

Natural Product Guided Research: Scaffolds, Biomimics, Glycolipids and Anti-tumour Macrolides

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School of Chemistry

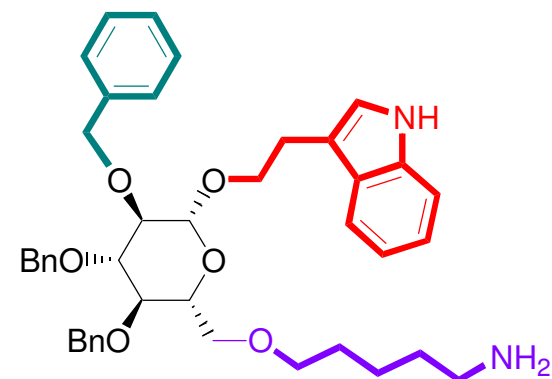
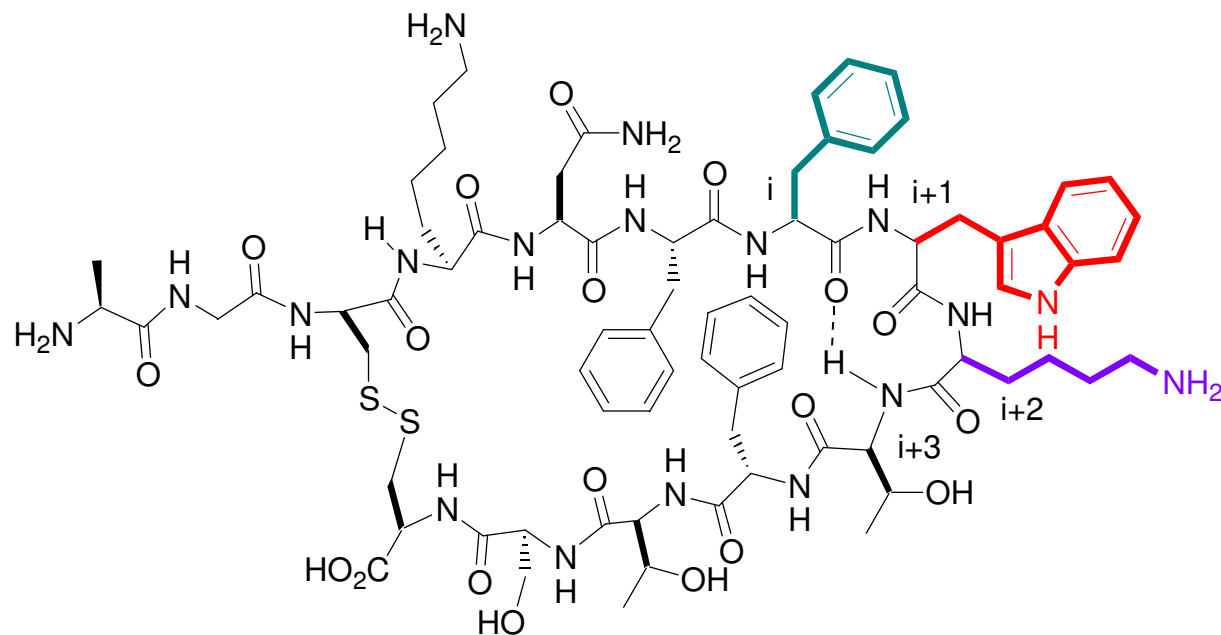
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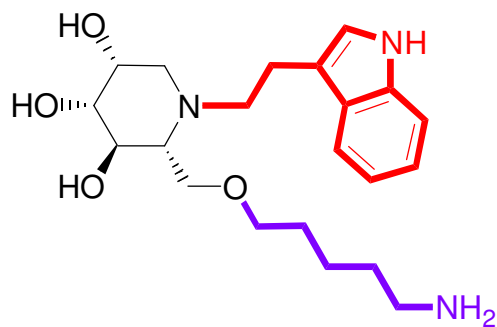
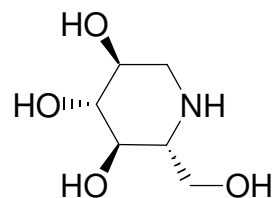


National University of Ireland, Galway
Ollscoil na hÉireann, Gaillimh

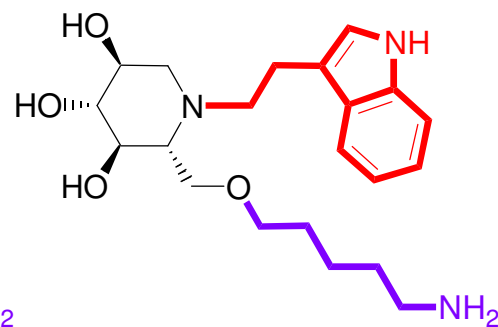
Iminosugars are privileged scaffolds for peptidomimetic development



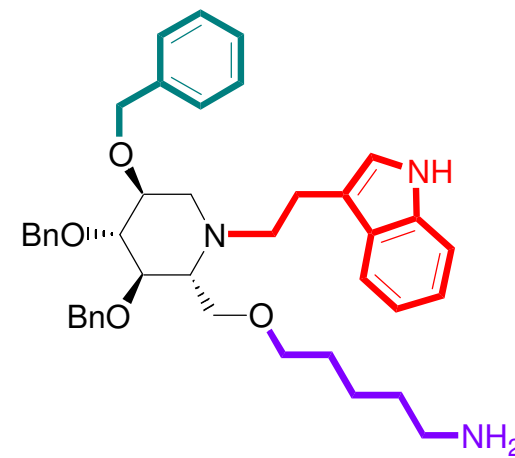
SST receptor ligand (μM)



