A Direct Synthesis of *C*-Glycosyl Compounds

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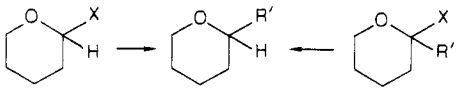
Lactone **4** (R = Bn) can be converted into *C*-glycosyl compounds by reaction with an organometallic reagent followed by reduction with Et_3SiH and $BF3{\cdot}Et_2O$.

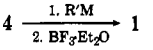
Glycosyl compounds have been important to organic chemists for almost a century. Recently, the subclass of *C*-glycosyl compounds has become a topic of high interest. In part, the interest stems from the increasing use of carbohydrates as synthetic intermediates for organic synthesis.[1] However, the isolation of the potent anticancer agents nogalamycin and lactoquinomycin, both of which are *C*-glycosyl compounds, and the attendant synthetic interest in these compounds and their analogues has also prompted new research into *C*-glycosyl compound synthesis.[2]

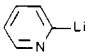
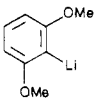
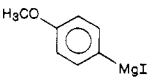
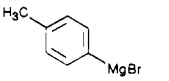
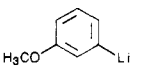
Danishefsky,[3] Kozikowski,[4] and Townsend[5] have formed *C*-glycosyl compounds by reacting carbohydrate esters with allylsilanes and Lewis acids. A related tact was taken by Williams[6] who reacted pyridyl thioglycosides with electron-rich aromatic compounds and enol silyl ethers in the presence of silver triflate. Schmidt has employed a similar strategy.[7] DeShong has prepared carbanions at C-1 on the way to *C*-glycosyl compounds.[8] Giese has generated *C*-glycosyl compounds by conjugate addition of a radical at C-1.[9] In all of the above cases, the crucial stereogenic center at C-1 was created by adding the R′ group last. The



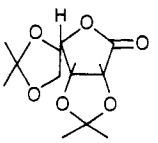
alternate possibility, adding the hydrogen atom last, has received almost no attention. Kishi and co-workers[10] examined cases in which X = OH and R′ was an aliphatic group. In each case the aliphatic group was in the equatorial position in the product. Nicolaou also employed this strategy in an elegant assembly of a tetracyclic precursor to the brevetoxins.[11] Our research in this area originated from our study of the reduction of cyclic hemiacetals to cyclic ethers.[12] We have extended this reduction reaction to the production of substituted cyclic ethers from hemiketals.[13] We now report the preparation of *C*-glycosyl compounds from carbohydrate hemiketals wherein R′ is an aryl or vinyl group.

Table I

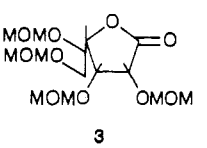


entry	R′M	% yield
1	PhMgCl	88
2	2-furyllithium	
3		65
4	$CH_2{=}CHMgBr$	60
5		
6		95
7		80
8		78

Initially, lactones **2**–**4**[14] were examined. Since both alkyl and aryl organometallics were known to add to carbohydrates lactones to form hemiketals,[15] the first important question was the compatibility of the alcohol protecting groups to the reaction conditions. Unfortunately, neither



2



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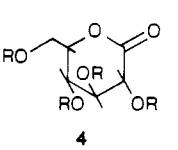
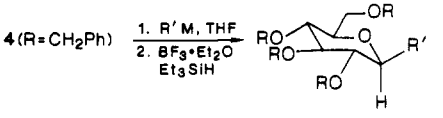


4

R = CH_2Ph
R = COPh

the methoxymethyl (MOM) groups in **2** nor the acetonide groups in **3** were stable to the reduction conditions ($BF_3{\cdot}Et_2O$, Et_3SiH). Additionally, the addition of phenylmagnesium chloride to the tetrabenzoate of **4** was not chemoselective. However, the benzylated derivative of **4** afforded good overall yields of *C*-glycosyl compounds.

The results of our study are depicted in Table I. The overall yields are very good. Several functional groups are compatible with the reaction conditions. The failure to



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reduce the furan adduct is presumably due to the well-known acid lability of furfuryl alcohols. The failure of the reaction involving (2,6-dimethoxyphenyl)lithium with **4** (R = Bn) may be due to enolization of the lactone.

