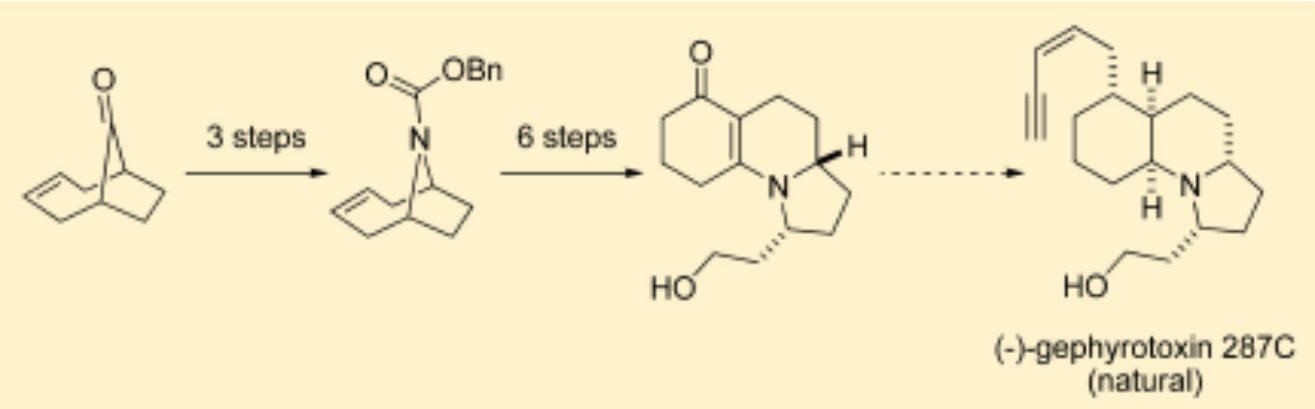
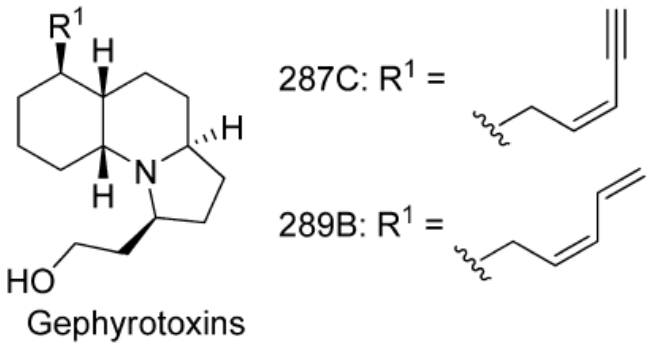


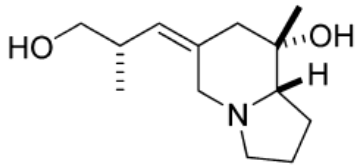
Converting Cycloalkanones into N-Heterocycles: Formal Synthesis of (−)-Gephyrotoxin 287C

Claude Spino *et al.*, *J. Org. Chem.* **2013**, *78*, 12532−12544.

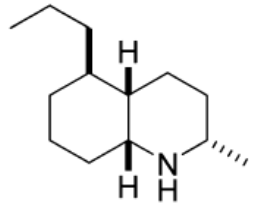
Poison frog alkaloids



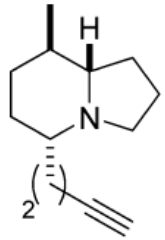
Gephyrotoxins



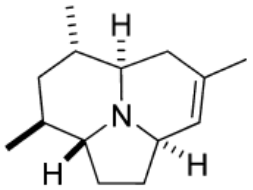
Pumiliotoxin 225F



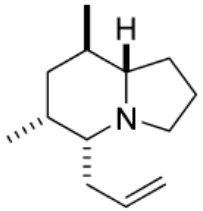
cis-Decahydroquinoline 195J



Indolizidine 205A



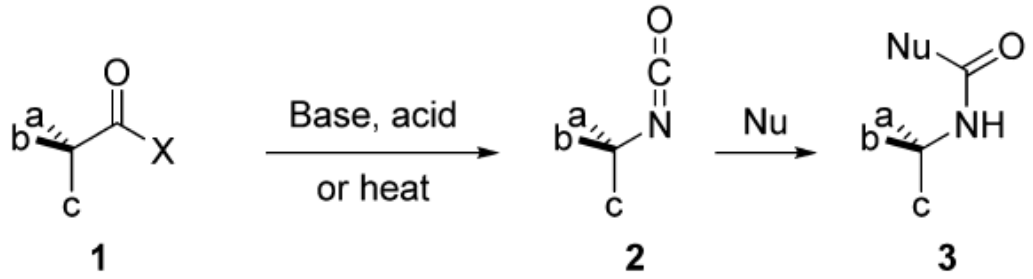
(-)-205B



Indolizidine 193G

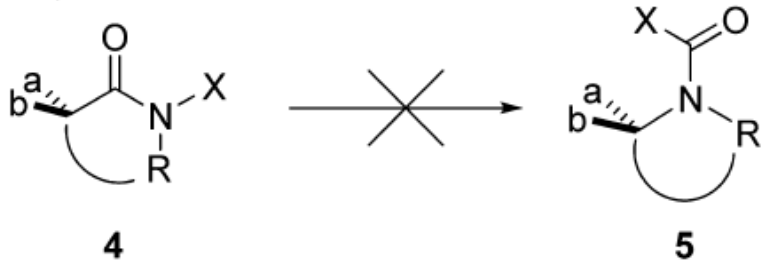
- Isolated from poison frog skin.
- Over 850 compounds isolated from frog skin over 40 years.
- Different classes : one stereogenic center at least α to nitrogen.
- 5 large classes + smaller ones.

