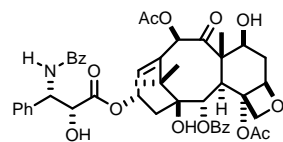
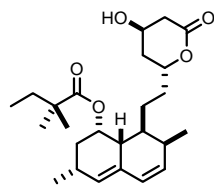


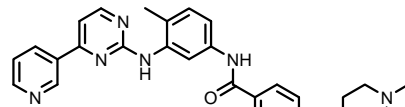
The Small Molecules of Life



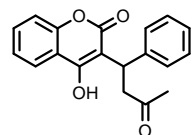
TAXOL (PACLITAXEL)
(Anticancer)



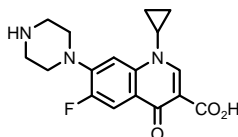
ZOCOR (SIMVASTATIN)
(Hypercholesterolemic)



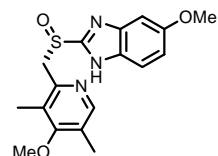
GLEEVEC (IMATINIB)
(Antileukemic)



COUMADIN (WARFARIN)
(Anticoagulant)



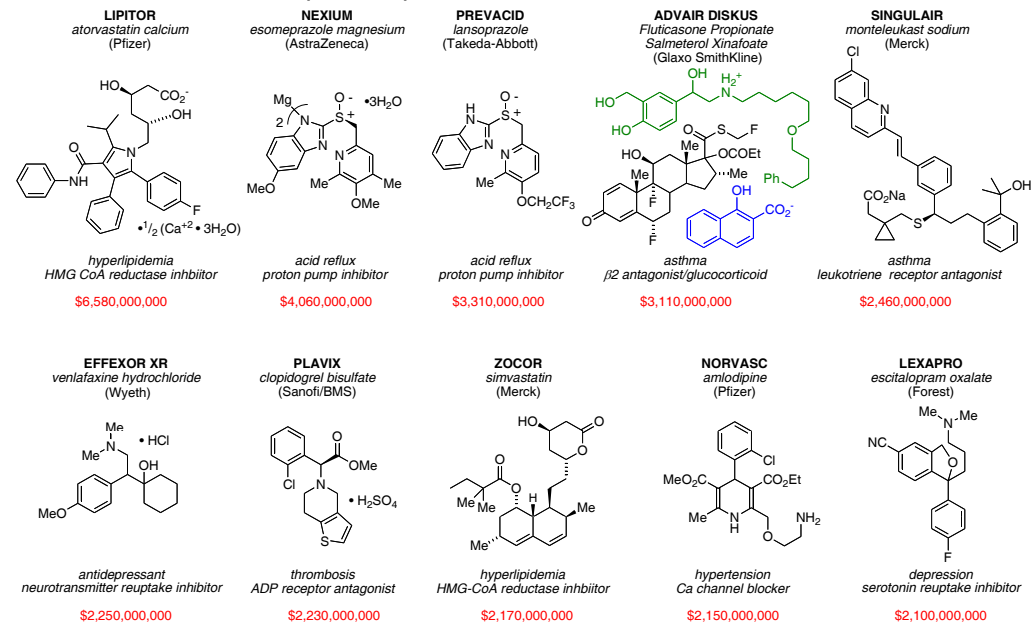
CIPRO (CIPROFLOXACIN)
(Antibiotic)



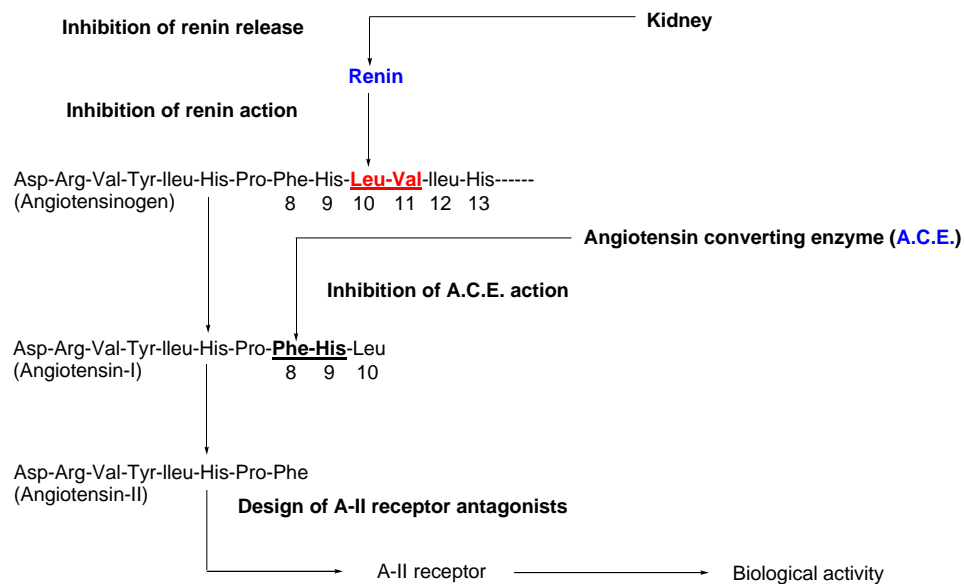
NEXIUM (ESOMEPRAZOLE)
(Proton pump inhibitor)

Most Top Drugs Require Synthesis

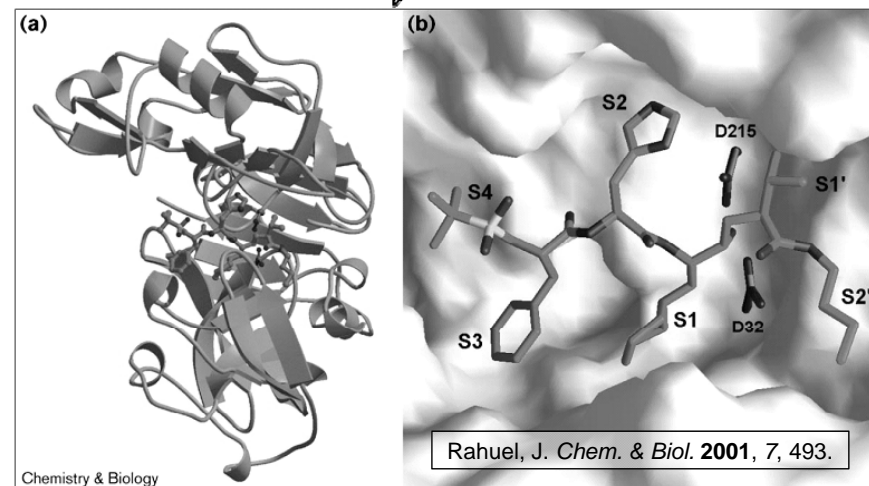
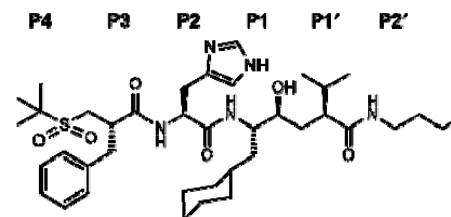
Top 10 Prescription Pharmaceuticals in the U.S. in 2006



