adduct of **1** [tBu$_4$PcInCl(tmed)], have been studied in toluene with laser pulses at 410 nm. These preliminary results show that **2** exhibits good optical-limiting response at this laser wavelength, whereas no response was found for compound **1** and its tmed adduct. Further studies on the NLO properties (including optical-limiting properties) displayed by **2** are currently in progress.

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Samarium Diiodide-Mediated Reductive Coupling of Epoxides and Carbonyl Compounds: A Stereocontrolled Synthesis of C-Glycosides from 1,2-Anhydro Sugars**

Jose Luis Chiara* and Esther Sesmilo

Dedicated to Professor Antonio Gómez-Sánchez on the occasion of his 75th birthday

The significant advances in the understanding of the biological function of carbohydrates and glycoconjugates achieved during the last two decades have stimulated the development of glycomimetics as fundamental tools for biological research and as potential agents for therapeutic intervention.[1] C-Glycosides are of special relevance in this context because of their resistance to hydrolysis and their occurrence in a number of natural products with interesting biological activities. Methods for their preparation using anomeric anions, cations, radicals, and carbenes have been extensively studied.[2] 1,2-Anhydro sugars, readily available and well-known donors for the stereoselective preparation of O-glycosides,[3] have also found application in the stereoselective synthesis of C-glycosides.[2] Because of their electrophilic nature, in all examples described to date, 1,2-anhydro sugars have reacted with metalated C-nucleophilic partners, which are often unstable and not readily available with a wide range of functionality. The regioselective and stereodefined umpolung of 1,2-anhydro sugars into nucleophilic C-glycosyl donors by reductive metalation could greatly extend the scope of these useful donors, by allowing the introduction of an expanded set of substituents at the anomeric position in a stereoselective way.[4,5]

To test the feasibility of this approach, we performed exploratory experiments with epoxide **2a**, readily available from the protected D-glucal **1a** by oxidation with DMDO

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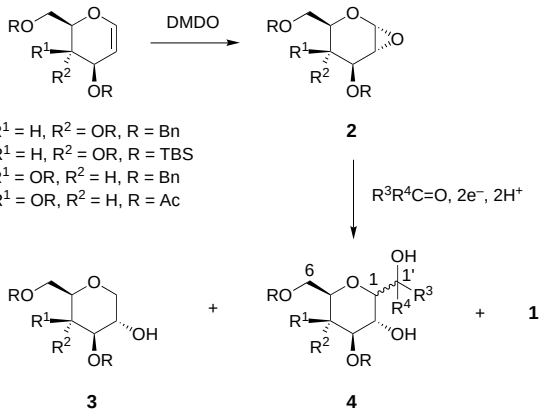
(Scheme 1).[10] Initial attempts to couple **2a** to isobutyraldehyde[11] in the presence of $[Cp_2TiCl]_2$[11i,12] as the reducing agent produced only minor amounts (< 20 %) of the C-glycoside **5a** (see Table 1 for structure)[6,9] as a 1:1 mixture of



Scheme 1. Synthesis of C-glycosides from glycals by a one-pot DMDO oxidation and intermolecular reductive coupling reaction with carbonyl compounds. DMDO = dimethyl dioxirane, TBS = *tert*-butyldimethylsilyl.

α diastereoisomers, irrespective of temperature (−78 °C to RT) and the order of addition of reagents (Table 1, entry 1). The major products obtained under these conditions were the corresponding glycal **1a** (35–45 %) and the 1-deoxy pyranose **3a** (25–40 %). We next tried samarium(II) diiodide as the reducing agent. Gratifyingly, addition of isobutyraldehyde (4 equiv) to a THF solution of SmI_2 containing a catalytic amount of NiI_2 (1 mol %),[7g,h,13,14] at −78 °C, followed immediately by dropwise addition of a THF solution of crude **2a** afforded the α-C-glycoside **5a** in 60 % overall yield, as a 4:1 mixture of diastereoisomers[15] together with minor amounts of **1a** and **3a** (Table 1, entry 1). This two-step/one-pot DMDO oxidation–SmI_2 reduction sequence was successfully applied to the coupling of differently protected glycals **1a–d** with a series of simple aldehydes and ketones to yield C-glycosides of D-*gluco* and D-*galacto* configuration in moderate to good overall yields (Table 1).

