New generations of organocatalysts suitable for the spiroacetal formation

Aim

To overcome the current limitations of organocatalysis in the field of spiroacetal formation, focusing on the synthesis of all aliphatic spiroacetals and the selective formation of kinetic (non-thermodynamic) spiroacetals.

Motivation

Spiroacetals are key components of several natural products with exceptionally interesting biological properties (Figure 1).[1–5] Our interest in this class of compounds is twofold:

1. Synthesis of derivatives of Ivermectin-like natural products to advance the optimization of their anthelmintic biological activity.
2. Development of a new generation of organocatalysts that will enable the stereoselective preparation of aliphatic spiroacetals with targeted structures for the first time. Additionally, these novel organocatalysts should be able to finely tune the cyclization step, allowing the generation of not only thermodynamically favored configurations of the spiroacetals but also the opposite stereoisomers.

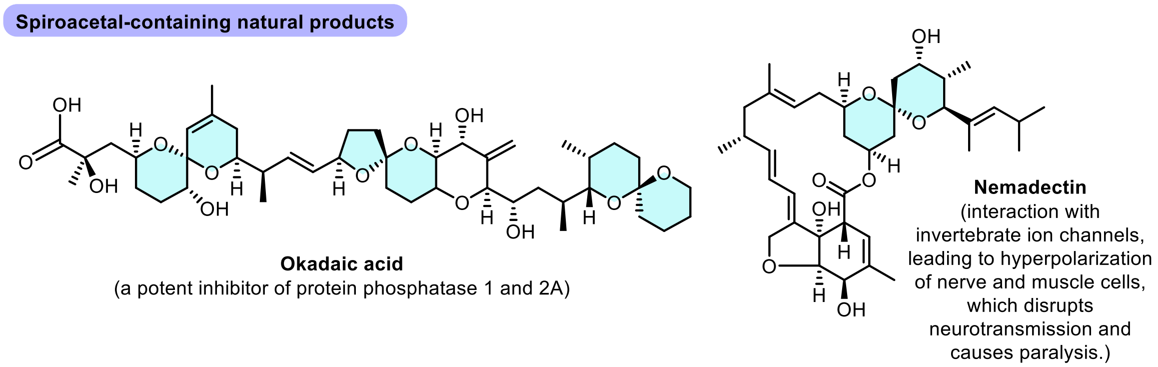


Figure 1. Selected examples of natural products that contains spiroacetal subunit.

State-of-the-art

The synthesis of aliphatic spiroacetals has garnered significant attention in the literature due to the intriguing properties of natural products containing these structural motifs (Scheme 1A and B). Typically, thermodynamically favored compounds are produced because of the anomeric effect-driven stability of the formed spiroacetals (Scheme 1C). However, this approach does not allow for the selective synthesis of the thermodynamically unfavored spiroacetals. Consequently, current synthetic methodologies do not enable the formation of new chemical structures. These structures, due to their rigidity, could serve as previously unknown chemical building blocks, occupying previously inaccessible chemical space and potentially leading to the discovery of novel biological activities.