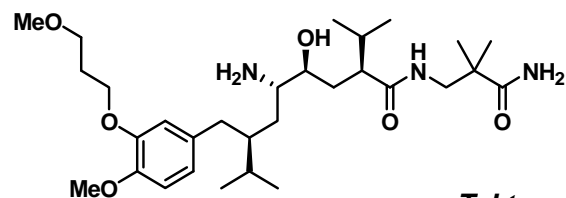
Sites available for the inhibition of the renin-angiotensin system (RAS)



Structure-based design of renin inhibitors



The First Marketed Renin Inhibitor for Hypertension



Tekturna
(aliskiren, SPP-100 CGP-60536B)

Publications (formal syntheses)

Maibaum *J. Med. Chem.* **2007**, *50*, 4818 (Novartis)
 Maibaum *J. Med. Chem.* **2007**, *50*, 4832 (Novartis)
 Skydstруп *J. Org. Chem.* **2006**, *71*, 4766
 Ma *Tetrahedron Lett.* **2005**, *46*, 6337
 Maibaum *Helv. Chim. Acta* **2003**, *86*, 2848 (Novartis)
 Hanessian *J. Org. Chem.* **2002**, *67*, 4261
 Dondoni *Tetrahedron Lett.* **2001**, *42*, 4819
 Sandham *Tetrahedron Lett.* **2000**, *41*, 10091 (Novartis)
 Maibaum *Tetrahedron Lett.* **2000**, *41*, 10085 (Novartis)

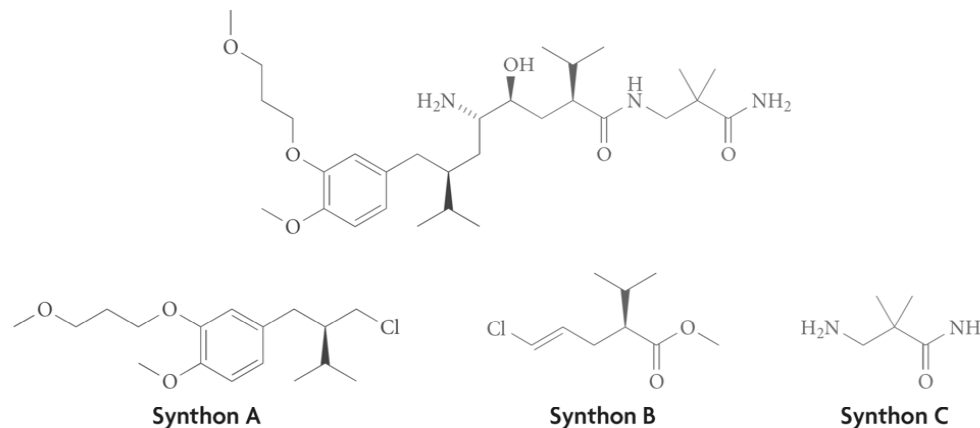
Patents:

WO 2007/045420 A2 (Novartis)
 WO 2007/039183 A1 (Novartis)
 WO 2006/131304 A2 (Novartis)
 WO 2006/024501 A1 (Novartis)
 WO 2002/08172 A1 (Speedel Pharma)
 WO 2002/02508 A1 (Speedel Pharma)

Reviews:

Maibaum, J.; Feldman, D. L. *Ann. Rep. Med. Chem.* **2009**, *44*, 105;
 Jensen, C.; Herold, P.; Brunner, H. R. *Nature Drug Discov.* **2008**, *7*, 399;
 Siragy, H. M.; Kavi, S.; Kirkpatrick, P. *Nature Drug Discov.* **2007**, *6*, 779.

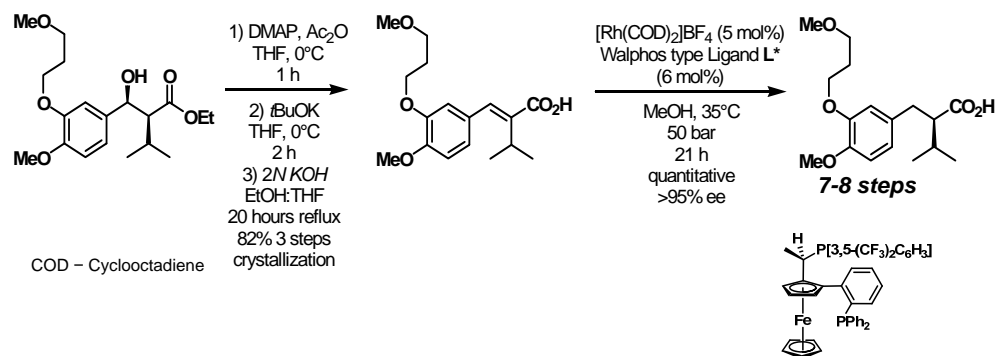
ex. Speedel process to Tekturna (aliskiren)



References

Synthon A synthesis: Peter Herold, Stefan Stutz Speedel Pharma AG *WO0202487* [2002]
 Synthon A synthesis: Peter Herold, Stefan Stutz Speedel Pharma AG *WO0202500* [2002]
 Synthon B synthesis: Peter Herold, Stefan Stutz Speedel Pharma AG *WO02092828* [2002]
 Aliskiren synthesis: Peter Herold, Stefan Stutz, Felix Spindler Speedel Pharma AG *WO0202508* [2002]

Synthesis of (*R*)- 2-isopropyl-3- phenylpropionic acid



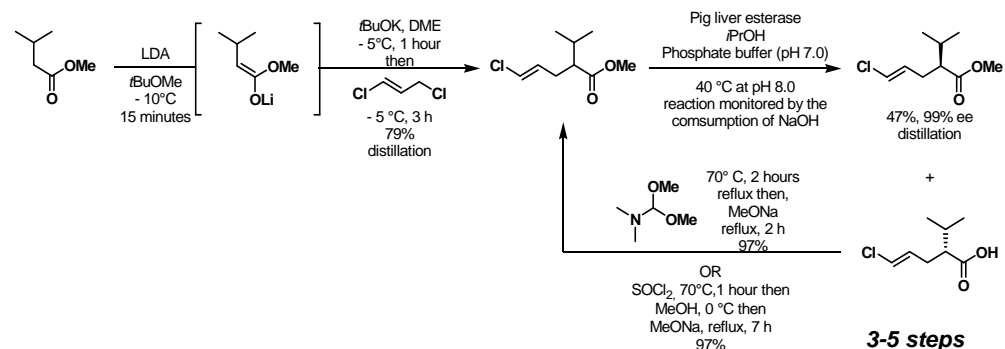
Walphos type Ligand L*

Catalyzed Enantioselective hydrogenation references (chiral ligands and metals):

- Sturm, T.; Weissensteiner, W.; Spindler, F. *Adv. Synth. Catal.* **2003**, *345*, 160-164.
 - Boogers, J. A. F.; Felfer, U.; Kotthaus, M.; Lefort, L.; Steinbauer, G.; de Vries, A. H. M.; de Vries, J. G. *Organic Process Research & Development* **2007**, *11*, 585-591.
 - Fox, M. E.; Jackson, M.; Lennon, I. C.; Klosin, J.; Abboud, K. A. *J. Org. Chem.* **2008**, *73*, 775-784.
 - Wang, Y.; Sturm, T.; Steurer, M.; Arion, V. B.; Mereiter, K.; Spindler, F.; Weissensteiner, W. *Organometallics* **2008**, *27*, 1119-1127.
 - Li, S.; Zhu, S.-H.; Zhang, C.-M.; Song, S.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2008**, *130*, 8584-8585.