SST4 ~ 48% at $1\mu\text{M}$
SST5 inactive at $1\mu\text{M}$

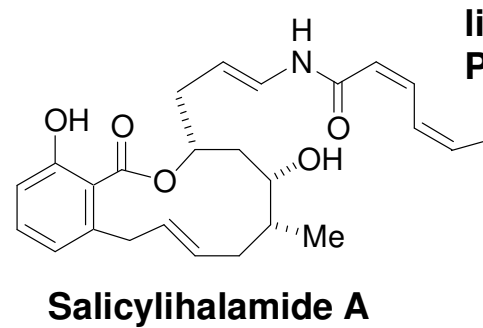
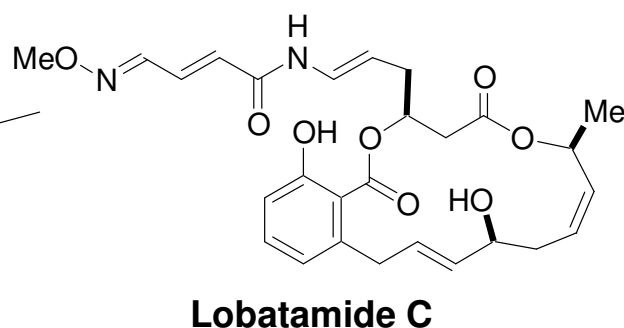
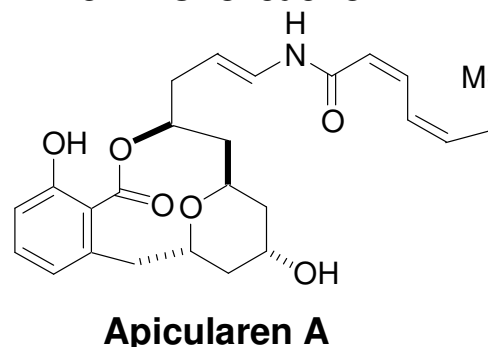
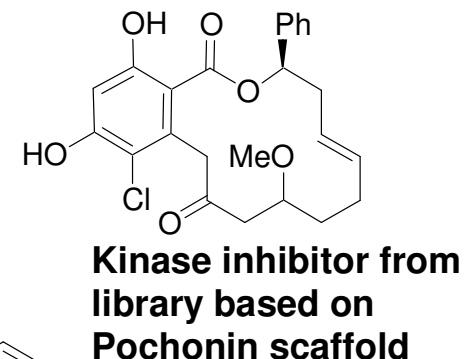
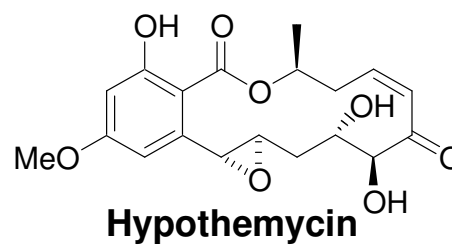
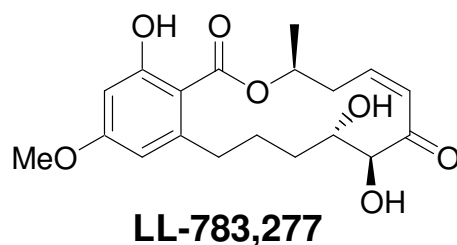
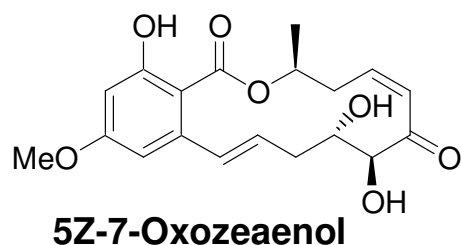
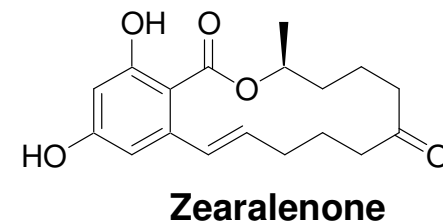
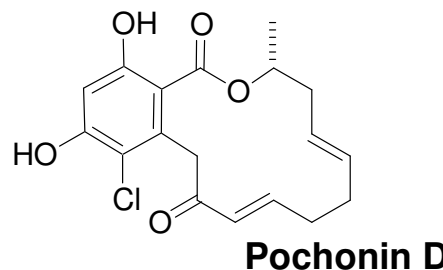
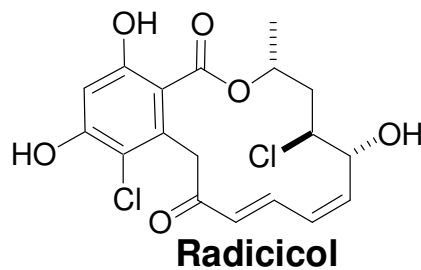
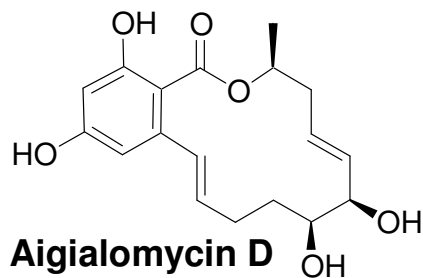


