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A PRACTICAL SYNTHESIS OF 2-DEOXY ALDONOLACTONES VIA A SmI_2-MEDIATED α-DEOXYGENATION REACTION

Stephen Hanessian*, Christian Girard and Jose Luis Chiara
Department of Chemistry, Université de Montréal
P.O. Box 6128, Station A, Montréal, P.Q., CANADA

Abstract: A one-step deoxygenation of 2-hydroxylactones or their acetates is possible using samarium diiodide as an electron-transfer reagent in conjunction with a proton source.

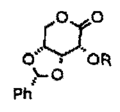
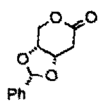
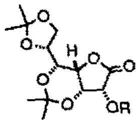
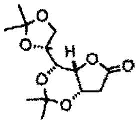
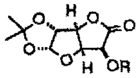
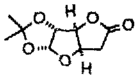
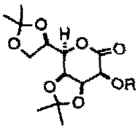
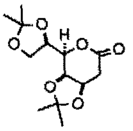
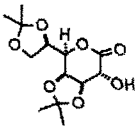
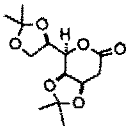
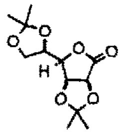
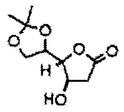
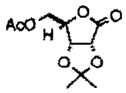
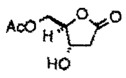
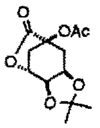
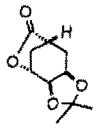
2-Deoxypentoses and hexoses are among the more important naturally occurring sugars, being constituents of nucleic acids, antibiotics and related biologically relevant molecules.[1] Only a few 2-deoxy aldoses are commercially available and these are not inexpensive. Although a number of methods have been reported for the synthesis of this class of carbohydrates,[2] they are, with few exceptions somewhat laborious and not general in scope. A convenient synthesis could rely on the reduction of the corresponding lactones,[3] provided these are readily available by a general procedure. A recent report by Fleet and coworkers[4] described the reductive cleavage of a 2-triflate ester in aldonolactones in the presence of lithium iodide (THF, aq. AcOH, reflux), to produce the corresponding 2-deoxy derivatives.

In continuing our studies[5] on the preparative utility of samarium diiodide[6] as a reagent in polyhydroxy compounds,[7] we report on the facile α-deoxygenation of aldonolactones to 2-deoxy lactones. This can be achieved either directly, through loss of a *free 2-hydroxyl group*, loss of an acetate ester, or of an 2,3-O-alkylidene acetal in excellent yields.

Table 1 illustrates several examples of α-deoxygenation of representative γ- and δ-lactones in the carbohydrate series. In general, unsubstituted 2-hydroxy lactones (entries 1-5) are efficiently reduced *directly* with 3 equiv. of SmI_2 in THF within 3h in the presence of HMPA and ethylene glycol as additives. The corresponding acetates undergo rapid reduction with or without the presence of HMPA (compare entries 1-4, 8, R=H, Ac). The 2,3-O-isopropylidene derivatives shown in entries 6,7 were readily reduced to the 2-deoxylactones in the absence of HMPA. A typical procedure is as follows: To a solution of **1** (236 mg, 1.0 mmol), anhydrous ethylene glycol (650 μL, 12 eq.) and HMPA (1.5 mL) in THF (10 mL), was added dropwise a solution of 0.1M SmI_2 in THF (30 mL, 3 mmol, 3 eq.) at room temperature under argon. After stirring for 3h, the mixture was quenched with satd. aq. $NaHCO_3$, then extracted with EtOAc. Washing the organic layer with aq. $Na_2S_2O_3$, brine and water, *followed by usual workup and chromatography afforded 199 mg (90%) of 3.*

The α-deoxygenation of α-epoxy and α-hydroxy esters using SmI_2 in the presence of an additive and/or a proton source was first shown by Inanaga and coworkers.[8] In an extension of this work to O-acetylated aldonolactones,[9] they recently reported the formation of 2,3-unsaturated aldonolactones and their saturated 2,3-dideoxy analogs. Under these conditions, and using peracetylated aldonolactones, Inanaga and coworkers[9] were not able to obtain selective deoxygenation at the 2-position. Thus, by avoiding the presence of an ester leaving

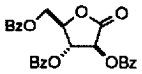
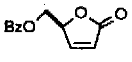
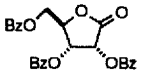
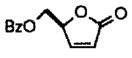
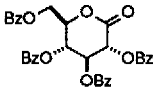
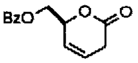
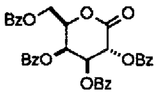
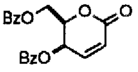
Table 1.