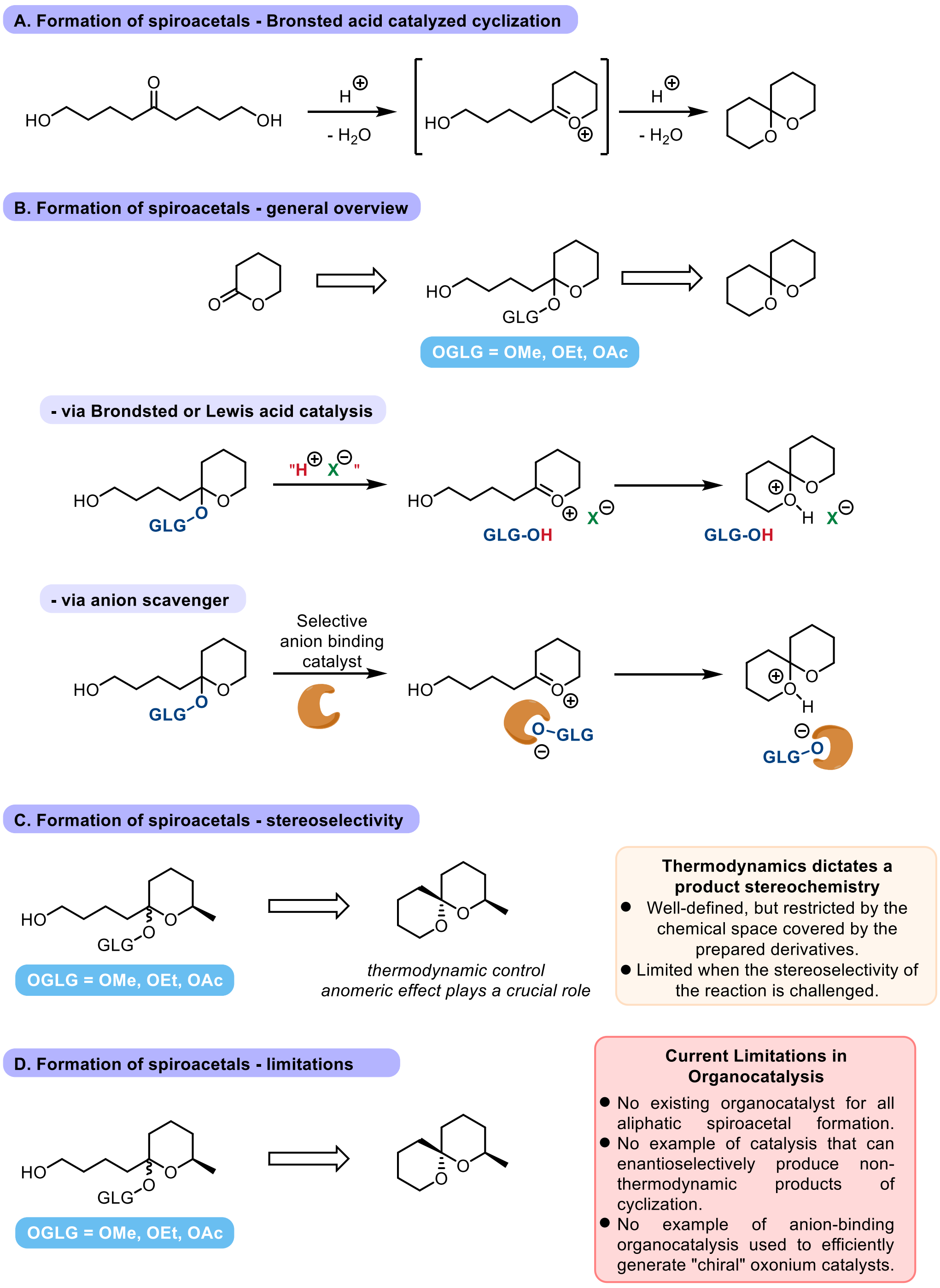
There are several limitations to known spiroacetal formation methodologies known from the literature (Scheme 1D). Currently, organocatalyzed spirocyclization reactions are limited to aryl-containing structures and very specific substrates. Examples of such cyclizations can be found in the following articles.[6–9] There is no anion-recognition organocatalytic system in the literature that allows for the stereoselective organocatalyzed formation of spiroacetals.

Objectives

The Ph.D. project aims to: (a) Identify organocatalytic systems capable of stereodefined spirocyclization of cyclic substrate **1** into spiro compound **2** in an enantioselective manner, considering both possible stereoisomers formed selectively. (b) Apply the developed strategy to the total synthesis of nematocide congener **3** (Scheme 2).

