fragments, especially those in the lower mass region, followed basically the pattern found in other isopropylidene derivatives of carbohydrates.[31] Of particular significance are the peaks M − 15 − 58 (A) derived by elimination of acetone from the M − 15 fragment and M − 15 − 60 (B) which arose by a loss of CH_3COOH. It was pointed out[31] that elimination of acetone from a diisopropylidene derivative must occur at a site different from that undergoing a methyl radical cleavage. Thus, it is not surprising that tetraisopropylidene derivatives such as **2** or **6** can generate ions M − 15 − 2 ×

(28) The suggested[26] ionic mechanism is, however, a less favored alternative.[17]

(29) Jorgenson, M. J. In "Organic Reactions"; Wiley: New York, 1970; Vol. 21, p 1.

(30) Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1979**, *62*, 1990.

(31) DeJongh, D. C.; Biemann, K. *J. Am. Chem. Soc.* **1964**, *86*, 67.

Table II. Selected Ions from the Mass Spectra of Starting Materials and Reaction Products[a]

compd	m/e (relative intensity)											
	M − 15	A	B	C	D	E	F	G	H	I	J	K
1b[b]	323, 321 (39.1, 38.9)	265, 263 (1.6, 1.8)		237, 235 (11.1, 11.2)		205, 203 (8.6, 7.3)	179, 177 (10.3, 12.9)					
1c	369 (79.3)	311 (1.1)		283 (34.8)		251 (13.2)	225 (30.3)					
1d	243 (100.0)	185 (6.7)		157 (85.7)		125 (50.7)	99 (73.6)					
2	499 (34.7)	441 (14.3)			383 (2.5)		355 (59.3)	325 (3.1)	323 (0.8)	297 (14.0)	265 (5.2)	239 (12.6)
4	359 (2.5)					241 (6.0)						
5b	229 (103.7)	171 (46.4)	169 (2.8)			111 (71.2)						
6	471[c] (79.0)	413 (13.3)			355 (12.8)				295 (22.1)		237 (10.8)	
8	215[d] (100.0)	157 (72.1)				97 (63.3)	71 (11.0)					
9	429 (100.0)	371 (6.6)		343 (7.1)	313 (1.4)	311 (36.2)	285 (64.9)		253 (62.7)	227 (6.6)		
10	485 (55.9)	427 (13.9)		399 (16.0)	369 (4.7)		341 (30.3)	311 (1.6)	309 (6.7)	283 (67.2)	251 (5.7)	225 (10.1)

[a] Low-mass ions such as m/e 113, 101, 100, 85, 59, 43, and others commonly found in isopropylidene pentoses and hexoses[31] are not listed. A = M − 15 − 58, B = M − 15 − 60, C = M − 101, D = M − 15 − 2 × 58, E = M − 15 − 60 − 58, F = M − 101 − 58, G = M − 15 − 3 × 58, H = M − 15 − 60 − 2 × 58, I = M − 101 − 2 × 58, J = M − 15 − 60 − 3 × 58, K = M − 101 − 3 × 58. [b] The doubling of m/e reflects the isotopic contribution of ^{79}Br and ^{81}Br. [c] m/e 428 (1.0, M − 58), 370 (12.3, M − 2 × 58), 312 (3.8, M − 3 × 58). [d] m/e 101 (39.1, cleavage of C_2-C_3), 114 (7.4, M − 2 × 58), 115 (24.7, M/2, cleavage of C_3-C_4).

Table III. Molecular Rotations [M] of Carbohydrate Dimers

compd	$[M]_{calcd}$,[a] deg	$[M]_{found}$, deg
2		+448.7
4		−199.2
6		−321.6
9	+124.8	+137.4
10	+63.6	+17

[a] Obtained from values for the corresponding symmetric dimers D_1 and D_2: $D_1 + D_2/2$. $[M] = [\alpha]M/100$.

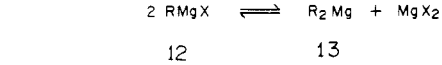
58 (D) and M − 15 − 3 × 58 (G) found in the respective mass spectra.

In dimers, **2**, **9**, and **10**, which all gave an abundant m/e 101 fragment resulting from the cleavage of C_4–C_5 bond, ions M − 101 − 58 (F) and M − 101 − 2 × 58 (I) are also found. However, M − 101 (C) was missing in **2**, but it was present in both unsymmetrical dimers **9** and **10**. As expected, fragment M − 101 − 3 × 58 (K) observed in the mass spectra of **2** and **10** was absent in **9**. The NMR spectra of compounds **9** and **10** clearly showed both carbohydrate moieties (Table I) and they were in complete agreement with conclusions derived from mass spectroscopy.

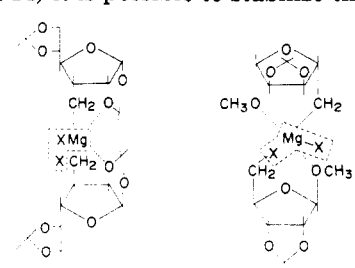
The structure of dimers **9** and **10** resembles somewhat the sugar–phosphate–sugar backbone found in nucleic acids, and, therefore, helicity effects could, at least theoretically, be expected. In that respect, a comparison of molecular rotations, [M], of unsymmetrical dimers **9** and **10** may be of interest (Table III). It can be seen that whereas [M] of compound **9** is close to the calculated value, a significant difference was observed in dimer **10**. A hypothetical helical contribution to the molecular rotation seems, therefore, greater in the furanose–pyranose dimer **10** than in the furanose–furanose derivative **9**. However, more data are necessary to support such a generalization.