Entry	Lactone	Method[a]	Time	Product	Yield[b]	Physical Properties[c]
1		1, R=H A 2, R=Ac B	3 h Inst.		3, R=H 90% R=Ac 92%	$[\alpha]_D$ -167.9° (c 1.47) m.p. 138-139°C
2		4, R=H A[d] 5, R=Ac B	Inst. Inst.		6, R=H 72% R=Ac 94%	$[\alpha]_D$ -89.3° (c 1.25) m.p. 81-82°C
3		7, R=H A 8, R=Ac B	Inst. Inst.		9, R=H 75% R=Ac 81%	$[\alpha]_D$ +91.3° (c 1.55) m.p. 89-90°C
4		10, R=H A 11, R=Ac A[e]	Inst. Inst.		12, R=H 99% R=Ac 99%	$[\alpha]_D$ +66.9° (c 1.01) m.p. 118-120°C
5		13 A	Inst.		12 98%	
6		14 B[f]	Inst.		15 98%	$[\alpha]_D$ +37.1° (c 0.95) m.p. 62-64°C
7		16 B[f]	Inst.		17 98%	$[\alpha]_D$ +28.1° (c 1.30)
8		18 A[e]	1 h		19 85%	$[\alpha]_D$ -29.5° (c 1.69) m.p. 94-96°C

a. Method: **A**: Ethyleneglycol (12 eq.), HMPA (5% v/v of SmI_2 solution), dropwise addition of SmI_2 (3 eq.) then 30 min. stirring at R.T. (Inst.=instantaneous). **B**: As **A** but without HMPA ; b. Isolated yield; c. Optical rotations in chloroform at 25°C, see ref. 11 ; d. Ethyleneglycol was added dropwise to the mixture; e. Slow reaction in the absence of HMPA; f. 4.5 eq. of SmI_2 were used, work-up by dilution with hexanes and filtration on a short pad of silica (CH_2Cl_2 / MeOH, 10 / 1) group, β-elimination can be circumvented to produce the desired α-deoxygenated lactones as reported herein(Table 1).

We have also found that perbenzoylated aldonolactones are versatile substrates for SmI_2-mediated elimination reactions. (Table 2). In the presence of 3 equiv. of reagent in THF, reaction is instantaneous and unsaturated lactones are formed in reasonable yields considering the ready accessibility of the starting lactones. It is of interest that the D-gluco and the D-galacto isomers differ in their patterns of reductive elimination, possibly due to the axial disposition of the benzoyloxy group in the latter. In spite of the moderate yields, the unsaturated lactones (dihydropyranones)[10] are easily produced from readily available starting materials (3 steps from commercial products).

Table 2.[a]

Entry	Lactone	Product	Yield[b]	Physical properties[c]
1	 20	 21	60%	[α]D -120.9° (c 1.08) m.p. 90-91°C
2	 22	 21	55%	
3	 23	 24	43%[d,e]	[α]D -64.5° (c 0.70) m.p. 88-91°C
4	 25	 26	48%[e,f]	[α]D +128.6° (c 1.09) m.p. 104-105°C

a. Typical procedure: To a solution of the lactone (0.2 mmol) in THF (1 ml) was added dropwise a 0.1 M solution of SmI_2 in THF (6 ml, 3 eq.) at room temperature under argon and the mixture was stirred for 30 min. Work-up in the usual way followed by flash chromatography afforded the product.; b. Isolated yields; c. Optical rotations in chloroform at 25°C, see ref. 11 ; d. Ethyleneglycol (12 eq.) and SmI_2 (5 eq.) were added (2-deoxy and α, β-unsaturated lactones are side-products); e. In the presence of pivalic acid, mixtures of the product, 2-deoxy and α, β-unsaturated compounds were obtained (see ref. 9) ; f. Work up by dilution with hexanes and filtration on a short pad of silica using hexanes / ethyl acetate (1 / 1 mixture)

In conclusion, we have shown that SmI_2 is a versatile reducing agent for the direct conversion of substituted or unsubstituted 2-hydroxy aldonolactones into the corresponding 2-deoxy lactones and in excellent yields.[11,12] Since carbohydrate lactones are readily converted into the corresponding lactols,[3] the method described herein offers an expedient route to 2-deoxyaldoses. Further progress on the mechanism of these electron transfer mediated α-deoxygenations, as well as in finding other practical uses for the versatile SmI_2 in organic transformations will be reported in due course.

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10. See for example, Qiu, D.; Schmidt, R.R. *Synthesis*, **1990**, 875; see also Lichtenthaler, F.W. *Pure Appl. Chem.* , **1978**, 50, 1343.
11. Lactones listed in Tables 1 and 2 were characterized by comparison of physical constants with known data from the literature. All new compounds gave correct microanalyses and they were further characterized by 300 MHz ^{1}H NMR spectra.
12. For examples of reductive elimination of α-alkoxy and α-halo carbonyl compounds, see Smith III, A.B.; Dunlap, N.K.; Sulikowski, G.A. *Tetrahedron Lett.*, **1988**, 29, 439; Holton, R.A.; Williams, A.D. *J. Org. Chem.*, **1988**, 53, 5981; White, J.D.; Somers, T.C. *J. Am. Chem. Soc.*; **1987**, 109, 4424; Molander, G.A.; Hahn, G. *J. Org. Chem.*, **1986**, 51, 1135 and 2596; see also Girard, P.; Namy, J.L.; Kagan, H.B. *J. Am. Chem. Soc.*, **1980**, 102, 2693.

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