To achieve such objectives, the following goals were established:

1. Development of the organocatalytic systems that would be able to carry out stereoselective spirocyclization as described in Scheme 2,Goal 1.
    a. Development of the organocatalysis protocol based on the Brondsted acid catalysis (Goal 1a)
    b. Development of the organocatalysis protocol based on the anion-recognition catalysis (Goal 1a)
2. Total synthesis of nematocide congener **3**.
    a. To achieve out the total synthesis.
    b. Apply the developed organocatalytic approach to north fragment synthesis.



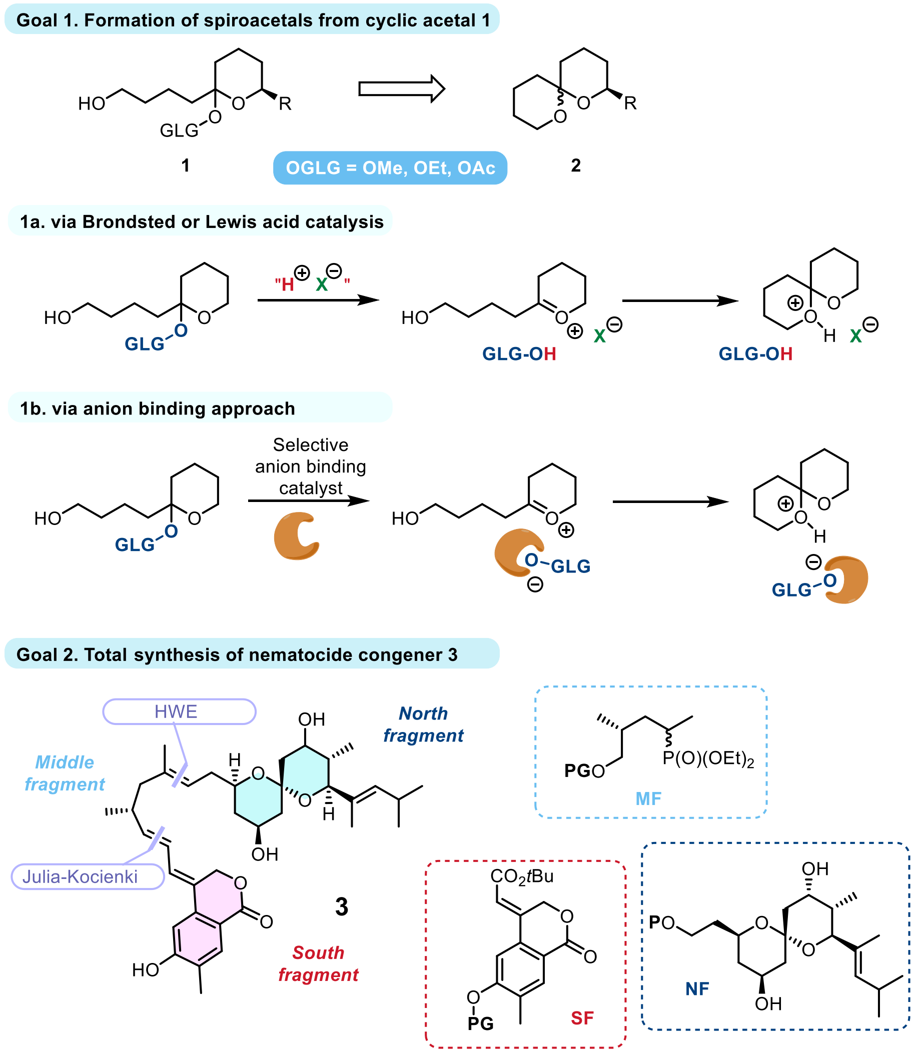
Thermodynamics dictates a product stereochemistry

- Well-defined, but restricted by the chemical space covered by the prepared derivatives.
- Limited when the stereoselectivity of the reaction is challenged.