Reaction Path. Although the purpose of our study was to investigate the scope of the reaction of halogeno carbohydrates with magnesium, some comments on the possible mechanism seem appropriate. As noted earlier, dimer formation was frequently observed during formation of more simple Grignard reagents capable of generating stabilized free radicals.[15] In such cases, iodides are more reactive than bromides, which is also the trend observed in this study. It is more difficult, however, to estimate radical stabilization in the complex polyoxygenated carbohydrate molecules. Clearer insights seem to derive from a consideration of magnesium complexes which may be involved in the reaction. Thus, any Grignard reagent can be viewed as an equilibrium mixture[32] of species **12** and **13** (Scheme VII). However, there is little to suggest that the dialkylmagnesium compound **13** is responsible for the reaction. It is more reasonable to assume that the coupling involves the Grignard reagent and unreacted halogeno sugar. Space-filling models have shown for all cases described in this study that an extensive stabilization by formation of magnesium complexes is possible in the corresponding transition state but not in the individual components. Thus, in the Grignard reagent derived from **1c** (formula **14**) it is possible to stabilize the magnesium

Scheme VII



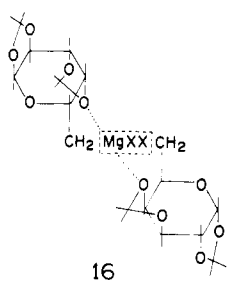
12 13



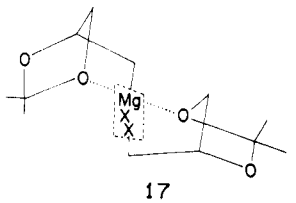
14 15

(32) Reference 3a, p 104.

complex by either O-2 or O-5, but not both at the same time. However, in the transition state (formula 14) full stabilization is feasible. Similar complexes can be invoked for other carbohydrate types included in our study (formulas 15 and 16). Less obvious is the possibility of sta-



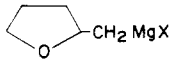
16



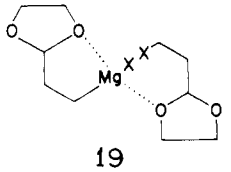
17

bilization in the magnesium complex derived from glycerol derivative **7b**. The structure 17 will be probably strained but similar sugar derivatives of norbornane type are quite stable.[33]

We have shown that the tendency toward dimer formation is surprisingly strong, and it cannot be overcome even by the presence of some very reactive Grignard-trapping agents such as thioester **11a**. This could add some weight to the argument that the stabilization of the transition state by magnesium complexes plays an important role. However, other data have indicated that this is not the only factor involved. Thus, reaction of bromo and iodo sugars **1b** and **1c** with *n*-butyllithium led to a significant formation of dimer **2**, although the possibility of stabilization of organolithium intermediates along the lines outlined for the magnesium complexes appears to be remote. In addition, (tetrahydrofuryl)methyl bromide, which can be considered as a simplified model of furanose devoid of exocyclic oxygen atoms, apparently afforded a "normal" Grignard reagent (formula 18) although an extensive



18



19

cleavage of the ring was observed.[34] A case somewhat related to our model **7b** also deserves some comment. Thus, 2-(2-bromoethyl)-1,3-dioxolane afforded the Grignard reagent, capable of stabilization by complexation (formula **19**), in at least 35% yield, and no formation of dimer has been reported.[27] However, the β-halogenoalkyl moiety is not attached to the "carbohydrate portion" which makes this case different from those reported in our study.

The C–C coupling reaction described above has inter alia a potential for synthesis of oligosaccharide analogues where the glycosidic oxygen will be replaced with a methylene group.

Experimental Section

General Procedures. All solvents and starting materials used were of the highest available purity or they were purified as specified. Tetrahydrofuran (THF) was distilled from $LiAlH_4$ or CaH_2, and it was kept over a sodium ribbon in the dark. Dimethylformamide (DMF) was distilled from P_2O_5, and it was stored over Linde molecular sieves (4A). TLC was performed on 6 × 2 cm precoated TLC sheets of silica gel 60 F_{254} (Merck) in the following solvents: S_1, benzene–ethyl acetate (EtAc), 9:1; S_2, benzene–EtAc, 1:1; S_3, benzene–EtAc, 3:2; S_4, CH_2Cl_2–CH_3OH (94:6); S_5, CH_2Cl_2–CH_3OH, 97:3; S_6, toluene–EtAc, 2:1; S_7, toluene–EtAc, 3:2; S_8, toluene–EtAc, 3:1; S_9, toluene–EtAc (4:1). Non-UV-absorbing carbohydrate derivatives were detected by charring (spraying with 10% $HClO_4$ and heating on a hot plate). For column chromatography silica gel 60 (70–230 mesh ASTM, Merck) was used. NMR spectra were obtained with an FX-100 Fourier transform NMR spectrometer (JEOL Ltd.) in $CDCl_3$ as solvent and $Si(CH_3)_4$ as an internal reference unless specified otherwise. Electron-impact mass spectra were determined with a JMS 01SG-2 or JMSD-100 mass spectrometer (JEOL Ltd.). Each spectrometer is interfaced with a gas chromatograph which permitted, in suitable cases, GC/MS analysis of products as an additional criterion of purity. For characterization of compounds, cf. Table I (NMR spectra and optical rotations) and Table II (mass spectra). Elemental analyses were performed by M-H-W Laboratories.