Some unique features of this new reductive coupling process are worth emphasizing. First, it shows wide protecting-group compatibility because of the very mild reaction conditions. Thus, apart from benzyl and silyl ethers, ester groups on the glycal are completely stable under the reaction conditions (Table 1, entries 4, 6, 15, 18). Second, the α/β stereoselectivity of the reaction is subtly sensitive to steric effects. In contrast to other reductive samariation procedures,[7] α-C-glycosides are predominantly or exclusively obtained with aldehydes (Table 1, entries 1–4, 6), independent of the protecting-group arrangement and the configuration of the starting glycal, while ketones give the corresponding β isomers as the major products (Table 1, entries 7, 9, 10, 12, 14, 15, 18).[16]

The new reductive coupling procedure was also successfully applied to the β epoxide **17**[17] affording C-glycosides of D-*manno* configuration in good yields (Table 2). In this case, α-C-glycosides are selectively obtained both with aldehydes and ketones.

A series of control experiments was carried out for mechanistic studies. First, fair yields of C-glycosides were still obtained by performing the reaction in the presence of a large excess (10 equiv) of D_2O (Table 1, entries 5, 8, 11, 13, 16; Table 2, entries 2, 4). This result is not consistent with the involvement of an anomeric organosamarium species in the C–C bond-forming step. Unexpectedly, the proton source affected the diastereoselectivity of the reaction. Thus, 1,2-*cis* C-glycosides are selectively formed under these protic conditions in all cases.[18] Second, addition of 10 equiv of *t*BuSH, a good hydrogen donor, severely affected the yield of C-glycoside (< 7 %), giving the corresponding 1-deoxy-pyranose as the major product.

A possible mechanistic rationalization for the above observations is illustrated in Scheme 2 for the case of 1,2-anhydro sugars **2**. Single electron transfer (SET) from SmI_2 to the epoxide group[19] of **2** regioselectively leads to an α-anomeric radical intermediate in the form of a solvated samarium(III) alkoxide **A**. Intermolecular radical addition of **A** to the Lewis acid- (Sm^{2+} or Sm^{3+}) activated carbonyl group[20] and subsequent (or concomitant) kinetic trapping of the generated alkoxyl radical (**B** or **D**) by a second SET from another molecule of SmI_2 (possibly by inner-sphere ET[21] from a chelated Sm^{2+} ion) produces the C-glycoside after hydrolysis. Destabilizing steric interactions between the solvated samarium(III) alkoxide at the C-2 atom in **A** and the incoming complexed carbonyl moiety along the kinetically favored axial trajectory of attack[22] (Path b) is more severe in the case of ketones, which could explain a preferential 1,2-*trans* approach in their case (Path a). Under protic conditions (Path c), fast protonation of the samarium alkoxide at the C-2 atom of **A** allows a hydroxy-directed[7d,23] approach of the Lewis acid-activated carbonyl compound **F**, generating predominantly the 1,2-*cis* C-glycoside **H**. A similar mechanistic rationalization can be proposed for the couplings of the 1,2-anhydro-D-*manno*-pyranose **17**. The glycal and 1-deoxypyranose are probably formed by competitive reduction of the anomeric radical **A** to an anomeric carbanion followed by β elimination or protonation, respectively.[24,25]

