1 H, CHOH), 3.17 (m, 1 H, benzylic), 2.4 (br s, 3 H, NH_2 and OH), 2.10 (m, 1 H), 1.98 (m, 1 H), 1.68 (m, 1 H), 1.51 (m, 3 H); ^{13}C NMR ($CDCl_3$) 143.58, 135.96, 130.53, 128.08, 126.47, 126.41, 76.91 (CHOH), 61.04 (CNH), 42.95, 39.05, 34.15, 34.00.

NMR Measurements. The exchangeable protons were removed with D_2O. Homonuclear and heteronuclear chemical shift correlation spectra (HOMCOR and HETCOR) were run with standard Varian software. The NOE difference spectrum was determined with the decoupler placed first well off resonance and then on resonance. The low-power decoupler was used, and the attenuation was maintained as high as possible as just to saturate the resonance. Subtraction of the second FID from the first was done with the standard add-subtract routine, and the transformation was performed.

Acknowledgment. This work was supported by National Institutes of Health Research Grants HL 34193 and GM 22988.

Synthesis of *C*-Glucosides by Reactions of Glucosyl Halides with Organocuprates

Ron Bihovsky,* Caryn Selick, and Irena Giusti

Department of Chemistry, State University of New York at Stony Brook, Stony Brook, New York 11794-3400

Received August 7, 1987

Lithium dimethylcuprate reacts with *trans*-2-chloro-6-methyltetrahydropyran (1) via nucleophilic substitution predominantly with inversion of configuration to afford *cis*-2,6-dimethyltetrahydropyran (2). Similarly, lithium dialkylcuprates displace protected α-glucosyl bromides (5) with inversion to afford the β-*C*-glucosides, β-1-alkyl-1,5-anhydroglucitols (6). In contrast, Grignard reagents gave mixtures of α- and β-*C*-glucosides 6 and 7, while organolithium reagents gave only elimination to 9.

α-Halo ethers have considerable utility in synthetic organic chemistry because of their high reactivity toward carbon nucleophiles.[1] Cyclic α-halo ethers are particularly attractive potential substrates for asymmetric induction in carbon–carbon bond formation. Thus axially disposed 2-halotetrahydropyrans (i.e. 1) are readily prepared since the anomeric effect[2] constrains the halogen atom to the axial orientation. If nucleophilic displacement by a carbon nucleophile with inversion of configuration ensues, stereospecific formation of the equatorially substituted product will result. Recently we exploited the reaction between *trans*-2-chloro-6-methyltetrahydropyran (1) and malonate anion, which occurred with nearly complete inversion of configuration, as the key step in a stereoselective synthesis of a civet constituent.[3] We hve also explored the reaction of a 2-chlorotetrahydrothiophene with several organometallic reagents during our synthesis of biotin.[4]

In the present investigation, we sought to determine whether organometallic reagents would react with 2-halotetrahydropyrans with inversion of configuration via an S_N2-like mechanism. If such displacements exhibited significant S_N1 or single-electron transfer character, however, the desired selective inversion of configuration would not be achieved. α-Halo ethers have frequenlty been reported to undergo substitution via an S_N1 mechanism in which the intermediate cation is stabilized by the adjacent oxygen.[2,5] Radical intermediates adjacent to oxygen are also stabilized.[6] Thus, the normal propensity of organolithium and Grignard reagents to displace halides via a single-electron transfer mechanism, with erosion of stereoselectivity,[7] would be expected to be particularly severe in α-halo ethers. Accordingly, we recently observed that organolithium and Grignard reagents attack a cyclic α-halo thio ether from the less hindered face, presumably via a single electron transfer process.[4]

The *C*-glycosides[8] represent one significant group of natural products that have been prepared by reactions between protected α-glycosyl halides and organometallic reagents.[9] Substitution with inversion is required for preparation of naturally occurring *C*-glycosides which generally possess the 1-β configuration. However Grignard,[10] organolithium,[11] and organocadmium[12] reagents

* Author to whom correspondence should be addressed at Berlex Laboratories, 110 East Hanover Avenue, Cedar Knolls, NJ 07927. All previous papers by R.B. were published under the name Hans Aaron Bates.

(1) (a) Summers, L. *Chem. Rev.* **1955**, *55*, 301. (b) Gross, H.; Höft, E. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 335.
(2) Kirby, A. J. In *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer-Verlag: New York, 1983.
(3) Bates, H. A.; Deng, P.-N. *J. Org. Chem.* **1983**, *48*, 4479.
(4) Bates, H. A.; Rosenblum, S. B. *J. Org. Chem.* **1986**, *51*, 3447.
(5) Pichler, J.; Korensky, J. *Collect. Czech. Chem. Commun.* **1974**, *39*, 1229.
(6) (a) Wallace, T. J.; Gritter, R. J. *Tetrahedron* **1963**, *19*, 657. Gritter, R. J. In *Chemistry of the Ether Linkage*; Patai, S., Ed.; Interscience: New York, 1967; pp 425–430. (b) Walling, C.; Mintz, M. J. *J. Am. Chem. Soc.* **1967**, *89*, 1515.
(7) (a) Guthrie, R. D. In *Comprehensive Carbanion Chemistry*; Buncel, E., Durst, T., Eds.; Elsevier: New York, 1980; pp 230–236. (b) Beletskaya, I. P.; Artamkina, G. A.; Reutuv, O. A. *Russ. Chem. Rev.* **1976**, *45*, 330.
(8) (a) Franz, G.; Grun, M. *Planta Med.* **1983**, 131. (b) Buchanan, J. G. *Prog. Chem. Nat. Org. Prod.* **1983**, *44*, 234. (c) Haynes, L. J. *Adv. Carbohydr. Chem.* **1963**, *18*, 227. (d) Haynes, L. J. *Adv. Carbohydr. Chem.* **1965**, *20*, 357.
(9) Reviews: (a) Bonner, W. A. *Adv. Carbohydr. Chem.* **1951**, *6*, 251. (b) Bonner, W. A. In *Methods in Carbohydrate Chemistry*; Whistler, R. L., Wolfrom, M. L., Eds.; Academic: New York, 1963; Vol. 2, pp 467–473. (c) Hanessian, S.; Pernet, A. G. *Adv. Carbohydr. Chem. Biochem.* **1976**, *33*, 111.
(10) (a) Hurd, C. D.; Bonner, W. A. *J. Am. Chem. Soc.* **1945**, *67*, 1972. (b) Hurd, C. D.; Holysz, R. P. *J. Am. Chem. Soc.* **1950**, *72*, 1732. (c) Zhdanov, Y. A.; Korol'chenko, G. A. *Proc. Acad. Sci. USSR* **1961**, *139*, 844. (d) Julia, M.; Jacquet, B. *Bull. Chem. Soc. Fr.* **1963**, 1983. (e) Tschesche, R.; Widera, W. *Justus Liebigs Ann. Chem.* **1982**, 902. (f) Crombie, L.; Wyvill, R. D. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1971. (g) Stone, T. E.; Daves, G. D. *J. Org. Chem.* **1977**, *42*, 2151. (h) Eade, R. A.; McDonald, F. J.; Simes, J. J. H. *Aust. J. Chem.* **1975**, *28*, 2011. (i) Preobrazhenskaya, M. N.; Suvorov, N. N.; *J. Gen. Chem. USSR* **1965**, *35*, 891. (j) Shul'man, M. L.; Shiyan, S. D.; Khorlin, A. Y. *Carbohydr. Res.* **1974**, *33*, 229. (k) Shiyan, S. D.; Shul'man, M. L.; Khorlin, A. Y. *Bull. Acad. Sci. USSR Div. Chem. Sci.* **1973**, *22*, 2335. (l) Berti, G.; Catelani, G.; Monti, L.; Ventresca, G. *Tetrahedron* **1986**, *42*, 3973. (m) Eliel, E. L.; Hargrave, K. D.; Pietrusiewicz, K. M.; Manoharan, M. *J. Am. Chem. Soc.* **1982**, *104*, 3635. (n) Hanessian, S.; Liak, T. J.; Dixit, D. M. *Carbohydr. Res.* **1981**, *88*, C14. (o) Hanessian, S.; Dixit, D. M.; Liak, T. J. *Pure Appl. Chem.* **1981**, *53*, 129. (p) Marquez, F.; Arriandiaga, M. V.; Urbieta, M. T. *An. Quim., Ser. C* **1983**, *79*, 428.
(11) (a) Hurd, C. D.; Holysz, R. P. *J. Am. Chem. Soc.* **1950**, *72*, 1735. (b) Hurd, C. D.; Miles, H. T. *J. Org. Chem.* **1964**, *29*, 2976. (c) Shapiro *J. Am. Chem. Soc.* **1961**, *83*, 3920.

