

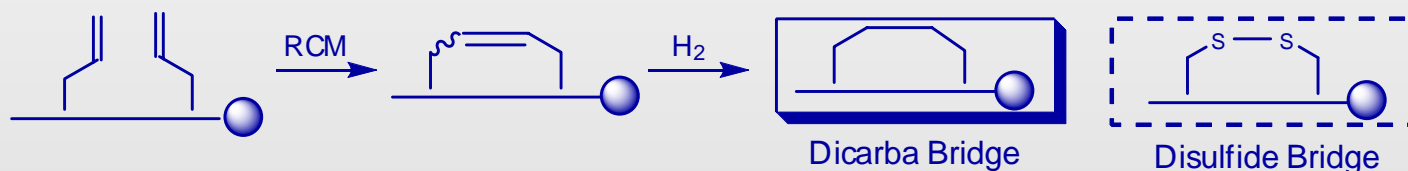
Catalytic Routes to Dicarba Mimics of Cystine Containing Peptides



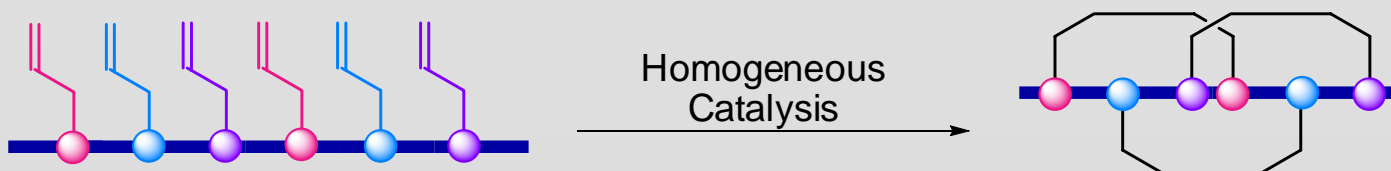
Bianca J. van Lierop, Jomana Elaridi,
Simon P. Gooding, W. Roy Jackson and
Andrea J. Robinson

Disulfide and Dicarba Bridges

- ★ Olefin metathesis has revolutionised peptidomimetics
 - ★ *Modern catalysts display high functional group tolerance and tunable reactivity*
 - ★ *Compatible with functionally diverse peptide-based substrates*
- ★ Replacement of disulfide bonds in cyclic peptides
 - ★ *Dicarba (unsaturated and saturated) links act as biostable structural mimics*
 - ★ *Drug candidates with enhanced stability?*

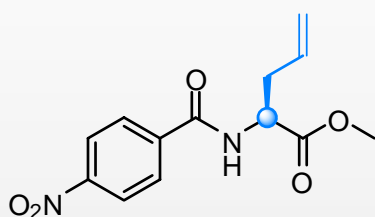


- ★ Achieved in single disulfide bond containing peptides
 - ★ *Many peptides contain multiple cysteine links: requires a REGIOSELECTIVE method*

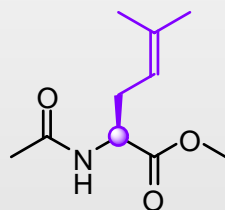


Constructing Multiple Dicarba Bridges

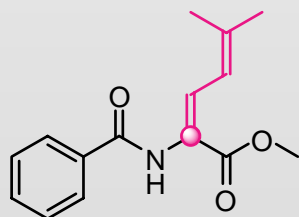
* * The unambiguous formation of 3 dicarba bridges * *



+

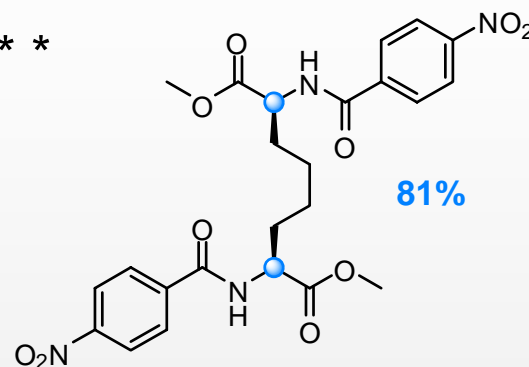


+



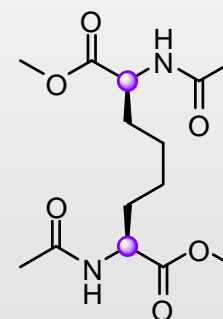
- i) 20 mol% 1st Gen. Grubbs', DCM, 50°C, 18h
ii) Rh(I)(PPH₃)₃Cl, 15 psi H₂, ^tBuOH : THF (1:1), 14h
iii) 5 mol% 2nd Gen. Grubbs', 15 psi C₄H₈, DCM, 50°C, 17h
iv) 5 mol% 2nd Gen. Grubbs', DCM, 50°C, 17h
v) Rh(I)(PPH₃)₃Cl, 50 psi H₂, THF, 4h

