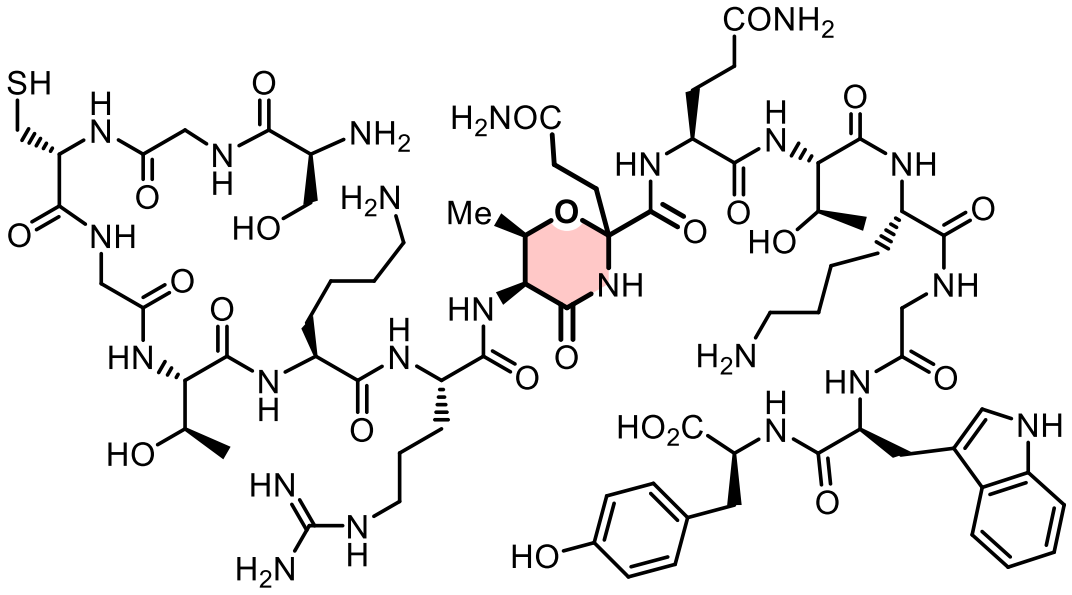
https://doi.org/10.17952/38EPS.2026.O46

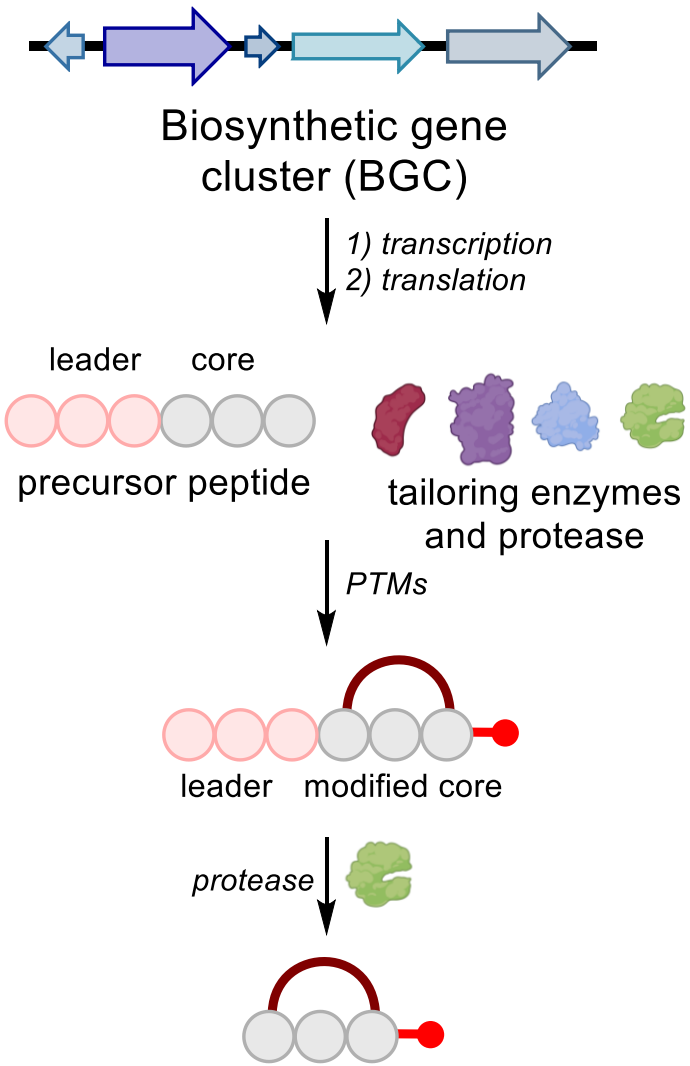
Total synthesis of the proposed structure of threoglucin A

Natalia Cano-Sampaio

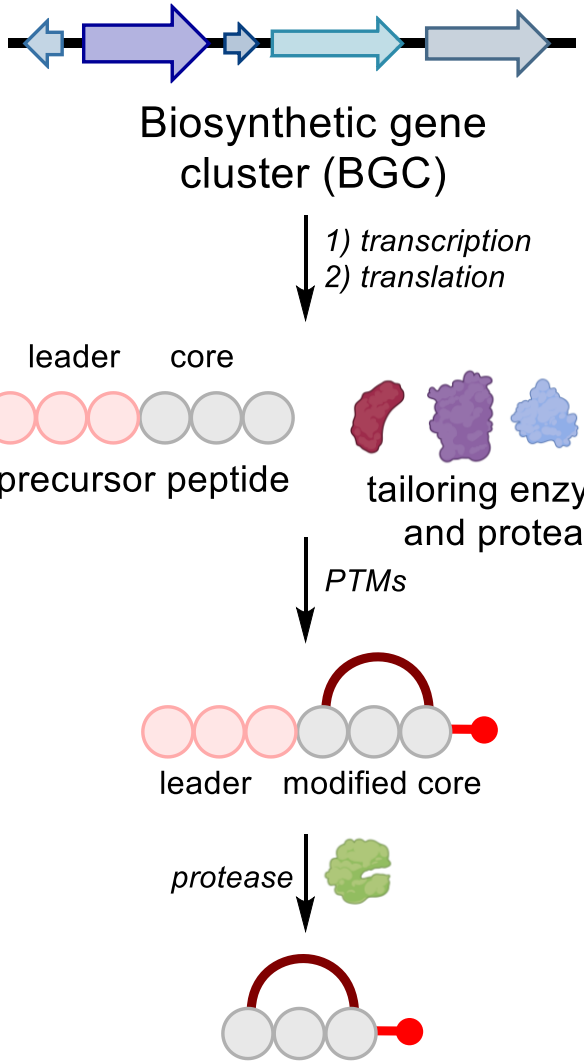


Del Valle Lab
University of Notre Dame
Department of Chemistry and Biochemistry

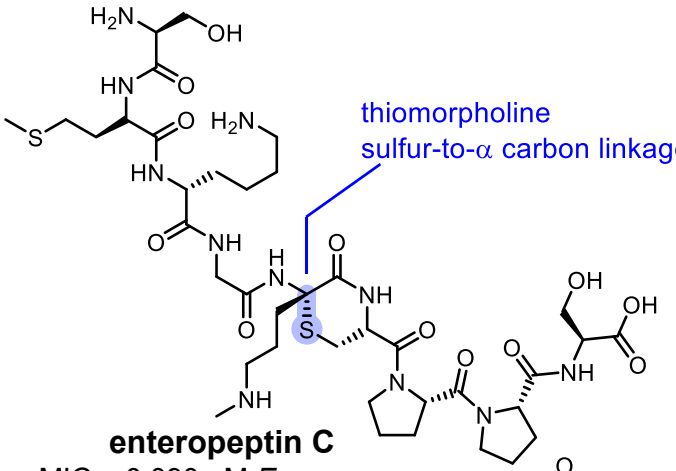
RiPP natural products biosynthesis and examples