0022-3263/88/1953-4026$01.50/0

Table I. Products from Reaction of α-2,3,4,6-Tetra-O-methylglucopyranosyl Bromide (5a) with Organometallic Reagents

reagent	mol %	temp, °C	time, h	R	yield (R′ = Me)[a] 6	7	8a	9a
MeLi	380	−35	4	Me	0	0	0	70
PhLi	205	20	140	Ph	0	0	0	60
MeMgBr	300	−15	12	Me	24	46	18	0
PhMgBr	210	20	140	Ph	27	22	0	0
Me_2CuLi	170	−35	17	Me	60	0	22	0
Bu_2CuLi	200	−35	18	Bu	56	0	28	0
Ph_2CuLi	195	20	95	Ph	39	2	12	4
$Me_2CuCNLi_2$	170	−35	22	Me	0	0	0	0

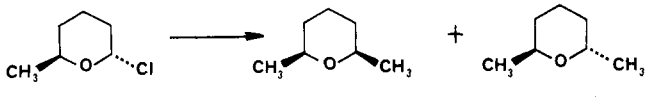
[a] Yields determined by gas chromatography before isolation.

Table II. Isolated Yields from Reactions of 3 with R_2CuLi and RMgBr

R′	R_2CuLi or RMgBr	mol %	temp, °C	time, h	yield[a] 6	ratio[b] 6:7
Me	Me_2CuLi	170	−35	17	46	>20:1
Me	Bu_2CuLi	200	−35	18	40	>20:1
Me	Ph_2CuLi	195	20	95	25	20:1
Bn	Me_2CuLi	185	−35	120	15	>20:1
Bn	Ph_2CuLi	180	20	140	18	>20:1
Ac	Me_2CuLi	180	−25	70	8	>20:1
Me	MeMgBr	300	−15	12	10	35:65
Me	PhMgBr	210	20	140	22	55:45
Bn	MeMgBr	324	5	18	11	35:65
Bn	PhMgBr	200	20	24	12	c
Ac	MeMgBr	1230	20	19	6[d]	50:50[d]

[a] Yields were not optimized. [b] Ratio of 6:7 was determined by GC for R′ = Me, and by isolated product for R′ = Bn and Ac. [c] Ratio was not determined. [d] Compounds 6c and 7c were isolated after reacetylation.

usually provide a mixture of α- and β-C-glycosides. Other organometallic reagents, allylsilanes, and radical coupling reactions give mixtures or α-C-glycosides.[13] This paper describes reactions of lithium dialkylcuprates with glucosyl halides to provide β-C-glucosides. Similar reactions with glycosyl halides or any other cyclic α-halo ethers do not appear to have been investigated; however, our previous results[4] suggested that β-C-glycosides would result.[14]



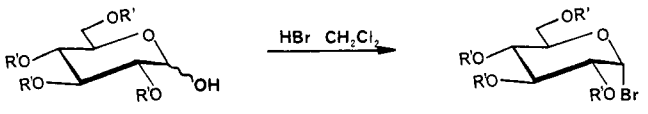
1 2 3

MeMgBr	25	75
MeLi	76	24
Me_2CuLi	90	10

Results

Reactions with Organometallic Reagents. As a prototypical example, *trans*-2-chloro-6-methyltetrahydropyran (1)[3] was treated with methylmagnesium bromide, methyllithium, and lithium dimethylcuprate in ether. Methylmagnesium bromide (140 mol %) reacted with 1 at −45 °C mainly with retention of configuration to afford a 25:75 mixture of *cis*- and *trans*-2,6-dimetyltetrahydropyran (2 and 3) in essentially quantitative yield after 45 min. Methyllithium (200 mol %) reacted more slowly with 1, giving a 74:26 mixture of 2 and 3 and 12% recovered starting material after 2 h at −40 °C. Lithium dimethylcuprate (102 mol %) reacted more rapidly than methyllithium to give an 87:13 mixture of 2 and 3 at −50 °C after 20 min or a 90:10 mixture at −70 °C after 75 min. Lithium dimethylcuprate is therefore the reagent of choice for substitution on 1 with inversion of configuration.

The protected α-D-glucosyl bromides **5a** and **5b**, required as substrates for C-glucoside synthesis, were easily prepared by treatment of 2,3,4,6-tetra-O-alkyl-D-glucose (**4a** or **4b**) with HBr in methylene chloride.[15] None of the epimeric β-glucosyl bromides could be detected spectroscopically. Direct conversion of 4 to 5 represents an improvement over conventional procedures, which unnecessarily utilize the acetate of **4a** or *p*-nitrobenzoate of **4b**.[10i,16] This procedure should find general application to glycosyl halide formation.



4 5

a; R′=Me
b; R′=Bn
c; R′=Ac

Initially we examined reactions of α-2,3,4,6-tetra-O-methyl-D-glucopyranosyl bromide (**5a**) with various organometallic reagents in diethyl ether. The distribution of products from these reactions, conveniently determined by gas chromatography, is shown in Table I. Isolated yields are shown in Table II. Methyllithium gave no substitution, but only elimination to 1,5-anhydro-2,3,4,6-tetra-O-methyl-D-*arabino*-hex-1-enitol (**9a**)[17] along with

(12) (a) Klein, R. S.; Kotick, M. P.; Watanabe, K. A.; Fox, J. J. *J. Org. Chem.* **1971**, *36*, 4113. (b) Hurd, C. D.; Holysz, R. P. *J. Am. Chem. Soc.* **1950**, *72*, 2005. (c) Sharma, R. A.; Bobek, M.; Bloch, A. *J. Med. Chem.* **1975**, *18*, 473. (d) Mertes, M. P.; Zielinski, J.; Pillar, C. *J. Med. Chem.* **1967**, *10*, 320.