Schmidt-type rearrangements



(Eq. 1)

X = N_3, NHOR, NHBr



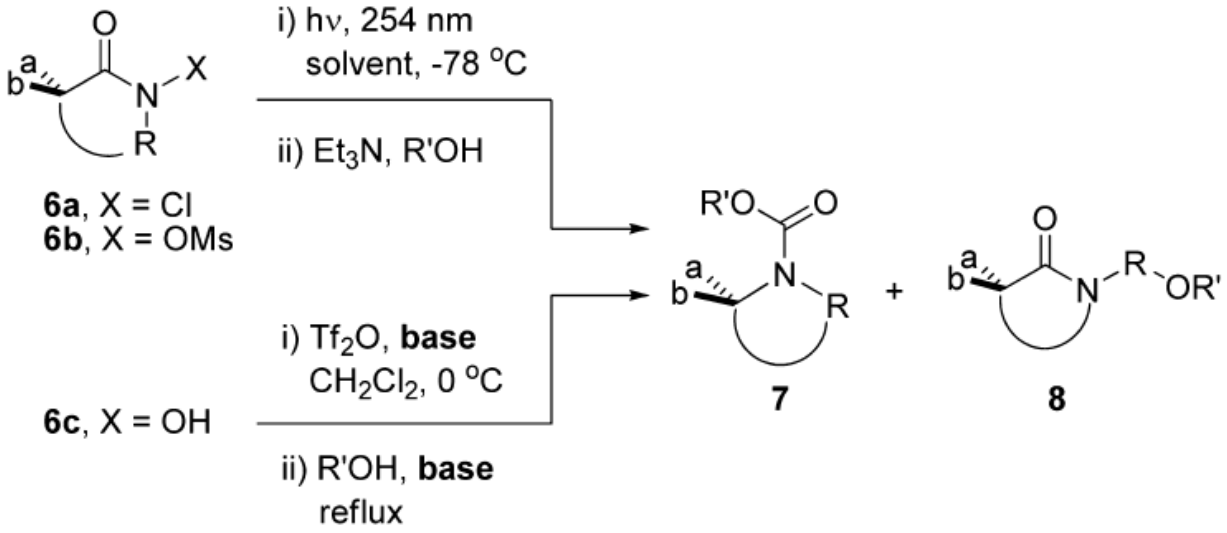
(Eq. 2)

- X = N_3, Curtius/Schmidt rearrangement
- X = NHOTs, Lossen rearrangement
- X = NHBr, Hofmann rearrangement

In each case, a primary amide derivative is used.

Rearrangements of *N*-activated lactams

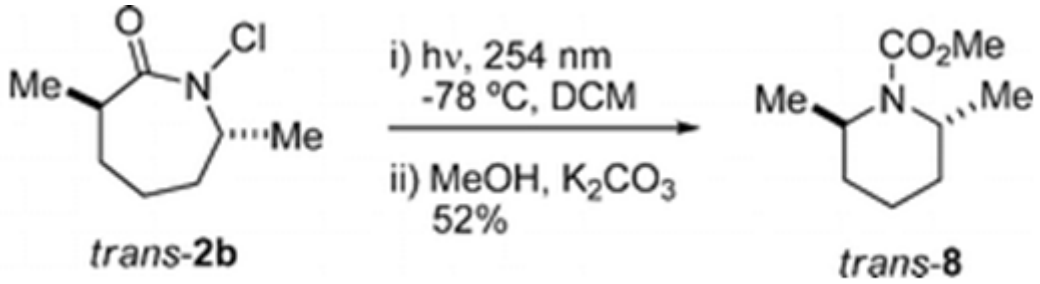
Scheme 1. Rearrangements of *N*-Activated Lactams



- Only applicable to cyclic or polycyclic systems

- (a) Drouin, A.; Lessard, J. Tetrahedron Lett. 2006, 47, 4285– 4288 (b) Winter, D. K.; Drouin, A.; Lessard, J.; Spino, C. J. Org. Chem. 2010, 75, 2610–2618(c) Drouin, A.; Winter, D. K.; Pichette, S.; Aubert-Nicol, S.; Lessard, J.; Spino, C. J. Org. Chem. 2011, 76, 164– 169 (d) Pichette, S.; Aubert-Nicol, S.; Lessard, J.; Spino, C. Eur. J. Org. Chem. 2012, 1328– 1335 (e) Pichette, S.; Aubert-Nicol, S.; Lessard, J.; Spino, C. J. Org. Chem. 2012, 77, 11216–11226