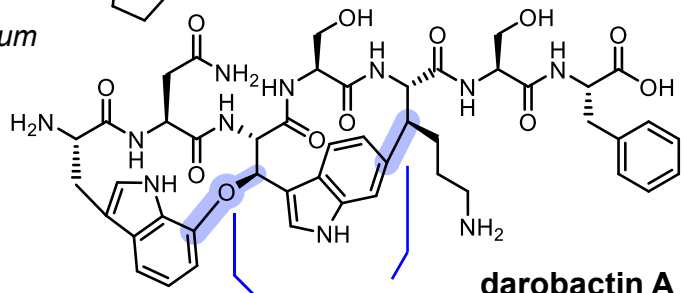
RiPP natural products biosynthesis and examples



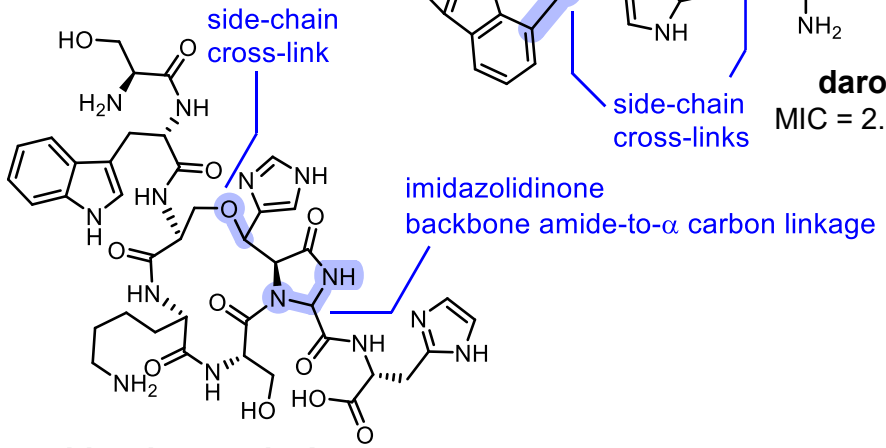
antimicrobial RiPPs



enteropeptin C
MIC = 0.090 μM *E. cecorum*

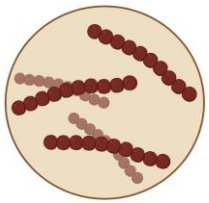


darobactin A
MIC = 2.07 μM *E. coli*

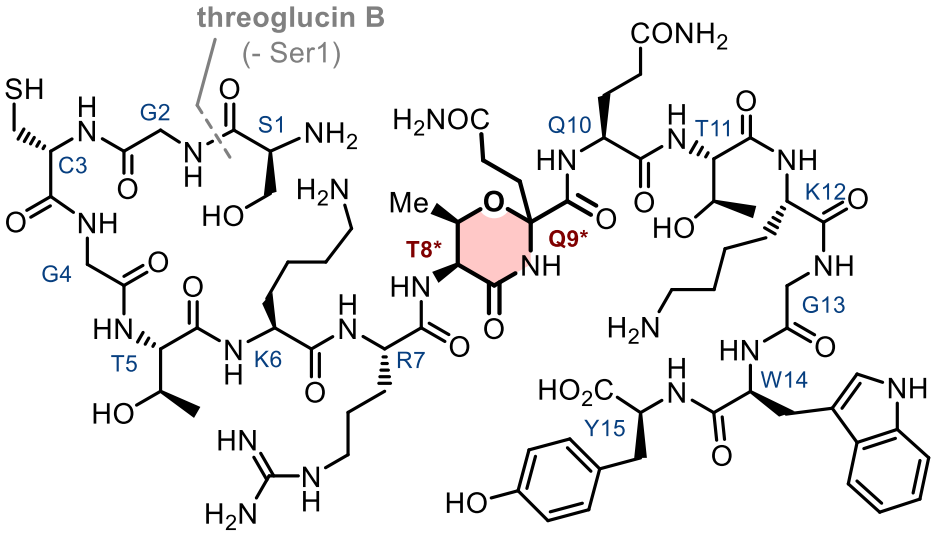


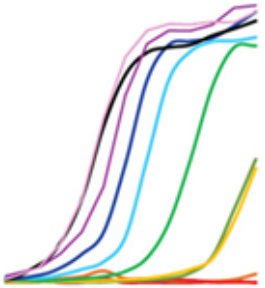
bicyclostreptin A
MIC = 0.27 μM *S. thermophilus*

Threoglucins: oxazinane-containing family of RiPPs



S. suis
(gram +)





bacteriostatic activity

Family of 22 congeners
(threoglucins A–R, *oxo*-variants A–D)

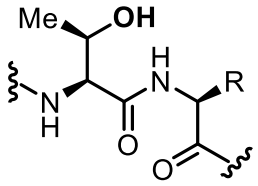
High selectivity against *S. suis (ThrA/B)*

Yield: 3.2 mg of an **inseparable** mixture of ThrA/B (from 10 L fermentation)

Non-toxic to human cells

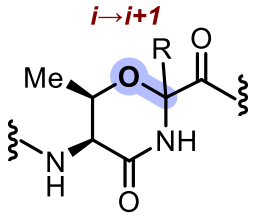
Unassigned Q9 Cα configuration

Cα amidoketal critical for biological activity



SPPS-derived
unmodified product

MIC > 30 µM *S.suis*



enzymatic
proposed product

MIC = 0.5 µM *S.suis* (ThrA/B)

Chemical synthesis required for structural validation and SAR studies

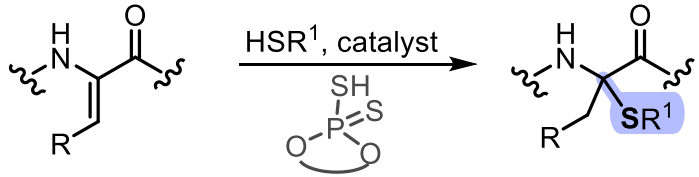
Synthetic approaches to heteroatom-to-α-carbon linkage

previous approaches

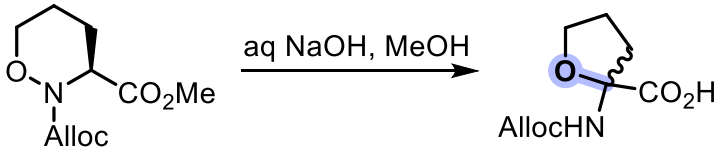
Waser, J. *et al.* (2024)



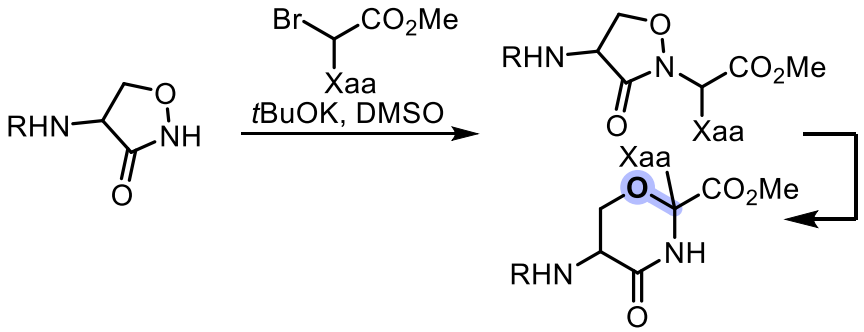
Ting, C. *et al.* (2025)