Starting Materials. For most experiments, sublimed magnesium (Dow Chemical Co.) was used. This material was powdered by filing with a new steel file.

***N*-Phthaloyl-L-phenylalanine 2-pyridyl Thioester (11a).** This compound was prepared by the dicyclohexylcarbodiimide method[35] in 90% yield: mp 102–104 °C (lit.[35] mp 103–105 °C), 104–107 °C, after recrystallization; $[\alpha]^{24}_D$ –229.7° (*c* 1, DMF) (lit.[35] $[\alpha]^{20}_D$ –237°).

Lithium *N*-Phthalyl-L-phenylalaninate. *N*-Phthaloyl-L-phenylalanine (0.59 g, 2 mmol) in water (15 mL) was neutralized with magnetic stirring by the addition of LiOH (1.95 mmol) in water (5 mL, pH 7–7.5). Additional acid (20 mg, 0.07 mol) was added to ensure that all the LiOH reacted. The excess acid was extracted with ether (4 × 15 mL). The aqueous phase was evaporated, the residue was co-evaporated several times with ethanol, and the resultant white solid was dried at 100 °C (0.01 mmHg) for 3 h. The yield was 0.56 g (95% based on LiOH used).

1,2:5,6-Di-*O*-isopropylidene-3-*C*-methylene-α-D-ribohexofuranose. The procedure described[13] on a 3.3-mmol scale was run routinely with 80–170 mmol of the starting material. For this purpose, the method was modified as follows. The crude product obtained from 34.5 g (0.14 mol) of ketone, after removal of triphenylphosphine oxide by filtration, was chromatographed on a column of silica gel (140 g, 17 × 4.5 cm) by using benzene as an eluant, and the fractions (50–100 mL) were monitored by TLC in solvent S_1. The UV-absorbing material was removed in the first 325-mL volume. Further elution with benzene (400 mL) followed by solvent S_1 (300 mL) gave, after evaporation and crystallization of the residue from petroleum ether, 20 g (58%) of the title product: mp 29–31 °C; $[\alpha]^{28}_D$ +102.4° (*c* 1, $CHCl_3$). The literature reports[13] $[\alpha]^{22}_D$ +104° for an oil. The NMR and mass spectra were identical with those described.[13,36]

3-Deoxy-3-*C*-(hydroxymethyl)-1,2:5,6-diisopropylidene-α-D-allofuranose (1a). We were unable to reproduce the described procedure[5] on a 23-mmol scale, and, therefore, the method was modified as follows. Diborane (1% in N_2; Union Carbide, Cryogenic Gases Division) was introduced with magnetic stirring into a solution of methylene sugar from the previous experiment (3.5 g, 13.7 mmol) in THF (30 mL) at 4 °C. The progress of the reaction was checked by removal of 0.2-mL aliquots which were treated with water, with 2 N NaOH, and with 30% H_2O_2, kept at room temperature for 5 min, and evaporated in vacuo. The residues were subjected to TLC in solvent S_2. The reaction mixture was stored overnight at 4 °C. TLC showed that the hydroboration was 90% complete. Aqueous THF (50%, 14 mL) was then added dropwise at 4 °C followed by 2 N NaOH (41.4 mL) and H_2O_2 (30%, 24 mL). The resultant milky white mixture was warmed to room temperature and stirred for an additional 1 h. Evaporation in vacuo afforded a gum which was partitioned between water (100 mL) and ether (4 × 50 mL). The dried ($MgSO_4$) ether extracts were evaporated to an oil (3.5 g) which was chromatographed on a silica gel column (110 g, 50 × 2.6 cm)

(33) (a) Doerr, I. L.; Codington, J. F.; Fox, J. J. *J. Org. Chem.* **1965**, *30*, 467. (b) Köll, P.; Deyhim, S. *Chem. Ber.* **1978**, *111*, 2913 and references therein.

(34) (a) Paul, R. *Bull. Soc. Chim. Fr.* **1933**, [4] *53*, 417. (b) Robinson, R.; Smith, L. H. *J. Chem. Soc.* **1936**, 195.

(35) Lloyd, K.; Young, G. T. *J. Chem. Soc. C* **1971**, 2890.

(36) Glangetas, A.; Gulacar, F. O., Tronchet, J. M. J.; Buchs, A. *Helv. Chim. Acta* **1980**, *63*, 1740.

in solvent S_3. The fractions (7 mL each) were examined by TLC in solvent S_2, and those containing only product **1a** (fractions 38–61) were pooled and evaporated to give 2.55 g (68%) of **1a**, mp 49–50 °C. The literature[5] reports **1a** as a sirup. The NMR spectrum was identical with that reported in the literature.[5]

Two further preparations run on a 38-mmol scale when combined gave an overall yield of 16 g (77%).

