BRANCHED CHAIN CARBOHYDRATE LACTONES FROM A TANDEM SmI_2 DEOXYGENATION-CARBONYL ADDITION REACTION

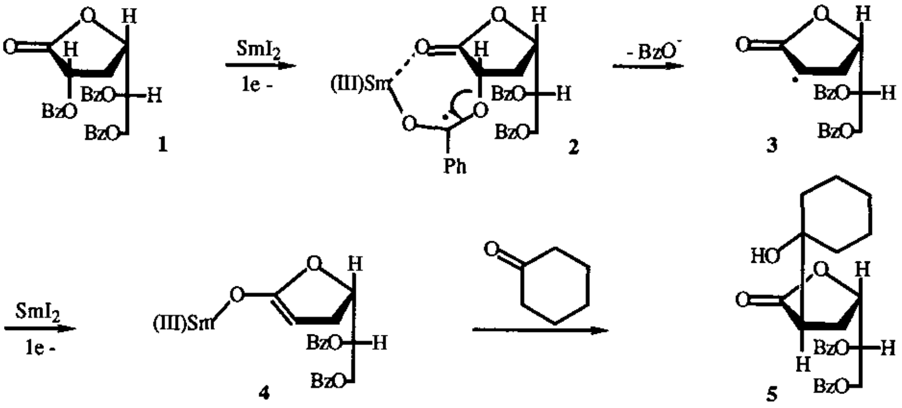
Eric J. Enholm* and Shujun Jiang

Department of Chemistry, University of Florida, Gainesville, Florida 32611, USA

Abstract--Treatment of a carbohydrate lactone with a ketone in the presence of SmI_2-HMPA produces a deoxygenation/carbonyl addition reaction to afford new C_2-branched chain carbohydrates.

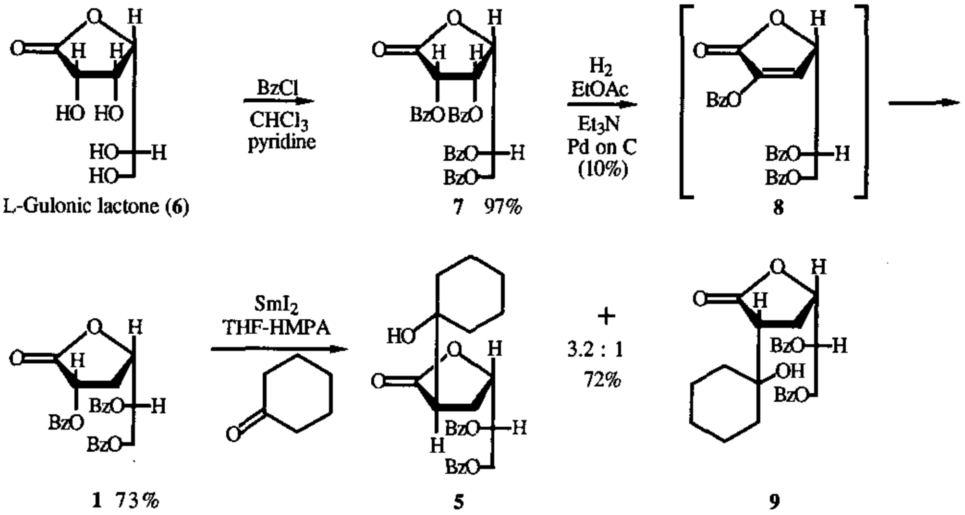
Branched chain carbohydrates are found in many biologically important molecules and widely occurring natural products.[1] These substrates are an intensely investigated area of organic synthesis,[2] however, most current technologies involve modifications of a ketone on a pyran or furan ring with the Wittig reaction,[3] CH_2N_2[4] or organometallic reagents.[5] A totally different synthetic approach to these branched chain sugars might involve reductive deoxygenation of a pyranose or furanose ring to produce an enolate anion which can then condense with an electrophile such as a ketone. The strong oxophilicity, stereoselectivity and regiocontrol of the one-electron reductant SmI_2, should be worthy of investigation in this capacity.[6] It is also noteworthy that there are many transformations of SmI_2 with simple achiral molecules, however, there exist few reactions of this one-electron reductant with more sophisticated, optically active substrates, such as carbohydrates.[7,8]

In this communication, we would like to report the results of a novel transformation of carbohydrate 3-deoxylactones in which deoxygenation[8] of a C_2-O-benzoate moiety is followed by the formation of a new carbon-carbon bond. Thus, an intermolecular carbonyl addition reaction affords a β-hydroxy lactone as a branched chain sugar in a subsequent tandem reaction after the deoxygenation. The overall process is outlined in Scheme I. A bidentate chelate of **1** with SmI_2 between the C_2-benzoate and the lactone carbonyl oxygen[8a] initiates the reaction to afford a one-electron reduction of the benzoate carbonyl to produce the benzylic stabilized radical species (**2**).