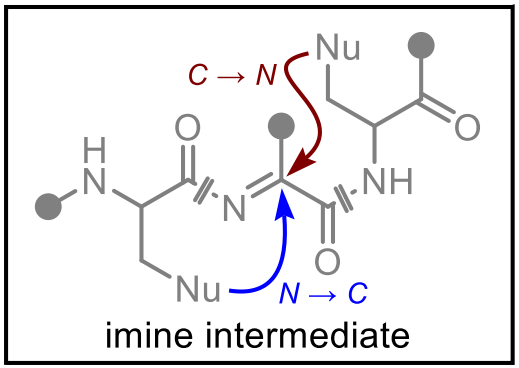


Del Valle, J. R. *et al.* (2020)



Gordon, E.M. *et al.* (1974)

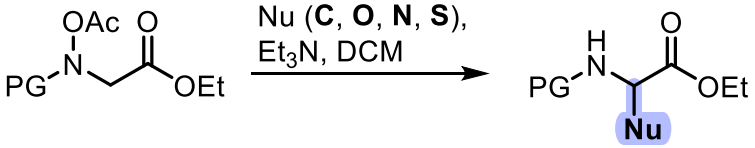




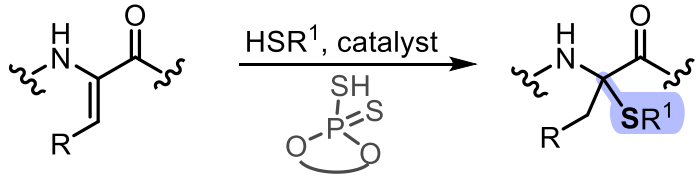
Synthetic approaches to heteroatom-to-α-carbon linkage

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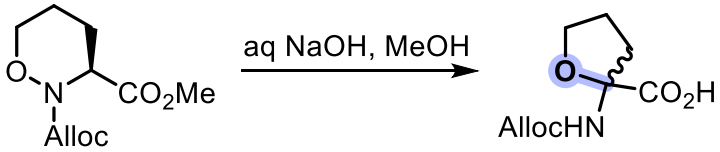
Waser, J. *et al.* (2024)



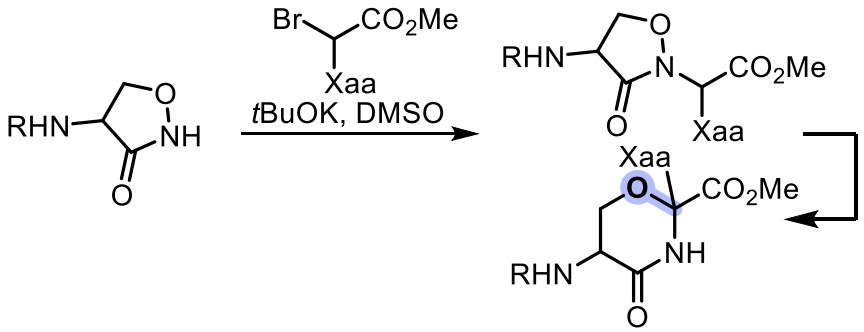
Ting, C. *et al.* (2025)

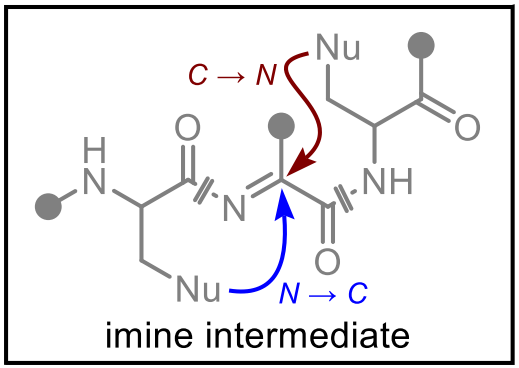


Del Valle, J. R. *et al.* (2020)

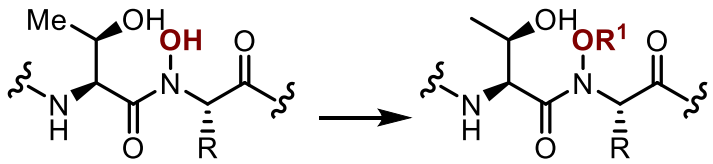


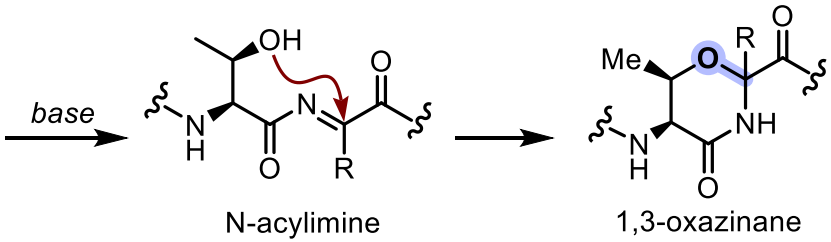
Gordon, E.M. *et al.* (1974)