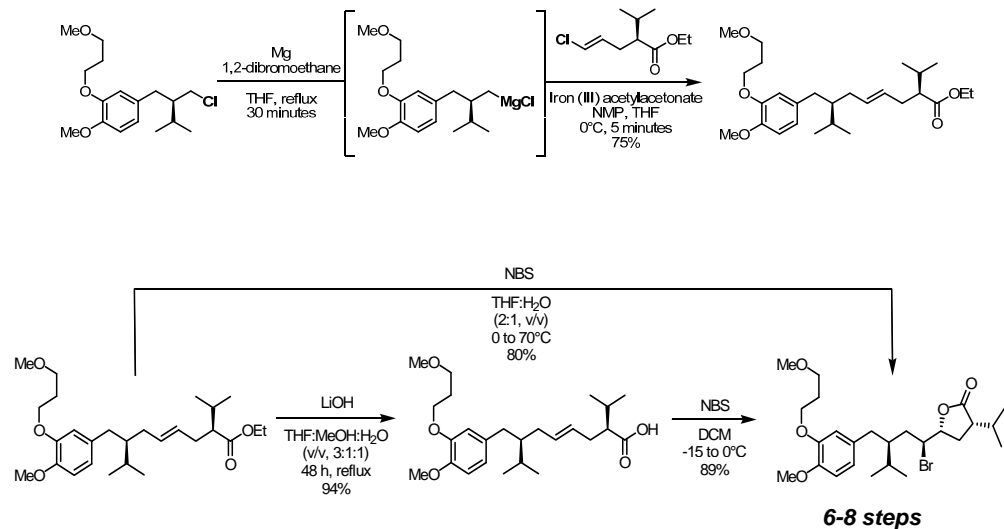
Herold, P.; Stutz, S. Speedel Pharma AG *WO0202500* [2002]

Process for the preparation of substituted carboxylic ester



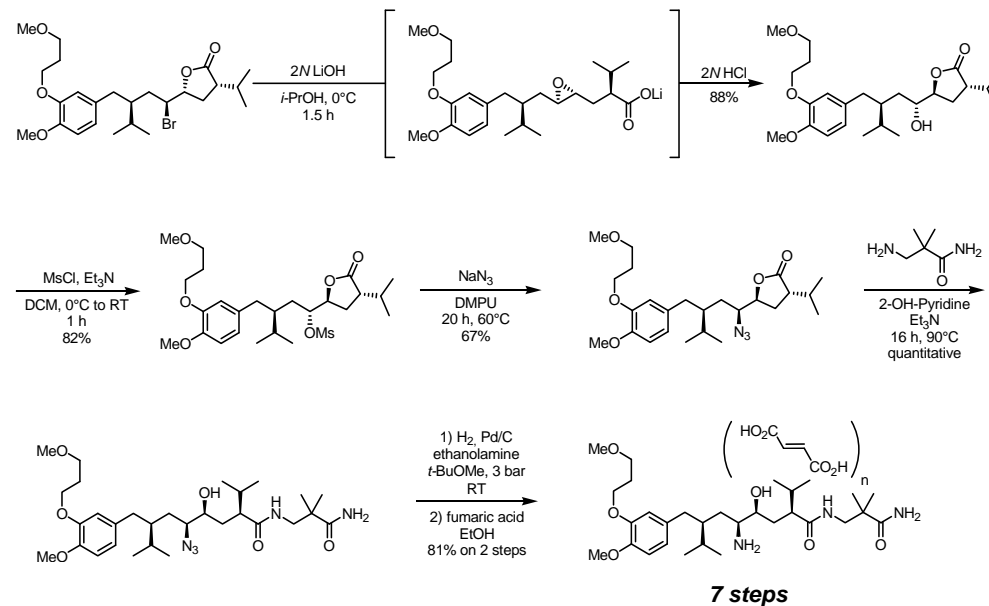
Herold, P.; Stutz, S. Speedel Pharma AG *WO0202500* [2002]

Coupling and bromolactonization reaction



Herold, P.; Stutz, S.; Spindler, F. Speedel Pharma AG WO0202508 [2002]

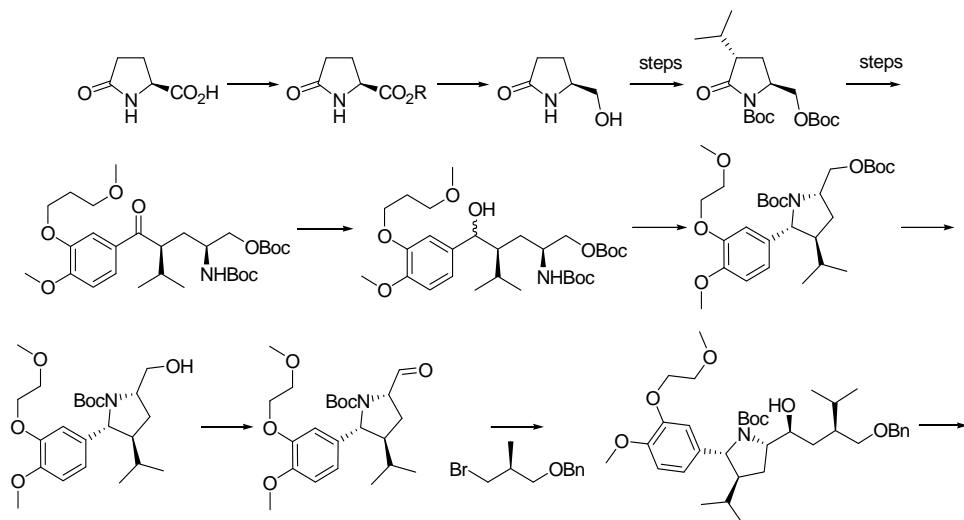
ex.Speedel synthetic route towards Tekturna



Herold, P.; Stutz, S.; Spindler, F. Speedel Pharma AG WO0202508 [2002]