SST4 $K_i = 3.3\mu\text{M}$
SST5 $K_i > 1\text{mM}$



SST4 $K_i = 4.4\mu\text{M}$
SST5 $K_i = 5.0\mu\text{M}$

Naturally occurring resorcylic acid lactones and salicylic acid lactones



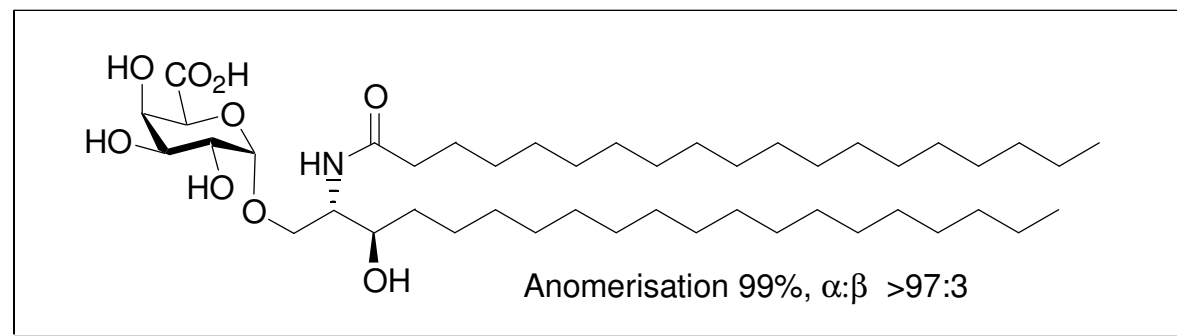
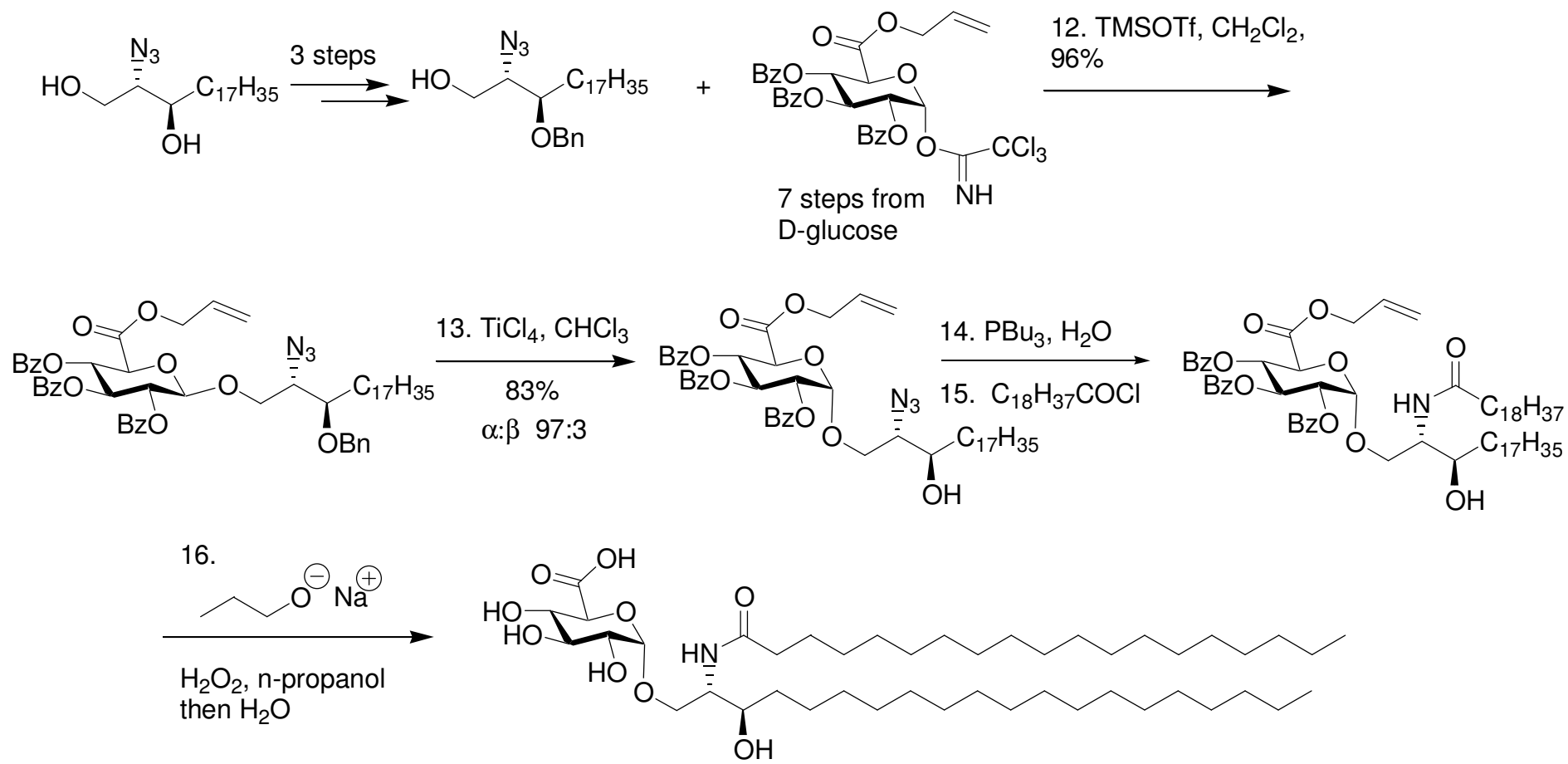
Hypothemycin inhibits MEK1, MEK2, FLT1, FLT3, KDR

5Z-7-Oxozeaenol inhibits TAK1 (8 nM) whereas LL-783,277 inhibits of MEK-1(4 nM)