In summary, we have developed an efficient preparation of C-glycosides by a new intermolecular reductive coupling reaction of 1,2-anhydro sugars with carbonyl compounds, promoted by samarium(II) diiodide. Outstanding features of the new approach are the following: 1) the starting 1,2-anhydro sugars are readily available with different stereochemistry, 2) good overall yields of C-glycoside are obtained, independent of the configuration of the starting 1,2-anhydro sugar, 3) the very mild reaction conditions allow a wide O-protecting group compatibility, 4) the stereoselectivity of the reaction is complementary to other syntheses of C-glycosides mediated by SmI_2, 5) C-glycosides with a free hydroxy group at C-2 are directly obtained, which facilitates further selective functionalizations, and 6) the stereoselectivity of the reaction can be significantly modified by adding a proton source. The extension of this process to other radical acceptors and its application to the solution- and solid-phase synthesis of C-glycosydic analogues of biologically important natural glycosides are being actively pursued in our laboratory.

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Table 1. One-pot DMDO oxidation–SmI_2 reductive coupling synthesis of C-glycosides from glycals and carbonyl compounds.

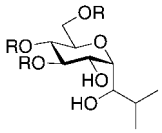
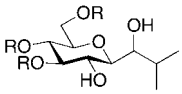
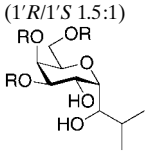
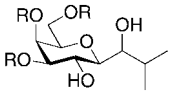
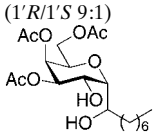
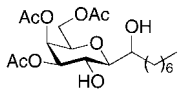
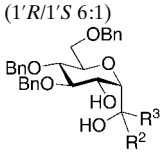
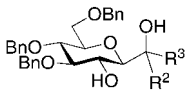
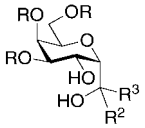
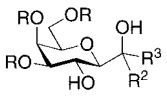
Entry	Glycal	Carbonyl compound	C-Glycoside		Glycal	1-Deoxypyranose
			Yield [%][a] (diastereoisomer ratio)			
						
1	**1a**	isobutyraldehyde	**5a**[b]	**5b**	**1a**	**3a**
			60	ND[c]	12	15
			(1′*R*/1′*S* 4:1)			
2	**1b**	isobutyraldehyde	**6a**	**6b**	**1b**	**3b**
			67	ND	27	ND
			(1′*R*/1′*S* 1.5:1)			
						
3	**1c**	isobutyraldehyde	**7a**[d]	**7b**	**1c**	**3c**
			76	ND	6	14
			(1′*R*/1′*S* 2.5:1)			
4	**1d**	isobutyraldehyde	**8a**	**8b**[e]	**1d**	**3d**
			73	9	8	7
			(1′*R*/1′*S* 5:1)			
5			61[f]	ND[f]	12[f]	14[f,g]
			(1′*R*/1′*S* 9:1)			
						
6	**1d**	1-octanal	**9a**	**9b**[h]	**1d**	**3d**
			52	18	16	2
			(1′*R*/1′*S* 6:1)			
						
7	**1a**	acetone	**10a**	**10b**	**1a**	**3a**
			12	64	3	8
8			53[f]	10[f]	23[f]	13[f,g]
			($R^2 = R^3 = Me$)			
9	**1a**	3-pentanone	**11a**	**11b**	**1a**	**3a**
			5	60	13	22
				$R^2 = R^3 = Et$		
10	**1a**	cyclohexanone	**12a**[i]	**12b**[i]	**1a**	**3a**
			12	48	3	32
11			51[f]	8[f]	20[f]	17[f,g]
				$R^2,R^3 = (CH_2)_5$		
						
12	**1c**	acetone	**13a**	**13b**	**1c**	**3c**
			ND	70	2	16
13			40[f]	2[f]	42[f]	2[f,g]
				$R^2 = R^3 = Me$		
14	**1c**	cyclohexanone	**14a**	**14b**[i]	**1c**	**3c**
			ND	77	3	18
				$R^2,R^3 = (CH_2)_5$		
15	**1d**	acetone	**15a**	**15b**	**1d**	**3d**
			15	46	9	9
16			40[f]	6[f]	15[f]	24[f,g]
17			44[j]	8[j]	19[j]	12[j]
				$R^2 = R^3 = Me$		