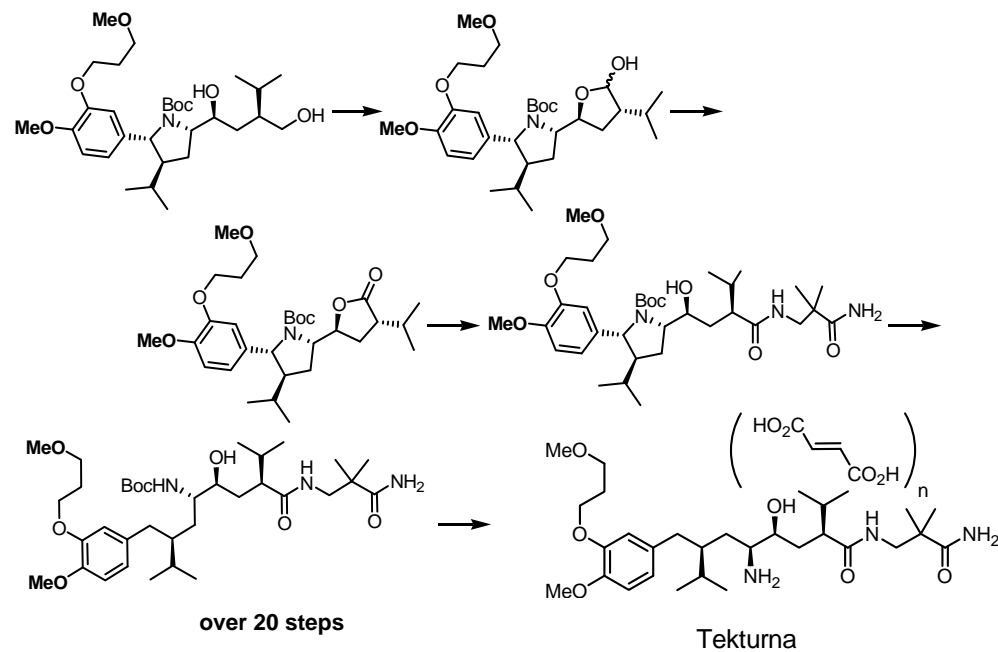
Summary of the Novartis Patent 2006/131304

Mickel, Sedelmeier, Hirt, Schäfer, Foulkes

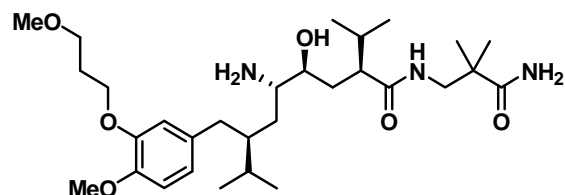


Summary of the Novartis Patent 2006/131304

Mickel, Sedelmeier, Hirt, Schäfer, Foulkes



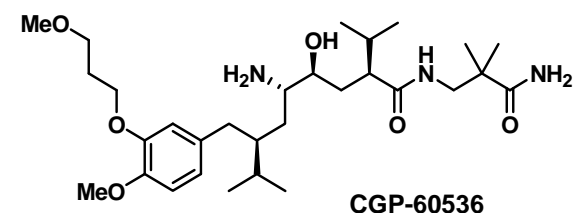
Formal syntheses of Tekturna (aliskiren)



Maibaum *J. Med. Chem.* **2007**, *50*, 4818 (Novartis)
 Maibaum *J. Med. Chem.* **2007**, *50*, 4832 (Novartis)
 Skydstrup *J. Org. Chem.* **2006**, *71*, 4766
 Ma *Tetrahedron Lett.* **2005**, *46*, 6337
 Maibaum *Helv. Chim. Acta* **2003**, *86*, 2848 (Novartis)
 Dondoni *Tetrahedron Lett.* **2001**, *42*, 4819
 Sandham *Tetrahedron Lett.* **2000**, *41*, 10091 (Novartis)
 Maibaum *Tetrahedron Lett.* **2000**, *41*, 10085 (Novartis)

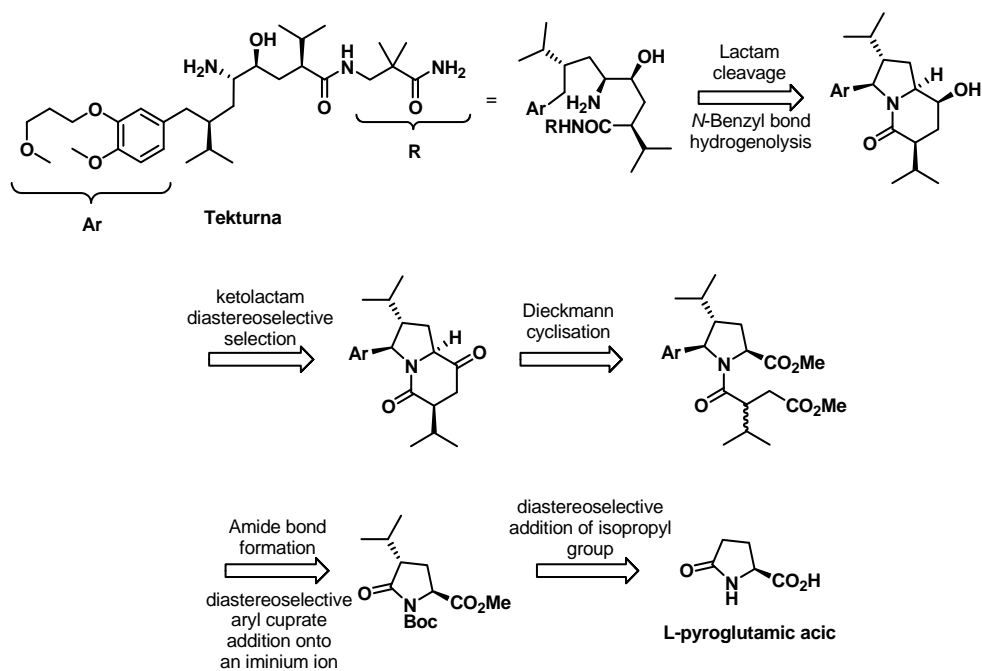
The ex.Ciba-Geigy Pharma Hanessian collaboration story (ca.1996-2000)

- Target molecule: CGP-60536
- Conditions: no azide; no chiral auxiliaries, no toxic reagents; amenable to scale-up; low cost



