DIRECT ACCESS TO LACTAM-FUSED LACTONES BY STEREOSELECTIVE AND REGIODIVERGENT HALOLACTONIZATION OF ALLYLIC LACTAMOYL ACIDS

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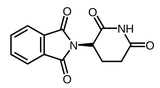
ABSTRACT

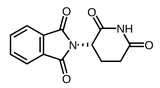
Lactam-lactones are ubiquitous structural motifs in pharmaceuticals such as omuralide (antibacterial) and salinosporamide A (anticancer). In this embodiment, a highly chemo-, regio-, and stereoselective, cost-effective-, high-yielding approach to lactam-lactones is described. This is achieved through halolactonization of lactamoyl acids, which are readily prepared from feedstock chemicals such as amines, enals and anhydrides. The approach is highly modular, which bodes well for late-stage diversification and high throughput screening studies. It is anticipated that the aforementioned merits will endear our methodology to the medicinal and synthesis communities.

BACKGROUND

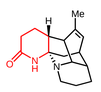
It is well known that the bioactivity of molecules is tremendously sensitive to any change in its structure, for even changing a single stereocenter from *R* to *S* can have profound effects. A tragic example of this is the birth defects only one isomer of the anti-morning sickness drug Thalidomide caused[1]. Consequently, it is imperative that the selectivity of reactions in each step of drug synthesis is controlled, especially to attain maximum yield of the desired drug conformation. This work offers a highly selective and economical lactam-lactone synthesis, as lactams, lactones, and lactam-lactones are common motifs in medicinal chemistry.



(*R*)-thalidomide
Still in use

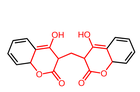


(*S*)-thalidomide
Responsible for birth defects



Neophleghenrine A
Anti-Alzheimer

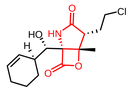
Diazepam
Anti-Anxiety



Dicoumarol
Anti-Coagulant

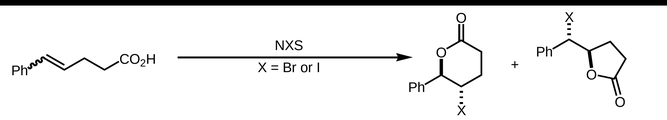
Efavirenz
Anti-HIV AIDs

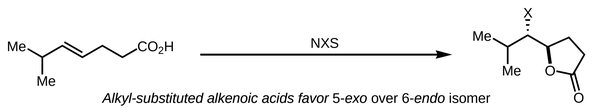
Omuralide
Anti-bacterial



Salinosporamide A
Anti-Cancer

PREVIOUS WORK

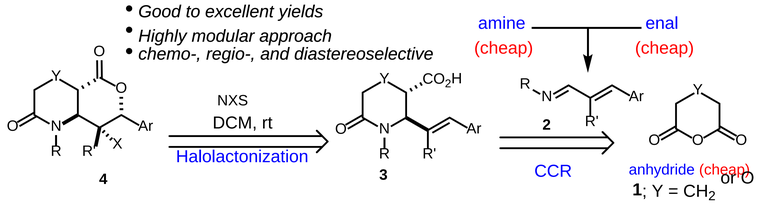




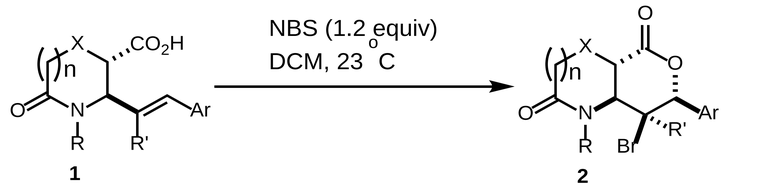
Alkyl-substituted alkenoic acids favor 5-*exo* over 6-*endo* isomer

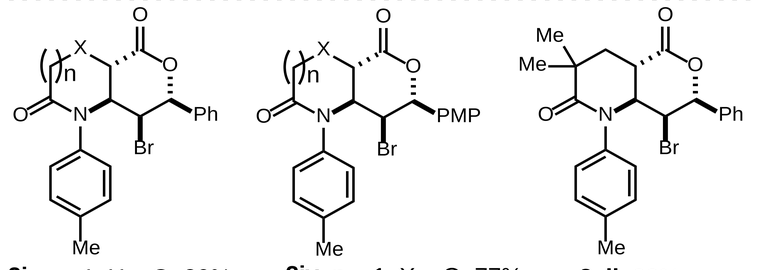
SYNTHETIC APPROACH

- *Good to excellent yields*
- *Highly modular approach*
- *chemo-, regio-, and diastereoselective*



