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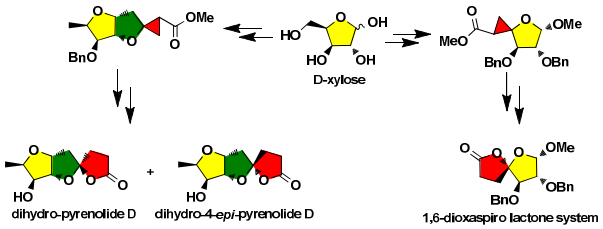
Graphical Abstract

A one-pot protocol for the stereoselective construction of γ-spiroketal γ-lactone frameworks from sugar derived spiro-cyclopropanecarboxylic acids involving a ring enlargement and cyclization reaction is revealed.



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Stereoselective synthesis of 1,6-dioxaspirolactones from spiro-cyclopropanecarboxylated sugars: Total synthesis of dihydro-pyrenolide D

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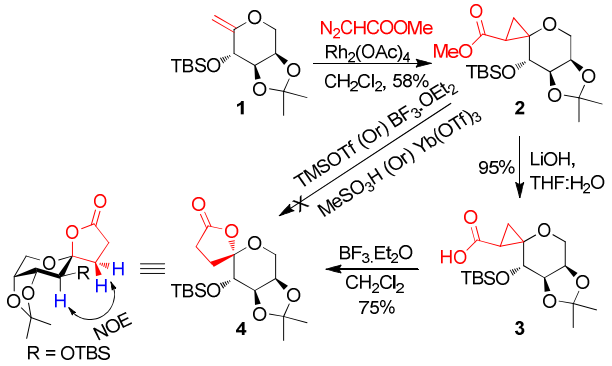
An efficient method for the stereoselective construction of 1,6-dioxaspiro[4.n]decan-2-one systems (n = 4, 5) from sugar derived spirocyclopropane carboxylic acids involving a one-pot ring-opening and cyclization reaction is revealed. The generality of the methodology and its application in the total synthesis of dihydro-pyrenolide D and 4-*epi*-dihydro-pyrenolide D are reported.

1,6-dioxaspiro system, particularly in the form of spiroketal[1] or spirolactone,[2] is one of the intriguing structural unit present in a number of highly bioactive natural products.[3] For example, marine toxins like azaspiracids,[4] pinnatoxins,[5] pteriatoxins,[6] spongistatins[7] and spirolides[8] etc. possess the spiroketal moiety as the core structure. The spiroketal framework provides the essential conformation that is essential to unveil the biological activity in these molecules. This was evidenced by some of the simplified spiroketal fragments which were found to retain the biological activity that was exhibited by the parent natural product.[9] Despite their wide occurrence, methods for the enantioselective construction of these frameworks are very limited.[1] A major challenge in the construction of these spirocycles is the stereoselective formation of quaternary ketal centre. The traditional method for the spiroketal synthesis involves an acid catalyzed ketalization of a dihydroxy ketone precursor, which often produces the thermodynamic product.[10] On the other hand, oxidative radical cyclization is a contemporary approach that offers an access to the kinetically controlled preparation of spiroketals.[11] Recently, IBX/Yb(OTf)$_3$ mediated ring enlargement of donor-acceptor cyclopropanes to give [n,5]-spiroketals in moderate yield has been reported.[12] Although several methods have been reported for the synthesis of spiroketals, the stereoselective protocols for the preparation of spirolactones (γ-spiroketal γ-lactones) are very scarce.[13] In addition, spirolactones are also an excellent synthons for the preparation of spiroketals[14] as well as for further functional group modifications. Apart from directed protocols,[15] photolytic oxidative cyclization of sugar derived nononamides[16] and gold phosphate-catalyzed one-pot three component coupling reaction of alkynols, anilines and glyoxylic acid towards the preparation of spirolactones[17] are noteworthy. In continuation of our investigation towards the application of cyclopropanecarboxylated sugars in the stereoselective synthesis of bicycilc architectures,[18] herein we report a general methodology for the preparation of carbohydrate derived 1,6-dioxa[n,5]-spiroketal butyrolactones (n = 5, 6) involving a one-pot ring expansion and cyclization reaction of sugar derived donor-acceptor spiro-cyclopropanecarboxylic acids.[19] Further, the developed methodology was successfully utilized in the total synthesis of pyrenolide D analogues, 2,3-dihydro-pyrenolide D and 2,3-dihydro-4-*epi*-pyrenolide D.

