Biomimetic oxidative strategies and alternative route for the synthesis of diketopiperazine natural products

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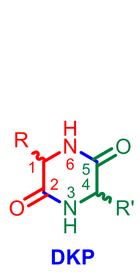
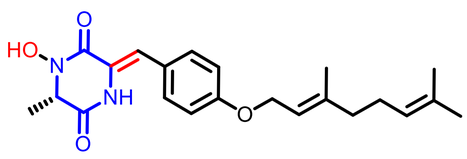
❶ Fact sheet

- **2,5-diketopiperazine (DKP)** is the smallest cyclopeptide alkaloid, usually made by cyclization of two amino acids, isolated from microorganism.[1,2]
- Post-oxidative transformations lead to high chemical diversity and therefore diverse interesting biological activities: antibacterial, antifungal, anticancer, anti-inflammatory…[3]
- **Examples:**

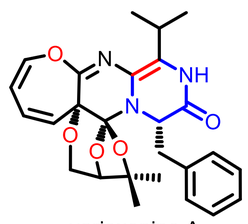


Gliocladride-DKP (anticancer)

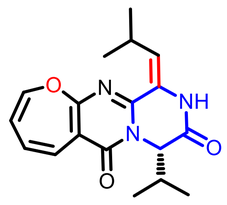


gliocladrid A (*gliocladium sp.*)[4]

Oxepino-DKP (plant growth inhibition)

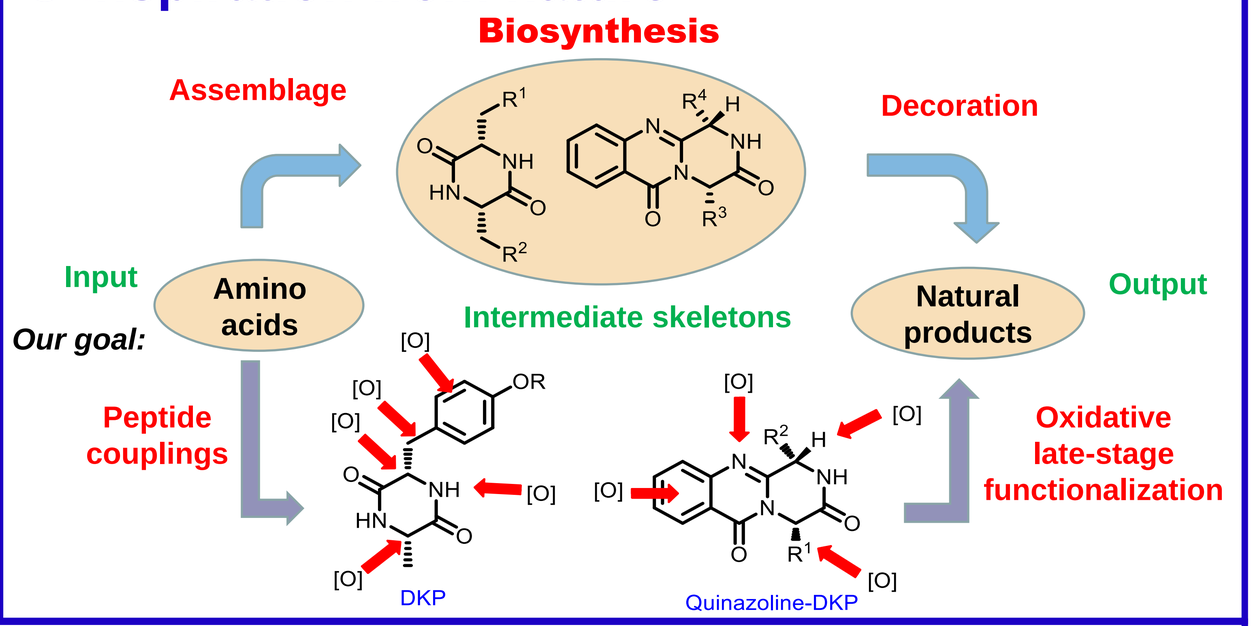


varioxepine A (*Paecilomyces variotii*)[5]