Scheme I

Expulsion of the benzoate produces a resonance stabilized radical species (**3**). A second equivalent of SmI_2 then reduces the radical to a Sm(III) enolate. The enolate (**4**) appears to be of reduced reactivity because it does not displace or condense with any benzoate functions. Subsequent carbonyl addition with a ketone such as cyclohexanone affords the C_2 branched sugar (**5**). Reduction of the lactone carbonyl in **2**, rather than the benzoate carbonyl can also provide **5**, however, SmI_2 reduces aromatic carbonyls much faster than aliphatic carbonyls such that species (**2**) is more favored for the first one-electron reduction.[9]

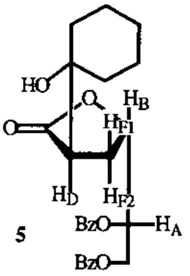


Scheme II

Because Sm(III) enolates have a marked tendency to eliminate α-oxo functions to afford α,β-unsaturated carbonyls,[8] C3-deoxygenated lactone carbohydrates were selected as starting substrates for these studies. We adopted a two-step protocol previously utilized to make C3-deoxyacetylated analogs.[10,11] Thus, exhaustive esterification of commercially available L-gulonic γ-lactone (**6**) with benzoyl chloride produced 2,3,5,6-tetra-*O*-benzoylgulonic γ-lactone (**7**) in 97% yield, shown in Scheme II.[12] Next, Et_3N-promoted elimination of benzoic acid followed by hydrogenation of the endocyclic olefin (via **8**) from the least hindered face of the furanose ring rendered 3-deoxy-2,5,6-tri-*O*-benzoylgulonic γ-lactone (**1**), isolated in highly crystalline form[12] (mp 124-125 °C) in 73% yield. With key precursor (**1**) in hand, it was next treated with an intensely dark blue solution of SmI_2 (4 equiv.) and cyclohexanone in THF/HMPA from -78 °C to 23 °C over 1 h. Two branched chain carbohydrates (**5**) and (**9**) formed in a ratio of *ca.* 3 : 1, as determined by 300 MHz ^1H nmr, in 72% yield. The products were easily separated and major product (**5**), was crystallized as colorless needles (mp 143.5-144.5 °C).[12] Difference

Table I. Difference NOE Data for Product (5)

Proton(s) Irradiated	DLP	Percent Effect Observed				
		H_A	H_B	H_D	H_{F1}	H_{F2}
H_B	22	12.1			5.6	
H_D	22					4.9
H_{F1}	25		14.2			24.4
H_{F2}	30			7.7	22.7	



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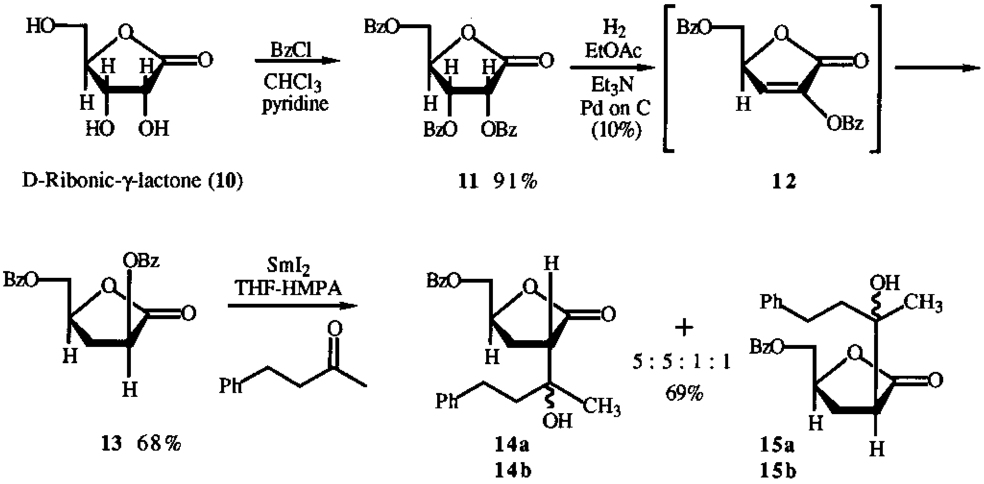


Scheme III

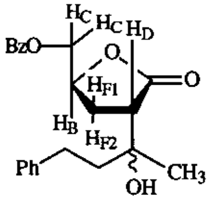
NOE studies of **5** indicated that cyclohexanone had a preference to add to the least hindered face of the lactone ring, as expected. These spectroscopic data are shown in Table I.