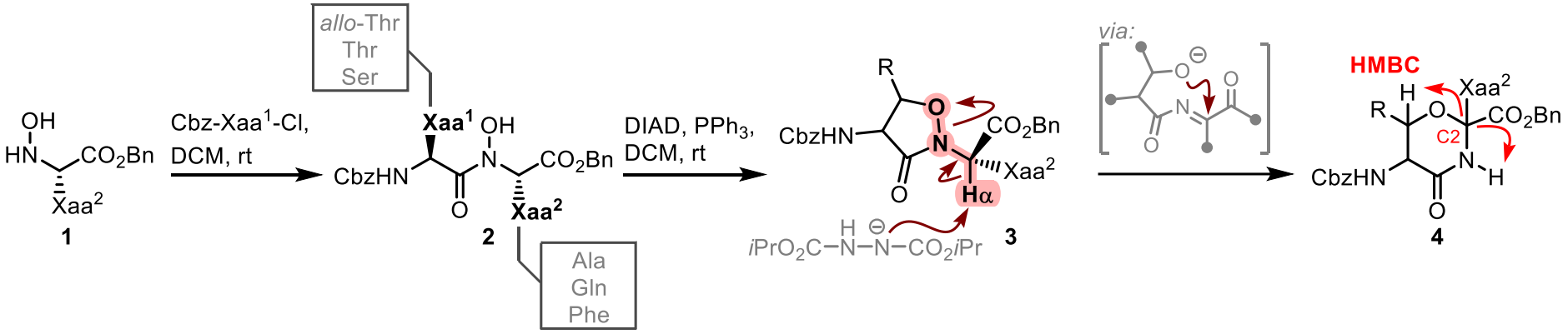


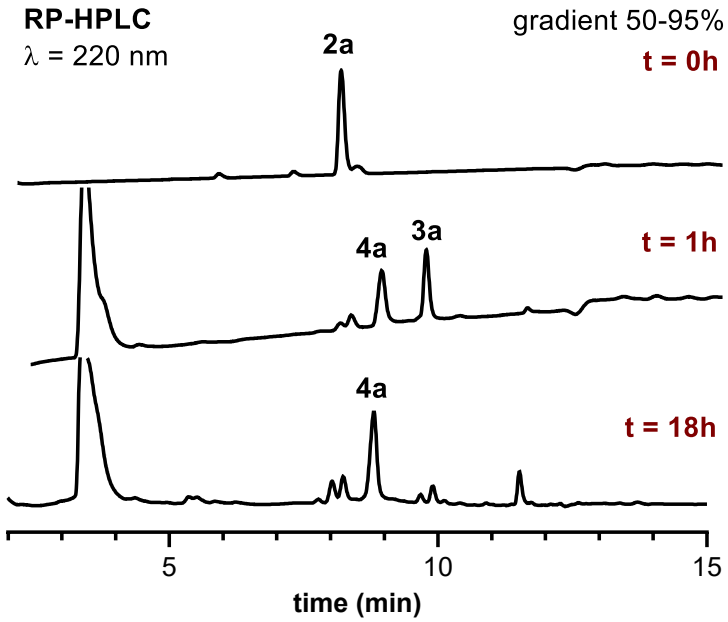
this work





Synthesis of 1,3-oxazinanes via cyclothreonine rearrangement

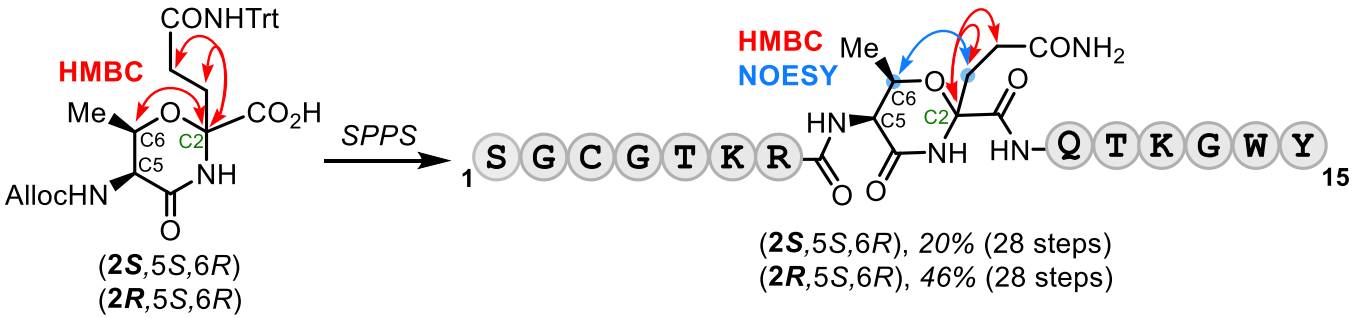




SM	Xaa^1	Xaa^2	time	product	yield	dr
2a	*allo*-Thr	Gln	18 h	**4a**	81%	60:40
2b	*allo*-Thr	Ala	18 h	**4b**	70%	75:25
2c	Thr	Gln	1 h	**4c**	99%	63:37
2d	Thr	Ala	1 h	**4d**	62%	88:12
2e	Thr	Phe	1 h	**4e**	82%	55:45
2f	Ser	Gln	18 h	**4f**	91%	53:47
2g	Ser	Ala	18 h	**4g**	88%	70:30
2h	Ser	Phe	1 h	**4h**	90%	50:50

Overall yields and dr values were determined based on ^{1}H NMR peak integration of Ser/Thr α/β ^{1}H signals relative to internal standard.

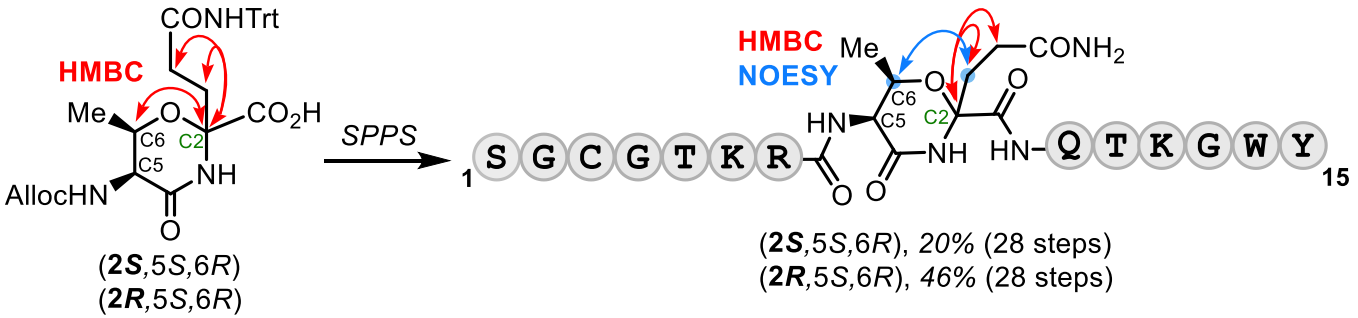
Synthesis of the proposed structure of threoglucin A and diastereomers



(**2*S***,5*S*,6*R*)
(**2*R***,5*S*,6*R*)

(**2*S***,5*S*,6*R*), *20%* (28 steps)
(**2*R***,5*S*,6*R*), *46%* (28 steps)

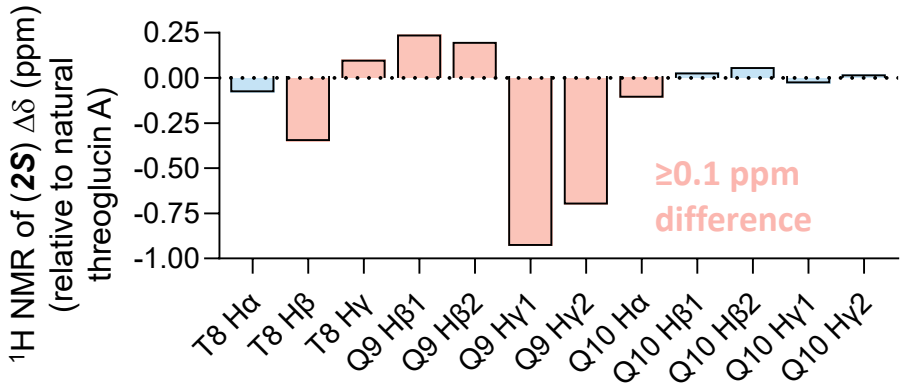
Synthesis of the proposed structure of threoglucin A and diastereomers

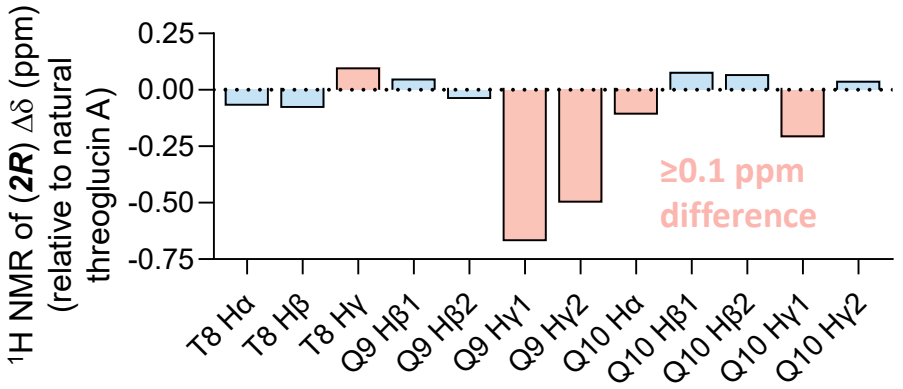


(**2*S***,5*S*,6*R*)
(**2*R***,5*S*,6*R*)

