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Efficient Synthesis of Fused Perhydrofuro[2,3-*b*]pyrans (and Furans) by Ring Opening of 1,2-Cyclopropanated Sugar Derivatives

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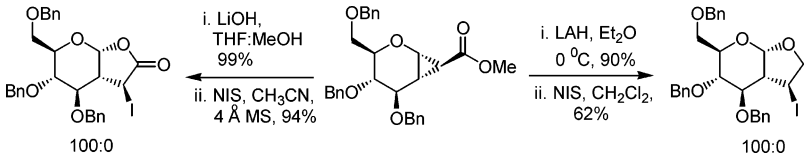
ABSTRACT



An efficient method has been developed for the construction of fused perhydrofuro[2,3-*b*]pyrans by diastereoselective ring opening of 1,2-cyclopropanated sugar derivatives. The methodology has been successfully applied to the synthesis of fused perhydrofuro[2,3-*b*]pyrano-γ-butyrolactone derivatives.

A wide range of linear-fused perhydrofuro[2,3-*b*]pyran or furan ring systems are encountered in a number of biologically active natural product structures. A few approaches are available for the construction of this kind of fused motif; these involve radical cyclization of substituted furans[1] or pyrans,[2] cycloadditions,[3] intramolecular dehydration reactions,[4] acid-catalyzed cyclization of hydroxyacetals,[5] and spontaneous intramolecular ketalization of acyclic dihydroxyaldehydes.[6] However, these strategies suffer from harsh reaction conditions, multistep reactions, and low overall yield. We recently reported an efficient methodology for the synthesis of 2-C-branched glyco-amino-acids by ring opening of 1,2-cyclopropanecarboxylated sugar derivatives.[7] Logically, a similar strategy can be utilized for the construction of fused perhydrofuro[2,3-*b*]pyran/furan ring systems by trapping the intermediate oxonium ion in an intramolecular fashion. In this report we describe the synthesis of perhydrofuro[2,3-*b*]pyran ring systems with defined stereochemistry, inherently present in the cyclopropanated sugar precursor, using NIS-mediated ring opening of 1,2-cyclopropanated sugar derivatives[8] (Scheme 1). Additionally

(1) (a) Mayer, S.; Prandi, J.; Bamhaoud, T.; Bakkas, S.; Guillou, O. *Tetrahedron* **1998**, *54*, 8753. (b) Harrison, T.; Pattenden, G.; Myers, P. L. *Tetrahedron Lett.* **1988**, *29*, 3869.

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(4) Duhamel, P.; Deyine, A.; Dujardin, G.; Plé, G.; Poirier, J. M. *J. Chem. Soc., Perkin Trans 1.* **1995**, 2103.

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(6) Alonso, F.; Lorenzo, E.; Meléndez, J.; Yus, M. *Tetrahedron* **2003**, *59*, 5199.

(7) Sridhar, P. R.; Ashalu, K. C.; Chandrasekaran, S. *Org. Lett.* **2004**, *6*, 1777 and references cited therein.

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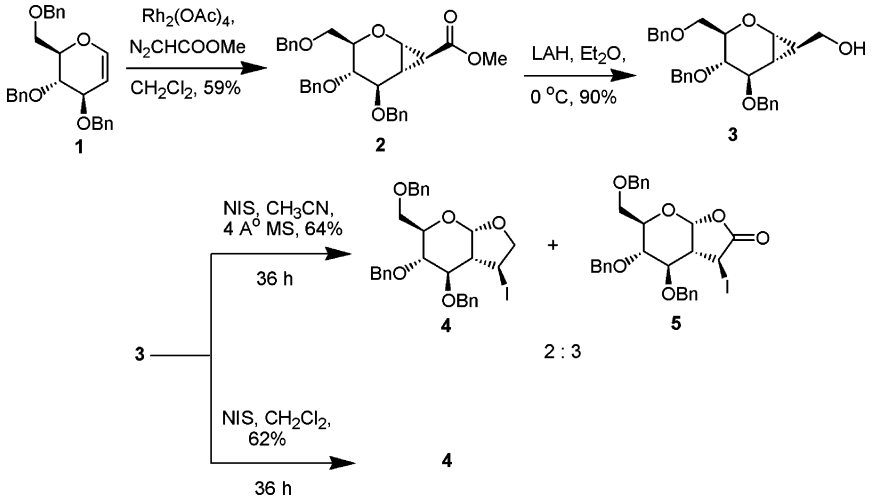
Scheme 1. NIS Mediated Ring Opening of 1,2-Cyclopropanated Sugar Derivatevs



we also describe an efficient method for the construction of perhydrofuro[2,3-*b*]pyrano-γ-butyrolactone derivatives under similar reaction conditons.