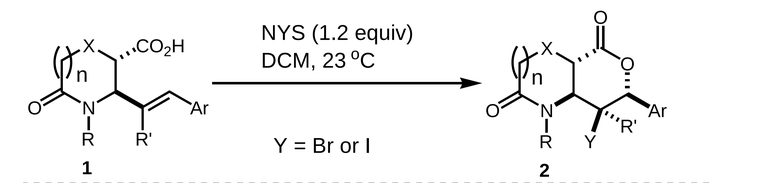
BROMOLACTONIZATION

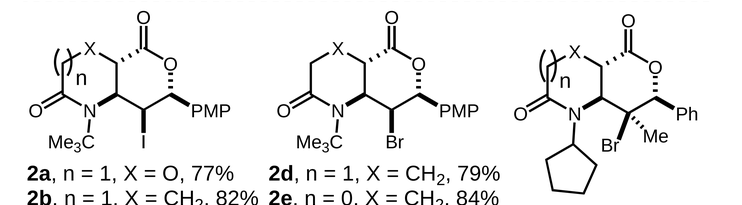




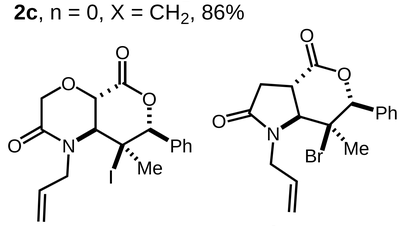
2i, n = 1, X = O, 80%
2ii, n = 1, X = CH_2, 87%
2iii, n = 0, X = CH_2, 91%
2iv, n = 1, X = O, 77%
2v, n = 1, X = CH_2, 83%
2vi, n = 0, X = CH_2, 86%
2vii, 83%

HALOLACTONIZATION OF *N*-ALKYL ALLYLIC LACTAMOYL ACIDS



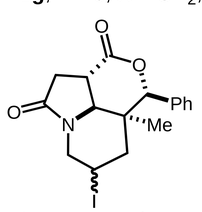


2a, n = 1, X = O, 77%
2b, n = 1, X = CH_2, 82%
2c, n = 0, X = CH_2, 86%
2d, n = 1, X = CH_2, 79%
2e, n = 0, X = CH_2, 84%
2f, n = 1, X = O, 81%
2g, n = 0, X = CH_2, 85%



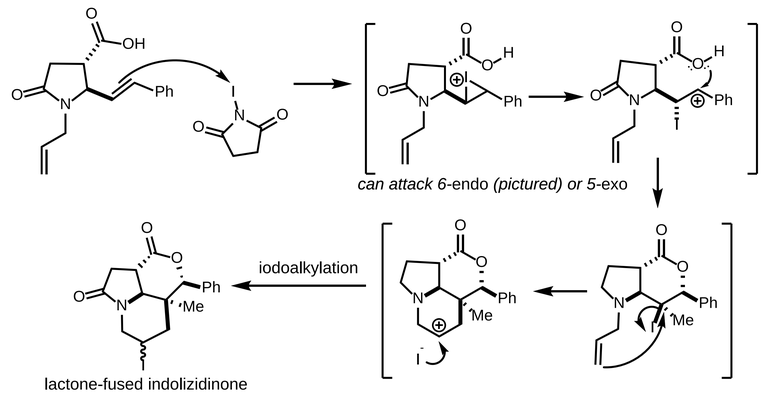
2h, 83%

2i, 83%

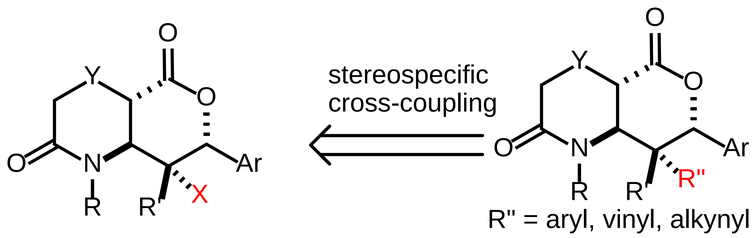


3, 77%, 1:1 dr
tandem iodolactonization and iodoalkylation

PROPOSED MECHANISM



FUNCTIONALIZATION POTENTIAL



REFERENCES

[1] Greene, J. A., & Podolsky, S. H. (2012). Reform, Regulation, and Pharmaceuticals — The Kefauver–Harris Amendments at 50. *The New England Journal of Medicine*, *367*(16), 1481–1483.

[2] *Proc. Nat. Acad. Sci*. **2010**, *107*, 20655-20660.

ACKNOWLEDGEMENTS

✯ Special thanks to the McNair Scholars Program and CWU for funding.

✯ We are grateful to Miss Cindy White and Mr. Emil Babik for NMR assistance.

✯ My fellow research group members are much appreciated for their support.