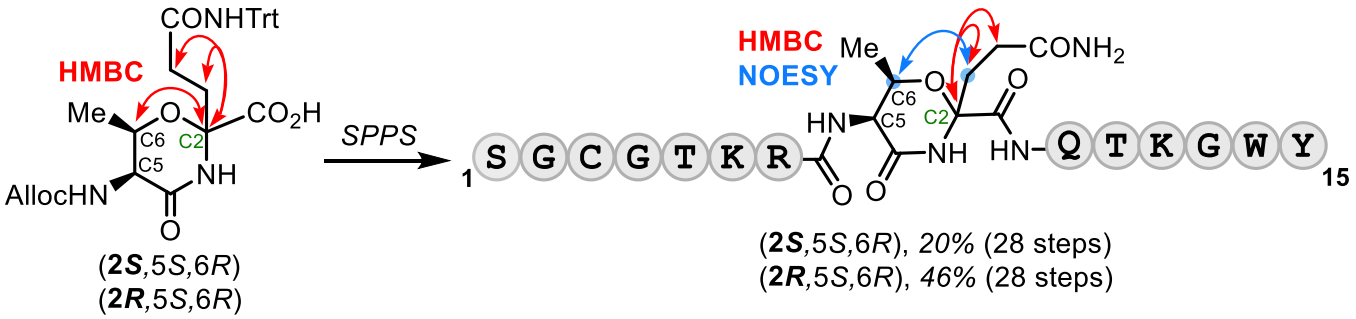
(**2*S***,5*S*,6*R*), *20%* (28 steps)
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^{1}H NMR chemical shift deviations for synthetic products relative to natural product

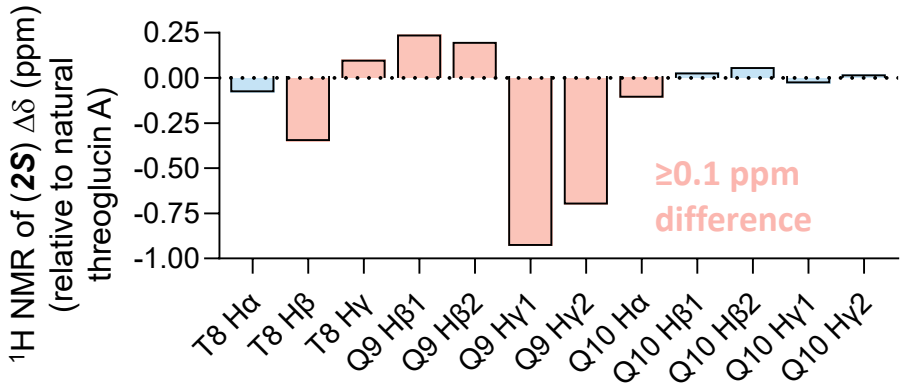


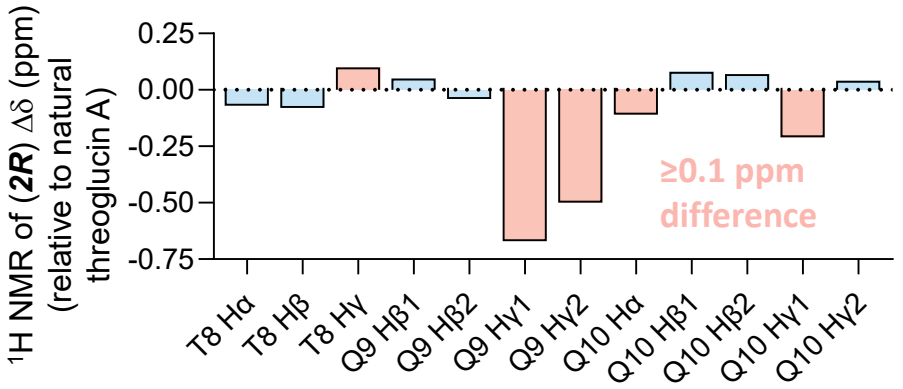


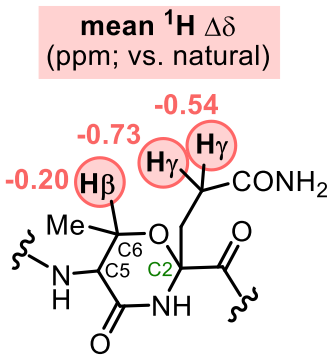
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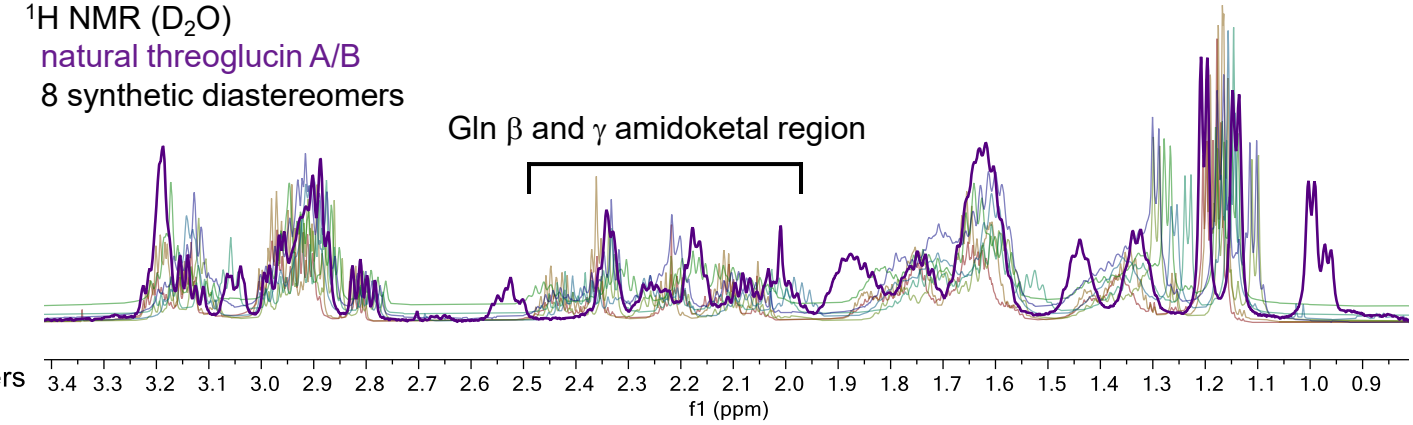
^{1}H NMR chemical shift deviations for synthetic products relative to natural product





