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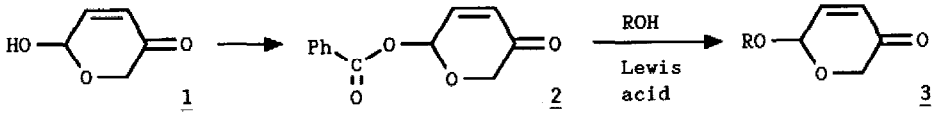
IMPROVED PROCEDURE FOR THE SYNTHESIS OF 6-ALKOXY-2,3-DIHYDRO-6H-PYRAN-3-ONES (2,3-DIDEOXY-DL-PENT-2-ENOPYRANOS-4-ULOSES). NEAT CONVERSION INTO POLYFUNCTIONALIZED CYCLOPENTENONES.

Bernd MUCHA and H.Martin R. HOFFMANN*
Department of Organic Chemistry, University of Hannover,
Schneiderberg 1B, D-3000 Hannover, F.R. Germany

Abstract - The glycosidic bond of 6-alkoxy-2,3-dihydro-6*H*-pyran-3-ones (**3**) is made advantageously in the presence of catalytic $ZnCl_2$·etherate. A palladium-assisted transformation of **3** affords *trans*-4-alkoxy-5-hydroxy-2-cyclopenten-1-ones (**4**) in good yield.

The construction of the glycosidic linkage is a key reaction in oligosaccharide chemistry.[1-3] In the instance of 6-alkoxy-2,3-dihydro-6*H*-pyran-3-ones (**3**), the classical Königs-Knorr reaction is not applicable, because a glycosyl halide of **1** cannot easily be obtained.[4] Instead, activation of **1** via the crystalline benzoate **2** is feasible. Treatment of **2** with a variety

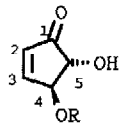
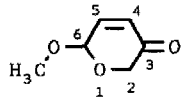
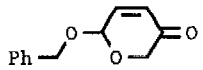
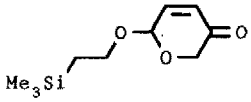
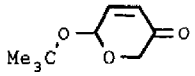
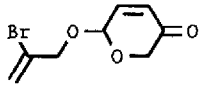
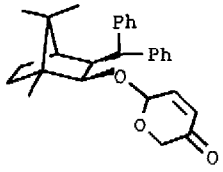
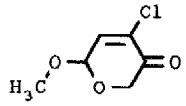
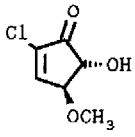
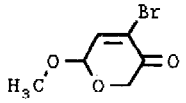
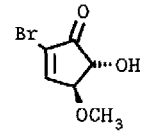


1 2 3

		this work	ref.5
3a	R = $CH_3C(=CH_2)C{\equiv}CCH_2O$-	61%	23%
3b	R = *l*-menthyl-O-	78%	58%

of alcohols in the presence of $SnCl_4$ has been shown to give 6-alkoxy-2,3-dihydro-6*H*-pyran-3-ones (**3**) (2,3-dideoxy-DL-pent-2-enopyranos-4-uloses).[5] We now report that $ZnCl_2$·etherate[6] in 1,2-dichloroethane is superior to $SnCl_4$ as a Lewis acid catalyst in this glycosidation. In a typical experiment, the sensitive 4-methyl-4-penten-2-yn-1-ol and benzoate **2** gave acetal **3a** in 61% yield,[7] whereas $SnCl_4$[5] gave the desired acetal in 23% yield only. In the case of *l*-menthol activated zinc chloride according to Mayr[6] gave **3b** in 78% yield, whereas $SnCl_4$ gave **3b** in 58% yield.[5] Glycoside **3a** and various other derivatives are of considerable interest for annulation reactions.[8] Further studies were aimed at converting the series of α-alkoxyethers **3**

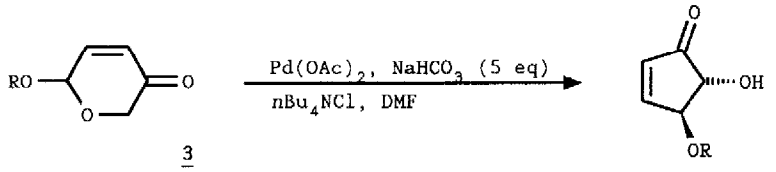
Table - Improved Route to 6-Alkoxy-2,3-dihydro-6*H*-pyran-3-ones (**3**). Palladium-assisted Diastereoselective Transformation into *trans*-4-Alkoxy-5-hydroxy-2-cyclopenten-1-ones (**4**).

