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Ring-Contraction vs Ring-Expansion Reactions of Spiro-cyclopropanecarboxylated Sugars

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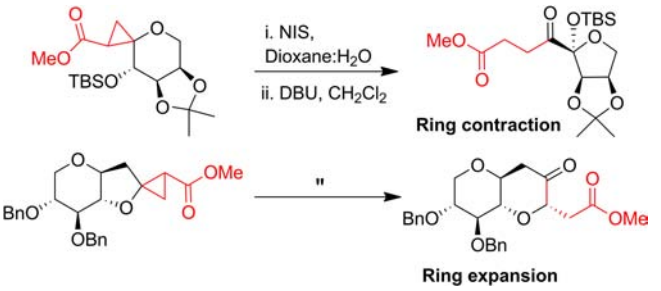
ABSTRACT



Electrophilic ring opening of spiro-cyclopropanecarboxylated sugars followed by reaction with DBU revealed interesting ring-contraction and ring-expansion reactions depending on the substrate and the kind of hydroxyl protective group present adjacent to the spiro center. A stereoselective method for accessing a new class of carbon chain extended keto-furanoses and C-glycosylated bicyclic compounds is reported.

Carbohydrates are ubiquitous chiral resources whose chemistry has underpinned the discovery of many awe-inspiring and fascinating new transformations in chemistry and biology.[1] Apart from designed methodologies, quite a few surprising reactions/rearrangements have emerged in "sugar chemistry", and some are even unusual.[2] In this context, ring-contraction[3] and ring-expansion[4] reactions involving carbohydrate derivatives are very significant. Of several published protocols, the ring-contraction of α-trifluoromethanesulfonylated aldonolactones[5] and Kirschning's hypervalent iodine-mediated oxidative ring-contraction of glycals[6] to formyl glycosyl analogues are noteworthy. Gin et al.[7] cleverly implemented the I^{III}-mediated ring-contraction of a glycal as a key step in the first total synthesis of (+)-pyrenolide D. However, the application of such ring-contraction reactions, and the conversion of pyranoses to C-branched furanoses, in the stereoselective total synthesis of complex natural products have been scarce.[8]

Likewise, there are very few reports of the conversion of carbohydrates into the corresponding ring-expanded versions. The classical Achmatowicz[9] reaction involving

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(2) Redlich, H. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1345–1347.

(3) Ring contraction of cyclic ethers to carbocycles: (a) Verner, E. J.; Cohen, T. *J. Am. Chem. Soc.* **1992**, *114*, 375–377. (b) Paquette, L. A. *J. Organomet. Chem.* **2006**, *691*, 2083–2088. (c) Alonso, R. A.; Vite, G. D.; McDevitt, R. E.; Fraser-Reid, B. *J. Org. Chem.* **1992**, *57*, 573–584. (d) Ito, H.; Motoki, Y.; Taguchi, T.; Hanzawa, Y. *J. Am. Chem. Soc.* **1993**, *115*, 8835–8836. (e) Enholm, E. J.; Trivellas, A. *J. Am. Chem. Soc.* **1989**, *111*, 6463–6465. (f) Aurrecoechea, J. M.; López, B. *Tetrahedron Lett.* **1998**, *39*, 2857–2860. Ring contraction of pyranoses to furanoses: (g) Bettelli, E.; D'Andrea, P.; Mascanzoni, S.; Passacantilli, P.; Piancatelli, G. *Carbohydr. Res.* **1998**, *306*, 221–230. (h) Hanessian, S.; Tyler, P. C.; Demailly, G.; Chapleur, Y. *J. Am. Chem. Soc.* **1981**, *103*, 6243–6246. (i) Kassou, M.; Castillón, S. *J. Org. Chem.* **1995**, *60*, 4353–4358. (j) Hanessian, S.; Pernet, A. G. In *Advances in Carbohydrate Chemistry and Biochemistry*; Academic Press: New York, 1976; Vol. 33, pp 111−188. (k) Pontén, F.; Magnusson, G. *J. Org. Chem.* **1997**, *62*, 7972–7977. (l) Pozsgay, V.; Neszmélyi, A. *Tetrahedron Lett.* **1980**, *21*, 211–212.

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(5) (a) Estevez, J. C.; Saunders, J.; Besra, G. S.; Brennan, P. J.; Nash, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **1996**, *7*, 383–386. (b) Bichard, C. J. F.; Brandstetter, T. W.; Estevez, J. C.; Fleet, G. W. J.; Hughes, D. J.; Wheatley, J. R. *J. Chem. Soc, Perkin Trans. 1* **1996**, 2151–2156.