The synthesis of carbohydrate derived donor-acceptor cyclopropanecarboxylic acid was planned starting from the *exo*-glycals of type **1**. Thus, $Rh_2(OAc)_4$ catalyzed cyclopropanation of *exo*-glycal[20] **1** using methyldiazoacetate provided the spiro-cyclopropanecarboxylate **2** as a mixture of diastereomers.[§] In contrast to the 1,2-cyclopropane carboxylated sugars which have been shown to undergo ring-opening followed by cyclization reaction,[21] direct exposure of spiro-cyclopropanecarboxylate **2** to a series of Lewis acids did not provide the expected spirolactone **4**. This might be attributed due to the higher stability and lower strain of spiro-cyclopropanecarboxylate, when compared to linearly fused systems.

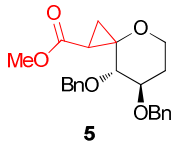
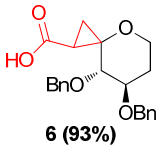
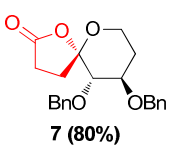
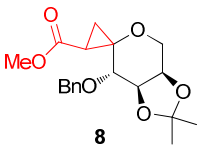
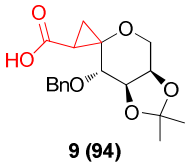
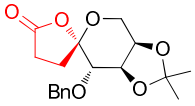
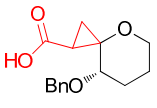
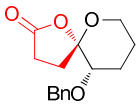
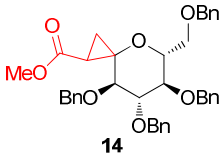
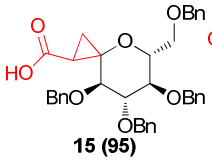
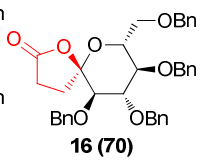
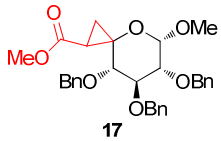
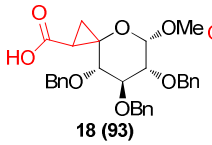
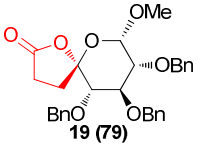
We assumed that, converting the cyclopropanecarboxylate to the corresponding carboxylic acid will increase the electrophilicity of the carbonyl group and facilitate the cyclopropane ring opening.

Thus, ester **2** was hydrolyzed to give spiro-cyclopropanecarboxylic acid **3** and reacted with catalytic $BF_3.Et_2O$. Under these conditions, **3** underwent a facile one-pot ring-opening and cyclization reaction to provide the expected spirolactone **4** as a single diastereomer. The formation of a single diastereomer clearly indicates the existence of oxonium ion intermediate that is trapped by the carboxylic acid, minimizing the anomeric effect of both the rings, which leads to the formation of thermodynamically more stable spirocyclic system. The stereochemistry at the spirocentre was unambiguously assigned by 2D NOESY experiment.



Scheme 1 Synthesis of 1,6-dioxaspiro[4.5]decan-2-one by a one-pot ring-opening and cyclization reaction.

Table 1. Stereoselective synthesis of pyranose derived 1,6-dioxaspiro[4.5] decan-2-one systems.

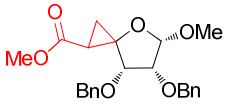
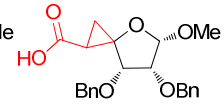
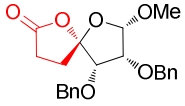
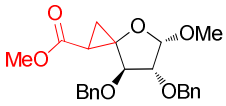
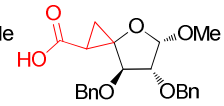
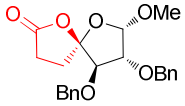
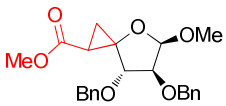
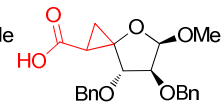
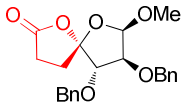
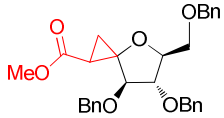
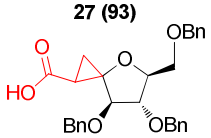
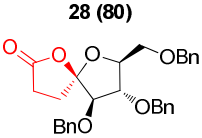
entry	spiro-cyclopropa--ne carboxylate[a]	spiro-cyclopropane carboxylic acid[a] (%)[b]	spirolactones (%)[b]
1	 **5**	 **6 (93%)**	 **7 (80%)**
2	 **8**	 **9 (94)**	 **10 (85)**
3	 **11**	 **12 (95)**	 **13 (85)** (55:45)[c]
4	 **14**	 **15 (95)**	 **16 (70)**
5	 **17**	 **18 (93)**	 **19 (79)**

[a] Mixture of diastereomers. [b] Yield refers to pure and isolated products. [c] Major diastereomer is represented.