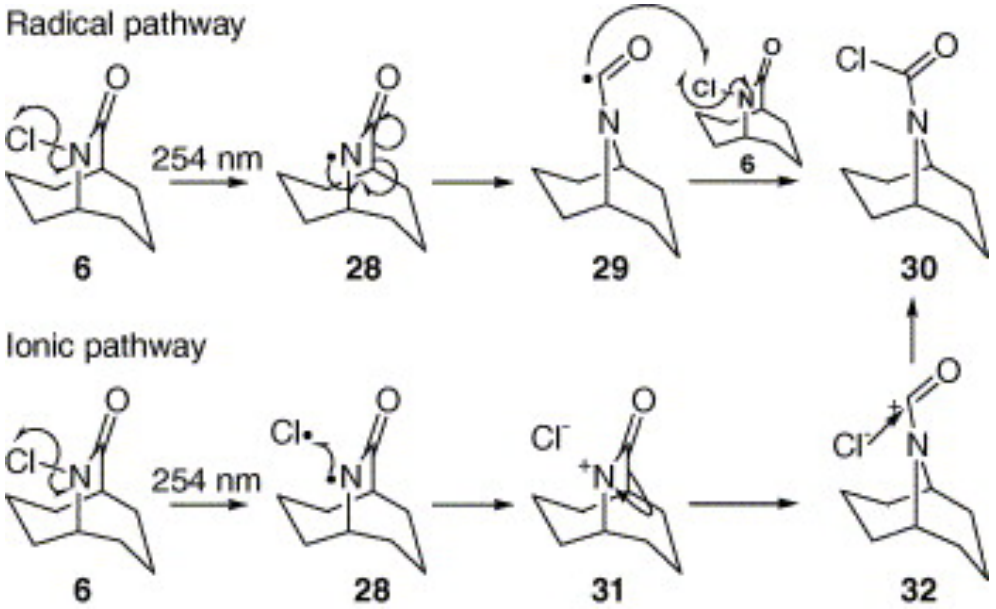
Rearrangements of *N*-chloro and *N*-mesyloxy lactams



- Starting compounds easy to access
- Mild conditions
- Main side-product : dechlorination. Can be recycled
- 5,6,7-membered rings obtained, 4,3 fail because of strain
- Substitution in α influences migration and therefore yield.
- OMs substrates give 30-40% higher yields than Cl.

Drouin, A.; Lessard, J. Tetrahedron Lett. 2006, 47, 4285– 4288. Winter, D. K.; Drouin, A.; Lessard, J.; Spino, C. J. Org. Chem. 2010, 75, 2610– 2618

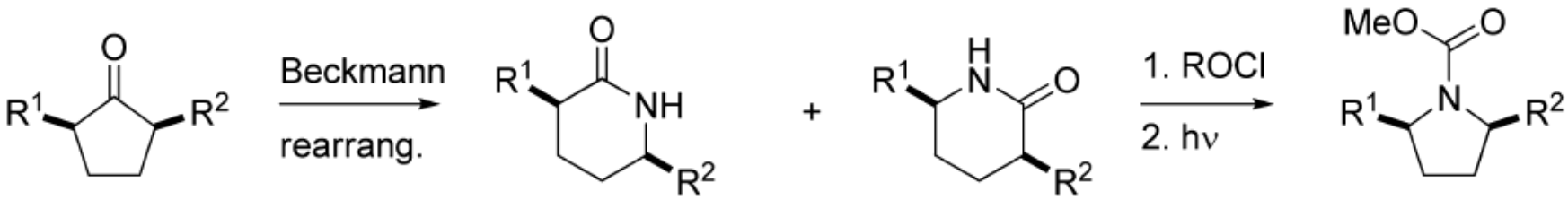
Proposed mechanism



- 100% stereoselective.
- Migration: concerted mechanism.
- Ionic pathway via acylnitrenium more probable.
- No thermic reaction with N-Cl, or N-OMs. Possible with N-OH.

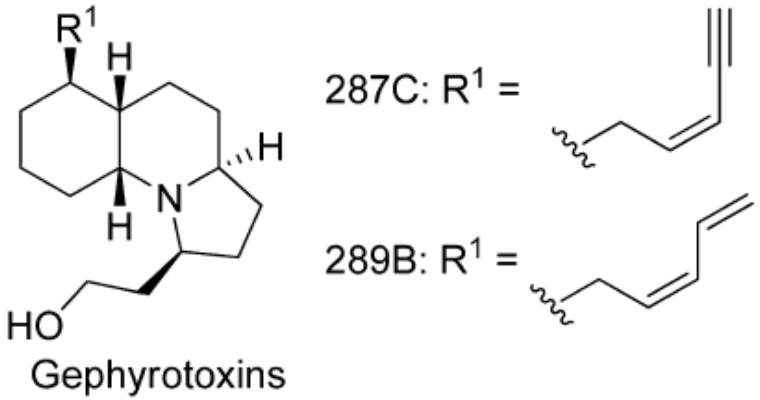
Drouin, A.; Lessard, J. Tetrahedron Lett. 2006, 47, 4285– 4288. Winter, D. K.; Drouin, A.; Lessard, J.; Spino, C. J. Org. Chem. 2010, 75, 2610– 2618

Sequence



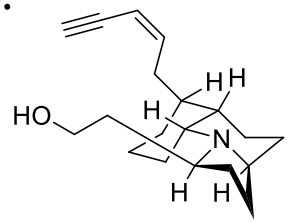
- Beckmann ring-expansion/Photochemical ring-contraction cascade
- In 3 steps transformation of a cycloalkanone into *N*-heterocycle of the same size
- Retention of stereochemistry
- Strategy applied to synthesis of (-)-gephyrotoxin 287C