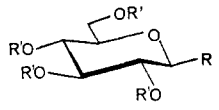
(13) (a) Maeba, I.; Iwata, K.; Usami, F.; Furukawa, H. *J. Org. Chem.* **1983**, *48*, 2998. (b) Posner, G. H.; Haines, S. R. *Tetrahedron Lett.* **1985**, *26*, 1823. (c) Nicolaou, K. C.; Dolle, R. E.; Chucholowski, A.; Randall, J. L. *J. Chem. Soc., Chem. Commun.* **1984**, 1153. (d) Hosomi, A.; Sakata, Y.; Sakurai, H. *Tetrahedron Lett.* **1984**, *25*, 2383. (e) Giese, B.; Dupuis, J. *Angew. Chem., Int. Ed. Engl.* **1983**, 622. (f) For alternative syntheses of C-glycosides, see footnotes 9–14, 22, 23, and references cited therein.

(14) For examples of organocuprate conjugate addition to carbohydrate derivatives, see: (a) Yunker, M. B.; Plaumann, D. E.; Fraser-Reid, B. *Can. J. Chem.* **1977**, *55*, 4002. (b) Goodwin, T. E.; Crowder, C. M.; White, R. B.; Swanson, J. S.; Evans, F. E.; Meyer, W. L. *J. Org. Chem.* **1983**, *48*, 376.

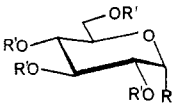
(15) Bates, H. A.; Selick, C. *J. Carbohydr. Chem.* **1985**, *4*, 273.

(16) (a) Ishikawa, T.; Fletcher, H. G. *J. Org. Chem.* **1969**, *34*, 563. (b) Koto, S.; Morishima, N.; Kusuhara, C.; Sekido, S.; Yoshida, T.; Zen, S. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2995.

unreacted starting material. Methylmagnesium bromide gave a 35:65 mixture of β-1,5-anhydro-1-*C*-methyl-2,3,4,6-tetra-*O*-methyl-D-glucitol (**6a**) and α-1,5-anhydro-1-*C*-methyl-2,3,4,6-tetra-*O*-methyl-D-glucitol (**7a**) accompanied by reductive elimination to 1,5-anhydro-3,4,6-tri-*O*-methyl-2-deoxy-D-*arabino*-hex-1-enitol (**8a**).[18] Lithium dimethylcuprate afforded **6a** as the only detectable substitution product, along with reductive elimination product **8a**. Reductive elimination appears to be caused by lithium dimethylcuprate itself since methyllithium gives only **9a**, and CuI did not react with **5a** even at 20 °C. While derivatives of *C*-glucoside **6a** have been synthesized by other routes,[10p,23] the present method is the most direct.

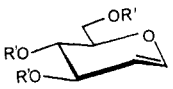


6

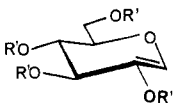


7

a; R=Me, R'=Me
b; R=Me, R'=Bn
c; R=Me, R'=Ac
d; R=Bu, R'=Me
e; R=Ph, R'=Me
f; R=Ph, R'=Bn



8



9

a; R'=Me
b; R'=Bn
c; R'=Ac

The reaction of glucosyl bromide **5a** with the higher order mixed cuprate, $Me_2CuCNLi_2$ was also examined. In other displacements, this reagent shows less tendency to cause elimination, as well as increased stability and superior reactivity compared to Me_2CuLi.[19] Surprisingly, treatment of **5a** with $Me_2CuCNLi_2$ at −50 °C or −35 °C for 22 h gave no reaction. A control reaction between $Me_2CuCNLi_2$ and 2-iodooctane[19] indicated that the reagent was satisfactory.

Lithium dibutylcuprate reacted with **5a** to afford β-1,5-anhydro-1-*C*-butyl-D-glucitol (**6d**) and reductive elimination product **8a**. Lithium diphenylcuprate reacted quite slowly with **5a** to provide β-1,5-anhydro-1-*C*-phenyl-D-glucitol (**6e**), accompanied by a trace of α-1,5-anhydro-1-*C*-phenyl-D-glucitol (**7e**), reductive elimination product **8a**, and elimination product **9a**. Under similar conditions, phenylmagnesium bromide gave a 55:45 mixture of **6e** and **7e** while phenyllithium caused elimination to **9a**.

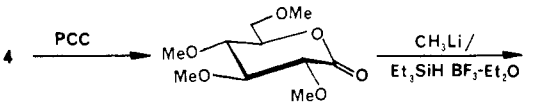
α-2,3,4,6-Tetra-*O*-benzyl-D-glucopyranosyl bromide (**5b**) underwent analogous stereoselective substitution with lithium dimethylcuprate and lithium diphenylcuprate, affording **6b** and **6f**, respectively. The nonoptimized isolated yields are shown in Table II. Methylmagnesium bromide, in contrast, gave a mixture of diastereomers **6b** and **7b**.

α-2,3,4,6-Tetra-*O*-acetyl-D-glucopyranosyl bromide (**5c**) reacted selectively with lithium dimethylcuprate to give a low yield of **6c**, accompanied by triacetylglucal (**8c**) and a small amount of starting material. The presence of considerable polar material suggests that the acetate protecting groups may be partially unstable to excess lithium dimethylcuprate after long reaction times. When **5c** was treated with a large excess of methylmagnesium bromide, cleavage of the acetyl groups occurred, followed by displacement of bromide.[10a] After reacetylation, we obtained equal quantities of **6c** and **7c** in low yield.

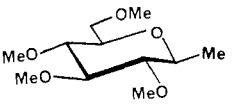
Stereochemical Assignments. The stereochemistry of *cis*- and *trans*-2,6-dimethyltetrahydroyran (**2** and **3**) was easily assigned by comparison of ^{13}C NMR chemical shifts with literature values.[20] A mixture of authentic **2** and **3** for use as a GC standard was also prepared by thermal dehydration of 2,6-heptanediol with catalytic toluenesulfonic acid.

Assignment of stereochemistry to **6** and **7** was more complicated. The stereochemistry of **6e** and **7e** was deduced from the ^1H NMR coupling constants (8.8 and 4.0 Hz, respectively) and chemical shifts (4.05 and 5.21 ppm, respectively) of the H_1 doublet. The correct stereochemistry of **6a–c** and **7a–c** was also suggested by the coupling constants and chemical shifts of H_1, but this evidence was deemed to be equivocal because H_1 is generally a low-amplitude, highly coupled signal in a congested portion of the spectrum. The correct assignments were also in accord with Hudson's rule, which generally,[9a] but not always,[21] holds for *C*-glycosyl compounds. Unequivocal evidence was therefore obtained by independent synthesis.