- vi) *S,S*-Et-DuPHOS-Rh(I), 75 psi H₂, MeOH, 2h, >99%ee
vii) 5 mol% 2nd Gen. Grubbs', 15 psi C₄H₈, DCM, 50°C, 17h
viii) 5 mol% 2nd Gen. Grubbs', DCM, 50°C, 17h
xi) Rh(I)(PPH₃)₃Cl, 50 psi H₂, THF, 4h



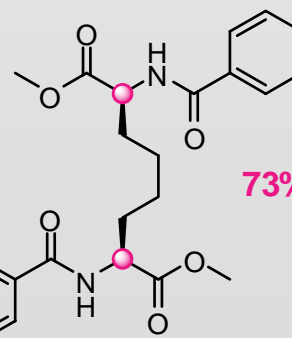
81%

+



70%

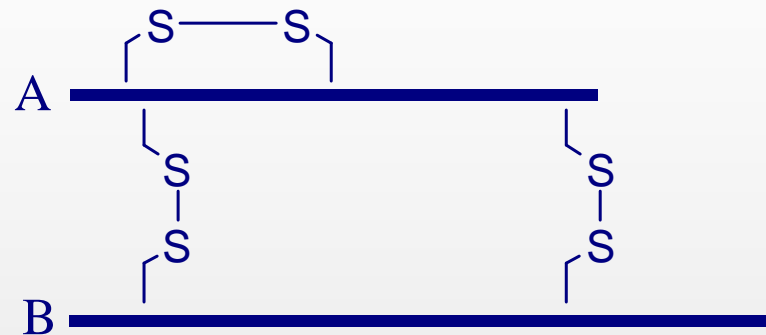
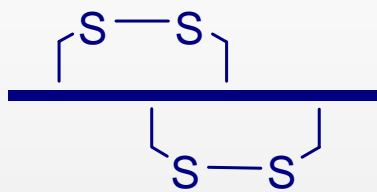
+



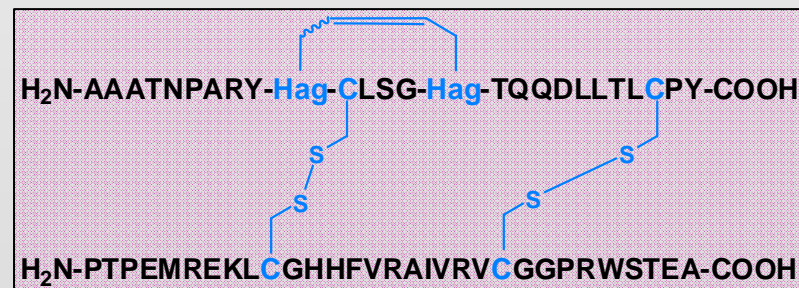
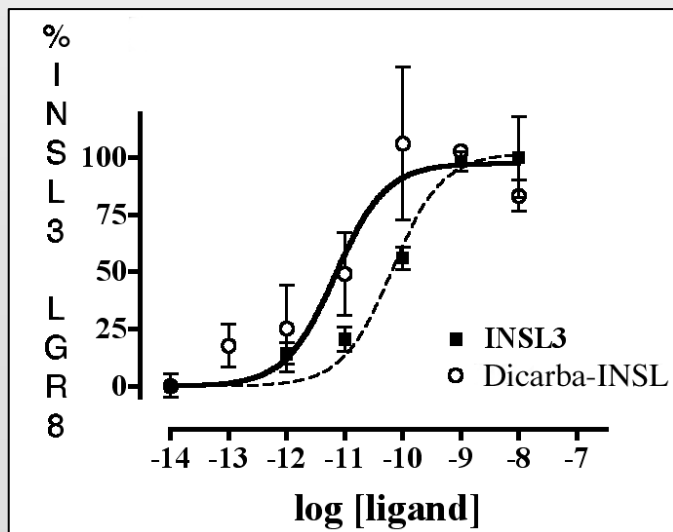
73%

Peptide-Based Substrates

- ★ Targeting *bis*- and *tris*- disulfide bond containing peptides



- ★ *c*[10,15]-Unsaturated dicarba INSL-3



Acknowledgements

ISOMXVII Organising Committee

Dr. Andrea Robinson (Supervisor)

Prof. Roy Jackson

Robinson/Jackson group (Monash University, Australia)



Please visit Poster 18 for further questions!