(-)-Gephyrotoxin 287C



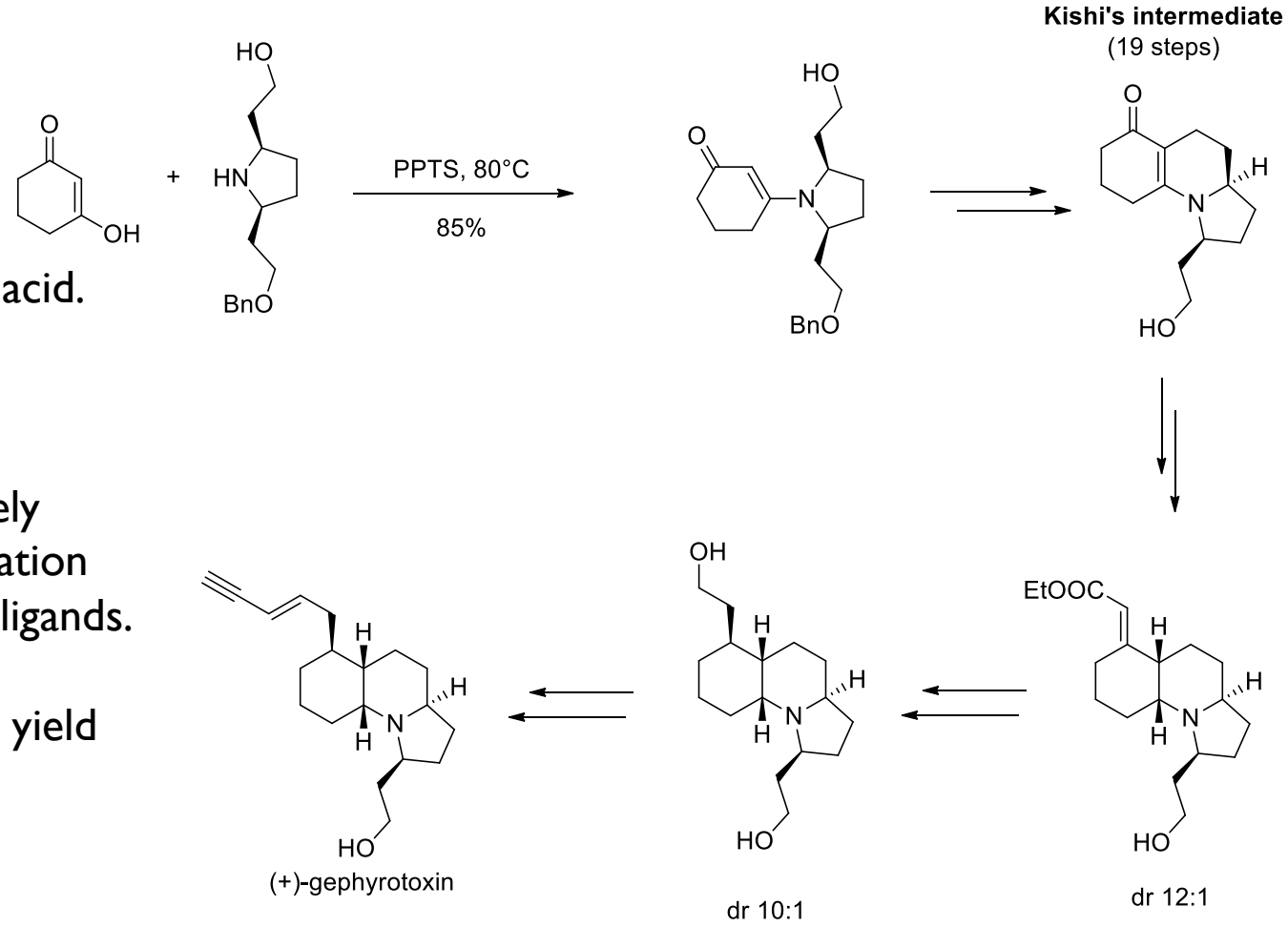
Gephyrotoxins

- Isolated from *Dendrobates histrionicus in 1974*.
- «<50 mg isolated from thousands of frog skins».
- First synthesized by Kishi in 1980. Absolute stereochemistry reassigned.
- Several total and formal syntheses.
- Mild neurological activity.



Tokuyama, T.; Yenoyama, K.; Brown, G.; Daly, J. W.; Witkop, B. Helv. Chim. Acta 1974, 57, 2597– 2604