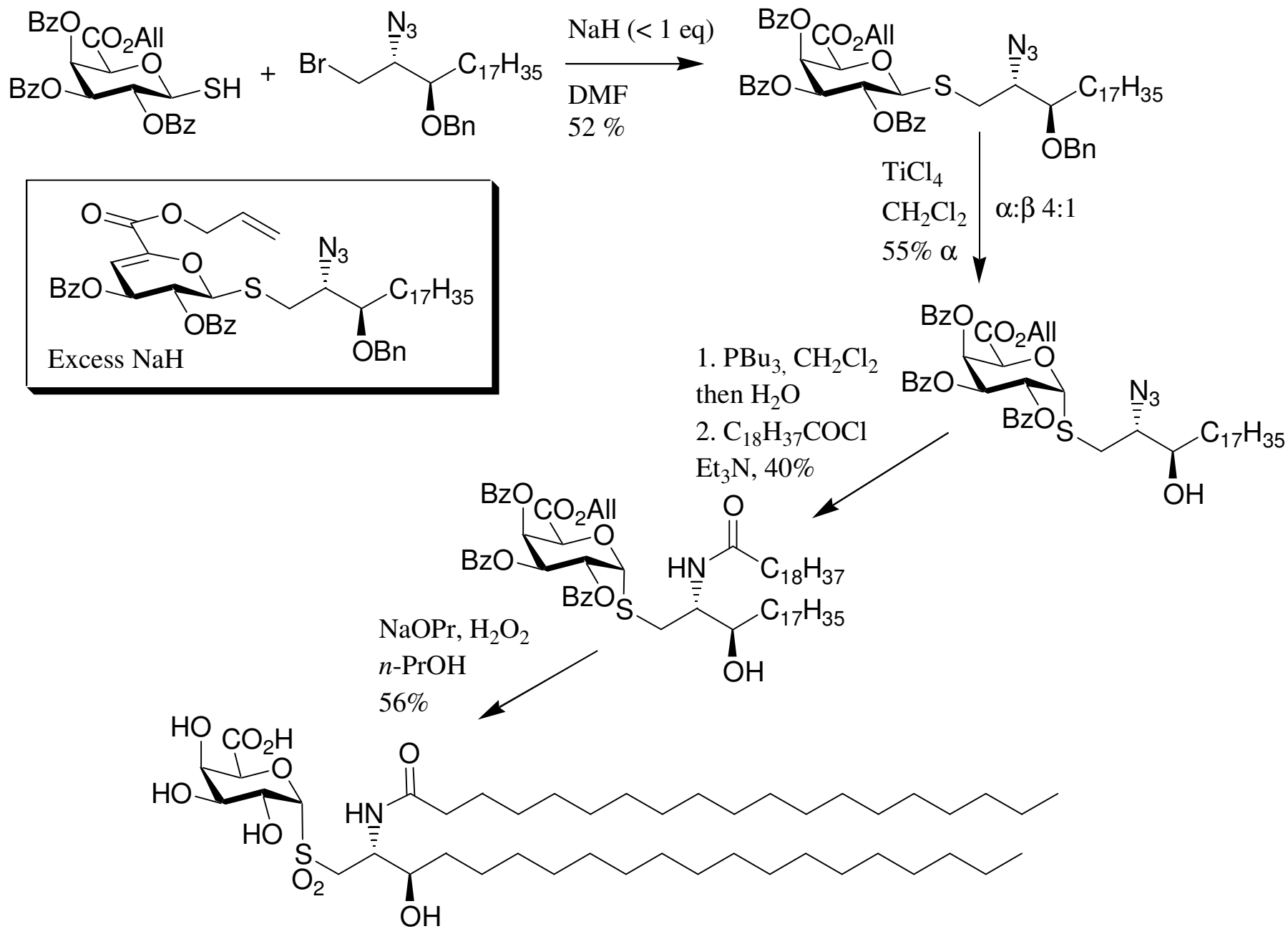
Aigialomycin D inhibits CDK1, CDK5 and GSK3

Common theme: salicylic acid macrolactone scaffolds recognise ATP binding proteins
Privileged or evolutionary selected scaffold