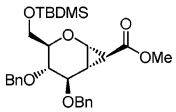
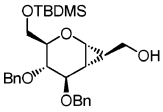
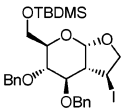
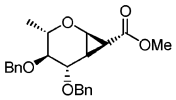
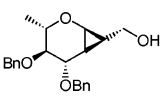
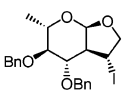
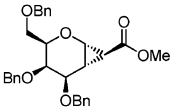
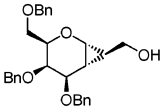
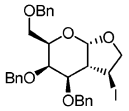
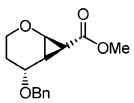
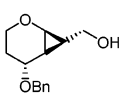
Cyclopropanation of tri-*O*-benzyl-D-glucal **1** was carried out by using methyl diazoacetate (MDA) in dichloromethane with catalytic rhodium acetate (23 °C, 90 min) to furnish the corresponding 1,2-cyclopropane carboxylated sugar derivative **2** in 59% yield.[9] LAH reduction of **2** in anhydrous ether at 0 °C afforded 1,5-anhydro-2-deoxy-1,2-C-(*exo*-hydroxymethylmethylene)-3,4,6-tri-*O*-benzyl-α-D-glucitol **3** in 90% yield. Treatment of alcohol **3** with *N*-iodosuccinimide (CH_3CN, 4 Å MS, 23 °C, 36 h) furnished the expected perhydrofurano[2,3-*b*]pyran derivative **4** along with an unexpected oxidized product, perhydrofuro[2,3,*b*]pyrano-γ-butyrolactone **5** (2:3 ratio).

Formation of the lactone **5** can be accounted for by the in situ oxidation of primary alcohol to the corresponding carboxylic acid, which can be an active competitor for the NIS-mediated ring opening reaction. It has been found that by changing the solvent from acetonitrile to dichloromethane, the required perhydrofuro[2,3-*b*]pyran derivative **4** was obtained as the exclusive product in 62% yield.

The generality of this methodology has been demonstrated by extending this reaction to a number of other sugar derivatives. The cyclopropyl methanols **7**, **10**, **13**, and **16** were readily obtained in high yield by LAH reduction of the corresponding cyclopropanated esters **6**, **9**, **12**, and **15**, respectively. The alcohols **7**, **10**, and **13** on treatment with 1 equiv of NIS (CH_2Cl_2, 23 °C, ~36 h) gave rise to the corresponding perhydrofuro[2,3-*b*]pyran derivatives **8**, **11**, and **14**, respectively, in good yield (58% to 66%) and with very high diastereoselectivity at the newly formed stereocenters (Table 1). The coupling constant for the anomeric proton ($J \approx 4.2$ Hz) in all the products showed that the fused ring systems have a α-[1,2-*b*]-*cis*-bicyclic stereochemistry.[2f,g] The stereochemistry at C1 and C2 was defined on the basis of the stereochemistry present in the 1,2-cyclopropanated sugar precursors. The configuration of the iodide in the product has been assigned based on nOe experiments between the C3 and C7 hydrogens (carbohydrate nomenclature).

However, in the reaction of **16** with NIS under similar reaction conditions the product **17** was obtained as a 1:1 mixture of diastereomers.