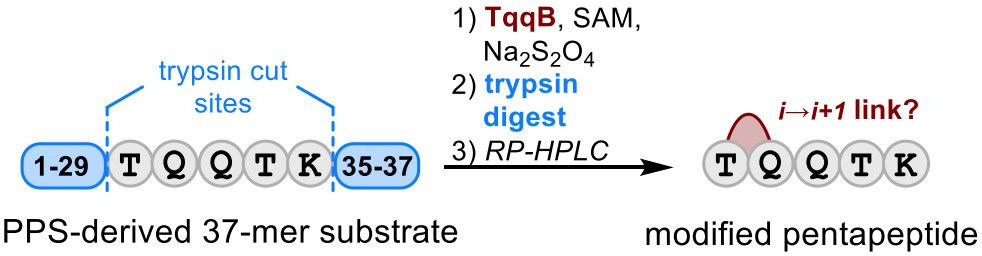


6 remaining oxazinane diastereomers



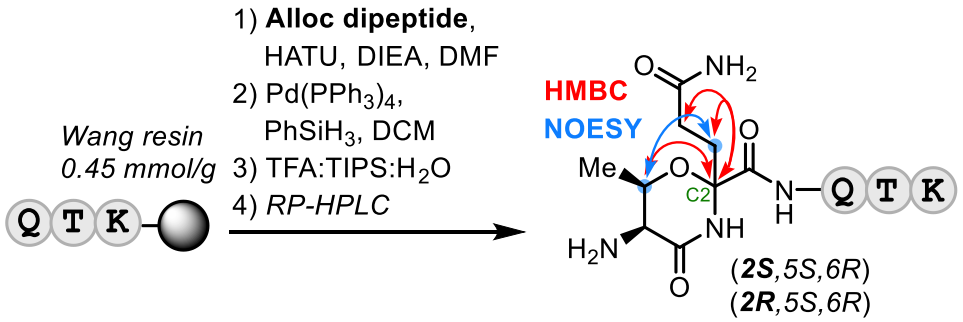
Synthesis of the proposed pentapeptides of the TqqB reaction

enzymatic synthesis



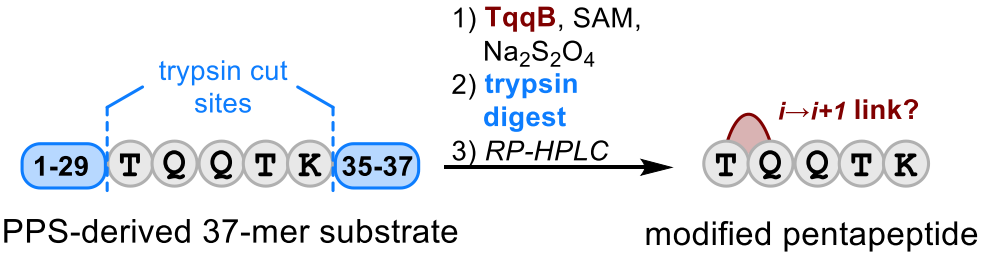
Clark, K. A.; Bushin, L. B.; Seyedsayamdost, M. R. (2019) *JACS. 141,* 27.

chemical synthesis



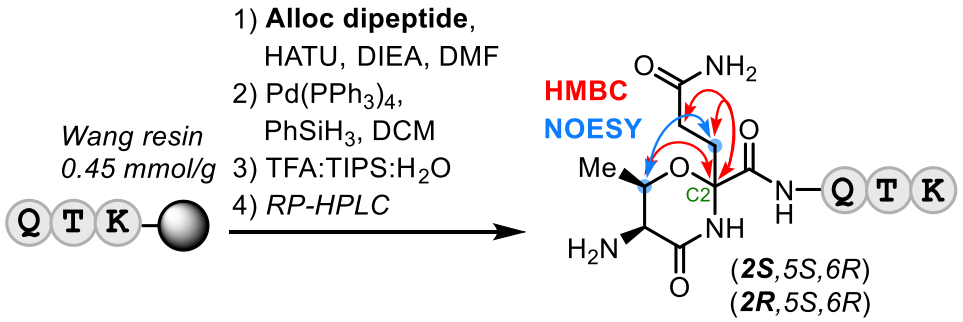
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enzymatic synthesis

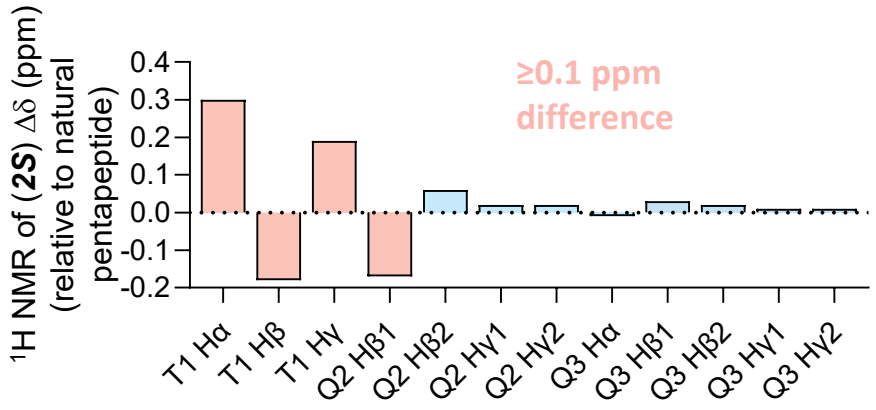


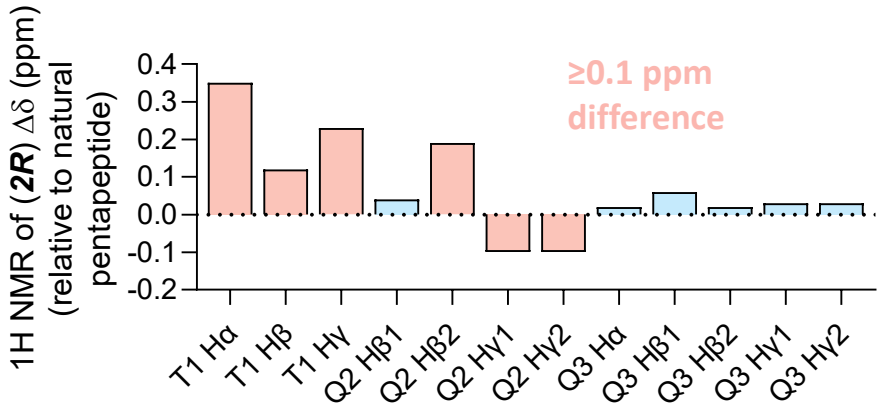
Clark, K. A.; Bushin, L. B.; Seyedsayamdost, M. R. (2019) *JACS. 141,* 27.

chemical synthesis

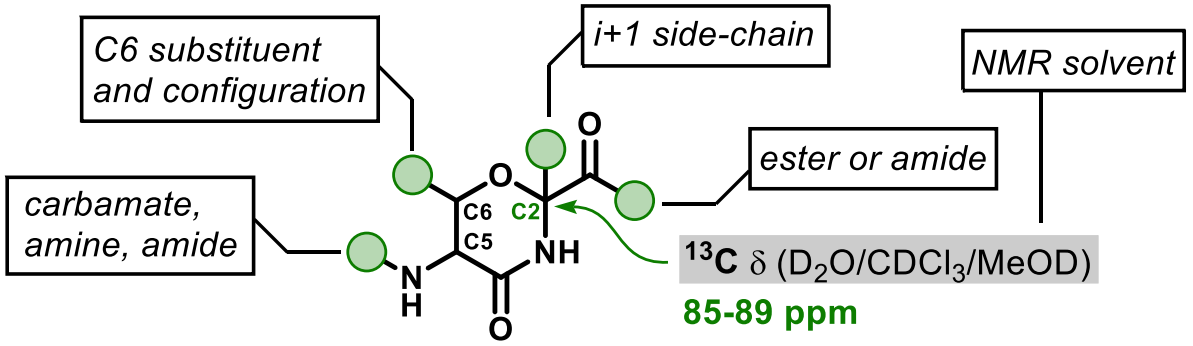


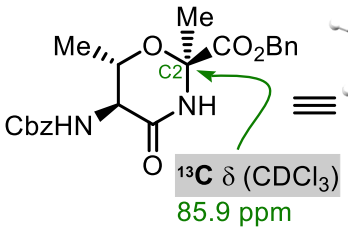
^{1}H NMR chemical shift deviations for synthetic products relative to enzymatic