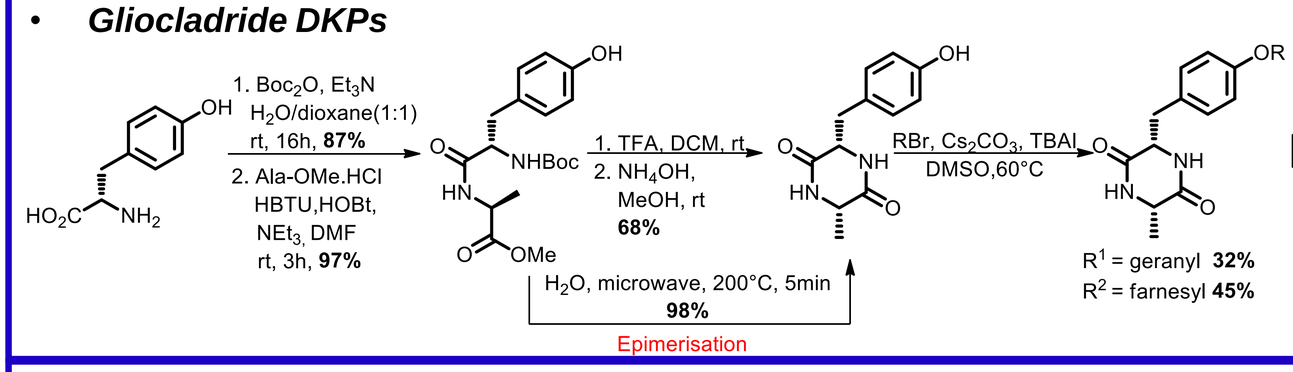
cinereain (*Botrytis cinerea*)[6]

❷ Inspiration from nature

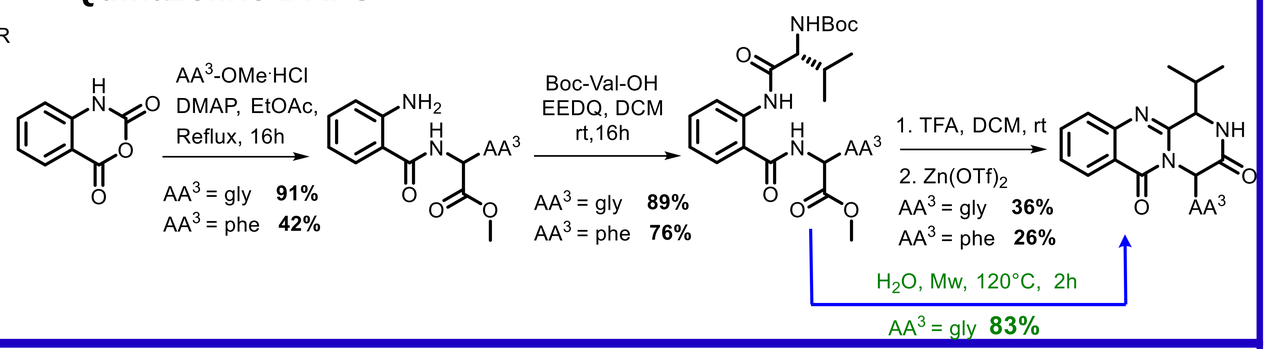


❸ Intermediate scaffold installations

- ***Gliocladride DKPs***



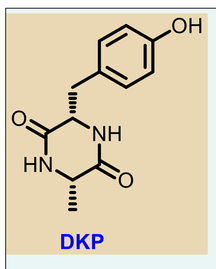
- ***Quinazoline-DKPs***



❹ Oxidative late-stage functionalization

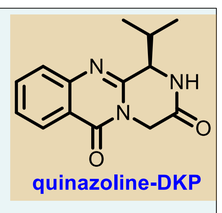
- ***Chemical oxidations***

✓ Screening of the oxidation toolbox for 2 DKP scaffolds

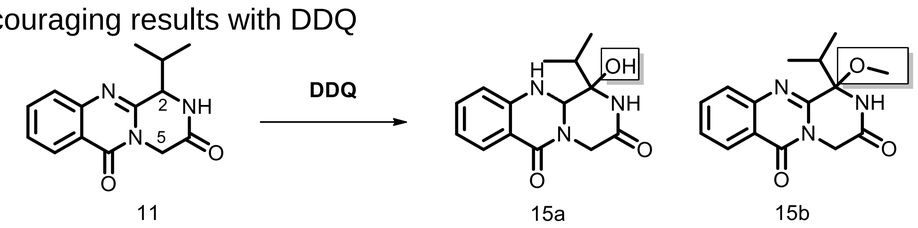


The oxidation box

Peroxides: *m*CPBA, DMDO, H_2O_2/NaOH, oxone,
Transition metal catalysts: $VO(acac)_2$ /TBHP, $FeCl_3/O_2$, $FeCl_3$/porphyrin/O_2
Photo-induced oxidation: O_2 (hv)/TPP or methylene blue
Others: CrO_3, NaOCl, IBX, DDQ, CAN, SeO_2