Kishi's synthesis



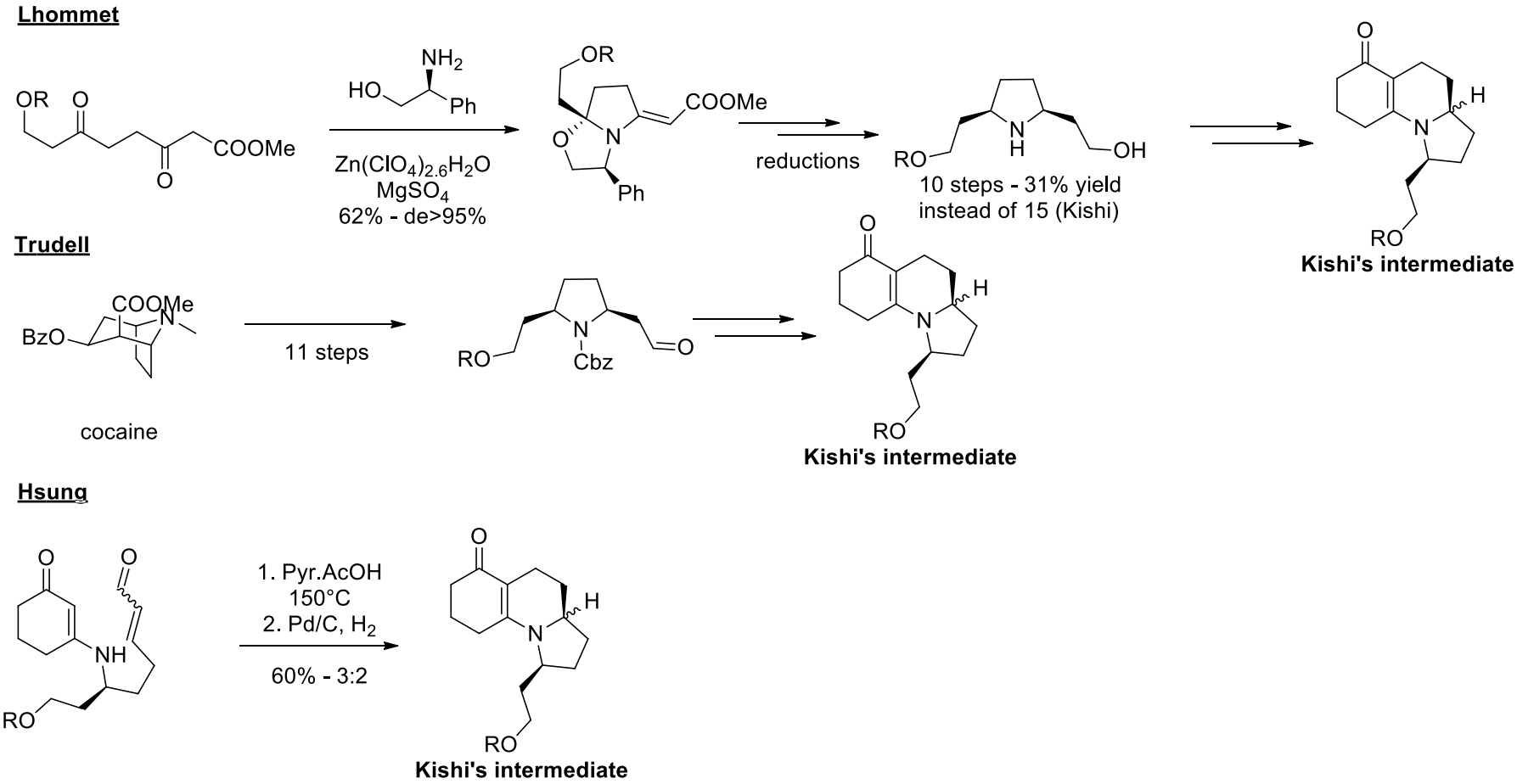
- From L-pyroglutamic acid.
15 steps to pyrrolidine.

- 1 existing center,
4 centers stereoselectively introduced via hydrogenation reactions without chiral ligands.

- 24 steps, 2.8% overall yield

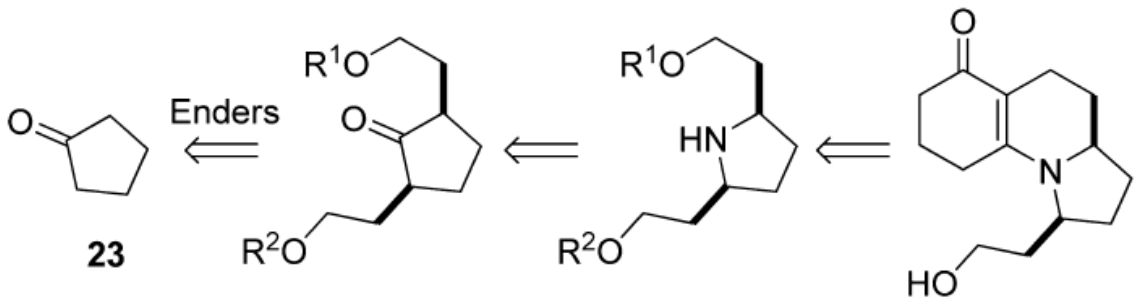
Fujimoto, R.; Kishi, Y.; Blount, J. G. J. Am. Chem. Soc. 1980, 102, 7154– 7156. Fujimoto, R.; Kishi, Y. Tetrahedron Lett. 1981, 42, 4197– 4198

Formal syntheses

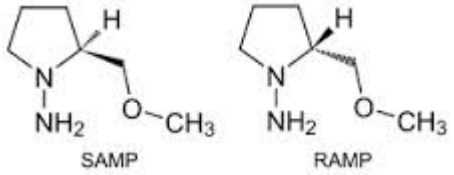


(a) Santarem, M.; Vannuci-Bacqué, C.; Lhommet, G. J. Org. Chem. 2008, 73, 6466– 6469 (b) Wei, L.-L.; Hsung, R. P.; Sklenicka, H. M.; Gerasyuto, A. I. Angew. Chem., Int. Ed. 2001, 40, 1516– 1518 (c) Miao, L.; Shu, H.; Noble, A. R.; Fournet, S. P.; Stevens, E. D.; Trudell, M. L. ARKIVOC 2010, 2010 (4) 6– 14.