	6-Alkoxypyran-3-one (3) Prepared[a]	Yield[%] Electrophilic Catalyst[b] $SnCl_4$	Yield[%] Electrophilic Catalyst[b] $ZnCl_2$·etherate	R in  4	Yield [%]
c		67(10)[c]	48-64(10)	CH_3	62
d		73(10)[c]	88-93(10)	CH_2Ph	50
e		--	77-82(10)	$CH_2CH_2SiMe_3$	50-67
f		50(10)[c]	49(10)	t-Bu	60
g		--	87-93(10)	CH_2-CBr=CH_2	30
h		--	84(10)[d]	exo-cis-diphenylmethylisoborneyl	84
i		Ref. 15			26
j		Ref. 15			24

[a]Acetals **3a-j** were purified by chromatography (silica gel, ether/light petroleum). [b]The number in brackets refers to the amount of catalyst (in mol%) with respect to benzoate. [c]Ref. 5. Methanol adds to **3c** in a consecutive Michael reaction. [d]Diastereomeric mixture, separable by column chromatography. Levorotatory diastereomer, $[\alpha_D]^{21}$= -26.3 ($CHCl_3$, c=0.615 g/100 ml), 74%; dextrorotatory diastereomer, $[\alpha_D]^{21}$= +26.4 ($CHCl_3$, c=0.935 g/100 ml), isolated in 10%yield.

into carbocycles. Much recent[9-11] and also earlier work[12] has centered on this general problem, viz. preparing carbocycles from carbohydrates. To date, many of the protocols are still lengthy and involve several operational steps, in which the new ring is often constructed "around" the carbohydrate[13] (the "annulated sugar" approach[11b]).

After exploratory experiments showed the cyclic acetals **3** to disappear slowly in the presence of base, we conceived of utilizing transition metal catalysis combined with solid/liquid phase transfer conditions. Thus, acetals **3c-j** were found to enter into a new **one-pot** reaction which afforded a wide range of functionalized 2-cyclopenten-1-ones (**4**) in simple manner. For



3 4

example, 6-(2-trimethylsilylethoxy)-2,3-dihydro-6*H*-pyran-3-one (**3e**) (0.35 g, 1.6 mmol) and freshly obtained $Pd(OAc)_2$ (36 mg, 10 mol%) were dissolved in anhydrous dimethylformamide (DMF) (48 ml). After addition of solid $NaHCO_3$ (0.67 g, 8 mmol) and nBu_4NCl (0.43 g, 1.6 mmol) the resulting mixture was vigorously stirred for ca. 24 h at 80°C (TLC control). The dimethylformamide was removed at reduced pressure, and the resulting residue was taken up in CH_2Cl_2, the filtrate was concentrated and chromatographed (silica gel, ether/light petroleum). The resulting carbocycles were fully identified by spectroscopy.[14] All cyclopentenones were formed diastereoselectively, i.e. the alkoxy group was always found *trans* to the hydroxy group in **4**. The formation of 2-halocyclopentenones **4i,j** from **3i,j** shows that the reaction tolerates additional sensitive functionality and has fairly broad scope.

In conclusion, we have described a useful method for preparing 6-alkoxy-2,3-dihydro-6*H*-pyran-3-ones (**3**) and have found a new and flexible palladium-assisted transformation of these carbohydrate building blocks. The resulting *trans*-4-alkoxy-5-hydroxy-2-cyclopenten-1-ones (**4**) are of obvious interest in natural products chemistry.

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References and Notes

(1) Reviews: Schmidt, R.R. *Angew.Chem.Int.Ed.Engl.* **1986**, *25*, 212; *Angew. Chem.* **1986**, *98*, 213; Castro, B.R. *Org.React.* **1983**, *29*, 1; Paulsen, H. *Angew.Chem.Int.Ed.Engl.* **1982**, *21*, 155; *Angew.Chem.* **1982**, *94*, 184.