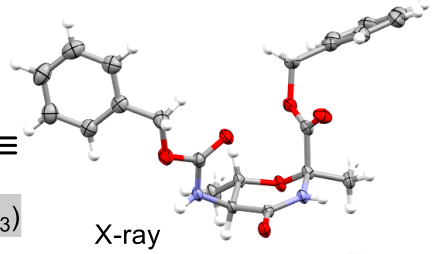


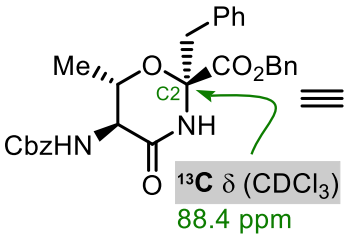


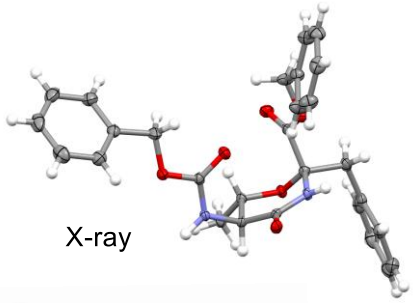
Diagnostic ^{13}C chemical shift in oxazinane amidoketals

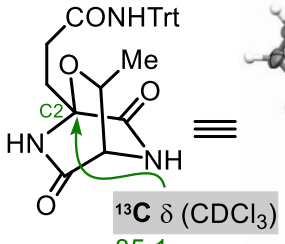


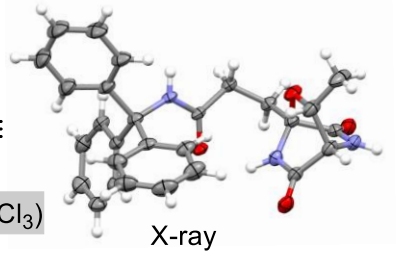


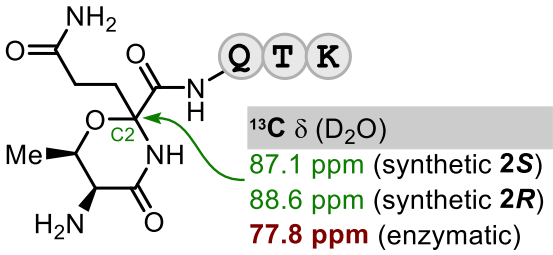


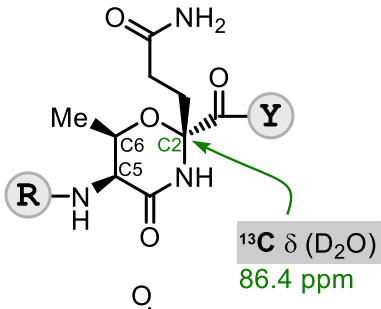


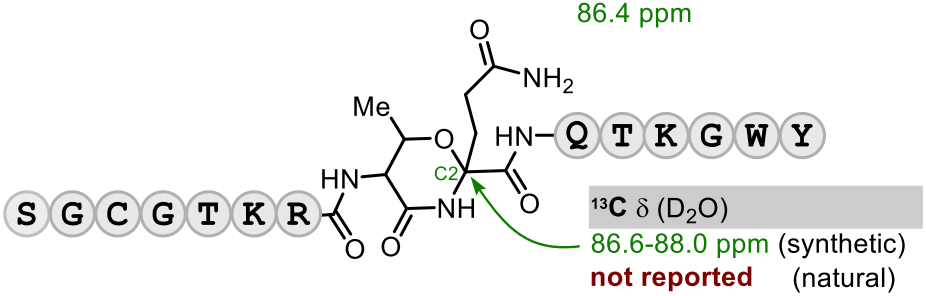




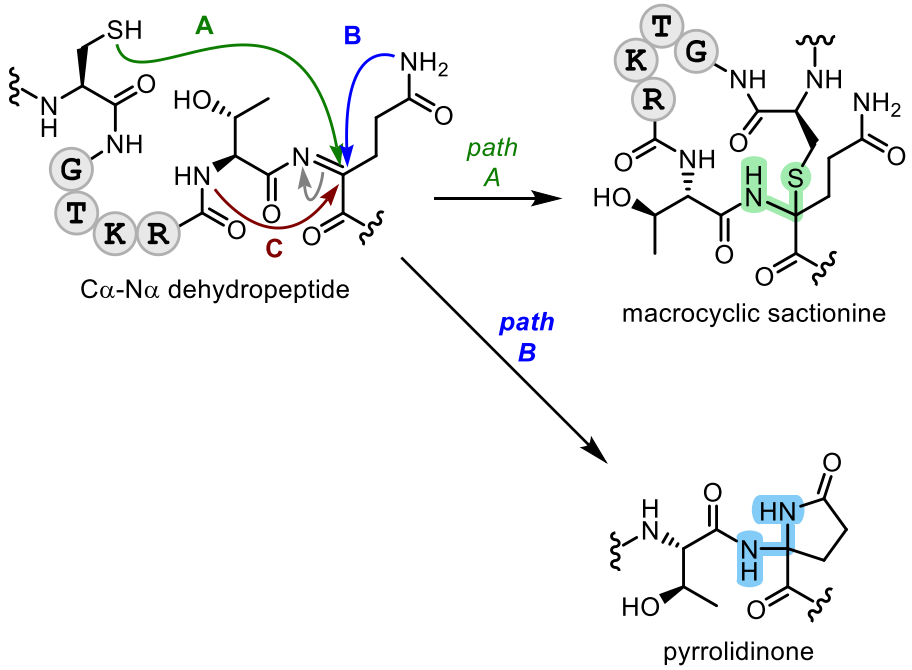