Encouraged with this result the generality of the reaction was investigated by applying it to a number of sugar derived spiro-cyclopropanecarboxylic acids. Thus, a series of pyranose fused cyclopropanecarboxylated sugar derivatives **5**, **8** and **11** were subjected to the base hydrolysis to obtain the corresponding spiro-cyclopropanecarboxylic acids **6**, **9** and **12**, respectively, in excellent yield. Subjecting these acid derivatives to the $BF_3.Et_2O$ mediated ring-opening cyclization reaction provided the sugar derived 1,6,-dioxaspirolactones **7**, **10** and **13**, respectively, in good yield. In the all ring-opening and cyclization reactions we observed the formation of thermodynamically more stable spirolactone as the only product, except in the case of spirolactone **13** in which a 55:45 ratio of thermodynamic *vs* kinetic product formation was observed (Table 1, entry 1-3). Towards the application of this methodology to fully substituted hexose derived spirocyclic systems, glucose based donor-acceptor cyclopropanecarboxylated compounds **14** and **17** were hydrolyzed to obtain the corresponding acids **15** and **18** which were upon exposure to $BF_3.Et_2O$ lead to the formation of 1,6-dioxaspiro[4.5]decan-2-one systems **16** and **19** as single diastereomers, respectively.

The methodology was further evaluated in the case of furanose fused spiro-cyclopropanecarboxylic acids. Thus, spiro-cyclopropanecarboxylates **20**, **23**, **26** and **29** were hydrolyzed to obtain furanose fused spiro-cyclopropanecarboxylic aicds **21**, **24**, **27** and **30**, respectively. Reaction of these acids with $BF_3.Et_2O$ provided the 1,6-dioxaspiro[4.4]nonan-2-one motifs **22**, **25**, **28** and **31** as single diastereomers in good yield. Interestingly, it was observed that in all the spirolactones that were synthesized, the oxygen of the lactone prefer to have a 1,2-*syn* relationship. These observations indicate that the stereochemistry at spirocentre is a cumulative outcome based on the stability of the chair-like oxonium ion intermediate and the anomeric effect, which will be substantially influenced by the stereocentre adjacent to the spirocentre.[22]

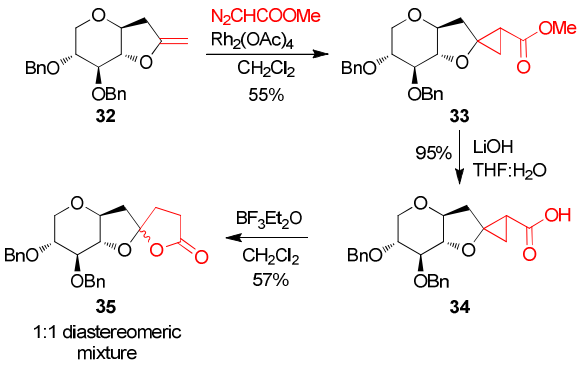
Table 2. Stereoselective synthesis of furanose derived 1,6-dioxaspiro[4.4] nonan-2-one systems.

entry	spiro-cyclopropane carboxylate[a]	spiro-cyclopropane carboxylic acid[a] (%)[b]	spirolactones (%)[b]
1	 **20**	 **21 (96)**	 **22 (80)**
2	 **23**	 **24 (91)**	 **25 (79)**
3	 **26**	 **27 (93)**	 **28 (80)**
4	 **29**	 **30 (94)**	 **31 (72)**

[a] Mixture of diastereomers. [b] Yield refers to pure and isolated products.

To examine the application of this methodology in bicyclic systems, *exo*-olefin **32** was cyclopropanated to give a diastereomeric mixture of tricyclic cyclopropanecarboxylate **33** which upon base hydrolysis provided the corresponding carboxylic acid **34**. $BF_3.Et_2O$ mediated

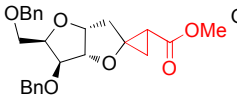
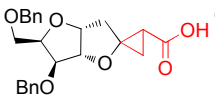
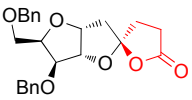
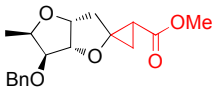
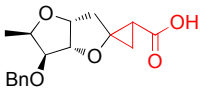
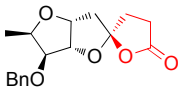
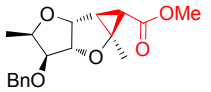
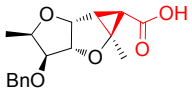
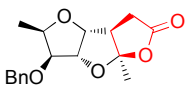
ring-opening and cyclization of **34** provided the tricyclic spirolactone **35** as a 1:1 diastereomeric mixture (Scheme 2).