A second study, shown in Scheme III, utilized the carbohydrate lactone D-ribonic γ-lactone (**10**) as a starting substrate which was exhaustively esterified and deoxygenated at the C_3 position by elimination/hydrogenation of the furanose ring in 91% and 68% yields respectively, in a manner similar to the Scheme II example. Crystalline 3-deoxy-2,5-di-*O*-benzoylthreo-γ-lactone (**13**),[10,12] (mp 156-158 °C) produced from the two-step process was then treated with SmI_2 and benzylacetone in THF/HMPA affording stereoisomers **14a** : **14b** : **15a** : **15b** in a *ca.* 5 : 5 : 1 : 1 ratio, respectively, in 69% yield. The stereochemistry reflects a preference for the carbonyl addition reaction of benzylacetone to the least hindered face of the furanose ring via the Sm(III) enolate. The stereorandom 1 : 1 ratio may indicate a lack of chelation with the Sm(III) and the ketone in the transition state of the carbonyl addition to the ester enolate. The stereochemistry of the major products was confirmed by difference NOE studies summarized in Table II for isomer (**14a**) and Table III for isomer (**14b**).[12]

Table II Difference NOE Data for Product (14a)

Proton(s) Irradiated	DLP	Percent Effect Observed				
		H_B	H_C	H_D	H_{F1}	H_{F2}
H_B	25	╲	7.3		1.5	5.0
H_D	25			╲	3.3	
H_{F1}	25	7.3	4.1	8.1	╲	*
H_{F2}	25	12.4	1.2	3.5	*	╲

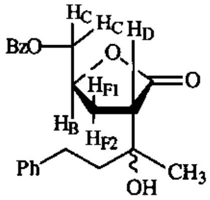
*Proton difficult to observe due to proximity with irradiated proton.



14a

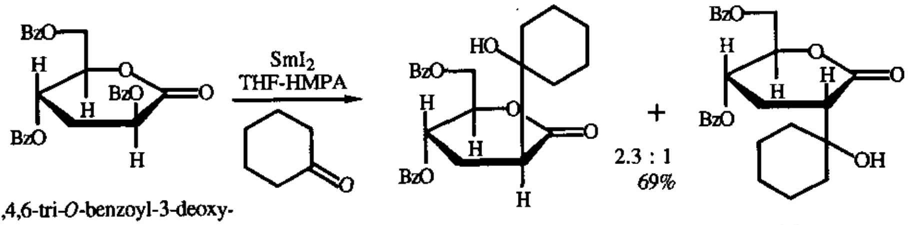
Table III Difference NOE Data for Product (14b)

Proton(s) Irradiated	DLP	Percent Effect Observed				
		H_B	H_C	H_D	H_{F1}	H_{F2}
H_B	25	╲	5.6			4.2
H_D	25			╲	3.3	1.5
H_{F1}	25	3.3	3.7	4.3	╲	17.7
H_{F2}	25	13.5	1.5	1.0	7.0	╲



14b

In a third study, shown in Scheme IV, crystalline 2,4,6-tri-*O*-benzoyl-3-deoxy-D-arabino-1,5-lactone (**16**), readily available in two steps from γ-gluconolactone,[11] was treated with SmI_2 and cyclohexanone in THF-HMPA. Products (**17**) and (**18**) were observed in a 2.3 : 1 ratio, respectively. In this example, the approach of the



2,4,6-tri-*O*-benzoyl-3-deoxy-D-arabino-1,5-lactone (**16**)

17

18

Scheme IV

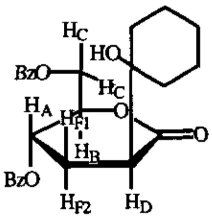
ketone to the β-face of the pyranose ring is favored for stereoelectronic reasons because axial approach to the Sm(III) enolate is preferred.[13] The difference NOE studies on the major product (**17**) are shown in Table IV.[12]

Table IV Difference NOE Data for Product (17)

Proton(s) Irradiated	DLP	Percent Effect Observed				
		H_A	H_B	H_C	H_D	H_{F1} & H_{F2} **
H_A	25		4.6	3.7	1.0	5.1
H_B	25	5.8		3.1	6.9	
H_C	25	5.5	8.5			1.3
H_D	25		13.2	1.6		3.6
H_{F1}	28	11.7	1.9	1.0	5.9	*
H_{F2}	28	10.8	1.1		9.3	*

*Proton difficult to observe due to proximity with irradiated proton.

**The two protons are too close to get the result separately.



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To summarize, a useful and novel condensation of simple ketones with carbohydrate 3-deoxylactones with SmI_2 has been achieved. After ejection of the C_2-benzoate, the approach of the ketone to the carbohydrate lactone in the major product is controlled by a combination of the steric bias of existent appendages on the ring and a favored stereoelectronic approach to the Sm(III) enolate.

ACKNOWLEDGEMENT

The authors acknowledge the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research (Grant ACS-PRF 23356-AC4). We also gratefully acknowledge support by the National Science Foundation (Grant CHE-9013121) for this work.

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Received, 29th June, 1992