3-*C*-(Bromomethyl)-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (1b). (A) Using CBr_4 and Triphenylphosphine. Triphenylphosphine (2.02 g, 7.7 mmol) and CBr_4 (2.69 g, 8.09 mmol) each in DMF (10 mL) were added with magnetic stirring to the solution of compound **1a** (2.11 g, 7.7 mmol) in DMF (10 mL), cooled externally by an ice bath, at such a rate that the temperature of the mixture did not exceed 10 °C. The stirring was then continued for 24 h at room temperature. Because TLC (S_2) showed no reaction, the solvent was evaporated in vacuo, the residue was dissolved in DMF (30 mL), and new reactants (see above) were added. The mixture was kept for 3 days at room temperature, whereupon only a little of **1a** remained. The solution was evaporated, and the oily residue was dissolved in solvent S_3, filtered, and chromatographed on a silica gel column (100 g, 40 × 2.6 cm) in the same solvent. The product was crystallized from petroleum ether and dried at 0.1 mm at room temperature overnight: yield 1.6 g (61%) of **1b**; mp 65–68 °C.

(B) Using *N*-Bromosuccinimide and Triphenylphosphine. *N*-Bromosuccinimide (592 mg, 3.4 mmol) and triphenylphosphine (890 mg, 3.4 mmol) in DMF (10 mL) were added to compound **1a** (822 mg, 3 mmol) in DMF (10 mL) at 0 °C with magnetic stirring which continued 1 h at room temperature. TLC (S_2) revealed the presence of ca. 30% of **1b**. The reaction was completed by heating at 50 °C for 1 h. The solution was evaporated in vacuo, and the residue was chromatographed on a silica gel column (28 g, 36 × 1.5 cm) in solvent S_3 as in method A. The obtained product was crystallized from petroleum ether to give 905 mg (90%) of **1b** (mp 65–68 °C) identical (TLC, NMR and mass spectra) with the material prepared by method A.

3-Deoxy-3-*C*-(iodomethyl)-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (1c). Compound **1a** (274 mg, 1 mmol) was dissolved in a mixture of CH_2Cl_2 (5 mL) and pyridine (79 mg, 1 mmol). The solution was cooled to 0 °C, and trifluoromethanesulfonic anhydride (310 mg, 1.1 mmol) was then added with magnetic stirring from a syringe in 0.2-mL portions over a period of 15 min. TLC (S_3) showed an almost complete reaction (formation of the trifluoromethanesulfonate). The solution was cooled to −78 °C with a dry ice–2-propanol mixture, and tetra-*n*-butylammonium iodide (369 mg, 1 mmol) was added with stirring which was continued for another 90 min at room temperature. TLC (S_3) showed an almost complete conversion to product **1c**. The mixture was then chromatographed on a silica gel column (25 g, 30 × 1.6 cm) in solvent S_3, and 5-mL fractions were collected and examined by TLC in the same solvent. Fractions 8–12 were combined and evaporated to give 280 mg (73%) of **1c**, mp 75–76 °C. This material was crystallized for analysis from petroleum ether; mp 76–77 °C.

Methyl 5-Deoxy-5-iodo-2,3-*O*-isopropylidene-β-D-ribofuranoside (3b). This compound was prepared by a modification of the method described for the synthesis of derivative **1c** using starting sugar **3a** (612 mg, 3 mmol). Trifluoromethanesulfonic anhydride was added at −6 °C over a period of 10 min, and the reaction was complete in 20 min at −6 °C. After addition of iodide, the mixture was stirred for 1 h at −78 °C, 1 h at room temperature, and, finally, 1 h at 50 °C. After evaporation of the solvent, the crude product was chromatographed on a column of silica gel (25 g, 30 × 1.6 cm) in solvent S_3. The appropriate fractions were evaporated to give **3b** as an oil (710 mg, 75%) containing, according to GC/MS, a trace of trifluoromethanesulfonate as the only impurity. The mass spectrum contained fragments described in the literature.[10]

2',3'-*O*-Isopropylidene-N^3-methyluridine (3c). The solution of 2',3'-*O*-isopropylideneuridine (1.42 g, 5 mmol) and dimethylformamide dimethyl acetal (6.6 mL, 50 mmol) in DMF (25 mL) was magnetically stirred for 48 h at room temperature, and then it was heated at 90 °C for 2 h. The solvent was evaporated, and the residue was crystallized from ethyl acetate–petroleum ether: yield 1.4 g (95%); mp 103–105 °C. Melting point values in the literature vary from 133.5–134[37] to 182–183 °C.[38]

5'-Deoxy-5'-iodo-2',3'-*O*-isopropylidene-N^3-methyluridine (3d). The triflate displacement method was followed (see compound **1c**) by starting from **3c** (1 g, 3.7 mmol), the reaction temperature during triflation was maintained between −7 and +5 °C, and the progress of the reaction was monitored by TLC in solvent S_4. The displacement with iodide was also performed as described: 1 h at −78 °C and overnight at −20 °C. After warming to 0 °C, the mixture was extracted with water (2 × 30 mL, 0 °C), the organic layer was evaporated, and the resultant oil was chromatographed on a silica gel column (26 g, 36 × 1.5 cm) in solvent S_5 to give a pale yellow oil, **3d**, ca. 93% pure according to GC/MS. This material was dissolved in ethanol, and the solution was decolorized with Norite and evaporated to give a colorless oil which was converted to a white foam at 0.02 mm and room temperature; yield 0.92 g (61%) of **3d**.