Scheme 2 Synthesis of tricyclic spiro systems possessing spirolactone moiety.

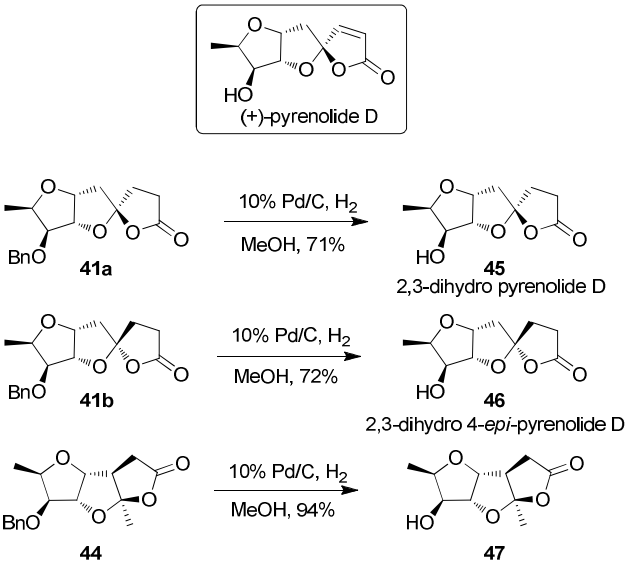
Application of the similar protocol on spiro-cyclopropane carboxylic acids **37** and **40**, synthesized from esters **36** and **39**, provided the spiro-lactones **38a** and **38b** (8:7) and **41a** and **41b** (3:2), respectively (Table 3, entry 1 and 2). The lower diastereoselectivity in these reactions might be due to the lack of stereocentre adjacent to the spirocenter. The methodology is also equally applicable to the synthesis of fused lactones that has been shown by synthesizing the cyclopropanecarboxylic acid **43**, prepared from **42**,[23] and treating with $BF_3.Et_2O$ to give linearly fused tricyclic lactone **44** as a single diastereomer (Table 3, entry 3).[24]

Table 3. Synthesis of tricyclic spirosystems.

entry	spiro-cyclopropa--ne carboxylate[a]	spiro-cyclopropane carboxylic acid[a] (%)[b]	spiro-lactone (%)[b]
1	 **36**	 **37** (92)	 **38a:38b** (8:7), (75)[c]
2	 **39**	 **40** (74)	 **41a:41b** (3:2), (77)[c]
3	 **42**	 **43** (95)	 **44** (83)

[a] Mixture of diastereomers. [b] Yield refers to pure and isolated products. [c] Major diastereomer is represented.

To demonstrate the significance of the developed methodology we planned to synthesize the analogues of a bio-active spirolactone containing natural product pyrenolide D[25] (IC_{50} = 4 µg/mL against HL-60). Thus, purified spirolactones **41a** and **41b** were treated with 10% Pd/C under hydrogen atmosphere to give the 2,3-dihydro-pyrenolide D **45**, and 2,3-dihydro-4-*epi*-pyrenolide D **46**. Surprisingly to the best of our knowledge, the synthesis of dihydro-pyrenolides **45** and **46** has not been reported to date. We assume that the biological activity of these compounds would reveal the importance of the unsaturated lactone moiety in the natural product pyrenolide D. Similarly hydrogenolysis of compound **44** provided the fused tricyclic lactone **47** (Scheme 3).



Scheme 3 Synthesis of pyrenolide D analogues and linearly fused tricyclic lactone.

Conclusions

In conclusion, a stereoselective protocol for the construction of spiro[6.5] and spiro[5.5]lactone using a diastereomeric mixture of carbohydrate derived spiro-cyclopropanecarboxylates was revealed. The generality of the reaction was investigated by applying the methodology to synthesize a variety of spirocyclic systems. In all the spiro-lactones that were synthesized it was observed that there is a pronounced effect of the stereocentre adjacent to the anomeric position which directs the chirality of emerging spirocentre. This methodology was also further applied to synthesize a series of tricyclic spiro[furan-2,2'-furo[3,2-*b*]furan] ring systems. A successful application of the developed methodology was shown by synthesizing dihydro-pyrenolide D and dihydro-4-*epi*-pyrenolide D. Exploitation of this protocol in the total synthesis of bioactive natural products and the investigation of controlling the stereochemistry at the spirocentre are in progress.

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Notes and references

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§ To the best of our knowledge highly diastereoselective cyclopropanation of exocyclic enol ethers has not yet been demonstrated.

Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data and copies of ^1H and ^{13}C spectra of all new compounds, copies of DEPT, COSY and NOESY spectra of all spirocyclic lactones. See DOI: 10.1039/c000000x/

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