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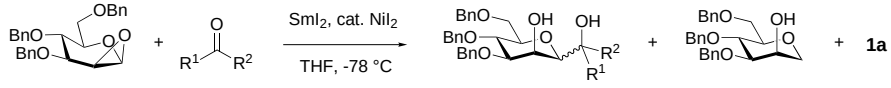
Table 2 (Continued)

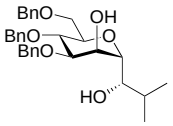
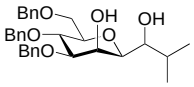
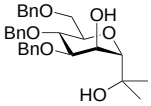
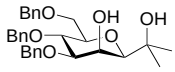
Entry	Glycal	Carbonyl compound	C-Glycoside		Glycal	1-Deoxypyranose
			Yield [%][a] (diastereoisomer ratio)			
18	**1d**	3-pentanone	**16a**	**16b**	**1d**	**3d**
			8	48	14	15
			$R^2 = R^3 = Et$			

[a] Overall yields of isolated products from starting glycal; diastereoisomeric ratios as determined by ^{1}H NMR spectroscopy of the crude reaction mixtures. [b] Ref. [6a, 9]. [c] ND = Not detected. [d] Ref. [6b]. [e] Single diastereoisomer (stereochemistry at the C-1′ atom not determined). [f] Reaction performed in the presence of 10 equiv of D_2O. [g] ^{1}H NMR spectroscopic analysis showed that compound **3** was $>80\%$ α-monodeuterated at the C-1 atom. [h] 1:1 mixture of diastereoisomers at the C-1′ atom. [i] Ref. [7b, d]. [j] Reaction performed in the presence of 2 equiv of D_2O.

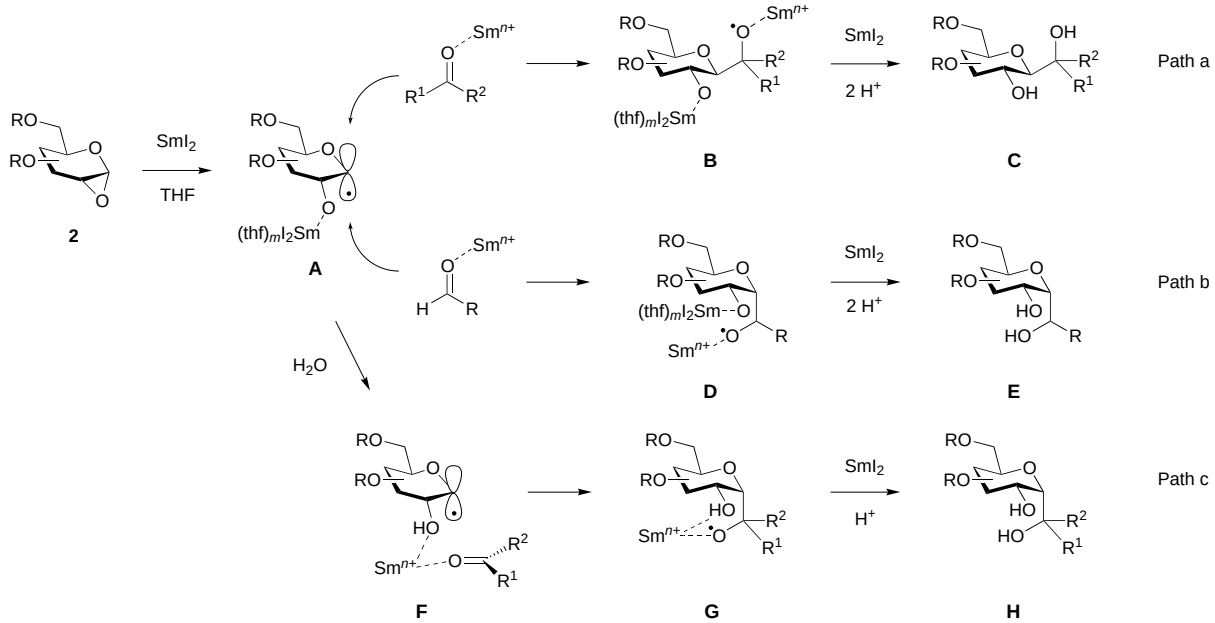
Table 2. SmI_2-promoted synthesis of C-glycosides from glycal **17**.