Current Limitations in Organocatalysis

- No existing organocatalyst for all aliphatic spiroacetal formation.
- No example of catalysis that can enantioselectively produce non-thermodynamic products of cyclization.
- No example of anion-binding organocatalysis used to efficiently generate "chiral" oxonium catalysts.

*Scheme 1. **A.** Most common approach to aliphatic spiroacetals – Bronsted acid catalyzed cyclization that yields thermodynamic spiroacetals. **B.** An alternative approach to spiroacetals that allows the key stereodetermining cyclization to carry out under Bronsted or Lewis acid catalysis or via selective anion chelating catalysis. **C**. Standard approach to spiroacetals that dictates stereoselectivity outcome. **D.** sum up of limitations and challenges in organocatalyzed spiroacetalyzation.*



Scheme 2. Goals of the project – an overview.

Litterature

(1) Paterson, I.; Coster, M. J.; Chen, D. Y. K.; Gibson, K. R.; Wallace, D. J. The Stereocontrolled Total Synthesis of Altohyrtin A/Spongistatin 1: The CD-Spiroacetal Segment. *Org Biomol Chem* **2005**, *3* (13), 2410–2419. https://doi.org/10.1039/B504148A.

(2) Han, X.; Floreancig, P. E. Spiroacetal Formation through Telescoped Cycloaddition and Carbon–Hydrogen Bond Functionalization: Total Synthesis of Bistramide A. *Angewandte Chemie International Edition* **2014**, *53* (41), 11075–11078. https://doi.org/10.1002/anie.201406819.

(3) Paterson, I.; Anderson, E. A.; Dalby, S. M.; Lim, J. H.; Maltas, P.; Moessner, C. Synthesis of the DEF-Bis-Spiroacetal of Spirastrellolide A Exploiting a Double Asymmetric

Dihydroxylation/Spiroacetalisation Strategy. *Chemical Communications* **2006**, No. 40, 4186–4188.

(4) Valdiglesias, V.; Prego-Faraldo, M. V.; Paśaro, E.; Meńdez, J.; Laffon, B. Okadaic Acid: More than a Diarrheic Toxin. *Marine Drugs 2013, Vol. 11, Pages 4328-4349* **2013**, *11* (11), 4328–4349. https://doi.org/10.3390/MD11114328.

(5) Kamat, P. K.; Nath, C. Okadaic Acid: A Tool to Study Regulatory Mechanisms for Neurodegeneration and Regeneration in Alzheimer's Disease. *Neural Regen Res* **2015**, *10* (3), 365–367. https://doi.org/10.4103/1673-5374.153679.

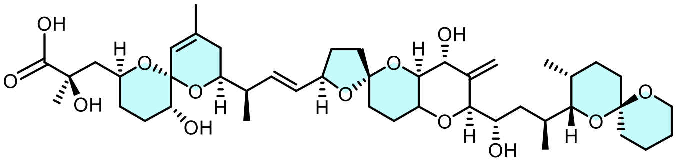
(6) Liu, C.; Liu, Y. K. Asymmetric Organocatalytic One-Pot, Two-Step Sequential Process to Synthesize Chiral Acetal-Containing Polycyclic Derivatives from Cyclic Hemiacetals and Enones. *Journal of Organic Chemistry* **2017**, *82* (19), 10450–10460. https://doi.org/10.1021/ACS.JOC.7B01915/SUPPL_FILE/JO7B01915_SI_004.CIF.

(7) Balha, M.; Pan, S. C. Organocatalytic Asymmetric Synthesis of Bridged Acetals with Spirooxindole Skeleton. *Journal of Organic Chemistry* **2018**, *83* (23), 14703–14712. https://doi.org/10.1021/ACS.JOC.8B02156/SUPPL_FILE/JO8B02156_SI_002.CIF.