Table 1. Synthesis of Linear Perhydrofuro[2,3-*b*]pyran Ring Systems by NIS-Mediated Ring Opening of 1,2-Cyclopropanated Sugar Derivatives

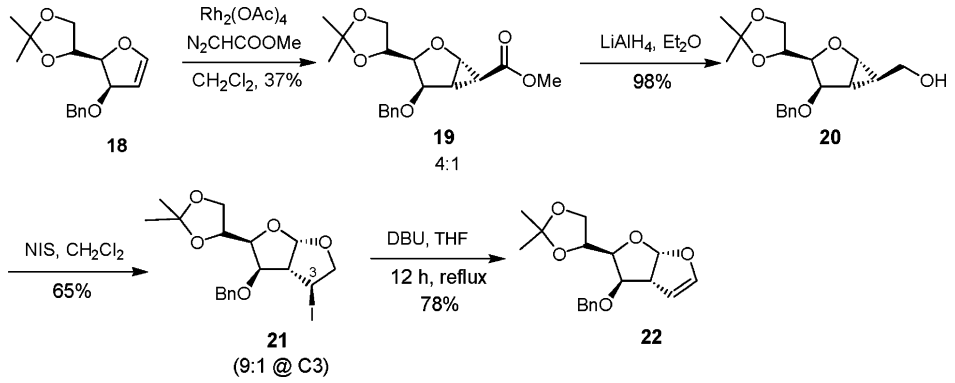
entry	ester(%)[a]	alcohol (%)[a]	iodoether (%)[a]	dr
1	 **6** (85)	 **7** (72)	 **8** (61)	100:0
2	 **9** (45)	 **10** (94)	 **11** (58)	100:0
3	 **12** (59)	 **13** (90)	 **14** (66)	100:0
4	 **15** (60)	 **16** (99)	 **17** (75)	50:50

[a] Isolated yield after column chromatography. Yield of iodoethers based on the corresponding alcohol precursors.

(8) For a review on the preparation and ring opening of cyclopropanated carbohydrates, see: Cousins, G. S.; Hoberg. J. O. *Chem. Soc. Rev.* **2000**, *29*, 165.

(9) Timmers, C. M.; Leeuwenburgh, M. A.; Verheijen, J. C.; van der Marel, G.; van Boom, J. H. *Tetrahedron*: *Asymmetry* **1996**, *7*, 49.

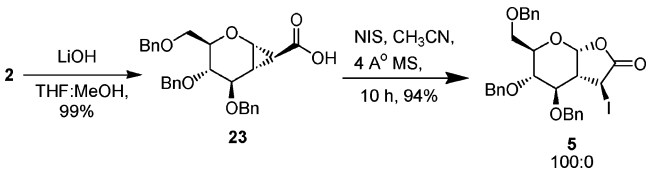
Scheme 2. Synthesis of the Furofuryl Glycal Ring System



There are many natural products that contain the perhydrofurofuran core such as clerodin and caryoptin[10] which show insect anti-feedant properties. With this in mind, the methodology was subsequently extended to the cyclopropanated tetrahydrofuran derivatives. The dihydrofuran derivative **18**[11] was treated with methyl diazoacetate in the presence of $Rh_2(OAc)_4$ to give the cyclopropanated ester **19** as a major product. Reduction of **19** with LAH gave rise to the required alcohol **20** in 98% yield. Compound **20** when subjected to the ring opening and cyclization reaction conditions (NIS 1 equiv, CH_2Cl_2, 25 °C, 36 h) led to the formation of perhydrofuro[2,3-*b*]furan derivative **21** in 65% yield as a mixture of diastereomers (9:1). This mixture was subjected to dehydrohalogenation with DBU (THF, reflux, 14 h) as a base to obtain the corresponding furofuryl glycal **22** in 78% yield (Scheme 2).

The low reactivity and moderate yield of these reactions with all the cyclopropyl methanol derivatives studied so far may be attributed to the lack of neighboring group participation and donor−acceptor functionality in the cyclopropane ring systems.[12] Consequently, we decided to incorporate these two features in the substrates to check the selectivity and yield under similar reaction conditons. Toward this end, 1,2-cyclopropane carboxylic acid **23** was synthesized by base hydrolysis of the 1,2-cyclopropane carboxylate **2** (Scheme 3).