First approach

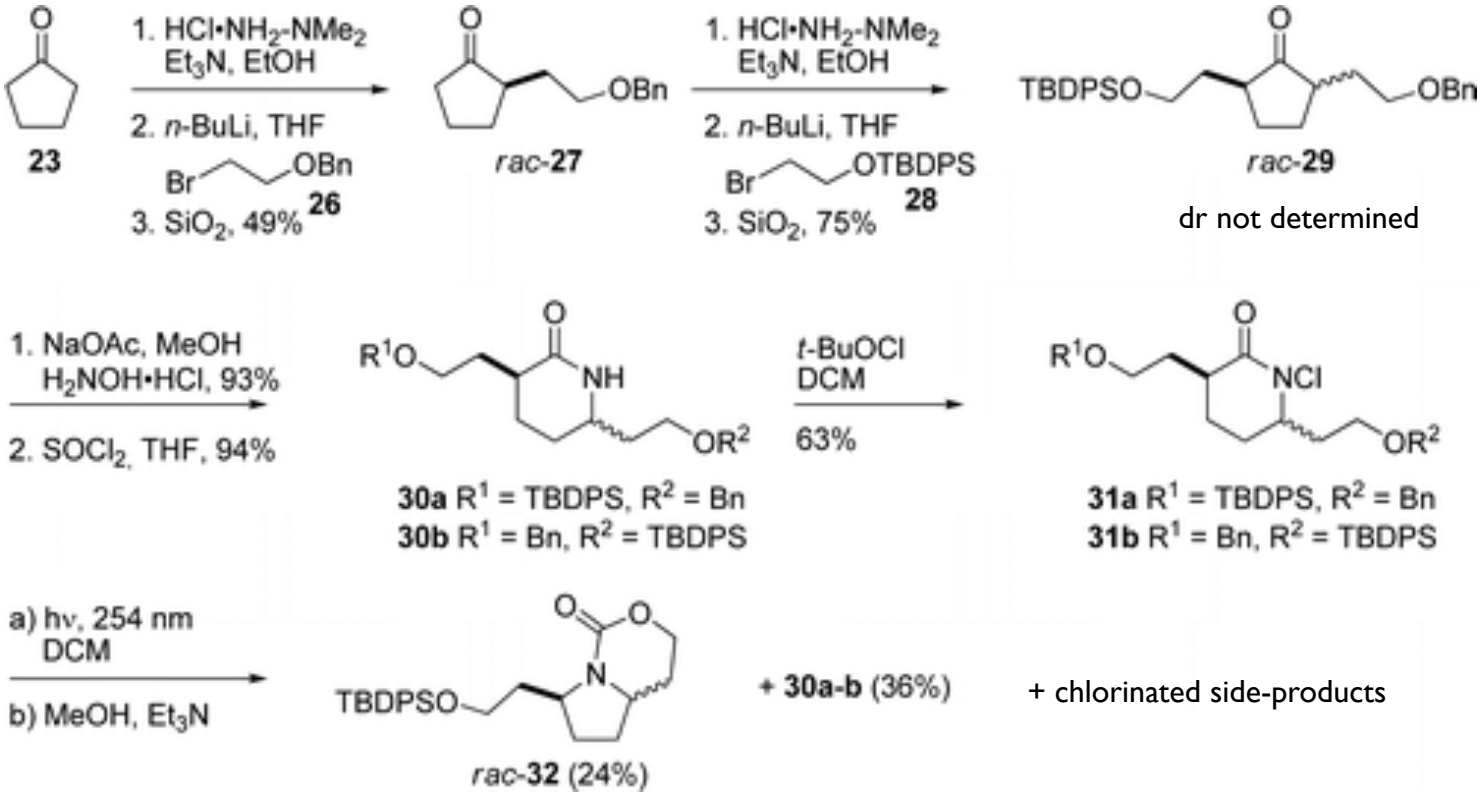


- Alkylations using Enders' chiral hydrazones



- Beckmann-ring contraction sequence to obtain dialkylated pyrrolidine.
- Synthesis of Kishi's intermediate.

Racemic approach



Mixture of Beckmann regioisomers gives the same product

Unexpected cyclization

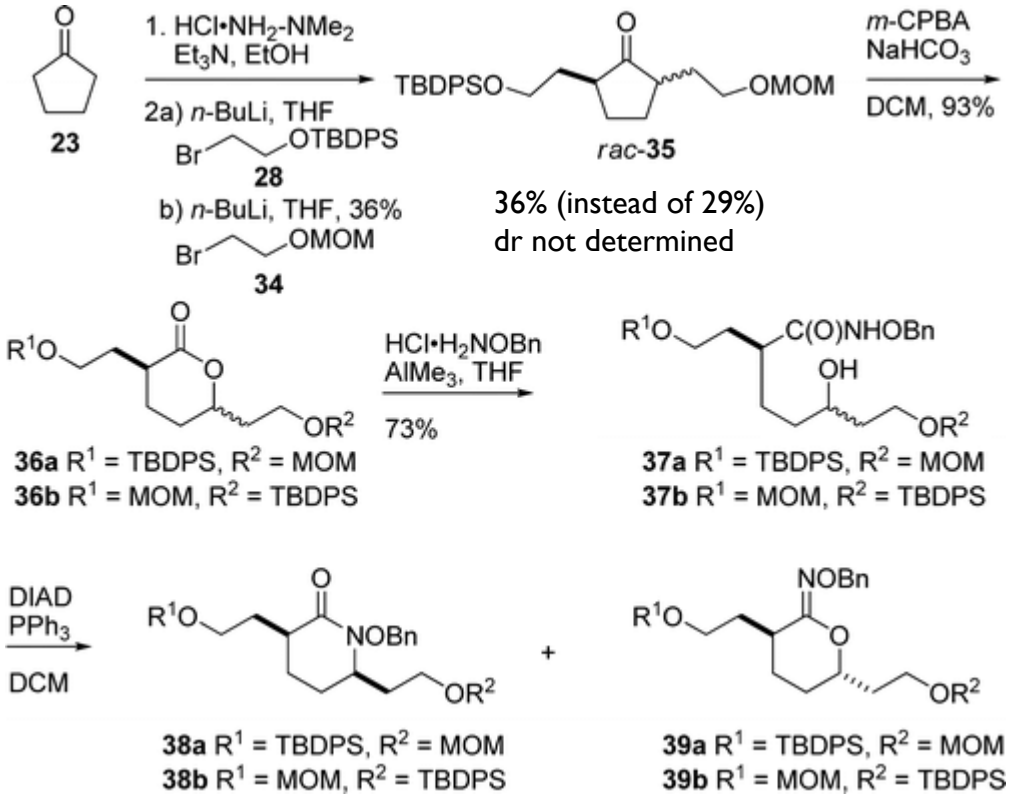
- Benzylated alcohol cyclized onto the intermediate.
- Weak nucleophile, unexpected cyclization in methanol.