2,2-Dimethyl-4-(iodomethyl)-1,3-dioxolane (7b). The method for preparation of compound **1c** was modified as follows. The reaction of **7a** (Solketal, 792 mg, 6 mmol) with trifluoromethanesulfonic anhydride at −20 °C and the subsequent displacement with iodide were performed as described before. The R_f values of the trifluoromethanesulfonate and compound **7b** (solvent S_3) were close, but the latter was readily detected as a weakly UV-absorbing spot. The mixture was kept at −78 °C for 1 h and then at room temperature until it reached a deep orange color. The workup followed the usual procedure, and the crude product was purified by column chromatography on silica gel (25 g, 1.5 × 38 cm) in solvent S_6. Fractions of 5 mL were collected, and fractions 23–37 were pooled and evaporated to give compound **7b** as a pale yellow oil, 850 mg (55%). The NMR and mass spectra were very similar to those reported.[20]

Coupling of Carbohydrate Halides by Using Magnesium in THF. (A) General Procedure for Symmetric "Dimers". The appropriate halide (ca. 0.5 mmol) was dissolved in THF (2 mL), and freshly powdered sublimed Mg (4 equiv) was added followed by a crystal (1–2 mg) of I_2. The mixture was then magnetically stirred in an atmosphere of dry N_2 for several hours at room temperature. TLC in solvent S_7 unless stated otherwise, revealed little or no reaction and, therefore, refluxing was commenced which was continued for several hours. A drying tube filled with P_2O_5 was attached to the condenser. After cooling, the solids were removed by filtration and were washed with THF, and the filtrate was evaporated in vacuo to give an oily residue. The latter was chromatographed on a column of silica gel (26 g, 35 × 1.5 cm) to give the appropriate dimer which was crystallized from petroleum ether. All products were pure according to TLC and GC/MS unless stated otherwise.

1,2-Bis(3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranos-3-yl)ethane (2). The reaction time was 2 h at room temperature and 8 h reflux. Chromatography in solvent S_7 yielded 57% of **2**, mp 127–128 °C.

5,5'-Bis(methyl-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranose) (4). The starting materials were **3b** (0.86 mmol) and Mg (2.6 mmol) (5 h reflux). The reaction products were chromatographed in solvent S_8. Compound **4** was obtained as an oil in 68% yield.

Attempted Dimerization of Iodo Nucleoside 3d. Compound **3d** (0.25 g, 0.6 mmol) and Mg (58 mg, 2.4 mmol) were refluxed in THF (2 mL) for 4 days after the usual entrainment with I_2. TLC (S_4) revealed that ca. 85% of the starting material was unchanged in addition to the presence of a slower moving UV-absorbing compound, lacking the sugar moiety (NMR, and mass spectra) which was not further investigated.

Attempted Dimerization of Iodo Derivative 1c in the Presence of Nucleoside 3d. The experiment was run as indicated before with equimolar amounts (0.26 mmol each) of **1c** and **3d** and with Mg (38 mg, 1.6 mmol) in refluxing THF (4 mL) for 3 days. TLC (S_7) revealed no product formation at all, including dimer **2**.

6,6'-Bis(1,2:3,4-di-*O*-isopropylidene-6-deoxy-α-D-galactopyranose) (6). Iodo derivative **5a** (0.7 g, 2 mmol) and Mg (0.19

(37) Kochetkov, N. K.; Budowsky, E. I.; Shibaev, V. N. In "Synthetic Procedures in Nucleic Acid Chemistry"; Wiley: New York, 1968; Vol. 1, p 497.

(38) Szer, W.; Shugar, D. In "Synthetic Procedures in Nucleic Acid Chemistry"; Wiley: New York, 1968; Vol. 1, p 433.

g, 8 mmol) were refluxed with stirring under N_2 in THF (5 mL) for 6 h. TLC (S_7) showed the presence of ca. 60% unreacted **5a** as being most mobile, a small amount of deoxy compound **5b** of intermediate mobility, and product **6** as the slowest. Chromatographic separation of the mixture was performed as described for previous dimers in solvent S_8, and 3-mL fractions were taken. Product **6** contaminated with **5a** and **5b** (TLC in S_7, GC/MS) was rechromatographed and crystallized from petroleum ether to give 0.15 g (31%) of **6**, mp 109–110 °C.

The intermediate fraction afforded 6-deoxygalactose derivative **5b** (20 mg, 4%) contaminated with a small amount of dimer **6** but identical according to NMR and mass spectra with an authentic sample of **5b**.