(1) Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach*; Pergamon: New York, 1983.
(2) Nogalamycin. See: Kawasaki, M.; Matsuda, F.; Terashima, S. *Tetrahedron Lett.*, **1986**, 2145 and references therein. Lactoquinomycin: Okabe, T.; Nomoto, K.; Funabashi, H.; Okuda, S.; Suzuki, H.; Tanaka, N. *J. Antibiot.* **1985**, *38*, 1336.
(3) Danishefsky, S.; Kerwin, J. F. *J. Org. Chem.* **1982**, *47*, 3803.
(4) Kozikowski, A.; Sorgi, K. L. *Tetrahedron Lett.* **1982**, *23*, 2281.
(5) Cupps, T. L.; Wise, D. S.; Townsend, L. B. *J. Org. Chem.* **1982**, *47*, 5115.
(6) Stewart, A. O.; Williams, R. M. *J. Am. Chem. Soc.* **1985**, *107*, 4289.
(7) Schmidt, R. R.; Hoffman, M. *Tetrahedron Lett.* **1982**, *23*, 409.
(8) DeShong, P.; Slough, G. A.; Elango, V. *J. Am. Chem. Soc.* **1985**, *107*, 7788.
(9) Dupuis, J.; Giese, B.; Hartung, J.; Leising, M.; Korth, H.-G.; Sustmann, R. *J. Am. Chem. Soc.* **1985**, *107*, 4332.
(10) Lewis, M. D.; Cha, K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976. Babirad, S. A.; Wang, Y.; Kishi, Y. *J. Org. Chem.* **1987**, *52*, 1370.
(11) Nicolaou, K. C.; Hwang, C.-K., Duggan, M. E.; Reddy, K. B.; Marron, B. E.; McGarry, D. G. *J. Am. Chem. Soc.* **1986**, *108*, 6800.
(12) Kraus, G. A.; Frazier, K. A.; Roth, B. D.; Taschner, M. J.; Neuenschwander, K. *J. Org. Chem.* **1981**, *46*, 2417.
(13) Kraus, G. A.; Molina, M. T.; Walling, J. A. *J. Chem. Soc., Chem. Commun.* **1986**, 1568. Kraus, G. A.; Molina, M. T.; Walling, J. A. *J. Org. Chem.* **1987**, *52*, 1273.
(14) Kuzuhara, H.; Fletcher, H. G., Jr. *J. Org. Chem.* **1967**, *32*, 2531.
(15) Ogura, H.; Takahashi, H. *J. Org. Chem.* **1974**, *39*, 1374.

0022-3263/88/1953-0752$01.50/0

Stereochemistry at C-1 in our products was determined by preparing tetraacetate 1 (R = Ac, R′ = Ph) by reduction (H_2, Pd/C) and acetylation (Ac_2O, pyr, DMAP). Both the melting point (158 °C) and the coupling constant of 9.7 Hz ($J_{1,2}$) agree with the literature values for a β-oriented phenyl group.[16] The recent observation that a vinyl C-glycosyl compound could be hydroxylated stereoselectively with osmium tetraoxide makes 1 (R′ = ethenyl) a precursor to eight-carbon sugars.[17]

The results described herein show that C-glycosyl compounds containing an aryl or vinyl moiety in the equatorial position can be readily synthesized. The reactions can be conducted under mild acidic conditions. We are extending this work to the synthesis of C-nucleosides.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. Dichloromethane was distilled from phosphorus pentoxide. Infrared spectra were determined on a Perkin-Elmer 1320 spectrometer. Nuclear magnetic resonance spectra were determined on a Nicolet 300 MHz instrument. Carbon-13 NMR spectra were determined on a Nicolet 300 MHz instrument. High-resolution mass spectra were determined on a Kratos mass spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc.

General Procedure. To a solution of lactone 4 (1 equiv in dry THF (10 mL/mmol of lactone) at −78 °C was added the organometallic reagent (1.5 equiv). The reaction mixture was stirred for 1 h and then allowed to warm to 0 °C. The reaction was then quenched with water and extracted with methylene chloride. The organic layer was dried and concentrated. The crude ketol was immediately dissolved in methylene chloride (10 mL/equiv) and cooled to −78 °C. Triethylsilane (3 equiv) and then BF_3·Et_2O (3 equiv) was added and the reaction mixture stirred for 1 h. The reaction was then allowed to warm slowly to room temperature over 3 h. The reaction was quenched by pouring onto ice-cold brine. After extraction and concentration, the crude product was chromatographed on silica gel by using hexanes/ethyl acetate.

1 (R = Bn, R′ = Ph): 300-MHz NMR ($CDCl_3$) δ 3.43–3.85 (m, 5 H), 4.24 (d, J = 10 Hz, 1 H) 4.37 (d, J = 10 Hz, 1 H), 4.42–4.70 (m, 4 H), 4.76–5.02 (m, 4 H), 6.89–6.95 (m, 2 H), 7.05–7.8 (m, 23 H); IR (film) 3030, 2860, 1600, 1495, 1452, 1358, 1090, 1735, 695 cm^{-1}. MS, *m/e* 91, 181, 253, 295, 509, 600; HRMS, *m/e* for $C_{40}H_{40}O_5$ calcd 600.27858, found 600.28565.