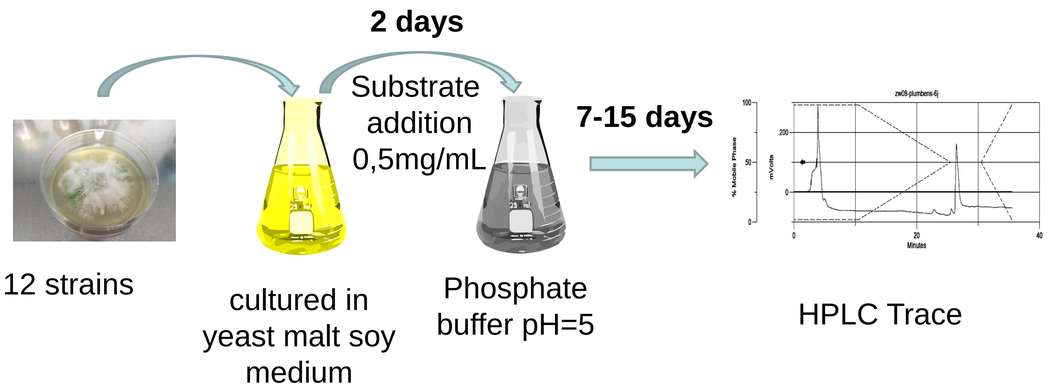
✓ Encouraging results with DDQ



Entry	Conditions	Results
1	DDQ, wet DCM, rt, 7 days	15a (39%)
2	DDQ, MeOH, 60°C, 16h	15b (71%)

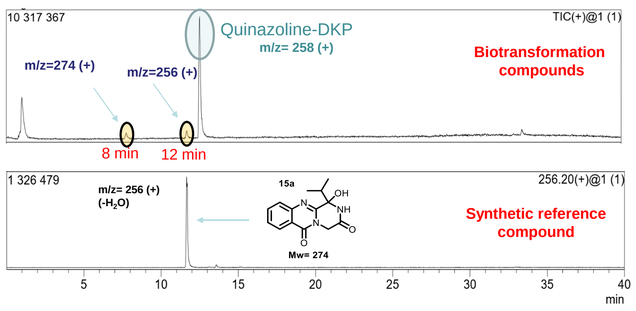
- ***Microbial oxidations***[7]

✓ Screening of microorganisms for the biotransfomations of quinazoline-DKP



✓ Results of *Mucor plumbeus*

LC-MS

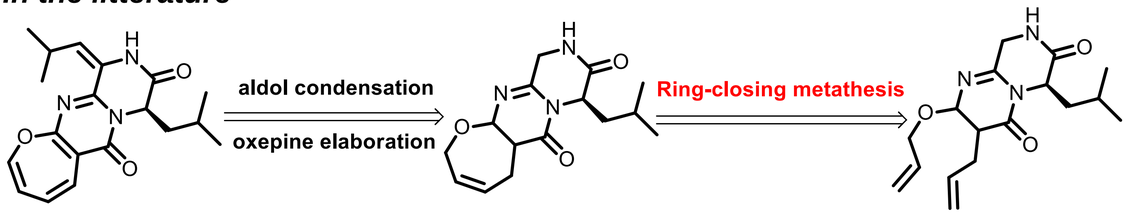


- Two compounds formed
- Compound at 12min could be 15a
- Compound at 8 min could be a new oxidative compound