Thus 2,3,4,6-tetra-*O*-methyl-D-gluconolactone (**10**), readily prepared by oxidation of 2,3,4,6-tetra-*O*-methyl-D-glucopyranose (**4a**) with pyridinium chlorochromate, was treated with methyllithium in ether followed by BF_3–Et_2O and triethylsilane at −78 °C to afford **6a**, identical in all respects with the reaction product from **5a** and Me_2CuLi.



10



6a

Since it is well established that triethylsilane hydride axially to an intermediate oxonium ion,[22] the structure of **6a** was confirmed. The stereochemistry of **6d** could now be assigned on the basis of the coincidence of relevant signals in the ^{13}C and ^1H NMR spectra of **6a** and **6d**.

The ^{13}C NMR spectra of **6a–c** vs **7a–c** reveal the expected tendency for the β-methyl group of **6a–c** to be deshielded compared with the α-methyl group of **7a–c** (approximately 18 and 12 ppm, respectively) because of

(17) (a) Wolfrom, M. L.; Husted, D. R. *J. Am. Chem. Soc.* **1937**, *59*, 2559. (b) Paulsen, H.; Thiem, J. *Chem. Ber.* **1973**, *106*, 115.

(18) (a) Eitelman, S. J.; Hall, R. H.; Jordan, A. *J. Chem. Soc., Perkin Trans. 1* **1978**, 595. (b) Kuhn, R.; Löw, I.; Trischmann, H. *Chem. Ber.* **1957**, *90*, 203. (c) Hirst, E. L.; Woolvin, S. *J. Chem. Soc.* **1931**, 1131.

(19) (a) Posner, G. *Org. React. (N. Y.)* **1975**, *22*, 253. (b) Goering, H. L.; Tseng, C. C. *J. Org. Chem.* **1983**, *48*, 3986. (c) Lipschutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A.; Parker, D. *J. Org. Chem.* **1984**, *49*, 3928. (d) Lipschutz, B. H; Wilhelm, R. S. *J. Am. Chem. Soc.* **1982**, *104*, 4696. (e) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Tetrahedron* **1984**, *40*, 5005. (f) Lipshutz, B. H.; Wilhelm, R. S.; Floyd, D. M. *J. Am. Chem. Soc.* **1981**, *103*, 7672.

(20) Eliel, E.; Manoharan, M.; Pietrusiewicz, K. M.; Hargrave K. D. *Org. Magn. Reson.* **1983**, *21*, 94.

(21) Dawe, R. D.; Fraser-Reid, B. *J. Org. Chem.* **1984**, *49*, 522.

(22) (a) Kraus, G. A.; Frazier, K. A.; Roth, B. D.; Taschner, M. J.; Neuenschwander, K. *J. Org. Chem.* **1981**, *46*, 2417. (b) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976. (c) Lancelin, J.-M.; Zollo, P. H.; Sinaÿ, P. *Tetrahedron Lett.* **1983**, *24*, 4833. (d) Babirad, S. A.; Wang, Y; Kishi, Y. *J. Org. Chem.* **1987**, *52*, 1370.

(23) (a) Pougny, J.-R.; Nassr, M. A. M.; Sinaÿ, P. *J. Chem. Soc., Chem. Commun.* **1981**, 375. (b) Lancelin, J. M.; Pougny, J.-R.; Sinaÿ, P. *Carbohydr. Res.* **1985**, *136*, 369. (c) Pougny, J.-R.; Sinaÿ, P., personal communication. (d) Horton, D.; Priebe, W. *Carbohydr. Res.* **1981**, *94*, 27. (e) Butler, R. N.; Johnston, S. M. *J. Chem. Soc., Chem. Commun.* **1981**, 376. (f) Hanessian, S.; Martin, M.; Desai, R. C. *J. Chem. Soc., Chem. Commun.* **1986**, 926.

the γ gauche effect. The spectra of **6b**, **6c**, **7b**, and **7c** were consistent with those reported by other authors,[23a-d] and the structures of **7b** and **7c** have been confirmed by X-ray crystallography on the deprotected α-1,5-anhydro-1-C-methyl-D-glucitol (**7**; R = Me, R′ = H).[23e]

Since spectral methods did not adequately define the stereochemistry of **6f**, an authentic sample was prepared by an independent method. The configuration of β-1,5-anhydro-1-C-phenyl-D-glucitol (**6**; R = Ph, R′ = H)[10a,b] has been established by degradative studies[24] and by the 9.8-Hz coupling constant of H_1 in the acetate.[25] β-1,5-Anhydro-1-C-phenyl-D-glucitol (**6**; R = Ph, R′ = H) was alkylated with benzyl bromide to give **6f**, identical in all respects with the sample prepared from **5b**.

Discussion

Cyclic α-halo ethers including glycosyl halides are known to react with organometallic reagents[9] including Grignard,[10] alkyllithium,[11] dialkylcadmium,[12] and other organometallic[13] reagents. Early investigators were sometimes unable to detect the diastereomeric composition of the products. However, in nearly all recent investigations, production of diastereomeric mixtures or formation of α-C-glycosides was reported. Thus our observation that Grignard reagents react with 2-chloro-6-methyltetrahydropyran (**1**) to give **2** and **3**, and with protected α-glucosyl bromides **5a–c** to give a mixture of diastereomers **6** and **7** is well precedented.[10] A recent report implying that **5c** reacts with Grignard reagents, including MeMgBr, to give β-C-glucosides exclusively[10p] contradicts previous studies and could not be reproduced in this laboratory.

Organolithium reagents react with **5a** to give elimination product **9a**. This is is accord with other reports that alkyllithium reagents are less effective than Grignard reagents in related substitution reactions[4,11] and may cause elimination.[11b]

In order to increase the tendency of the protected α-glucosyl bromides **5** to undergo substitution with inversion, we have utilized lithium dialkylcuprates. Although the precise mechanism has not been established, lithium dialkylcuprates generally displace secondary alkyl halides with inversion of configuration.[19] Reactions of lithium dialkylcuprates with primary acyclic α-halo ethers have occasionally been reported,[26] and we have utilized a related displacement on a cyclic α-halo thioether in our recent synthesis of biotin,[4] but to our knowledge reactions with cyclic secondary α-halo ethers have not previously been attempted.

Lithium dimethylcuprate displaced the chloride of **1** mainly with inversion of configuration. Likewise, as shown in Tables I and II, we have found that lithium dialkylcuprates generally displace α-glucosyl bromides **5** with inversion of configuration to give β-C-glucosides **6**. None of the α-C-glucosides **7** were isolated except in the reaction of Ph_2CuLi with **5a** where 5% **7e** was detected. Thus lithium dialkylcuprates can displace secondary cyclic α-halo ethers with inversion via an S_N2-like mechanism. Single-electron transfer or S_N1 mechanisms evidently do not interfere to a significant extent. Inversion of configuration has also been demonstrated recently in the reactions of protected α-glucosyl halides with sodium (η-cyclopentadienyl)dicarbonylferrate,[27a] and $Mn(CO)_5$.[27b]

The present method represents a direct route to β-C-glucosides, a significant group of natural products.[8,9] We are currently investigating reactions of other α-glycosyl halides with more complex organocuprates for the synthesis various naturally occurring C-glycosides.