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(8) Stoltz, B. M.; Wood, J. L. *Tetrahedron Lett.* **1996**, *37*, 3929–3930.

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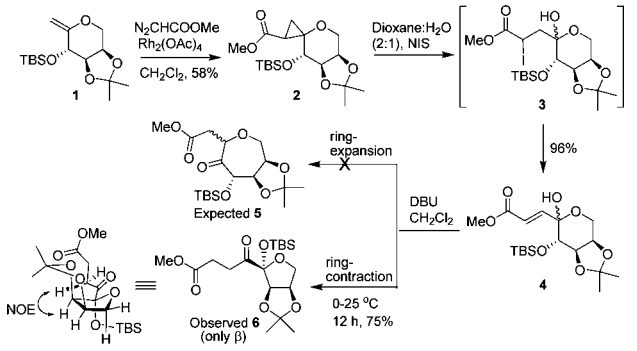
the rearrangement of furfuryl alcohol derivatives to dihydropyran systems has been used successfully in total synthesis[10] as well as in combinatorial chemistry.[11] Ring-expansion through the formation of a cyclopropane has been effectively utilized to synthesize 7-membered oxygen heterocycles, oxepines, as well as septanosides.[12] 1,2-Cyclopropanated sugar derivatives have also been converted to the corresponding ring-contracted counterparts.[13] Very recently, spiroannulated donor−acceptor cyclopropane derivatives were successfully converted to [*n*,5]-spiroketals ($n = 5, 6$) via ring enlargement of the cyclopropane moiety.[14] However, to the best of our knowledge, ring-expansion of a furanose derivative to a C-glycosylated pyranose has not been reported in the literature. In continuation of our investigations on the application of cyclopropanated sugar motifs,[15] in the preparation of novel chiral architectures, and in the total synthesis of natural products, herein we disclose an interesting ring-contraction reaction of spiro-cyclopropanecarboxylated sugar scaffolds to give keto-furanose derivatives, as well as a ring-expansion methodology for the diastereoselective synthesis of sugar-fused bicyclic systems.

Cyclopropanation of exocyclic-glycal[16] **1** using methyldiazoacetate in CH_2Cl_2 under catalytic $Rh_2(OAc)_4$ conditions provided the spiro-cyclopropane derivative **2** as a mixture of diastereomers[17] in 58% yield. Electrophilic ring-opening of this donor−acceptor cyclopropane **2** with *N*-iodosuccinimide (NIS) in dioxane:water (2:1) provided the α,β-unsaturated ester **4** through the formation of the iodo alcohol **3** followed by dehydrohalogenation, in excellent yield. We assumed that compound **4,** under basic conditions, would undergo an intramolecular hetero Michael addition (IHMA) reaction and provide the septanoside derivative **5**.

Scheme 1. Ring Expansion vs Ring Contraction of a Spiroannulated Sugar Derivative



Interestingly, treatment of compound **4** with DBU in CH_2Cl_2 provided a single diastereomer. Detailed spectral analysis revealed that the product was a keto-furanose derivative **6** instead of a septanoside **5** (Scheme 1). The structure of compound **6,** and stereochemistry at the newly formed quaternary center, were assigned by observing the NOE between the pseudoequatorial hydrogen and the methylene group adjacent to the carbonyl group.[18]

The generality of this serendipitous ring-contraction reaction was investigated by applying it to a series of spiro-cyclopropanecarboxylated sugar derivatives. Thus, compound **7** was subjected to NIS mediated solvolytic ring-opening to give α,β-unsaturated ester **8** which, upon reaction with DBU in CH_2Cl_2, gave the furanoside **9** as a 1:1 mixture of diastereomers. Similarly, spiro-compounds **10**, **13**, **16**, **19**, and **22** upon NIS mediated ring-opening provided the hemiketals **11**, **14**, **17**, **20**, and **23**, respectively. Reaction of these hemiketals with DBU resulted the formation of C-glycosylated keto-furanose derivatives **12**, **15**, **18**, **21**, and **24** in good yield and stereoselectivity (Table 1, entries 2−6).[19] These compounds can serve as excellent synthons for the preparation of bistetrahydrofuran derivatives particularly present in annonaceous acetogenins[20] by selective reduction of the ketone to the alcohol followed by lactonization, as well as furan-annulated spirocyclic natural products.[21] Further, anomeric deoxygenation could provide an access to the preparation of C-glycoside derivatives.