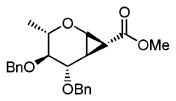
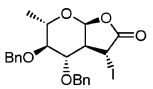
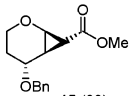
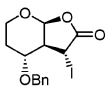
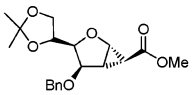
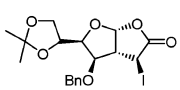
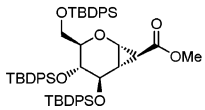
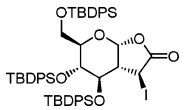
Scheme 3. Synthesis of Fused Perhydrofuro[2,3-*b*]pyrano-γ-butyrolactone



Treatment of carboxylic acid **23** with NIS/CH_3CN (4 Å MS, 10 h) furnished the corresponding 3-iodoperhydrofuro[2,3-*b*]pyrano-γ-butyrolactone derivative **5** as a single diastereomer in excellent yield (94%). There are some reports that cleverly use the acid-catalyzed rearrangement strategy for the formation of fused tetrahydrofuro[2,3-*b*]furano-γ-butyrolactone motif,[13] by using donor−acceptor 1,2-cyclopropane carboxylated derivatives. The present strategy is complementary to the existing methods and it is useful since it incorporates an additional chiral center in the molecule under milder conditions which can be used for further transformations.

The methodology has been validated by applying it to a few other 1,2-cyclopropanecarboxylic acid derivatives. Thus, treatment of cyclopropane carboxylic acids **24**, **26**, **28**, and **30** with NIS/CH_3CN (4 Å MS, 10 h) gave rise to the corresponding iodobutyrolactones **25**, **27**, **29**, and **31**, respectively, in very good yield (83−92%) with very high diastereoselectivity at the newly formed stereocenters (Table 2).

Table 2. Synthesis of Linear Perhydrofuro[2,3-*b*]pyrano-γ-butyrolactone Ring Systems by NIS-Mediated Ring Opening of Sugar Derived 1,2-Cyclopropancarboxylic Acids

entry	ester (%)[a]	carboxylic Acid (%)[a]	iodolactone (%)[a]	dr
1	 **9** (45)	**24** (100)	 **25** (89)	100:0
2	 **15** (60)	**26** (99)	 **27** (92)	100:0
3	 **18** (37)	**28** (99)	 **29** (83)	100:0
4	 **28** (58)	**30** (78)	 **31** (83)	100:0

[a] Isolated yield after column chromatography. Yield of iodolactones based on the corresponding carboxylic acid precursors.

(10) (a) van Beek, T. A.; de Groot, A. *Trav. Chim. Pays-Bas* **1986**, *105*, 513. (b) Merritt, A. T.; Ley, S. V. *Nat. Prod. Rep.* **1992**, *9*, 243.

(11) Kim, C.; Hoang, R.; Theodorakis, A. *Org. Lett.* **1999**, *1*, 1295.

In conclusion, we have developed an efficient method for the stereoselective construction of linear-fused perhydrofuro-[2,3-*b*]pyran motifs using NIS-mediated ring opening and cyclization of 1,2-cyclopropanated sugar derivatives. We also describe herein a general method for the synthesis of fused perhydrofuro[2,3-*b*]pyrano-γ-butyrolactone systems under similar reaction conditions using sugar-derived 1,2-cyclopropanecarboxylic acids. Application of this methodology for the synthesis of caryoptin is underway.

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Supporting Information Available: ^{1}H and ^{13}C NMR data for cyclopropyl methanols (**3**, **7**, **10**, **13**, **16**, **20**), cyclopropane carboxylic acids (**23**, **28**),d fused bicycles (**4**, **8**, **11**, **14**, **17**, **21**), and fused lactones (**5**, **25**, **27**, **29**, **31**). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) For reviews on donor - acceptor cyclopropanes: (a) Reissig, H.−U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151. (b) Reissig, H.−U. *Top. Curr. Chem.* **1988**, *144*, 73. (c) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321.

(13) (a) Kim, C.; Hoang, R.; Theodorakis, E. A. *Org. Lett.* **1999**, *1*, 1295. (b) Kim, C.; Brady, T.; Kim, S. H.; Theodorakis, E. A. *Synth. Commun.* **2004**, *34*, 1951. (c) Weisser, R.; Yue, W.; Reiser, O. *Org. Lett.* **2005**, *7*, 5353.