Experimental Section

NMR spectra were obtained on a Varian HFT-80 (^1H NMR, 80 MHz), a Varian CFT-20 (^{13}C NMR, 20 MHz), and a Nicolet NT-300NB spectrometer. Low-resolution mass spectra were obtained on a Hewlett-Packard 5980A spectrometer with 70 eV electron impact ionization, and high-resolution mass spectra were recorded on a Kratos MS-30 spectrometer. Infrared spectra were recorded on a Unicam SP1000 spectrophotometer. Gas chromatography was performed on a 10% SE-30 column in a HP-5830A chromatograph. Melting points are uncorrected. Analytical thin-layer chromatography (TLC) was performed on EM 5539 silica gel 60 plates, and preparative flash chromatography was performed on EM silica gel 60 (0.040–0.063 mm).

All reactions were carried out under nitrogen and stirred magnetically unless otherwise stated. All reaction temperatures were measured internally. Commercial anhydrous diethyl ether free of ethanol was used for organometallic reactions. Organic phases were dried over anhydrous $MgSO_4$ unless otherwise stated. Solents were evaporated in vacuo on a rotary evaporator.

Lithium dialkylcuprates were prepared from alkyllithium and CuI (Aldrich), which was purified by recrystallization from aqueous KI, washed with ether.[4] MeLi (1.6 M, low halide concentration in ether), BuLi (2.5 M in hexanes), PhLi (1.8 M in cyclohexane–ether, 70:30), and MeMgBr (2.4 M in ether) were purchased from Aldrich and titrated before use. PhMgBr (1.05 M in ether) was prepared in by standard procedures.

2,6-Heptanediol. Aqueous glutaraldehyde (30 mL, 25% by weight) was treated with NaCl (7 g) and extracted five times with ether. The organic layer was dried, the solvent was removed, and the residue was Kugelrohr distilled (85–170 °C, 30 mmHg) to give glutaraldehyde (4.47 g). MeMgBr (10 mL, 2.39 M, 23.9 mmol, 239 mol %) was added dropwise over 20 min to freshly distilled glutaraldeyde (1.00 g, 10 mmol) in ether (10 mL) at 0 °C. The very viscous mixture was then stirred as well as possible at 20 °C. After 25 h, the reaction was quenched with saturated NH_4Cl, extracted with ether, and dried over Na_2SO_4. The solvent was evaporated, and the residue was Kugelrohr distilled (80–120 °C, 0.5 mmHg) to afford 2,6-heptanediol (550 mg, 49% yield). Spectra were in accord with literature.[29]

***cis*- and *trans*-2,6-Dimethyltetrahydropyran (2 and 3).**

A. 2,6-Heptanediol (150 mg) and toluenesulfonic acid monohydrate (15 mg) were heated to 180 °C in a Kugelrohr bulb at atmospheric pressure for several minutes, and the distillate was condensed. Accompanying water was removed, and the distillate was Kugelrohr distilled (110–150 °C) to give product (96 mg, 74% yield). GC and ^{13}C NMR analyses indicated a 43:57 mix of **2** and **3**. With this method, rearrangement to tetrahydrofurans[20] was avoided.

B. MeLi (1.1 mL, 1.6 M, 1.76 mmol, 205 mol %) was added dropwise to CuI (200 mg, 103 mmol, 126 mol %) at −25 °C. After 30 min at −30 °C, the solution was cooled to −70 °C and a solution of 2-chloro-6-methyltetrahydropyran[3] (**1**, 0.86 mmol) in ether (1.5 mL) was added dropwise. After 75 min, the reaction was quenched with 1 M HCl and extracted three times with ether. GC indicated 76% yield of **2** and **3** (90:10). Evaporation of the ether left 65 mg (66% yield) of **2** and **3** (86:14): ^1H NMR (**2**, $CDCl_3$) δ 1.17 (6 H, d), 1.2 (2 H, m), 1.5 (4 H, s), 3.40 (2 H, m); ^{13}C NMR was consistent with literature.[20]

C. MeMgBr (0.5 mL, 2.39 M, 1.2 mmol, 140 mol %) was added over 2 min to *trans*-2-chloro-6-methyltetrahydropyran[3] (**1**, 0.86 mmol) in ether (1.5 mL) at −45 °C. After 45 min, the reaction was quenched with 1 M HCl and extracted three times with ether.

(24) Bonner, W. A.; Hurd, C. D. *J. Am. Chem. Soc.* **1951**, *73*, 4290.
(25) (a) Hillis, W. E.; Horn, D. H. S. *Aust. J. Chem.* **1965**, *18*, 531. (b) Bihovsky, R.; Li, H. unpublished results.
(26) (a) Alexakis, A.; Cahiez, G.; Normant, J. F. *Synthesis* **1979**, 826. (b) Posner, G. H.; Harrison, W.; Wettlaufer, D. G. *J. Org. Chem.* **1985**, *50*, 5041.
(27) (a) Trainor, G. L.; Smart, B. E. *J. Org. Chem.* **1983**, *48*, 2447. (b) DeShong, P.; Slough, G. A.; Elango, V.; Trainor, G. L. *J. Am. Chem. Soc.* **1985**, *107*, 7788.
(28) (a) Purdie, T.; Irving, J. C. *J. Chem. Soc.* **1903**, *83*, 1021. (b) Moeller, P. *Justus Liebigs Ann. Chem.* **1972**, *755*, 191.
(29) Overberger, C. G.; Merkel, T. F. *J. Org. Chem.* **1981**, *46*, 442.

GC indicated 100% yield of **2** and **3** (25:75). Evaporation of the ether left 85 mg (87% yield) of **2** and **3** (18:82): ^{1}H NMR (**3**, $CDCl_3$) δ 1.17 (6 H, d), 1.2 (2 H, m), 1.6 (4 H, s), 3.95 (2 H, m); ^{13}C NMR was consistent with literature.[20]

2,3,4,6-Tetra-*O*-methyl-α-D-glucopyranosyl bromide (5a) was prepared by a modification of our previous procedure.[15] HBr gas was bubbled into a solution of 2,3,4,6-tetra-*O*-methyl-D-glucopyranose (100 mg, 0.424 mmol) in dichloromethane (1 mL) at 20 °C for 5 min. The solvent was evaporated in vacuo at 35 °C, and remaining solvent was removed with a stream of N_2. The residue was extracted with anhydrous ether (2 × 0.5 mL). The cooled ether extract was quickly rinsed with cold water (0.1 mL) and then dried over $CaCl_2$ and Na_2CO_3, under which conditions it was stable for at least 18 h. The ether solution was generally utilized directly; however, evaporation of the solvent afforded **5a** (105 mg, 0.351 mmol, 83% yield). Physical and spectral properties were in accord with authentic material.[15]