1,2:5,6-Di-*O*-isopropylidenehexane-1,2,5,6-tetrol (8). Iodo derivative **7b** (484 mg, 2 mmol) was stirred with Mg (8 mmol) in THF (5 mL) for 48 h at room temperature (10% reaction as shown by TLC in S_7). The mixture was then refluxed for 14 h. The workup and chromatography (solvent S_7) was performed as usual to yield 0.16 g (70%) of crystalline **8**, mp 65–68 °C.

(B) General Procedure for "Unsymmetrical Dimers". Method A was followed by using equimolar amounts of the corresponding iodo derivatives (usually 0.35 mmol each) and 4.3 equiv of Mg in THF (0.6–4 mL). The separation of reaction products was also performed as described in method A.

3-Deoxy-3-*C*-[(methyl-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranos-5-yl)methyl]-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (9). The coupling of iodo derivative **1c** and **3b** was performed as described above for 2 days at room temperature (no reaction) and then at reflux for 8 h. TLC (S_7) showed the presence of dimers **2**, **9**, **4**, and starting iodides **1c** and **3b** in the order of increasing mobility. The products were separated by the usual column chromatography in solvent S_9 (2.5-mL fractions were taken). Fractions 62–90 were combined and evaporated to give crystalline **9**: 83 mg (53%); mp 105–106 °C.

3-Deoxy-3-*C*-[(6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-6-yl)methyl]-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (10). (A) Coupling of Iodo Compounds 1c and 5a. The reaction was performed in THF (0.6 mL), with a reaction time 14 h at room temperature (no reaction) and 8 h at reflux (starting materials virtually disappeared). The order of mobility on TLC (S_7) was **2** < **10** (major product) < **6** < **1c** and **5a**. After the usual workup and chromatography in solvent S_9 (3-mL fractions were taken), pure compound **10** (60 mg) was obtained from fractions 61–72. Fractions 73–79 afforded product **10** contaminated with dimer **2**, and they were rechromatographed to give pure **10** (30 mg, total yield 51%) as a colorless glass.

(B) Coupling of Bromo Compound 1b with Iodo Derivative 5a. The experiment was performed as in method A. The equimolar mixture of **1b** and **5a** (1.2 mmol each) was refluxed for 3 days in THF (4 mL) with Mg (9.2 mmol). TLC (S_7) revealed the presence of dimers **6** and **10**, but compound **2** was virtually absent. A significant portion of starting material (predominantly **1b**) remained unchanged. Chromatography gave dimer **6** (36% yield) and derivative **10** (8% yield) in addition to traces of **2**.

***N*-Phthaloyl-L-phenylalanyl Methyl Ketone (11b).** The solution of the Grignard reagent for the reaction was prepared by dilution of commercial 3 M CH_3MgBr in ether with THF. The dilute reagent (1.1 mmol) was added by using a syringe into a solution of thioester **11a** (388 mg, 1 mmol) in THF (4 mL) with magnetic stirring at 0 °C in 0.2-mL portions over a period of 30 min. TLC (S_1) showed that at the end of the addition of the reagent the starting material **11a** virtually disappeared. The product **11b** was isolated by preparative TLC on silica gel 6F (2 mm thick, 20 × 20 cm layer; Uniplate, Analtech) in solvent S_1. The major UV-absorbing band was eluted with the same solvent, the eluate was evaporated, and the residue was crystallized from petroleum ether to yield 225 mg (76%) of **11a** in three crops; mp 130–131 °C. The material for analysis was recrystallized: mp 133–134 °C; $[\alpha]^{24}_D$ −237.3° (*c* 0.9, DMF). The literature[39] described racemic **11b** as a "dark heavy liquid" without further characterization: NMR ($CDCl_3$) δ 7.74 (m, 4, phthaloyl), 7.14 (s, 5, C_6H_5), 5.00 (q, 1, CH), 3.45 (d, 2, CH_2), 2.23 (s, 3, CH_3); mass spectrum, *m/e* (relative intensity) 293 (15.9, M), 250 (100.0, M − 43), 232 (30.4), 146 (13.2), 103 (30.2), 91 (7.7, $C_6H_5CH_2$), 77 (21.2, C_6H_5), 43 (10.2, CH_3CO). Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.70; H, 5.16; N, 4.78. Found: C, 73.58; H, 4.89; N, 4.85.

Dimerization in the Presence of Grignard-Reactive Components. (A) Thioester 11a. A small crystal of I_2 was added to the solution of iodo derivative **1c** (100 mg, 0.26 mmol) and Mg (12.5 mg, 0.52 mmol) in THF (2 mL). The stirred mixture was warmed until the color of I_2 disappeared (15–30 s). Thioester **11a** (100 mg, 0.26 mmol) was then added and the stirring under N_2 continued for 12 h at room temperature. TLC (S_7) showed no reaction. The mixture was then refluxed for 2 h and TLC indicated presence of dimer **2**, in addition to starting materials **1c** and **11a**. Iodo compound **1c** was still the major component after refluxing overnight, but several new UV-absorbing spots appeared which did not char with $HClO_4$ (absence of carbohydrate moiety). The amount of dimer **2** did not increase.