Implementation of the electrophilic ring-opening reaction on spiroannulated compounds **25** and **27**, in which the protecting group adjacent to the spiro center was a benzyl group, provided the hemiketals **26** and **28**, respectively,

(9) Achmatowicz, O.; Bukowski, P.; Szechner, B.; Zwierzchowska, Z.; Zamojski, A. *Tetrahedron* **1971**, *27*, 1973–1996.

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(15) (a) Sridhar, P. R.; Venukumar, P.; Seshadri, K.; Satyavathi, R. *Chem.—Eur. J.* **2009**, *15*, 7526–7529. (b) Sridhar, P. R.; Venukumar, P. *Org. Lett.* **2012**, *14*, 5558–5561.

(16) For reviews on cyclopropanated sugars, see: (a) Cousing, G. S.; Hoberg, J. O. *Chem. Soc. Rev.* **2000**, *29*, 165–174. (b) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321–347. All of the exocyclic glycals were synthesized by elimination of HI from the corresponding iodomethyl pyranose/furanose or by methylenation of the corresponding protected lactone with Petasis reagent.

(17) The two newly formed stereocenters will be destroyed in the course of the reaction. Thus, no attempts were made to analyze the diastereomeric ratio of this mixture.

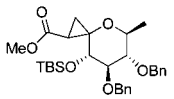
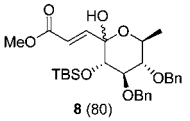
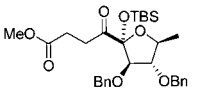
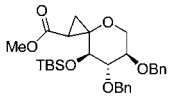
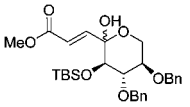
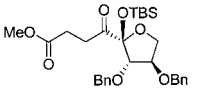
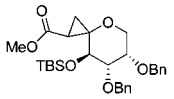
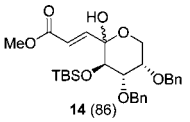
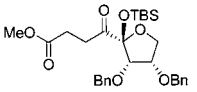
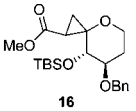
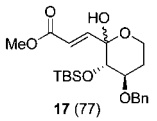
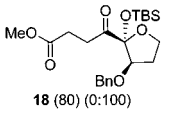
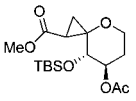
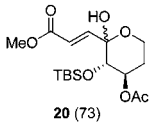
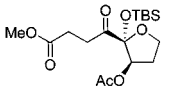
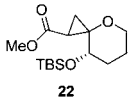
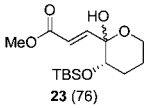
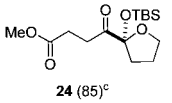
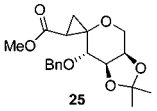
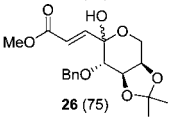
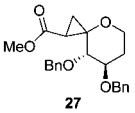
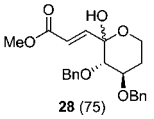
(18) A 3D (energy minimized) structure of compound **6** is provided in the Suporting Information.

(19) In all of the products, stereochemistry at the quaternary center was assigned by NOE experiments. The reported diastereomeric ratio is based on ^{1}H NMR of the crude reaction mixture after workup.

(20) (a) Figadere, B. *Acc. Chem. Res.* **1995**, *28*, 359–365. (b) Zeng, L.; Ye, Q.; Oberlies, N. H.; Shi, G.; Gu, Z.-M.; He, K.; McLaughlin, J. L. *Nat. Prod. Rep.* **1996**, *13*, 275–306. (c) Kojima, N.; Maezaki, N.; Tominaga, H.; Yanai, M.; Urabe, D.; Tanaka, T. *Chem.—Eur. J.* **2004**, *10*, 672–680.

(21) (a) Aho, J. E.; Pihko, P. M.; Rissa, T. K. *Chem. Rev.* **2005**, *105*, 4406–4440. (b) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617–1661.