2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl Bromide (5b). HBr gas was bubbled into a small flask containing a solution of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (400 mg, 0.741 mmol) in dichloromethane (3.5 mL) at 0 °C for 1 min. The flask was capped for 4 min, the solvent was evaporated in vacuo at 35 °C, and remaining solvent was removed with a stream of N_2. The residue was extracted with anhydrous ether, rinsed, and dried as above. The ether solution was generally utilized directly, however evaporation of the solvent afforded **5b** (438 mg, 0.726 mmol, 98% yield). Chromatographic and spectral properties were in accord with authentic material prepared from the *p*-nitrobenzoate of **4b**.[10i,16]

β-1,5-Anhydro-1-*C*-methyl-2,3,4,6-tetra-*O*-methyl-D-glucitol (6a). A. MeLi (0.85 mL, 1.6 M in ether, 1.36 mmol, 387 mol%) was added dropwise to a suspension of CuI (152 mg, 0.80 mmol, 228 mol%) in anhydrous ether (1 mL) at −30 °C. After 15 min at −35 °C, the mixture was nearly homogenous, and a solution of **5a** (0.351 mmol) in ether (1.5 mL) was added over 2 min, causing formation of a yellow precipitate. After 17 h at −35 °C, 1 M HCl (1 mL) was added. The mixture was warmed to 20 °C and extracted four times with ether and dried, and the solvent was evaporated to afford crude product (71 mg). GC before evaporation indicated **8a** (22%), **6a** (60%), and **5a** (18%). Much **8a** was lost during evaporation. Kugelrohr distillation (60–120 °C, 0.2 mm) afforded **6a** (42 mg, 51% yield), which was pure by GC and NMR. An analytical sample was prepared by chromatography on silica gel (50:50 ether–pentane).

B. MeLi (7.1 mL, 0.81 M, 5.75 mmol, 135 mol %) was added dropwise to a solution of 2,3,4,6-tetra-*O*-methyl-D-gluconic acid δ-lactone (**10**) (1.00 g, 4.27 mmol) in ether (10 mL) at −78 °C. After 7 min, the reaction was quenched with water. The lactol (800 mg, 75 % yield) was isolated as usual. Triethylsilane (93 mg, 0.80 mmol, 200 mol%) and this lactol (100 mg, 0.40 mmol) were dissolved in dichloromethane at −78 °C, and BF_3–Et_2O was added dropwise until the reaction was complete. The reaction was quenched with aqueous $NaHCO_3$ (5 mL), and the product was extracted into ether. The organic phase was washed and dried. The solvent was evaporated, and the residue was Kugelrohr distilled (80–120 °C, 0.2 mm) to afford **6a** (50 mg, 53 % yield): $[\alpha]^{22}_D$ +36.8° (*c* 4.4, $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 18.0 (q), 59.2 (q), 60.3 (q), 60.7 (q, 2 signals), 71.6 (t), 75.4 (d), 78.3 (d), 80.1 (d), 85.8 (d), 88.6 (d); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.29 (3 H, d, J = 6.2 Hz), 2.75 (1 H, t, J = 6.2 Hz), 3.15 (1 H, dq, J = 7.0, 8.8 Hz), 3.2–3.3 (2 H, m), 3.39 (3 H, s), 3.53 (3 H, s), 3.56 (3 H, s), 3.65 (3 H, s), 3.5–3.7 (3 H, m); IR (neat) 2930, 1460, 1390, 1310, 1110 cm^{-1}; mass spectrum, *m/e* (relative intensity) 101 (100), 175 (8), 189 (5), 218 (2). Anal. Calcd for $C_{11}H_{22}O_5$: C, 56.39; H, 9.46. Found: C, 55.98; H, 9.46.

β-1,5-Anhydro-2,3,4,6-tetra-*O*-benzyl-1-*C*-methyl-D-glucitol (6b) was purified by chromatography on silica gel (87:13 pentane–ethyl acetate: $[\alpha]^{22}_D$ +12.5° (*c* 4.1, $CHCl_3$); ^{13}C NMR (acetone-d_6) δ 18.5, 70.3, 73.7, 75.2, 75.4, 75.7, 75.9, 79.6, 84.8, 87.7, 128.1, 128.5, 128.9, 129.3, 129.3, 139.6, 139.6, 140.0; ^{1}H NMR ($CDCl_3$) δ 1.31 (3 H, d, J = 5.8 Hz), 3.28 (1 H, dq, J = 6, 8.5 Hz), 3.2–3.7 (6 H, m), 4.55 (2 H, s), 4.86 (2 H, s), 4.4–5.0 (4 H, m), 7.25 (20 H, s);[23a,c] IR (neat) 3070, 2930, 1500, 1460, 1120 cm^{-1}.

β-2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-1-*C*-methyl-D-glucitol (6c) was purified by chromatography on silica gel (60:40 pentane–ether): $[\alpha]^{22}_D$ +13.2° (*c* 8.9, $CHCl_3$); ^{13}C NMR (acetone-d_6) δ 18.1, 20.8, 63.5, 70.0, 74.4, 74.7, 75.0, 76.4, 170.3, 170.4, 170.6, 171.0; ^{13}C and ^{1}H NMR were consistent with literature;[23] IR (neat) 3000, 1760, 1440, 1380, 1240 cm^{-1}.

β-1,5-Anhydro-1-*C*-butyl-2,3,4,6-tetra-*O*-methyl-D-glucitol (6d) was purified by chromatography on silica gel (50:50 ether–pentane): $[\alpha]^{22}_D$ −3.7° (*c* 4.6 $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.7, 27.9, 31.4, 59.3, 60.3, 60.7, 60.7, 71.6, 78.7, 79.4, 80.1, 84.4, 89.1; ^{1}H NMR ($CDCl_3$) δ 0.95 (3 H, br d), 1.4 (6 H, m), 2.7–3.8 (7 H, m), 3.38 (3 H, s), 3.51 (3 H, s), 3.52 (3 H, s), 3.63 (3 H, s); IR (neat) 2980, 1460, 1390, 1310, 1120 cm^{-1}; mass spectrum, *m/e* (relative intensity) 101 (100), 175 (6), 199 (3), 202 (2), 231 (2). Anal. Calcd for $C_{14}H_{28}O_5$: C, 60.84; H, 10.21. Found: C, 60.64; H, 10.21.