(2) Smith, A.B.; Rivero, R.A. *J.Am.Chem.Soc.* **1987**, *109*, 1272; Matsumoto, T.; Katsuki, M.; Suzuki, K. *Chem.Lett.* **1989**, 437.

(3) Kahne, D.; Yang, D.; Lim, J.J.; Miller, R.; Paguaga, E. *J.Am.Chem.Soc.* **1988**, *110*, 8716; Barrett, A.G.M.; Bezuidenhout, B.C.B.; Howell, A.R.; Lee, A.C.; Russell, M.A. *J.Org.Chem.* **1989**, *54*, 2275.

(4) Grynkiewicz, G.; Zamojski, A. *Synth.Commun.* **1978**, *8*, 491.
(5) Grynkiewicz, G.; Barszczak, B.; Zamojski, A. *Synthesis* **1979**, 364.
(6) Mayr, H.; Striepe, W. *J.Org.Chem.* **1985**, *50*, 2995.
(7) Illustrative procedure for preparing **3**. Benzoate **2** (0.5 g, 2.3 mmol) and 4-methyl-4-penten-2-yn-1-ol (0.26 g, 2.75 mmol) (2 eq. were used when the alcohol was inexpensive) in 1,2-dichloroethane (4 ml) were mixed with $ZnCl_2$·etherate[6] (104 µl of a 2.2 M solution in CH_2Cl_2, 10 mol%). After 45 min the reaction mixture was poured into saturated $NaHCO_3$, and the organic layer was separated, washed several times with water and dried ($MgSO_4$). The resulting acetal **3a** was purified by column chromatography (silica gel, ether/light petroleum).
(8) Hoffmann, H.M.R.; Mucha, B. Unpublished experiments.
(9) Five-membered rings: Mezzina, E.; Savoia, D.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J.Chem.Soc. Perkin Trans.I* **1989**, 845; Rajan-Babu, T.V. *J.Org.Chem.* **1988**, *53*, 4522; RajanBabu, T.V. *J.Am.Chem.Soc.* **1987**, *109*, 609; RajanBabu, T.V.; Nugent, W.A.; Taber, D.F.; Fagan, P.J. *J.Am.Chem.Soc.* **1988**, *110*, 7128; Bartlett, P.A.; McLaren, K.L.; Ting, P.C. *J.Am.Chem.Soc.* **1988**, *110*, 1633; Bélanger, P.; Prasit, P. *Tetrahedron Lett.* **1988**, *29*, 5521; Wilcox, C.S.; Gaudino, J.J. *J.Am.Chem.Soc.* **1986**, *108*, 3102; Wilcox, C.S.; Thomasco, L.M. *J.Org.Chem.* **1985**, *50*, 546; Ferrier, R.J.; Furneaux, R.H.; Prasit, P.; Tyler, P.C.; Brown, K.L.; Gainsford, G.J.; Diehl, J.W. *J.Chem.Soc. Perkin Trans.I* **1983**, 1621 and subsequent publications; Bernet, B.; Vasella, A. *Helv.Chim.Acta* **1979**, *62*, 1990, 2400, 2411.
(10) Six-membered rings: Ferrier, R.J. *J.Chem.Soc. Perkin Trans.I* **1979**, 1455 and subsequent papers; Fleet, G.W.J.; Shing, T.K.M.; Warr, S.M. *J.Chem.Soc. Perkin Trans.I* **1984**, 905.
(11) (a) Vite, G.D.; Alonso, R.; Fraser-Reid, B. *J.Org.Chem.* **1989**, *54*, 2268; (b) Fraser-Reid, B.; Tsang, R. in: *Strategies and Tactics in Organic Synthesis*, Vol.2, ch. 4. Lindberg, T., ed. Academic Press, San Diego, 1989; (c) Fraser-Reid, B. *Acc.Chem.Res.* **1985**, *18*, 347.