Table 1. Electrophilic Ring Opening Followed by Ring-Contraction Reaction of Spiro-cyclopropanecarboxylated Sugar Derivatives

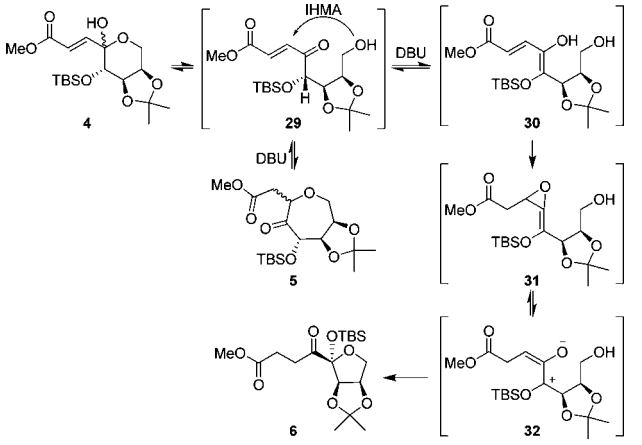
entry	spiro-cyclopropane carboxylate	α,β-unsaturated ester (%)[a]	product[b] (%)[a] (α:β)
1	 **7**	 **8** (80)	 **9** (78) (1:1)
2	 **10**	 **11** (88)	 **12** (78) (4:1)
3	 **13**	 **14** (86)	 **15** (72) (1:4)
4	 **16**	 **17** (77)	 **18** (80) (0:100)
5	 **19**	 **20** (73)	 **21** (65) (30:70)
6	 **22**	 **23** (76)	 **24** (85)[c]
7	 **25**	 **26** (75)	[d]
8	 **27**	 **28** (75)	[d]

[a] Yield refers pure and isolated products. [b] Major diastereomer is represented. [c] Obtained in 30% ee (by HPLC). Stereochemistry at anomeric center was not assigned. [d] No product was observed and the starting material was recovered.

in good yield. However, treating these compounds with DBU gave neither ring-contracted nor ring-expanded product even after an extended period of time (~3 days) (Table 1, entries 7 and 8).

On the basis of the above observations, a plausible mechanism is proposed for the formation of the ring-contracted keto-furanoside **6** from the pyranosyl hemiketal **4**. It is believed that cyclic hemiketal **4** exists in equilibrium with hydroxy ketone **29** that likely can undergo intramolecular hetero Michael addition to give ring-expanded septanose **5**. However, under the reaction conditions **5** can undergo a reverse Michael addition reaction to give **29**, to set up an equilibrium between **5** and **29**. On the other hand, ketone **29**, under basic conditions, can undergo enolization to form the corresponding enol **30**. Baldwin et al.,[22] reported that enols of type **30** may form favorable allene epoxides instead of cyclopropanone intermediate, which is commonly observed in the classical Favorskii rearrangement.[23] Thus, we assumed that enol **30** could convert to the allene epoxide **31** and this could eventually open to give the planar dipole intermediate **32**.[24] Finally, an intramolecular addition of *O*-nucleophile at the carbocation would provide the ring-contracted furanose derivative **6** (Scheme 2). Based on this, we believe that the conversion of hemiketal **4** to keto furanoside **6** depends on the formation of allene epoxide **31**. The driving force for the formation of intermediate **31** may be a consequence of the steric hindrance in intermediate enol **30**. Thus, the presence of a bulky silyloxy group on the enolic carbon might push the enol **30** to form the allene epoxide **31**. On the other hand, when the silyloxy group was replaced with a benzyloxy group (Table 1, entries 7 and 8), where as the steric hindrance would be lower for an OBn compared to an OTBS, the reaction did not proceed further to form the corresponding keto furanoside derivative.

Scheme 2. Proposed Mechanism for the Ring-Contraction Reaction



Keeping the above results in mind, we envisaged that replacing the spiroannulated pyran with a furan moiety might give the five membered hemiketal, upon NIS mediated ring-opening, which could then undergo a ring-expansion to a pyran derivative. Thus, compound **33** was subjected to electrophilic ring-opening to give the furanosyl-hemiketal **34** in 67% yield. However, compound **34** did not provide the expected ring expansion product **35** in the presence of DBU (Scheme 3).