β-1,5-Anhydro-2,3,4,6-tetra-*O*-methyl-1-*C*-phenyl-D-glucitol (6e). PhLi (0.75 mL, 1.8 M, in cyclohexane–ether, 70:30, 1.36 mmol, 387 mol %) was added dropwise to a suspension of CuI (128 mg, 0.672 mmol, 191 mol %) in anhydrous ether (1 mL) at −20 °C and then stirred for 4 min at 0 °C. The resulting green solution of cuprate containing some black precipitate was cooled to −35 °C, and a solution of **5a** (0.351 mmol) in ether (1.5 mL) was added over 2 min, causing formation of a precipitate. After the mixture was stirred 2 h at −35 °C and then 95 h at 20 °C, 1 M HCl (1 mL) was added and the mixture was extracted with ether. The organic layer was dried, and the solvent was evaporated. Chromatography on silica gel (pentane–ether, 60:40) gave **6e** (26 mg, 25 % yield): $[\alpha]^{22}_D$ +18.0° (*c* 6.0, $CHCl_3$);[30a] ^{1}H NMR ($CDCl_3$) δ 2.97 (3 H, s), 3.39 (3 H, s), 3.56 (3 H, s), 3.63 (3 H, s), 3.0–3.5 (6 H, m), 4.05 (1 H, d, J = 8.8 Hz); ^{13}C NMR ($CDCl_3$) δ 59.5, 60.2, 60.4, 60.9, 71.8, 79.1, 79.9, 81.6, 86.1, 88.5, 127.5, 128.0, 128.2 139.3; IR (neat) 2940, 1460, 1380, 1110 cm^{-1}; mass spectrum, *m/e* (relative intensity) 88 (37) 101 (100), 121 (16). Anal. Calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16. Found: C, 64.86; H, 8.11.

β-1,5-Anhydro-2,3,4,6-tetra-*O*-benzyl-1-*C*-phenyl-D-glucitol (6f). A. Ph_2CuLi reacted with **5b** to give **6f** (18 % yield) after purification by chromatography on silica gel (70:30 pentane–ether).

B. β-1,5-Anhydro-1-*C*-phenyl-D-glucitol (purified by crystallization of its acetate)[30] (48 mg, 0.20 mmol) was dissolved in anydrous dioxane (1 mL) and DMF (1 mL). Benzyl bromide (320 mg, 1.87 mmol, 935 mol %) and KH (154 mg, 3.85 mmol, 1925 mol %) were added, and a slightly exothermic reaction commenced. After 17 h, the solvent was evaporated in vacuo, water was added, and the mixture was extracted three times with ether. The organic phase was washed with water and dried, and the solvent evaporated. Chromatography on silica gel (75:25 pentane–ether) afforded **6f** (100 mg, 83% yield): mp 57–60 °C; $[\alpha]^{22}_D$ +27.6° (*c* 10.7 $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 69.3, 73.5, 74.7, 75.0, 75.5, 78.5, 79.5, 81.7, 84.4, 86.8, 127.6, 127.7, 128.0, 128.2, 128.3, 137.8, 138.4, 138.5, 138.8, 139.4; ^{1}H NMR ($CDCl_3$) δ 3.1–4.1 (7 H, m), 4.1–4.9 (8 H, m), 7.25 (25 H, m); IR (neat) 3070, 2930, 1500, 1460, 1110 cm^{-1}. Anal. Calcd for $C_{40}H_{40}O_5$: C, 79.97; H, 6.71. Found: C, 79.72; H, 6.51.

α-1,5-Anhydro-1-*C*-methyl-2,3,4,6-tetra-*O*-methyl-D-glucitol (7a). MeMgBr (0.50 mL, 2.4 M, in ether, 1.20 mmol, 342 mol %) was added dropwise to a solution of **5a** (0.351 mmol) in ether (1.5 mL) at −40 °C. A viscous solid precipitated, and stirring became difficult. After 18.5 h at −15 °C, standard workup gave crude product (55 mg). GC before evaporation indicated **5a** (12%), **6a** (24%), **7a** (46%), and **8a** (18%). The **8a** was removed (0.2 Torr), and the products were purified by column chromatography on silica gel (50:50 ether–pentane), providing **6a** (8 mg, 10% yield) and **7a** (24 mg, 29% yield). $[\alpha]^{22}_D$ +74° (*c* 5.8, $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 11.9, 58.4, 59.2, 60.4, 60.6, 69.6, 70.9, 71.9, 80.2, 81.8, 83.6; ^{1}H NMR (300 MHz) δ 1.20 (3 H, d, J = 7.0 Hz), 3.1–3.7 (6 H, m), 3.40 (3 H, s), 3.43 (3 H, s), 3.53 (3 H, s), 3.62 (3 H, s), 4.28 (1 H, dq, J = 5.5, 7 Hz); IR (neat) 2980, 1460, 1390, 1330, 1120 cm^{-1}; mass spectrum, *m/e* (relative intensity) 101 (100), 189 (23), 202 (1). Anal. Calcd for $C_{11}H_{22}O_5$: C, 56.39; H, 9.46. Found: C, 56.06; H, 9.46.

α-1,5-Anhydro-2,3,4,6-tetra-*O*-benzyl-1-*C*-methyl-D-glucitol (7b) was purified by chromatography on silica gel (85:15 pentane–ethyl acetate). $[\alpha]^{22}_D$ +19.8° (*c* 5.6, $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 12.2, 69.3, 70.2, 71.3, 73.0, 73.6, 75.1, 75.5, 78.4, 80.2, 82.2, 127.8, 128.0, 128.4, 138.1, 138.3, 138.8; ^{1}H NMR ($CDCl_3$) δ

(30) (a) Bonner, W. A.; Craig, J. M. *J. Am. Chem. Soc.* **1950**, *72*, 3481. (b) Hurd, C. D.; Bonner, W. A. *J. Am. Chem. Soc.* **1945**, *67*, 1664. (c) Bonner, W. A.; Koehler, W. L. *J. Am. Chem. Soc.* **1948**, *70*, 314.

1.27 (3 H, d, J = 6.8 Hz), 3.45–3.85 (6 H, m), 4.26 (1 H, pentet, J = 6.8 hz), 4.4–4.9 (8 H, m), 7.25 (20 H, br s); ^{13}C NMR and ^{1}H NMR data were consistent with literature;[23] IR (neat) 3060, 2950, 1500, 1460, 1100 cm^{-1}.

α-2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-1-*C*-methyl-D-glucitol (7c). Reaction of **5c** with excess MeMgBr followed by reacetylation,[10n] gave a light yellow oil (68% crude yield), which was purified by chromatography on silica gel (60:40 ether–pentane) to afford **6c** (6% yield) and **7c** (6% yield): ^{13}C NMR (acetone-d_6) δ 13.1, 20.9, 63.5, 69.7, 70.0, 70.2, 70.9, 71.7, 170.4, 170.8; ^{1}H NMR ($CDCl_3$) δ 1.29 (3 H, d, J = 6.9 Hz), 2.02 (3 H, s), 2.04 (3 H, s), 2.08 (3 H, s), 2.10 (3 H, s), 3.9–4.3 (2 H, m), 4.37 (1 H, pentet, J = 6.5 Hz), 4.9–5.4 (3 H, m); ^{13}C NMR and ^{1}H NMR were consistent with literature;[23] IR (neat) 2950, 1750, 1500, 1460, 1230, 1070 cm^{-1}.