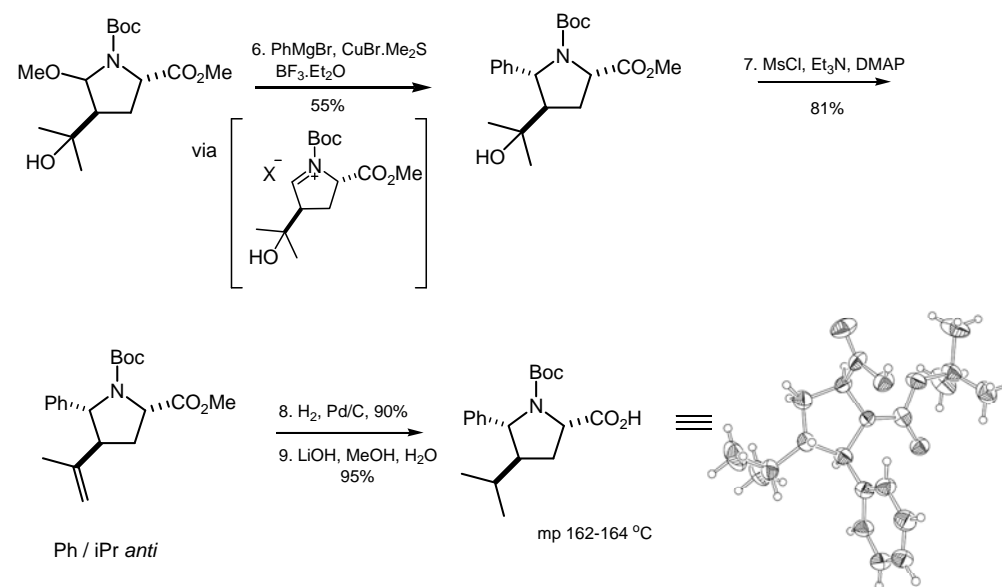
CGP-60536
 (Tekturna, Rasilez, aliskiren)

Retrosynthetic considerations

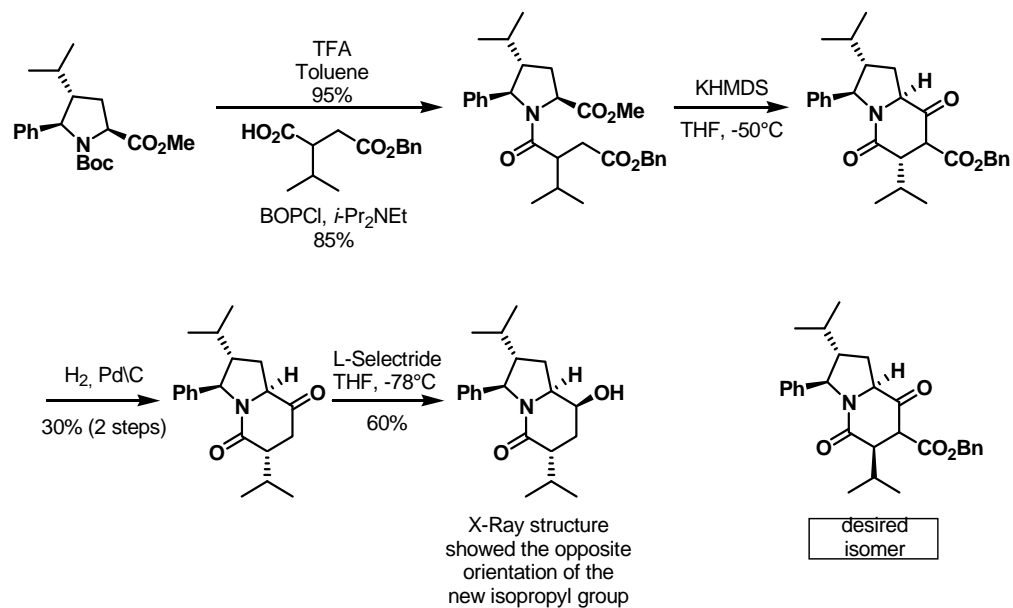


with S. Claridge and S. Johnstone *J. Org. Chem.* **2002**, *77*, 4261-4274

The first isopropyl hurdle

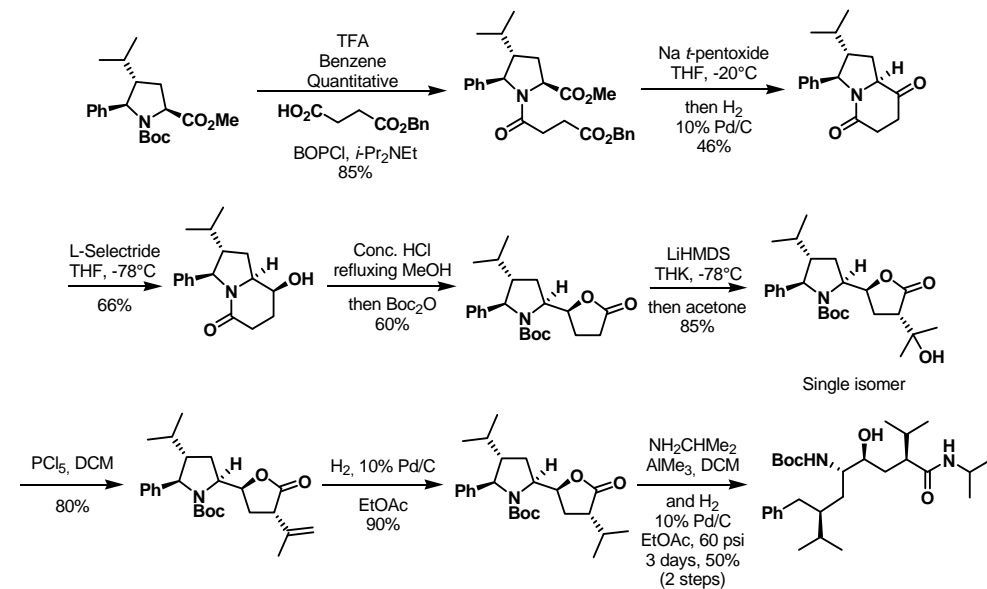


Synthetic route towards a Tekturna prototype: Dieckmann cyclization



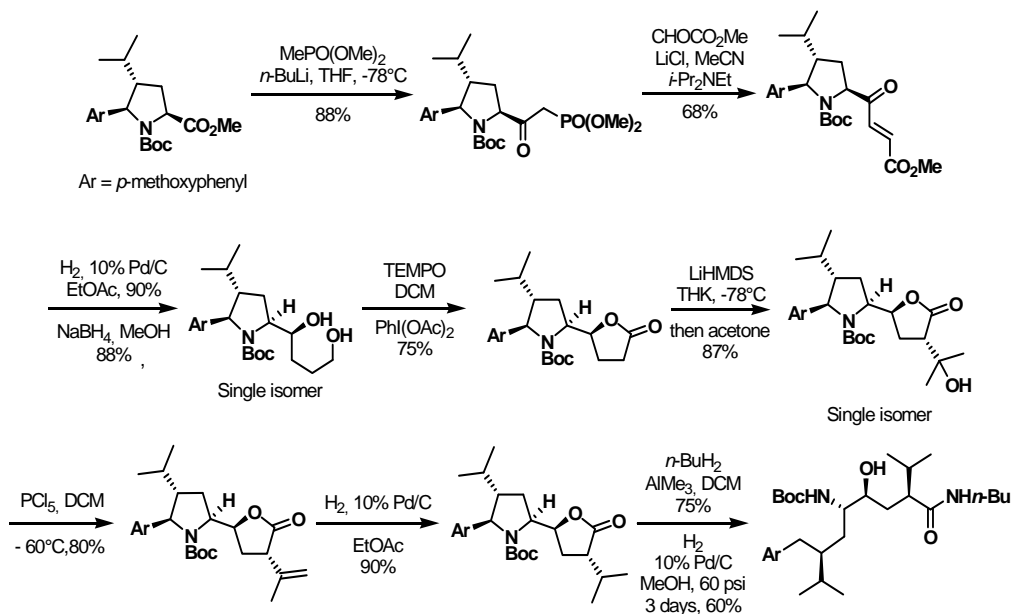
With Claridge, S.; Johnstone, S. *J. Org. Chem.* **2002**, *77*, 4261-4274