(12) Lichtenthaler, F.W. *Angew.Chem.Int.Ed.Engl.* **1964**, *3*, 211; *Angew.Chem.* **1964**, *76*, 84; Grosheintz, J.M.; Fischer, H.O.L. *J.Am.Chem.Soc.* **1948**, *70*, 1479.
(13) Review: Hanessian, S. *Total Synthesis of Natural Products: The "Chiron" Approach.* Pergamon Press, Oxford, 1983, ch. 13; Krohn, K. *Nachr.Chem.Tech.Lab.* **1987**, *35*, 1155.
(14) Selected spectral data. **3a**: ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.91 (dd, J=1 Hz, J<1 Hz, CH_3), 4.12 (d, ^2J=17 Hz, H-2), 4.49 (d, ^2J=17 Hz, H-2), 4.50 (s, CH_2), 5.27 (bs, sp^2 CH), 5.34 (bs, sp^2 CH), 5.44 (d, $J_{5,6}$=3.5 Hz, H-6), 6.19 (d, $J_{4,5}$=10 Hz, H-4), 6.93 (dd, $J_{4,5}$=10 Hz, $J_{5,6}$=3.5 Hz, H-5); IR (film) 1710, 1105, 1065, 1035 cm^{-1}. **3c**: ^{1}H NMR (90 MHz, $CDCl_3$, TMS) δ 3.55 (s, 3 H, OCH_3), 4.09 (d, ^2J=17 Hz, H-2), 4.48 (d, ^2J=17 Hz, H-2), 5.14 (d, $J_{5,6}$=3.5 Hz, H-6), 6.14 (dd, $J_{4,5}$=10 Hz, $J_{5,6}$=3.5 Hz, H-5); IR (film) 1710, 1690, 1105, 1060 cm^{-1}. **3e**: ^{1}H NMR (90 MHz, $CDCl_3$, without TMS) δ 0.02 (s, 9 H, $Si(CH_3)_3$), 1.07 (m, 2 H, CH_2SiMe_3), 3.46-4.11 (m, 2 H, $CH_2CH_2SiMe_3$), 4.06 (d, ^2J=17 Hz, H-2), 4.47 (d, ^2J=17 Hz, H-2), 5.21 (d, $J_{5,6}$=3.5 Hz, H-6), 6.11 (d, $J_{4,5}$=10 Hz, H-4), 6.87 (dd, $J_{4,5}$=10 Hz, $J_{5,6}$=3.5 Hz, H-5); IR (film) 2950, 1710, 1250, 1105 cm^{-1}. **4c**: ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 3.29 (bs, OH), 3.60 (s, OCH_3), 4.21 (d, $J_{4,5}$=2.5 Hz, H-5), 4.38 (m, H-4), 6.30 (dd, $J_{2,3}$=6 Hz, $J_{2,4}$=2 Hz, H-2), 7.51 (dd, $J_{2,3}$=6 Hz, $J_{3,4}$=2 Hz, H-3); IR ($CHCl_3$) 3560, 1725, 1120 cm^{-1}. **4e**: ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ -0.01 (s, 9 H, $Si(CH_3)_3$), 0.96 (m, 2 H, CH_2SiMe_3), 3.53-4.02 (m, 3 H, $CH_2CH_2SiMe_3$ and OH), 4.15 (d, $J_{4,5}$= 2.5 Hz, H-5), 4.40 (m, H-4), 6.21 (dd, $J_{2,3}$=6 Hz, $J_{2,4}$=2 Hz, H-2), 7.44 (dd, $J_{2,3}$=6 Hz, $J_{3,4}$=2 Hz, H-3); IR (film) 3530, 1730, 1250, 1120 cm^{-1}. **4i**: ^{1}H NMR (200 MHz, CD_2Cl_2, TMS) δ 3.09 (bs, OH), 3.55 (s, OCH_3), 4.25 (d, $J_{4,5}$=2.5 Hz, H-5), 4.34 (dd, $J_{3,4}$=2 Hz, $J_{4,5}$=2.5 Hz, H-4), 7.44 (d, $J_{3,4}$=2 Hz, H-3); IR (KBr) 3340, 1735 cm^{-1}.
(15) Hajivarnava, G.S.; Overend, W.G.; Williams, N.R. *Carbohydr.Res.* **1976**, *49*, 93. Preparation of epoxide precursors: Torii, S.; Tanaka, H.; Anoda, T.; Simizu, Y. *Chem.Lett.* **1976**, 495.

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