Application of anomerisation in bacterial glycosphingolipid synthesis

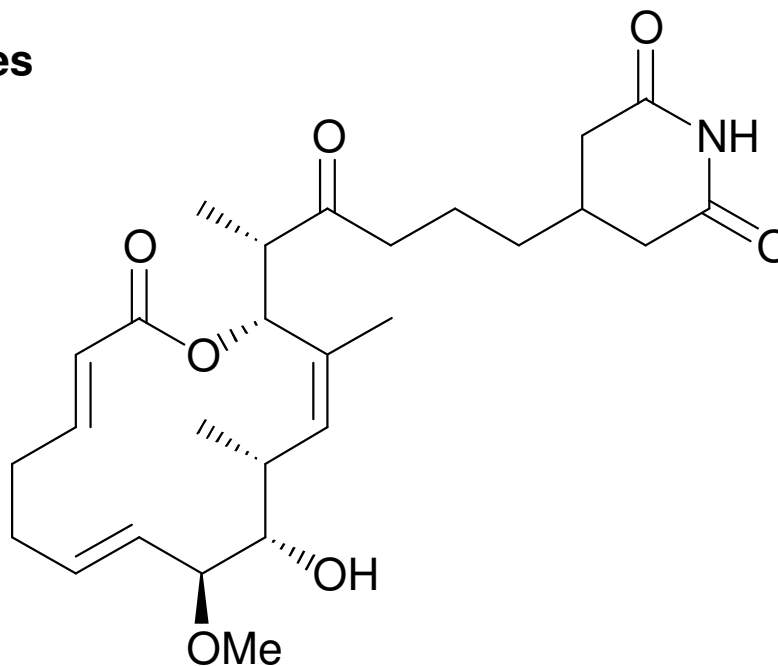


Anomerisation of uronic acids gives α -S-glycolipids



Migrastatin – A Novel Cell Migration Inhibitor

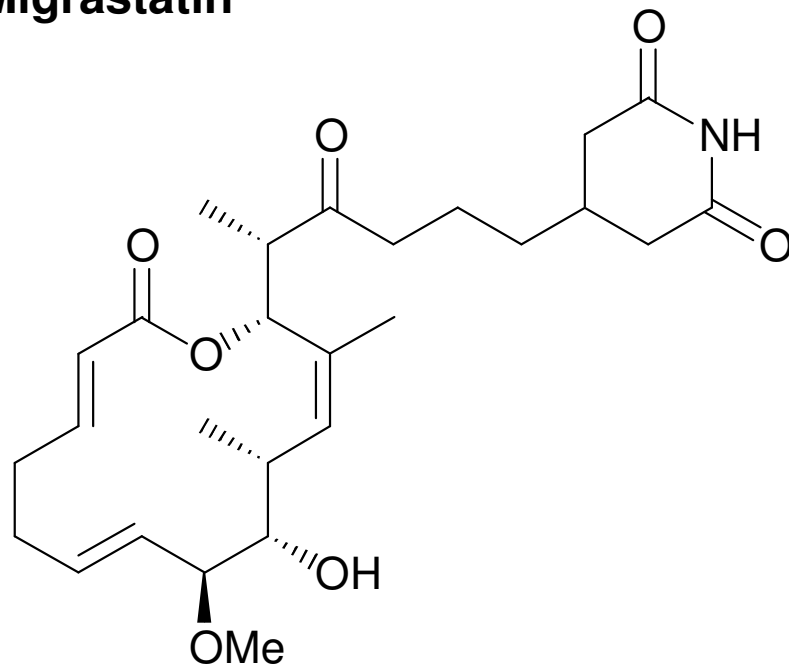
Isolated from streptomyces



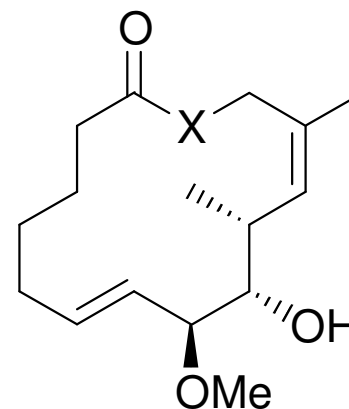
Cell migration inhibitors offer a novel approach to cancer and angiogenesis related therapy. Cell migration physiologically infrequent – possibility for drugs of lower toxicity

Nakae, K.; Yoshimoto, Y.; Sawa, T.; Homma, Y.; Hamada, M.; Takeuchi, T.; Imoto, M. *J. Antibiot.* **2000**, *53*, 1130-1136.

Migrastatin¹



Danishefsky analogues



Macrolide **3a** X = O

Macrolactam **3b** X = NH

Macroketone **3c** X = CH₂

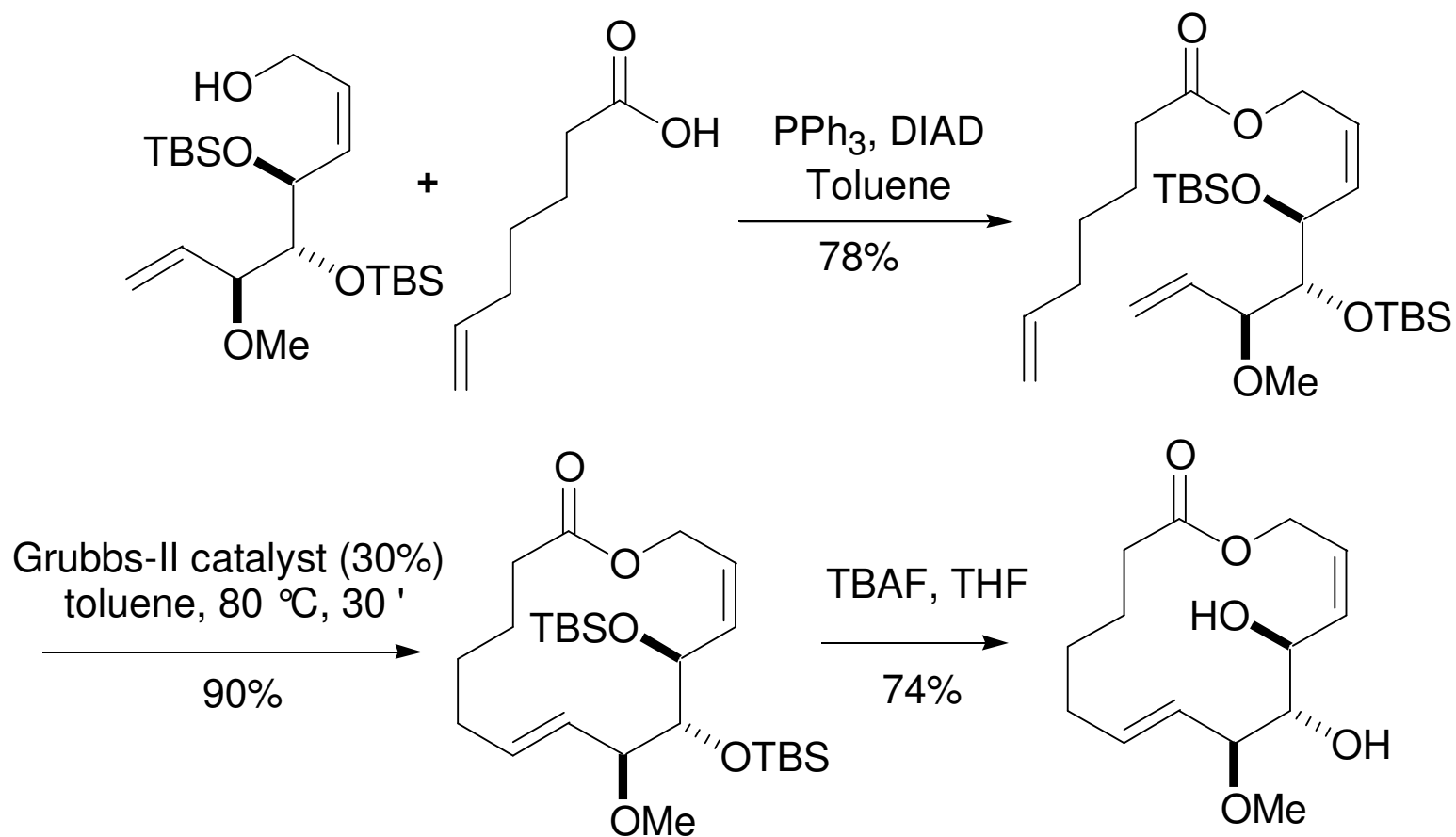
- A.** **3b** and **3c** inhibit breast cancer and lung cancer metastases in mouse model.³ Mechanism involves blocking of Rac activation and, thus, lamellipodia formation. **3a** not active *in vivo* (not stable to esterases)
- B.** **3a** is an inhibitor of HUVEC migration in chamber assay (125 nM).² Migrastatin = 65 μM; **3b** = 18 μM.