- Increasing nucleophilicity to increase yield ?
- Other protecting groups tried, but no yield increase.

change of strategy :

- Use N-OMs, but no way to oxidize lactams into cyclic hydroxamic acids.
- Change scaffold : use bicyclic system.

Hydroxamic derivative route

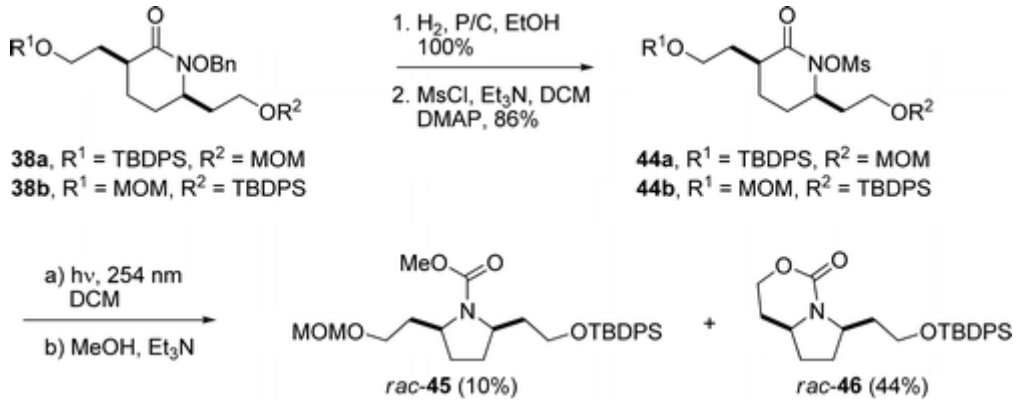


- First steps improved
- No efficient method for lactam oxidations.
- BV oxidation and opening of cycle with hydroxylamine.

  (2 regioisomers)
- Cyclization with hydroxylamine using Mitsunobu:

O- vs N-alkylation depending on stereochemistry.

Hydroxamic derivative route



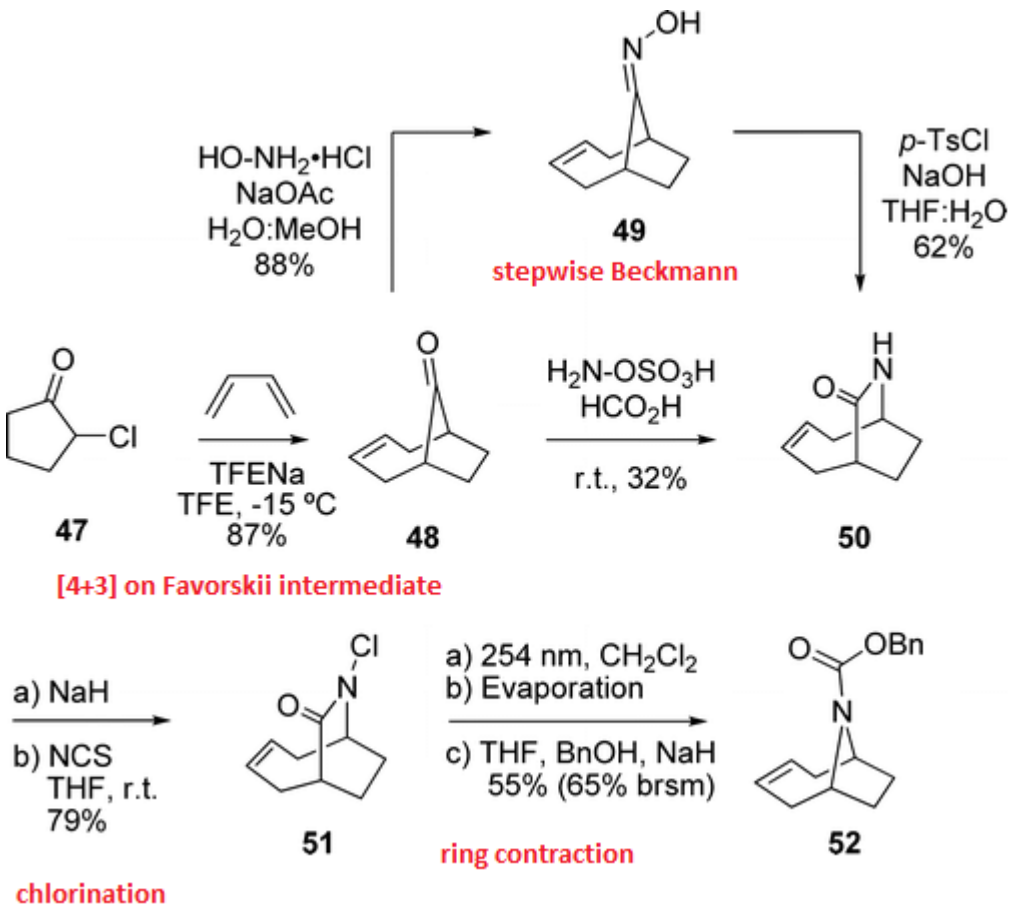
Advantage of approach :