17 **18**

Entry	Carbonyl compound	C-Glycoside		Glycal	1-Deoxy sugar
		Yield [%][a] (diastereoisomer ratio)			
					
1	isobutyraldehyde	**19a**[b]	**19b**	**1a**	**18**
		68	ND	9	12
2		8[c]	25[c,d]	9[c]	34[c,e]
					
3	acetone	**20a**	**20b**	**1a**	**18**
		63	ND	9	11
4		11[c]	27[c]	9[c]	26[c,e]

[a] Overall yields of isolated products from crude mixture; diastereoisomeric ratios as determined by ^{1}H NMR spectroscopy of the crude reaction mixtures. [b] Single diastereoisomer at the C-1′ atom (ref. [7d]). [c] Reaction performed in the presence of 10 equiv of D_2O. [d] 1:1 mixture of diastereoisomers at the C-1′ atom. [e] ^{1}H NMR spectroscopic analysis showed that compound **18** was $>80\%$ β-monodeuterated at the C-1 atom.



Scheme 2. Proposed mechanistic pathway for the reductive coupling of 1,2-anhydro sugars with carbonyl compounds, promoted by SmI_2.

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Experimental Section

General procedure for the preparation of C-glycosides: To a freshly prepared solution of SmI_2 (6 equiv) in THF, containing 1 mol% of NiI_2 at −78 °C under argon, a carbonyl compound (4 equiv) was added in one portion, followed immediately by dropwise addition of a 0.1 M THF solution of the crude 1,2-anhydro sugar[10,17] (1 equiv) over 30 min. After stirring at −78 °C for 1.5 h, the reaction mixture was allowed to attain RT slowly (1 h). A 10:1 mixture of saturated aqueous Rochelle salt (potassium sodium tartrate) and saturated aqueous $NaHCO_3$ was added and the mixture was extracted with EtOAc (3×). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The residue was chromatographed on silica gel to obtain the products.

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[16] Interestingly, reductive samariation of anomeric sulfones of pyranoses with a free hydroxy or an acetamido group in the C-2 position in the presence of aldehydes or ketones also affords 1,2-*cis* C-glycosides preferentially.[7d,e]

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[24] 1-Monodeuterated 1-deoxypyranose (>80% deuterium incorporation by ^{1}H NMR spectroscopic analysis) is obtained when the coupling is performed in the presence of D_2O. Interestingly, deuterium incorporation is stereospecific. Thus, α-deuterated **3** and β-deuterated **18** are exclusively formed from α epoxides **2** and β epoxide **17**, respectively, as expected for deuteration of a (chelated) 1,2-*cis* anomeric organosamarium intermediate. The corresponding 1,2-*trans* organosamarium compound should undergo a fast β elimination to give the glycal. We believe that these observations cast doubt on the commonly accepted carbanionic nature of other C-glycoside syntheses mediated by SmI_2[7] and the assumption of a preferred *syn*-elimination pathway[7b,d] for organosamarium compounds, which is unprecedented for other metal carbanions.

[25] A referee has argued that a mechanism involving anions may still be plausible, which suggests that carbonyl addition could be faster than protonation at −78 °C. However, we think this is unlikely since previous work from our group[23b] has shown that primary radicals are not readily reduced by SmI_2 at −78 °C and that intermolecular addition of a postulated organosamarium intermediate to acetone is efficiently suppressed in the presence of an excess of D_2O (see also ref. [24]). In spite of recent progress,[20] the nature of the intermediate involved in the key carbon–carbon bond-forming step of samarium Barbier reactions remains elusive.

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