1. Nakae, K.; Yoshimoto, Y.; Sawa, T.; Homma, Y.; Hamada, M.; Takeuchi, T.; Imoto, M. *J. Antibiot.* **2000**, *53*, 1130-1136.

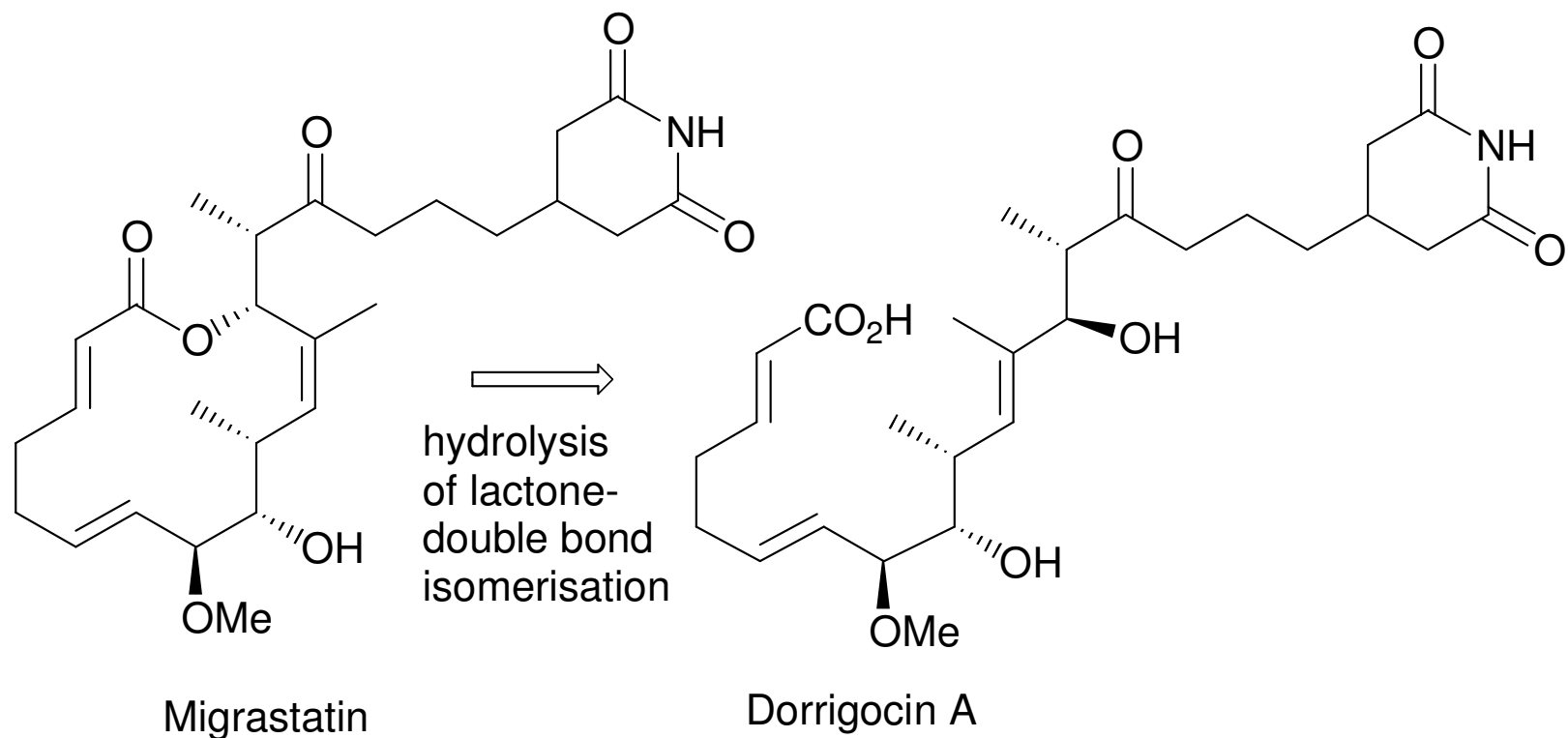
2. C. Gaul, J. T. Njardarson, D. Shan, D. C. Dorn, K.-D. Wu, W. P. Tong, X.-Y. Huang, M.A.S. Moore, and S. J. Danishefsky, *J. Am. Chem. Soc.* **2004**, *126*, 11326-37.

3. D. Shan, L. Chen, J. T. Njardarson, C. Gaul, X. Ma, S. J. Danishefsky, and X.-Y. Huang, *Proc. Natl. Acad. Sci.(USA)*, **2005**, *102*, 3772.