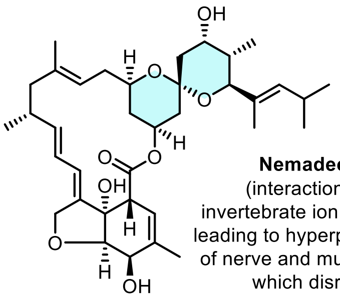
(8) Parida, C.; Mondal, B.; Ghosh, A.; Pan, S. C. Organocatalytic Asymmetric Synthesis of Spirooxindole Embedded Oxazolidines. *Journal of Organic Chemistry* **2021**, *86* (18), 13082–13091. https://doi.org/10.1021/ACS.JOC.1C00644/ASSET/IMAGES/LARGE/JO1C00644_0005.JPEG.

(9) Balha, M.; Vagadiya, N.; Manhas, A. Strategies for the Organocatalytic Asymmetric Synthesis of Bridged Acetal. *Mater Today Proc* **2022**, *62* (P13), 7007–7018. https://doi.org/10.1016/j.matpr.2021.12.546.

Spiroacetal-containing natural products

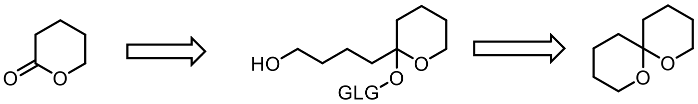


Okadaic acid
(a potent inhibitor of protein phosphatase 1 and 2A)



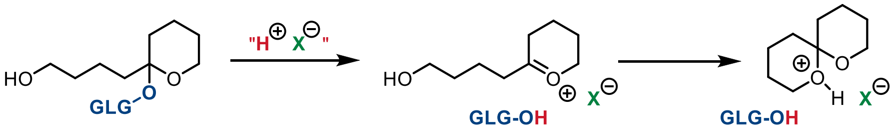
Nemadectin
(interaction with invertebrate ion channels, leading to hyperpolarization of nerve and muscle cells, which disrupts neurotransmission and causes paralysis.)

Formation of spiroacetals - general overview

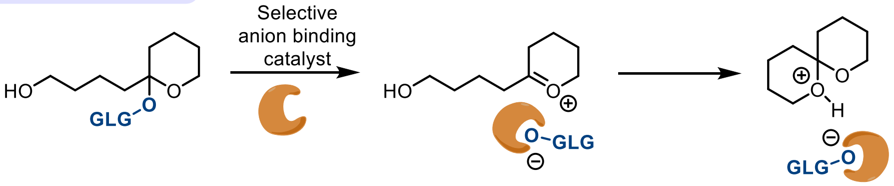


OGLG = OMe, OEt, OAc

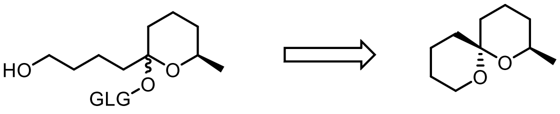
- via Brondsted or Lewis acid catalysis



- via anion scavenger



Formation of spiroacetals - stereoselectivity



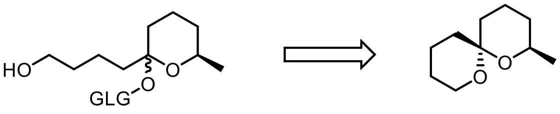
OGLG = OMe, OEt, OAc

thermodynamic control
anomeric effect plays a crucial role

Thermodynamics dictates a product stereochemistry

- Well-defined, but restricted by the chemical space covered by the prepared derivatives.
- Limited when the stereoselectivity of the reaction is challenged.

Formation of spiroacetals - challenges



OGLG = OMe, OEt, OAc

Goals

- New organocatalyst development suitable for all aliphatic systems
- Develop organocatalysts able to inverse the stereoselectiivty of the cyclization

Current Limitations in Organocatalysis

- No existing organocatalyst for all aliphatic spiroacetal formation.
- No example of catalysis that can enantioselectively produce non-thermodynamic products of cyclization.
- No example of anion-binding organocatalysis used to efficiently generate "chiral" oxonium catalysts.