α-1,5-Anhydro-2,3,4,6-tetra-*O*-methyl-1-*C*-phenyl-D-glucitol (7e). PhMgBr (0.70 mL, 1.05 M, in ether, 0.734 mmol, 210 mol %) was added dropwise to a solution of **5a** (0.351 mmol) in ether (1.5 mL) at −60 °C. Stirring became impossible. After the reaction was stirred at 20 °C for 140 h, standard workup gave crude product (157 mg), which was purified by column chromatography on silica gel (50:50 ether–pentane), providing **6e** (23 mg, 22% yield) and **7a** (20 mg, 19% yield): $[\alpha]^{22}_D$ +66.6° (c 3.9, $CHCl_3$);[30a] ^{13}C NMR ($CDCl_3$) δ 58.7, 59.2, 60.1, 60.2, 71.6, 72.0, 73.2, 79.9, 83.0, 83.5, 127.5, 128.3, 128.3, 137.8; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.40 (3 H, s), 3.46 (3 H, s), 3.52 (3 H, s), 3.68 (3 H, s), 3.0–3.7 (6 H, m), 5.21 (1 H, d, J = 4.0 Hz), 7.3 (3 H, m), 7.68 (2 H, d); IR (neat) 2910, 1750, 1440, 1090 cm^{-1}; mass spectrum, m/e (relative intensity) 88 (46) 101 (100), 121 (19). Anal. Calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16. Found: C, 60.94; H, 7.70.

1,5-Anhydro-3,4,6-tri-*O*-methyl-2-deoxy-D-*arabino*-hex-1-enitol (8a) was purified by chromatography on silica gel (60:40 pentane–ether) followed by careful evaporation to prevent loss of volatile **8a**:[18] ^{13}C NMR ($CDCl_3$) δ 55.65, 59.08, 59.19, 70.63, 75.70, 76.07, 77.09, 99.38, 144.42; ^{1}H NMR ($CDCl_3$, 80 MHz) δ 3.33 (3 H, s), 3.34 (3 H, s), 3.47 (3 H, s), 3.3–3.7 (5 H, m), 3.86 (1 H, dm), 4.75 (1 H, dd, J = 3, 6 Hz), 6.32 (1 H, dd, J = 1, 6 Hz); mass spectrum, m/e (relative intensity) 71 (100), 101 (100).

1,5-Anhydro-2,3,4,6-tetra-*O*-methyl-D-*arabino*-hex-1-enitol (9a). MeLi (0.75 mL, 1.6 M in ether, 1.20 mmol, 342 mol %) was added dropwise to a solution of **5a** (0.351 mmol) in ether at −35 °C. After 3.5 h at −35 °C, standard workup gave crude product (62 mg), a mixture of **5a** (30%) and **9a** (70%). The product was purified by column chromatography on silica gel (50:50 ether–pentane: ^{13}C NMR ($CDCl_3$) δ 55.79, 57.43, 58.48, 59.19, 70.56, 75.48, 76.66, 125.25, 139.75; ^{1}H NMR ($CDCl_3$, 80 MHz) δ 3.36 (3 H, s), 3.46 (3 H, s), 3.50 (3 H, s), 3.6 (2 H, m), 3.9 (3 H, m), 6.13 (1 H, s);[17] mass spectrum, m/e (relative intensity) 71 (58), 86 (33), 101 (63), 116 (100), 218 (14).

2,3,4,6-Tetra-*O*-methyl-D-gluconic Acid δ-Lactone (10). Pyridinium chlorochromate (1.80 g, 8.35 mmol, 195 mol %) in dichloromethane (7.5 mL) was added to 2,3,4,6-tetra-*O*-methylglucopyranose (**4a**) (1.00 g, 4.27 mmol) dissolved in dichloromethane (7.5 mL), and the mixture was refluxed for 7.5 h. The cooled mixture was diluted with ether (75 mL), decanted, and filtered through magnesium silicate. Evaporation of the solvent followed by Kugelrohr distillation (90–120 °C, 0.2 mmHg) afforded **10** (855 mg, 86% yield) as an oil. The classical oxidation of **4a** to **10** with bromine affords a lower yield and requires a tedious isolation procedure:[28] ^{1}H NMR ($CDCl_3$) δ 3.41 (3 H, s), 3.51 (3 H, s), 3.53 (3 H, s), 3.57 (3 H, s), 3.1–3.9 (5 H, m), 4.5 (1 H, ddd).

Acknowledgement is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, the National Institutes of Health (Grant AI 23281), and the New York State Science and Technology Foundation for support of this research. We thank Drs. Stuart Rosenblum and Edmund Marinelli for assistance in obtaining spectra.

Methods for the Introduction of a Phenylselenium Dichloride Group into the α-Position of Carbonyl Compounds. Syntheses of Enones

Lars Engman

Department of Organic Chemistry, Royal Institute of Technology, S-100 44 Stockholm, Sweden

Received March 8, 1988

Phenylselenium trichloride, $PhSeCl_3$, directly introduced, in fair yield, a $PhSeCl_2$ group into the α-position of ketones with loss of HCl. To some extent, depending on the substrate, this reagent was also shown to act as a chlorinating agent toward ketones, yielding α-chloro ketones and α-phenylselenenyl ketones. The latter compounds were readily converted to selenium(IV) dichlorides by SO_2Cl_2 chlorination to significantly improve the overall yields of the selenation process. The consecutive treatment of ketones with PhSeCl and SO_2Cl_2 could also be used for the introduction of a $PhSeCl_2$ group, but this procedure was usually less efficient than the $PhSeCl_3$-based one. Unsymmetrical ketones were selenated with poor regiocontrol. Aldehydes were primarily chlorinated by treatment with $PhSeCl_3$, but consecutive treatment with $PhSeCl_3$ and SO_2Cl_2 introduced a $PhSeCl_2$ group into the α-position. Carboxylic acids and esters were unreactive toward $PhSeCl_3$ and PhSeCl. $PhSeCl_3$ underwent addition reactions with enones to introduce a $PhSeCl_2$ group α or β to the carbonyl group, depending on the substrate. The carbonyl compounds substituted in the α-position with a $PhSeCl_2$ group were easily converted to the corresponding α,β-unsaturated carbonyl compounds after hydrolysis/selenoxide elimination. Since the selenium(IV) intermediates involved were highly crystalline and easy to purify, the preparation of enones from symmetrical ketones via $PhSeCl_2$ introduction/hydrolytic elimination was especially convenient to perform from the operational point of view.

Introduction

The selenoxide syn-elimination reaction represents one of the most important methods for the introduction of unsaturation into organic molecules.[1] In order to make use of the reaction, selenium is commonly introduced in the *divalent* state into an organic molecule, starting from commercially available reagents like benzeneselenenyl halides or diphenyl diselenide. Oxidation of the resulting organyl phenyl selenide to a selenoxide is then usually accompanied by a rapid syn-elimination process to yield the desired olefinic product.

We recently reported a new variation of this reaction using phenylselenium trichloride for the introduction of *tetravalent* selenium into an organic molecule (eq 1).[2]

(1) Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*; Pergamon: Oxford, 1986.

0022-3263/88/1953-4031$01.50/0