Synthetic route towards a Tekturna prototype: alternative substrate for the Dieckmann cyclization



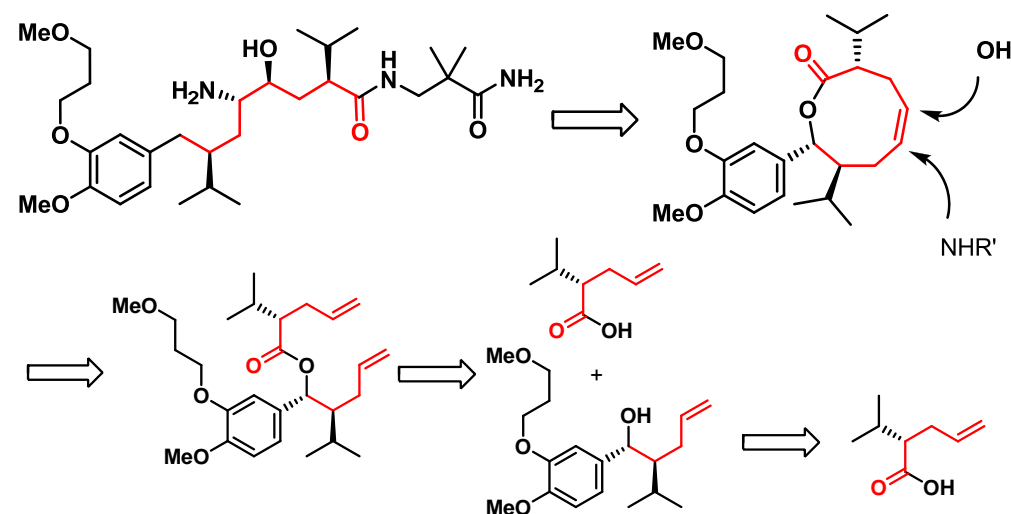
with Claridge, S.; Johnstone, S. *J. Org. Chem.* **2002**, *77*, 4261-4274

Synthetic route towards a Tekturna prototype: Beta-ketophosphonate route

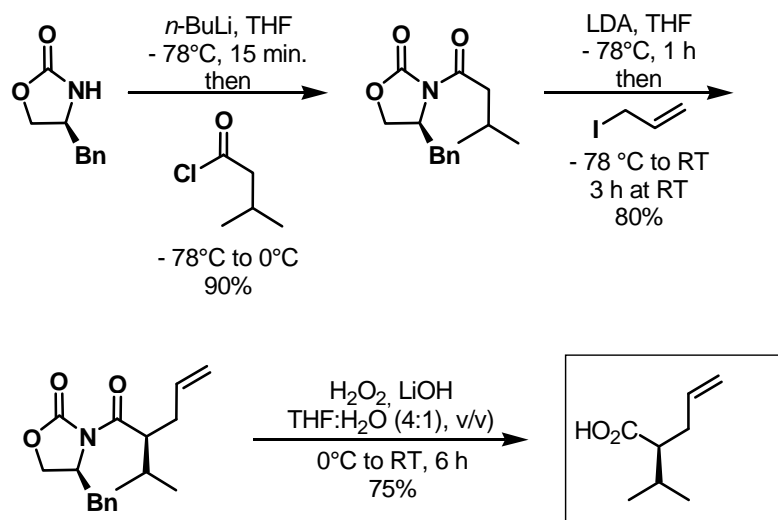


with Claridge, S.; Johnstone, S. *J. Org. Chem.* **2002**, *77*, 4261-4274

The Montreal macrocyclic total synthesis of Tekturna

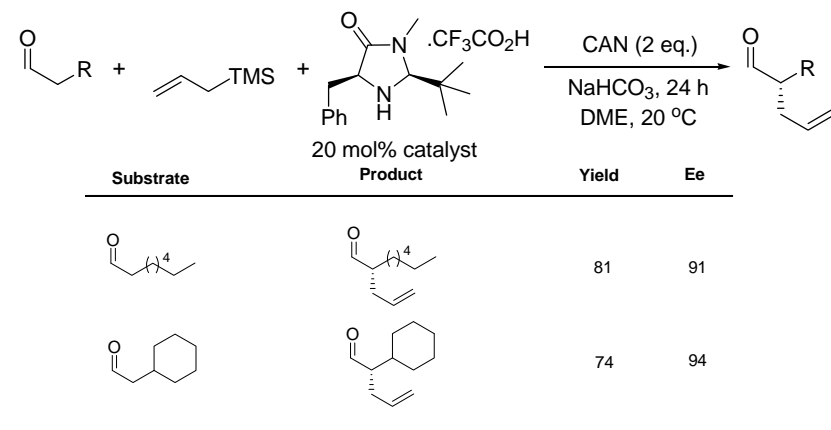


(2S)-Isopropyl-4-pentenoic acid: a diastereoselective approach

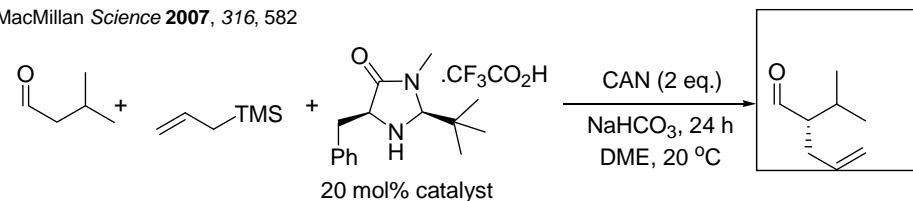


- Gage, J.R., Evans, D. A. *Org. Synth., Coll. Vol. VIII* **1991**, 339.
 - Hodgson, D. M. and all. *J. Chem. Soc. Perkin Trans 1* **1999**, 2911.