- Improved yield for the reaction (24% previously).
- Could be improved
- Mitsunobu selectivity can help purification

Disadvantage :

- Strategy longer (BV, opening, Mitsunobu, debenzylation and mesylation) to substrate

Bicyclic derivative route

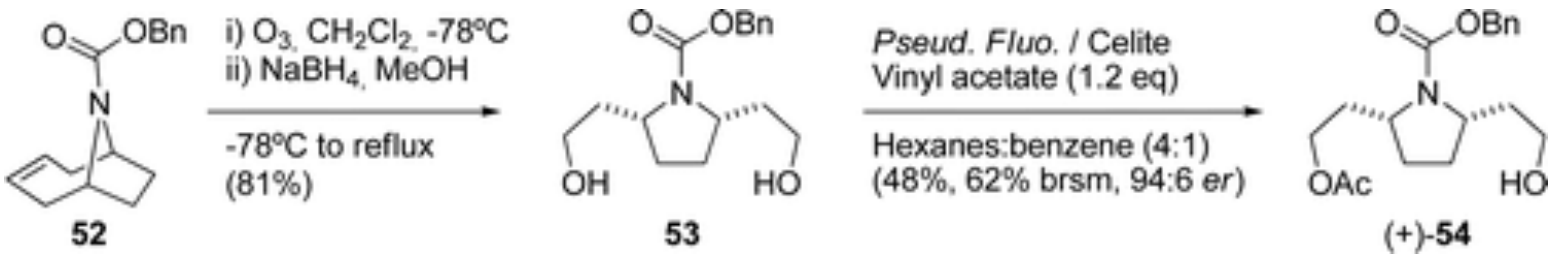


Advantages :

- Easy access to substrate
- Expected yields higher for the cascade
- Right *cis* stereochemistry

One of the best yields for the cascade obtained.

Bicyclic derivative route

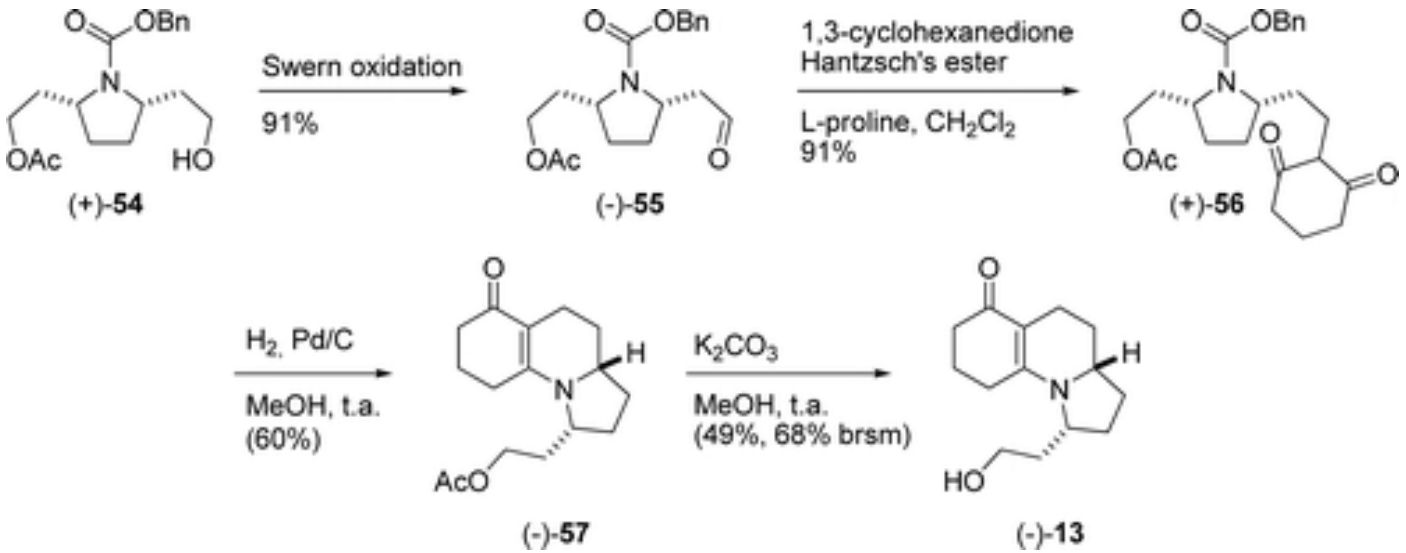


Advantages:

- Yield for cascade compares with OMs substrate.
- Substrate easy to access.
- Only the desired enantionmer is obtained.
- No side products.

The best way to access alkylated pyrrolidine.

Access to Kishi's intermediate



- Kishi's intermediate obtained in 10-12 steps.

Conclusion

- Development of a methodology for Schmidt-type rearrangement applied to lactams.

- Development of a cascade to transform a cycloalkanone into *N*-heterocycle of the same size

- Application to the formal synthesis of (-)-gephyrotoxin 287C.

Kishi's intermediate in 10-12 steps.

Key steps : Beckmann ring expansion/ring contraction cascade

Desymmetrization of a *meso* diol.