1 (R = Bn, R′ = 2-pyridyl): 300-MHz NMR ($CDCl_3$) δ 3.70 (d, *J* = 12 Hz, 1 H), 3.83–3.98 (m, 3 H), 4.08 (d, *J* = 12 Hz, 1 H), 4.24–4.31 (m, 2 H), 4.52 (d, *J* = 12 Hz, 2 H), 4.60–4.72 (m, 2 H), 4.97 (s, 2 H), 6.86 (d, *J* = 8 Hz, 1 H), 7.13 (d, *J* = 8 Hz, 1 H), 7.23–7.47 (m, 20 H), 7.66 (br t, *J* = 8 Hz, 1 H), 8.56 (d, *J* = 8 Hz, 1 H); IR (film) 3020, 1592, 1495, 1452, 1090, 1075, 740, 696 cm^{-1}; MS, *m/e* 91, 107, 253, 268, 358, 418, 447, 526, 601, 617.

1 (R = Bn, R′ = ethenyl): 300-MHz NMR ($CDCl_3$) δ 3.3–3.38 (m, 1 H), 3.42–3.52 (m, 1 H), 3.59–3.80 (4 H), 4.52–4.93 (m, 8 H), 5.26–5.5 (m, 3 H), 5.70–6.10 (m, 1 H), 7.1–7.4 (m, 20 H); IR (film) 3030, 2920, 1450, 1060, 749, 696 cm^{-1}; MS, *m/e* 91, 181, 253, 353, 459, 550; HRMS, *m/e* for $C_{36}H_{38}O_5$ calcd 550.27193,found 550.27130.

1 (R = Bn, R′ = *p*-MeOC$_6$H$_4$): 300-MHz NMR ($CDCl_3$) δ 3.46–3.72 (m, 2 H), 3.80 (s, 3 H), 3.75–4.0 (m, 3 H), 4.07–4.14 (m, 1 H), 4.20 (d, *J* = 10 Hz, 1 H), 4.37 (d, *J* = 10 Hz, 1 H), 4.42–4.74 (m, 5 H), 4.84–5.00 (m, 2 H), 6.82–6.97 (m, 2 H), 7.12–7.40 (m, 22 H); IR (film) 3025, 2900, 1610, 1510, 1450, 1100, 1065, 736, 695 cm^{-1}; MS, *m/e* 91, 181, 253, 522, 539, 630; HRMS, *m/e* for $C_{41}H_{42}O_6$ calcd 630.29815, found 630.29944.

1 (R = Bn, R′ = *p*-CH$_3$C$_6$H$_4$): 300-MHz NMR ($CDCl_3$) δ 2.36 (s, 3 H), 3.45–3.85 (m, 6 H), 4.22 (d, *J* = 10 Hz, 1 H), 4.35 (d, *J* = 10 Hz, 1 H), 4.42–4.70 (m, 4 H), 4.76–5.02 (m, 3 H), 6.92–6.97 (m, 2 H), 7.14–7.40 (m, 22 H); IR (film) 3025, 2860, 1495, 1451, 1357, 1095, 1067, 734, 696 cm^{-1}; MS, *m/e* 91, 191, 253, 523, 614; HRMS, *m/e* for $C_{41}H_{42}O_5$ calcd 614.30323, found 614.30218.

1 (R = Bn, R′ = *m*-MeOC$_6$H$_4$): 300-MHz NMR ($CDCl_3$) δ 3.45–3.87 (m, 5 H), 3.76 (s, 3 H), 4.02–4.09 (m, 1 H), 4.22 (d, *J* = 9 Hz, 1 H), 4.39 (d, *J* = 9 Hz, 1 H), 4.43–5.00 (m, 7 H), 6.78–7.45 (m, 24 H); IR (film) 3025, 1600, 1495, 1442, 1092, 735, 695 cm^{-1}; MS, *m/e* 91, 181, 253, 325, 341, 415, 433, 539, 630; HRMS, *m/e* for $C_{41}H_{42}O_6$ calcd 630.29815, found 630.29751.

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Registry No. 1 (R = Bn, R′ = Ph), 112219-64-4; 1 (R = Bn, R′ = 2-pyridyl), 112219-65-5; 1 (R = Bn, R′ = ethenyl), 112219-66-6; 1 (R = Bn, R′ = *p*-MeOC$_6$H$_4$), 93414-73-4; 1 (R = Bn, R′ = *p*-MeC$_6$H$_4$), 112219-67-7; 1 (R = Bn, R′ = *m*-MeOC$_6$H$_4$), 112219-68-8; 4 (R = Bn), 13096-62-3; CH_2=CHMgBr, 1826-67-1; MeOC$_6$H$_4$-*p*-MgI, 112219-63-3; MeC$_6$H$_4$-*p*-MgBr, 4294-57-9; MeOC$_6$H$_4$-*m*-Li, 31600-88-1; 2-lithiopyridine, 17624-36-1.

(16) Chen, S.; Gao, Y.; Cai, M. *Huaxue* Tongbao **1985**, 19.
(17) Brimacombe, J. S.; Kabir, A. K. M. S. *Carbohydr. Res.* **1986**, *150*, 35.