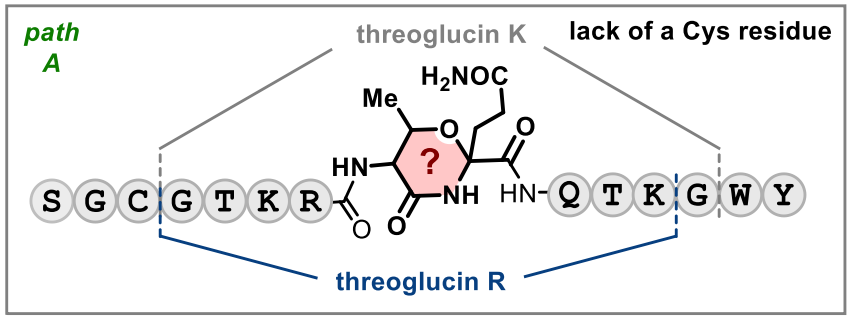


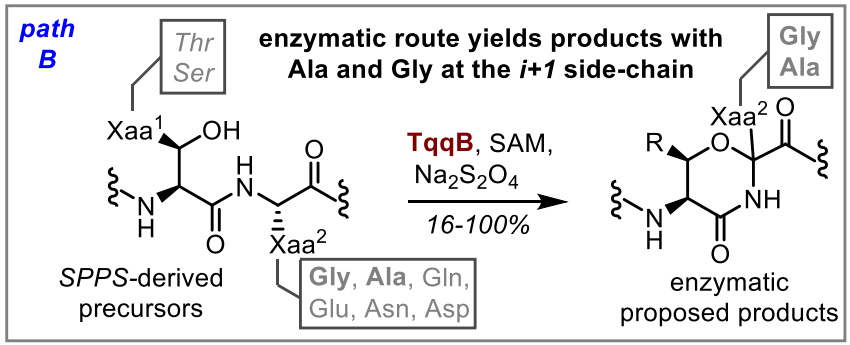




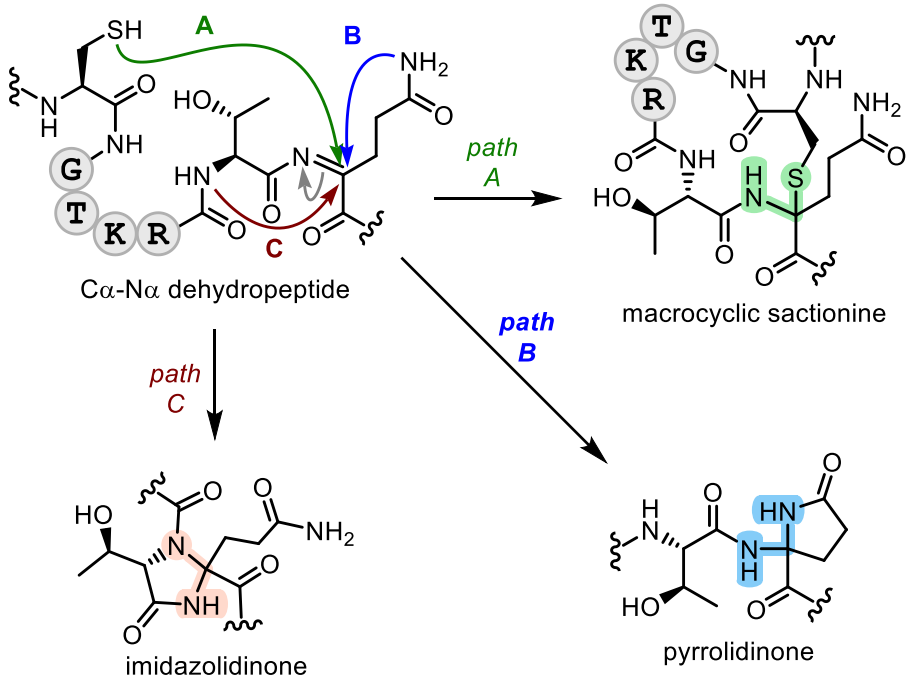
Potential connectivities in natural threoglucin A

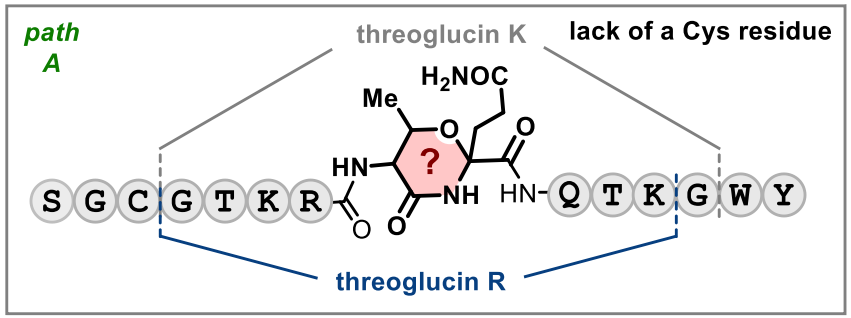


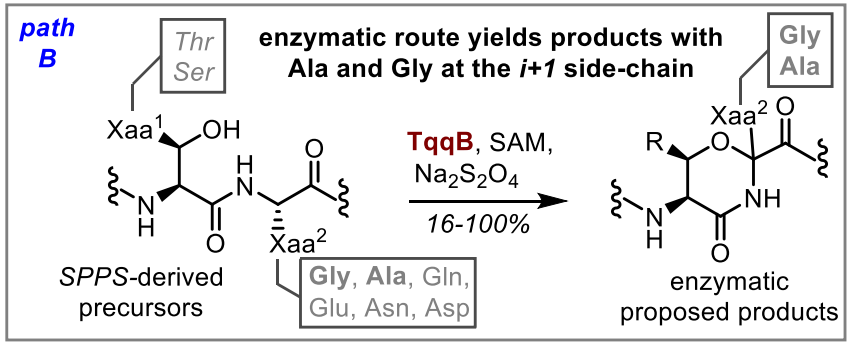


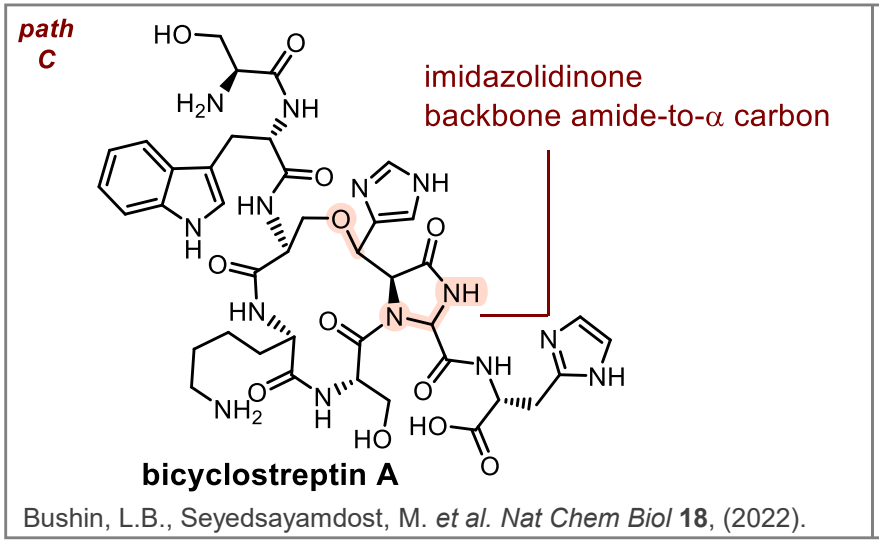


Potential connectivities in natural threoglucin A

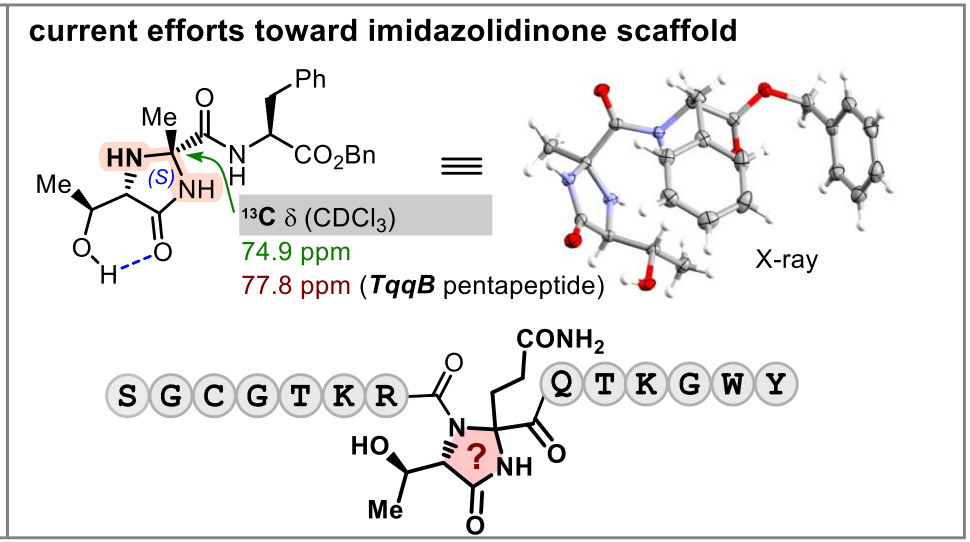








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