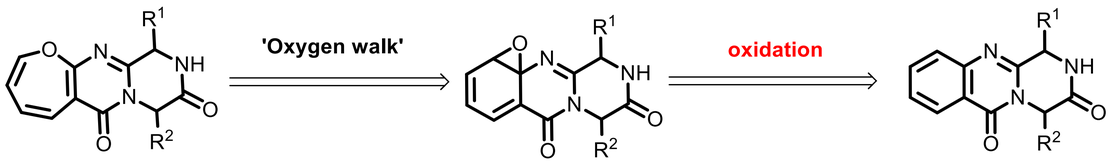
Large scale culture needed

❺ Alternative synthesis route for oxepine-DKP

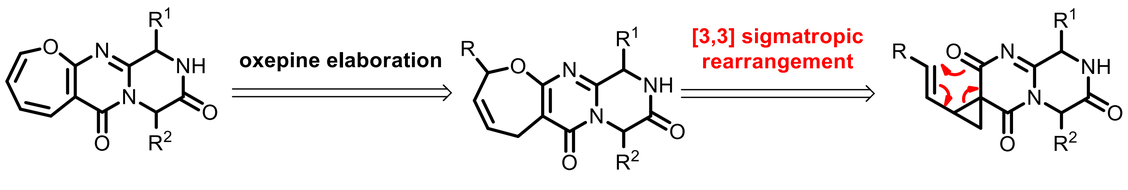
- ***In the litterature***[8]



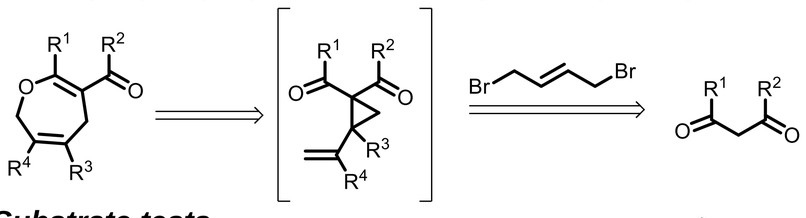
- ***Biomimetic strategy***



- ***Our new strategy***

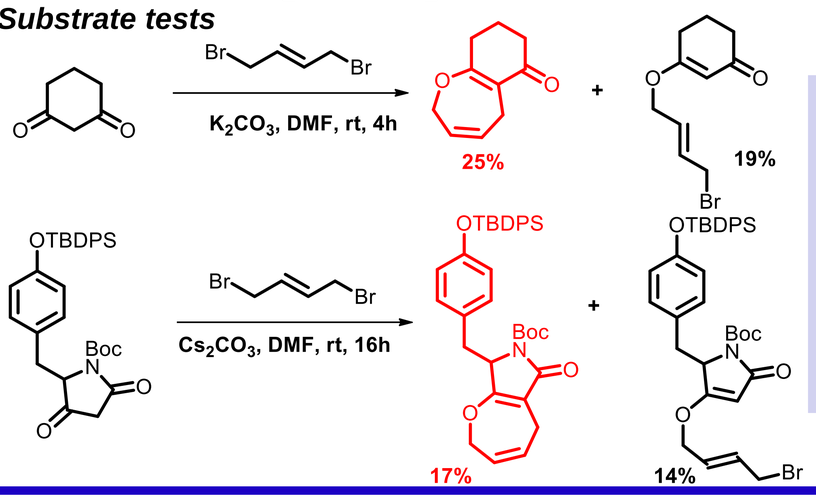


- ***From vinyl cyclopropanes to 2,5-dihydrooxepins synthesis***



- Cheap
- Metal-free

➢ ***Substrate tests***



Next work steps

➢ Improvement of the oxepin formations

➢ Apply to oxepine-DKP synthesis to get desired natural products

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- **References**: [1] A.B. Pomilio, M.E. Battista, A. A. Vitale, *Curr. Org. Chem.* **2006**, 10, 2075-2121; [2] A.D. Borthwick, *Chem. Rev.* **2012**, 112, 3641-3716; [3] A.Schueffler, T. Anke, *Nat. Prod. Rep.* **2014**,31,1425-1448; [4] Y. Yao, L. Tian, J. Li, J. Cao, Y. Pei, *Pharmazie* **2009**, 64, 616-618; [5] H. G. Cutler, J. P. Springer, R.F. Arrendale, B. H. Arison, *Agric. Biol. Chem*, **1988**, 52, 1725-1733; [6] P. Zhang, A. Mandi, X.-M. Li, F.-Y. Du, *Org. Lett.* **2014**, 16, 4834-4837; [7] R. Joyeau, M. Planchon, J. Abessolo, K. Aissa, C. Bance, D. Buisson, *J. Mol. Catal. B-Enz*, **2013**, 85-86, 65-70; [8] R. G. Doveston, R. Steendam, S. Jones, and R. J. K. Taylor, *Org. Lett.*, **2012**, 14 (4), 1122–1125