Ring Closing Metathesis: Effect of TBS Protecting Groups



Dorrigocin A and its relationship to Migrastatin

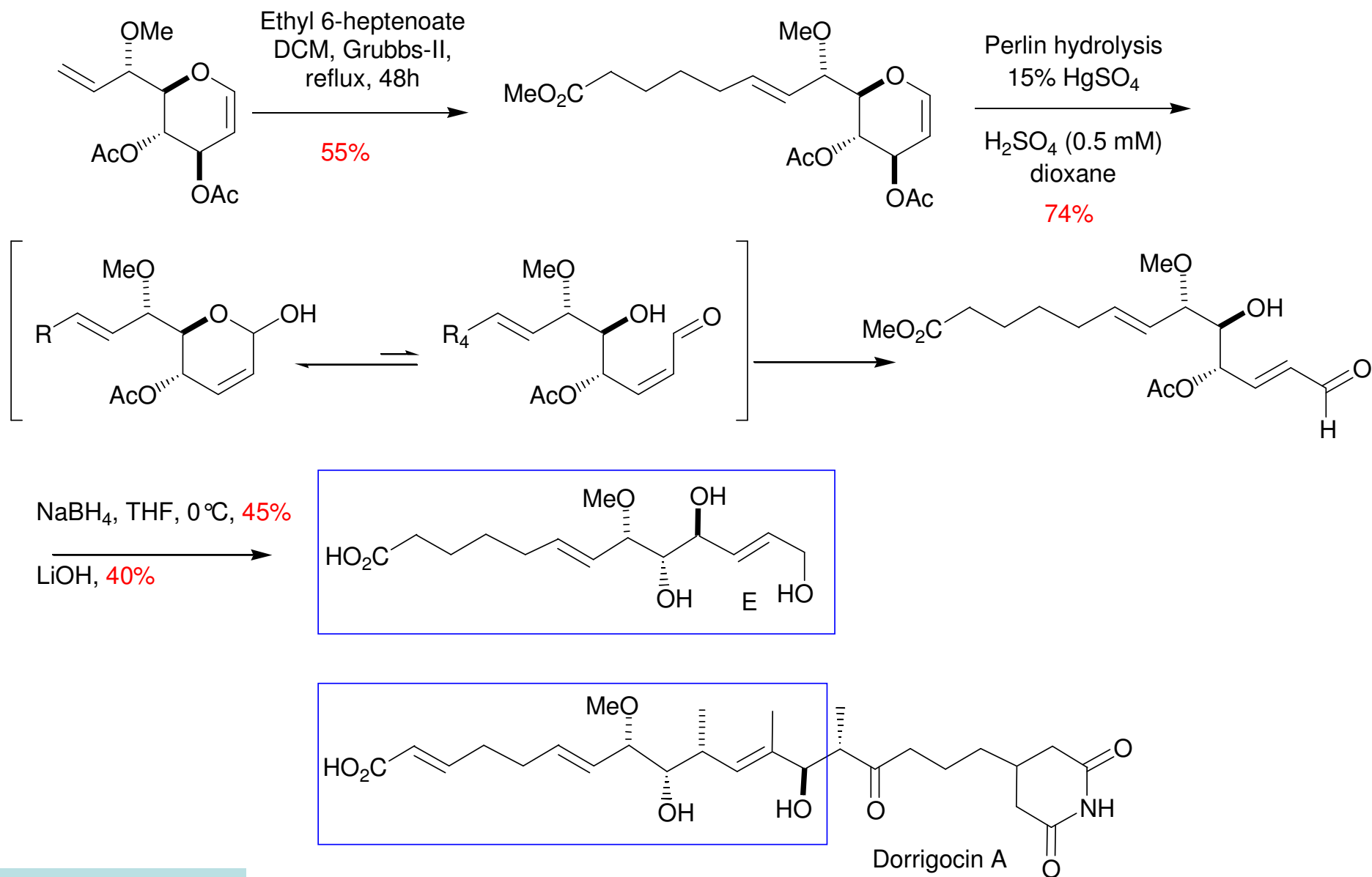


Dorrigocin A reverses the morphology of *ras*-transformed NIH/3T3 cells from a transformed phenotype to a normal one.

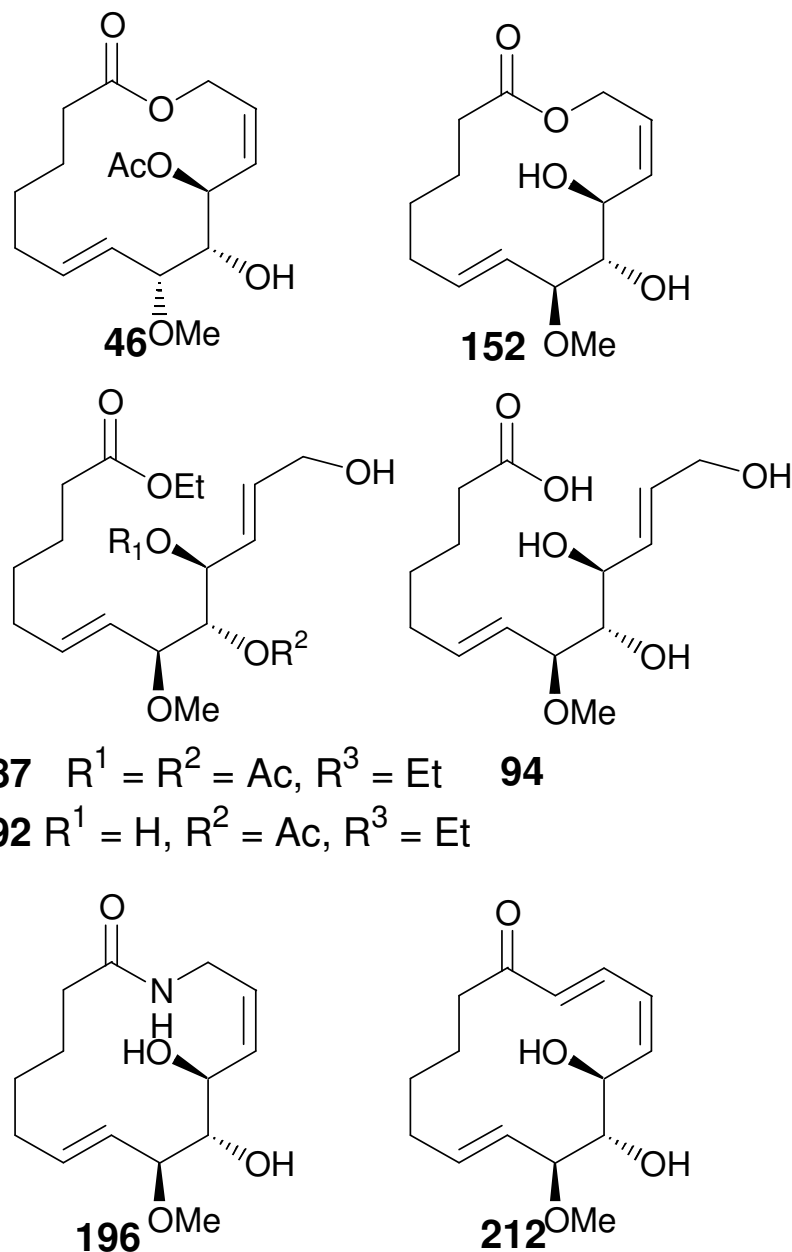
Inhibitor of the carboxyl methyltransferase involved in Ras processing.