(B) Benzonitrile. The experiment was conducted as described above (method A) with iodo compound **1c** (60 mg, 0.16 mmol), Mg (8 mg, 0.33 mmol), and benzonitrile (17 mg, 0.17 mmol). TLC (S_7) showed no reaction after 4 h at room temperature. The only compounds detected after 14 h of refluxing were starting material **1c** and dimer **2**.

6-Deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (5b). Hydrogen gas was introduced above the surface of the mixture of iodo derivative **5a** (0.35 g, 1 mmol), triethylamine (0.5 mL), and Pd/C (10%, 0.1 g) in methanol (5 mL) which was magnetically stirred at room temperature until no further hydrogenolysis occurred as indicated on TLC (S_7). The catalyst was then filtered off, the filtrate was evaporated, the residue was extracted with solvent S_9, and the extract was chromatographed on a silica gel column in the same solvent as in the preceding experiments. Fractions (5 mL) were taken, and fractions 23–27 were combined and evaporated to give an oil (**5b**; 0.1 g, 41%) which was pure according to TLC (S_6) and GC/MS; $[\alpha]^{22}_D$ −53.9° (*c* 0.6, $CHCl_3$). The literature[18,19] reports melting points of 30–35 and 37 °C and $[\alpha]^{19}_D$ −52.4° (neat). The NMR ($CDCl_3$) contained the expected signals reported[18] for the spectrum in CD_3COCD_3.

3-Deoxy-1,2:5,6-di-*O*-isopropylidene-3-*C*-methyl-α-D-allofuranose (1d). Bromo compound **1b** (50 mg, 0.15 mmol) in methanol (85%, 5 mL) was hydrogenated in a Parr apparatus at 30 psi in the presence of sodium acetate (50 mg, 0.61 mmol) and Pd/C (10%, 30 mg) at room temperature for 14 h. The reaction was complete as shown by TLC in solvent S_7. Celite was added, and the mixture was filtered by using a Millipore 0.45 membrane filter. The filtrate was evaporated, and the residue was partitioned between petroleum ether (5 mL) and water (5 mL). After evaporation of solvent, product **1d** was obtained as a colorless oil: 25 mg (66%); $[\alpha]^{22}_D$ +36° (*c* 0.45, $CHCl_3$) [lit.[13] $[\alpha]^{22}_D$ +37° (*c* 1)]. The NMR ($CDCl_3$) was identical with that described[13].

Reaction of Bromo Compound 1b with *n*-Butyllithium. The solution of derivative **1b** (100 mg, 0.3 mmol) in THF (2 mL) was cooled to −70 °C, and *n*-butyllithium in *n*-hexane (15%, 0.185 mL, 0.3 mmol) was introduced under N_2 by using a syringe. After 15 min, TLC (S_7) of an aliquot showed the presence of unreacted **1b** and deoxy compound **1d**. Addition of lithium *N*-phthaloyl-L-phenylalaninate (86 mg, 0.3 mmol), subsequent warming to room temperature (14 h), and refluxing did not afford any additional products. Column chromatography in solvent S_7 gave compound **1d** as an oil (20 mg, 26%) containing according to GC/MS ca. 8% of the starting material **1b**. The mass spectrum corresponded to that of an authentic sample of **1d**.

Reaction of Iodo Compound 1c with *n*-Butyllithium. The experiment was run as in the preceding case with derivative **1c** (0.26 mmol). TLC (S_7), after 2 min at −70 °C, showed an extensive formation of dimer **2** and a small amount of deoxy compound **1d**. The starting material **1c** virtually disappeared.

Reaction of Iodo Derivative 1c with Lithium in THF. Compound **1c** (77 mg, 0.2 mmol) and Li (3.5 mg, 0.25 mmol) were

(39) Ghosh, T. N.; Dutta, S. *J. Indian Chem. Soc.* **1953**, *30*, 863.
(40) Kissman, H. M.; Baker, B. R. *J. Am. Chem. Soc.* **1957**, *79*, 5534.
(41) Kim, K. S.; Szarek, W. A. *Can. J. Chem.* **1981**, *59*, 878.

magnetically stirred under N_2 in THF (0.2 mL) at room temperature. After 3 days, a large portion of **1c** remained unchanged, and dimer **2** appeared as the only product in a significant amount (TLC, S_7). A small amount of deoxy derivative **1d** was also present. Relative proportions of materials were unchanged after 1 week.

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Registry No. **1a**, 69832-48-0; **1a** triflate, 79068-95-4; **1b**, 79068-96-5; **1c**, 79068-97-6; **1d**, 26293-58-3; **2**, 79068-98-7; **3a**, 4099-85-8; **3a** triflate, 70209-11-9; **3b**, 38838-06-1; **3c**, 32471-59-3; **3c** triflate, 79068-99-8; **3d**, 79083-82-2; **4**, 79069-00-4; **5a**, 4026-28-2; 5b, 4026-27-1; 6b, 61252-75-3; DL-**7a**, 22323-83-7; DL-**7a** triflate, 79120-24-4; DL-**7b**, 23737-52-2; **8**, 79069-01-5; **9**, 79069-02-6; **10**, 79101-57-8; **11a**, 33861-65-3; **11b**, 79069-03-7; *N*-phthaloyl-L-phenylalanine, 5123-55-7; lithium *N*-phthaloyl-L-phenylalaninate, 79069-04-8; 1,2:5,6-di-*O*-isopropylidene-3-*C*-methylene-α-D-ribohexofuranose, 21665-16-7; 1,2:5,6-di-*O*-isopropylidene-3-deoxy-3-oxo-α-D-ribohexofuranose, 2847-00-9; 2',3'-*O*-isopropylideneuridine, 362-43-6.