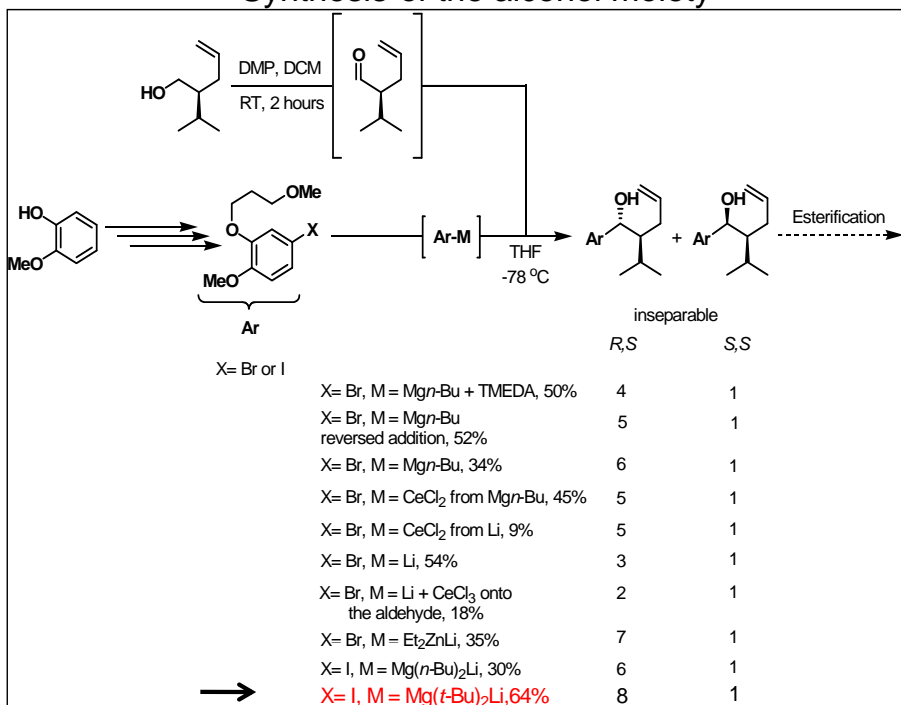
(2S)-Isopropyl-4-pentenoic acid: a catalytic enantioselective approach