Promotes apoptosis (in endothelial cells)

Synthesis of Dorrigocin A analogues



Inhibition of gastric cancer cell migration by novel migrastatin and dorrigoicin A derivatives

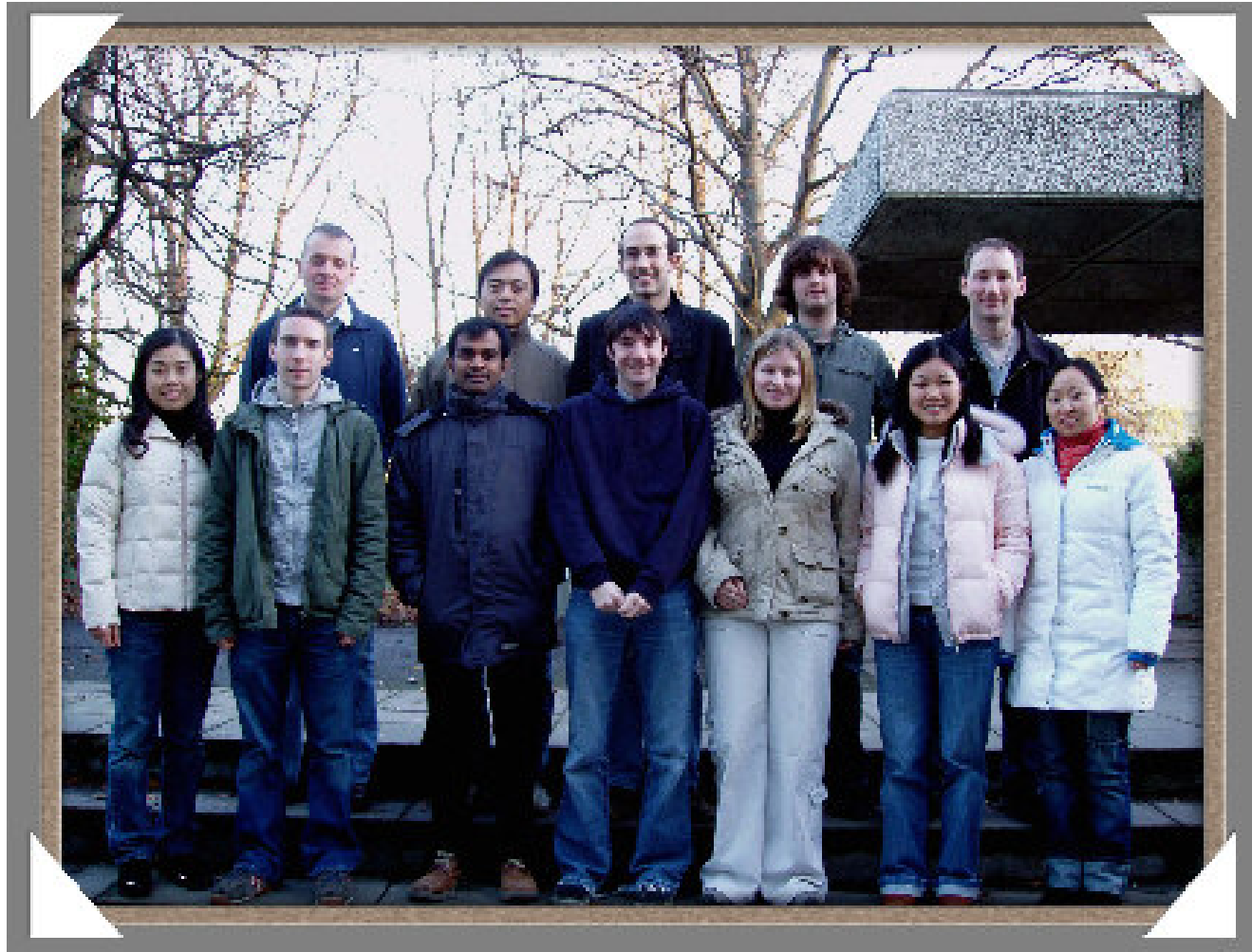


Inhibition of the migration of AGS Gastric Cancer Cells (transwell assay)

Compd	IC ₅₀ (μM)
46	17
152	not active
87	29
92	not active
94	0.032
196	50 % at 1 μM
212	38 % at 1 μM

^aCompounds **94-212** were inactive at concentrations >1 μM

Gareth Horgan, David Murray,
Peter Doran, Padraic MacMathuna
Mater Hospital Gastrointestinal Unit



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PRTL I Cycle 3

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