Notes

Synthetic Methods and Reactions. 104.[1] Silylations with in Situ Generated Trimethylsilyl Triflate Reagent Systems

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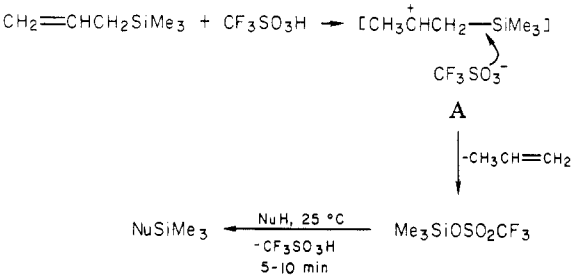
The trimethylsilyl group is a widely used protecting group for carboxylic acids, alcohols, mercaptans, carbonyl, and nitro compunds.[2] Recently, its usefulness was also demonstrated as an activating group, for example, for carboxylic acids, in the transesterification of carboxylic esters under essentially neutral conditions.[3] Although there are numerous reports on different silylation methods, most of them involve basic conditions.[2,4] Recently, silylations under acidic conditions with hexamethyldisiloxane have been reported. This method, however, necessitates high temperatures and long reaction times. Previously, we have reported a very mild silylation method with chlorotrimethylsilane/lithium sulfide.[4]

We also carried out extensive studies in an attempt to prepare stable trivalent silicenium ions such as $(CH_3)_3Si^+$. So far these attempts have been unsuccessful, due to the high affinity of the developing silicenium ion toward fluorine and oxygen containing donors, even in sysems of low nucleophilicity where related carbocations are stable. In these systems we instead observed quenching of the incipient silicenium ions by fluoride, fluorosulfonate, or triflate ions present in the medium. Trimethylsilyl trifluoromethanesulfonate (triflate)[6] is a powerful silylating reagent. However, it is expensive and highly moisture sensitive, thus making it difficult to handle. As a continuation of our interest in the development of in situ equivalents of trimethylsilylating agents, we have now studied the silylation of carboxylic acids, alcohols, phenols, mercaptans, and ketones with trimethylsilyl triflate, generated in situ from allyltrimethylsilane and trifluoromethanesulfonic acid.

Scheme I[a]



[a] NuH = RC(=O)OH or ROH.

Trimethylsilylation of carboxylic acids and alcohols took place almost instantaneously when 2–3 drops of triflic acid was added to a mixture of the substrate (10 mmol) and allyltrimethylsilane (12 mmol) in carbon tetrachloride solution, with the immediate liberation of propene (Scheme I). Recently, Morita et al.[7] have also reported a similar approach, using *p*-toluenesulfonic acid catalyst. However, under their reaction conditions silylation of alcohols and carboxylic acids was achieved only by heating at 70–80 °C for 1.5–3.0 h. The authors suggested that an ionic tosylated intermediate related to A may be the active silylating agent in the reactions. We believe, under our reaction conditions, the silylations are taking place via in situ formed trimethylsilyl triflate, which must be causing the instantaneous silylations in the case of carboxylic acids and alcohols. The formation of trimethylsilyl triflate from allyltrimethylsilane and triflic acid was confirmed by ^1H, ^{13}C, and ^{29}Si NMR spectroscopy.

The wide utility and general superiority of the present silylating system have been further demonstrated by the silylaton of mercaptans and thiophenols, albeit at a higher

(1) For part 103, see G. A. Olah, S. C. Narang, and L. D. Field, *J. Org. Chem.* **46**, 3727 (1981).
(2) (a) C. B. Reese, *Prot. Groups Org. Chem.*, 95–143 (1973); (b) J. F. Klebe, *Acc. Chem. Res.*, **3**, 299 (1970); (c) B. E. Cooper, *Chem. Ind.*, 194 (1978).
(3) G. A. Olah, S. C. Narang, G. F. Salem, and B. G. B. Gupta, *Synthesis*, 142 (1981).
(4) G. A. Olah, B. G. B. Gupta, S. C. Narang, and R. Malhotra, *J. Org. Chem.*, **44** 4272 (1979), and references cited therein.
(5) H. W. Pinnick, B. S. Bal, and N. N. Lajis, *Tetrahedron Lett.*, 4261 (1978).
(6) G. Simchen and W. Kober, *Synthesis*, 259 (1976).
(7) T. Morita, Y. Okamoto, and H. Sakurai, *Tetrahedron Lett.*, 835 (1980).
(8) H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969).
(9) K. A. Andrianov and T. N. Ganina, *Zh. Obshch. Khim.*, **29**, 601 (1959).

0022-3263/81/1946-5212$01.25/0