The reason for the lack of reactivity of compound **34** is certainly due to its higher stability in the furanose form compared to the keto-pyranose **35**. Hence, decreasing the flexibility of furanose-hemiketal might be expected to giverise to the ring-expansion product. Therefore,

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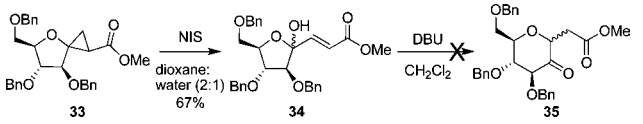
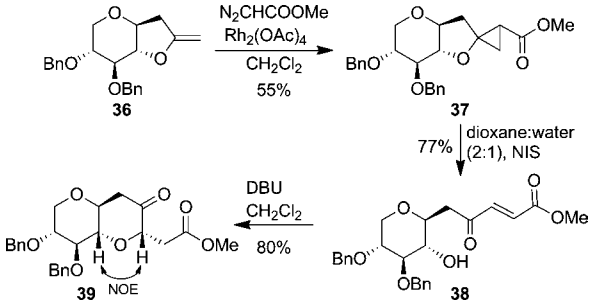
Scheme 3. Electrophilic Ring Opening of Spiro-cyclopropane-Carboxylated Furanose Derivative



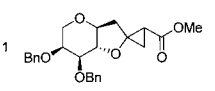
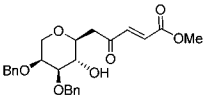
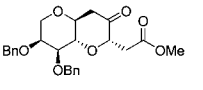
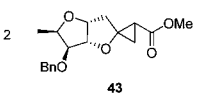
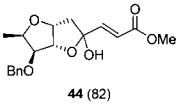
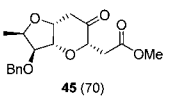
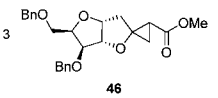
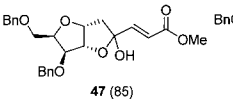
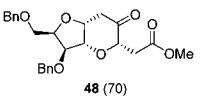
Scheme 4. Ring Expansion of Spiro-cyclopropanecarboxylated Sugar Derivative



spiro-cyclopropanecarboxylated fused bicycle **37** was synthesized by cyclopropanation of the exocyclic vinyl ether **36**. Exposure of compound **37** to NIS resulted in C-glycoside **38** which, upon reaction with DBU, provided the expected ring-expanded bicyclic pyrano[3,2-*b*]pyran derivative **39** as a single diastereomer. The stereochemistry at the newly formed chiral center was assigned from the NOE between the 1,3-diaxial hydrogen atoms present in bicycle **39** (Scheme 4).

Similarly, the spiroannulated sugar derivative **40**, upon electrophilic ring opening, provided the C-glycoside **41**, which smoothly ring-expanded to the bicyclo-pyrano[3,2-*b*]-pyran derivative **42** in excellent yield upon exposure to DBU (Table 2, entry 1). On the other hand, reaction of cyclopropanecarboxylated furo[3,2-*b*]furan derivatives **43** and **46** with NIS provided exclusively the bicyclic hemiketals **44** and **47**. However, in the presence of DBU, the hemiketals **44** and **47** furnished the expected ring-expansion products **45** and **48**, respectively, in good yield. These types of bicyclo-tetrahydrofuro- or pyrano[3,2-*b*]pyran ring systems are present in a number of bioactive natural products.[25] The present ring-expansion methodology will provide a straightforward access to this kind of bicyclic architecture from inexpensive sugar-based raw materials.

Table 2. Stereoselective synthesis of Fused Pyrano- or Furo[3,2-*b*]pyrans from Spiro-cyclopropanecarboxylated Sugar Derivatives

entry	spiro-cyclopropane carboxylate	α,β-unsaturated ester (%)[a]	product (%)[a,b]
1	 **40**	 **41** (75)	 **42** (84)
2	 **43**	 **44** (82)	 **45** (70)
3	 **46**	 **47** (85)	 **48** (70)

[a] Yield refers pure and isolated products. [b] Only a single diastereomer was obtained.

In conclusion, an interesting ring contraction of spiro-cyclopropanecarboxylated sugar derivatives to keto-furanoses, involving NIS-mediated electrophilic ring-opening followed by a DBU-mediated cyclization reaction, has been discovered. The generality of this methodology was investigated, and a plausible mechanism for the process was proposed. Additionally, a ring-expansion protocol for the diastereoselective synthesis of fused pyrano- or furo[3,2-*b*]pyran frameworks has been developed. Further investigations and applications of this methodology in the synthesis of bioactive natural products are in progress.

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Supporting Information Available. Experimental procedures, full spectroscopic data, and ^1H, ^{13}C and DEPT of all new compounds; COSY and NOESY of all final products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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