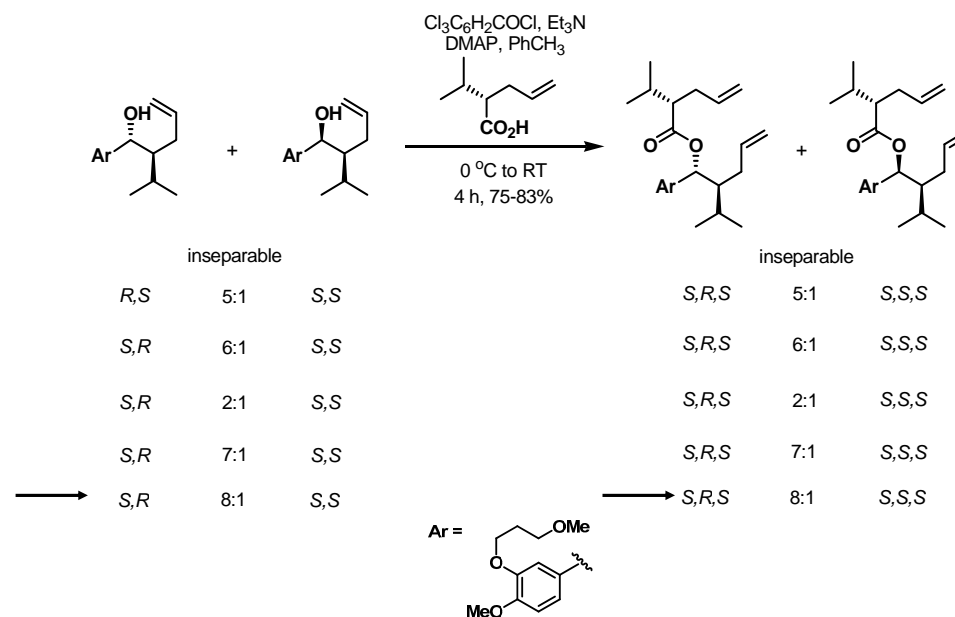
MacMillan *Science* **2007**, 316, 582



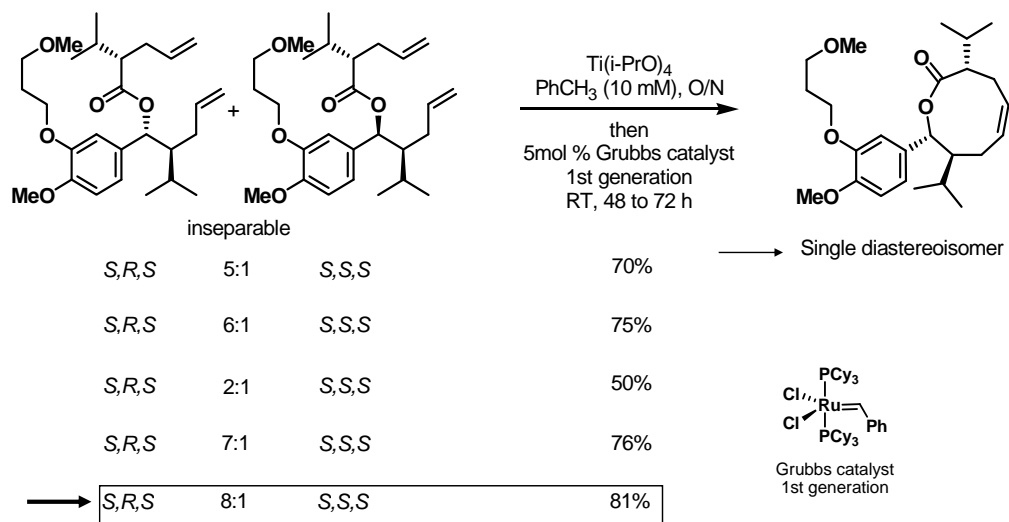
Synthesis of the alcohol moiety



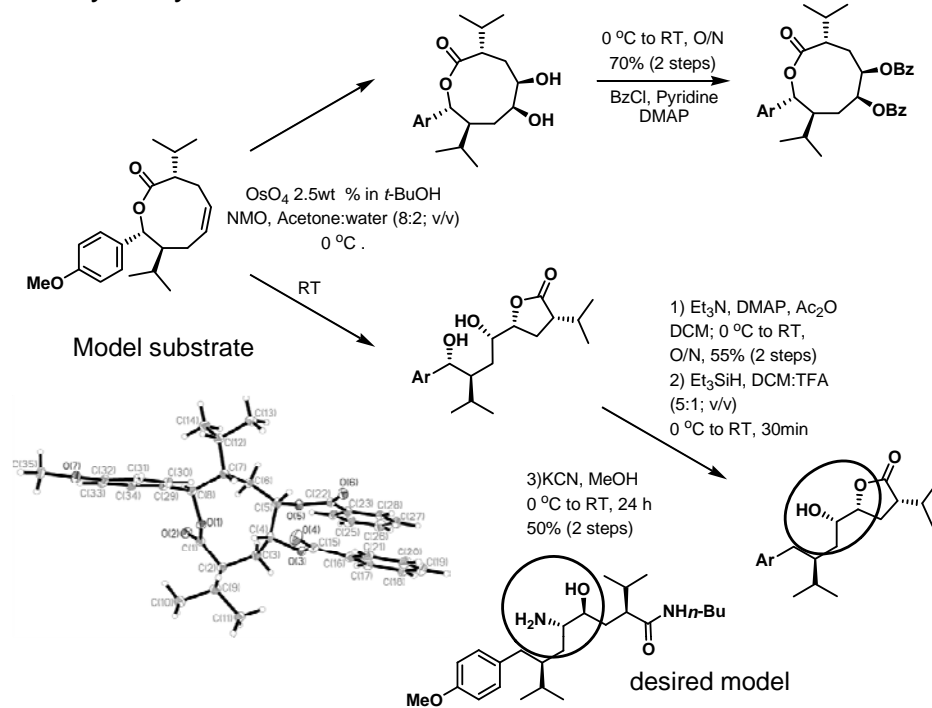
Esterification



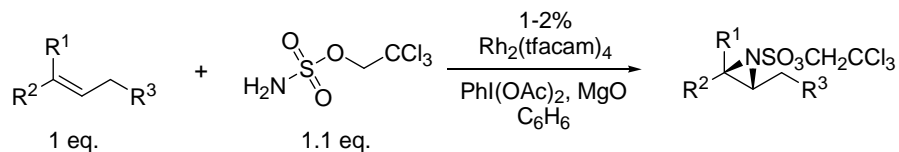
Ring closing metathesis reaction



Dihydroxylation reaction: confirmation of the stereochemistry

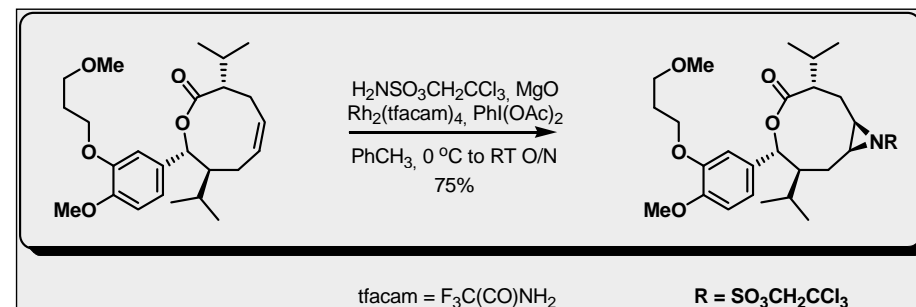
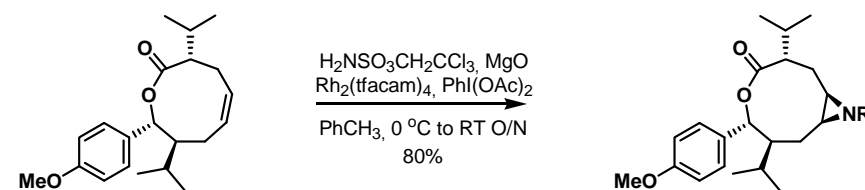


Du Bois catalytic olefin aziridination

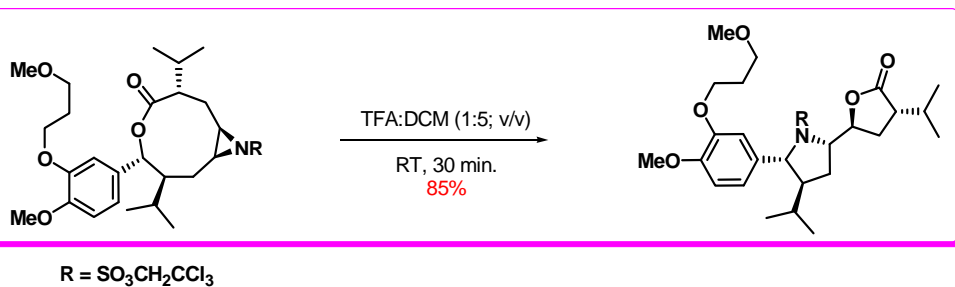
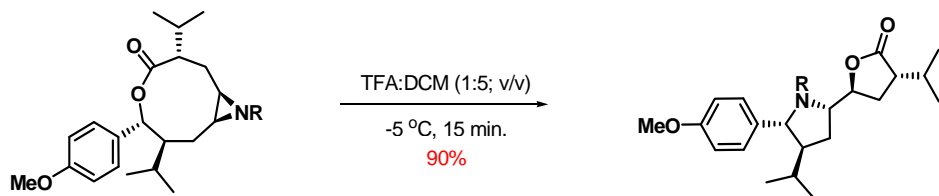


Substrate	Product	Yield
		85%
		85%
		82%
		72%
		84%

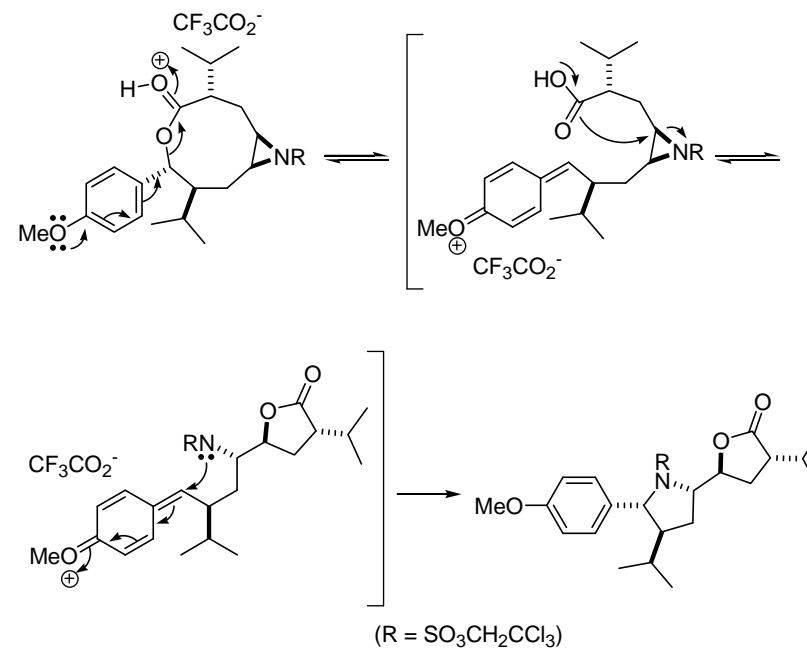
Du Bois aziridination reaction



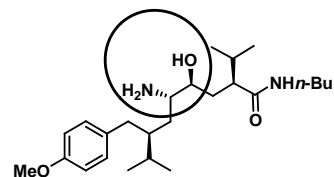
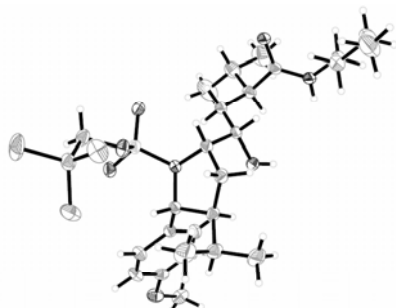
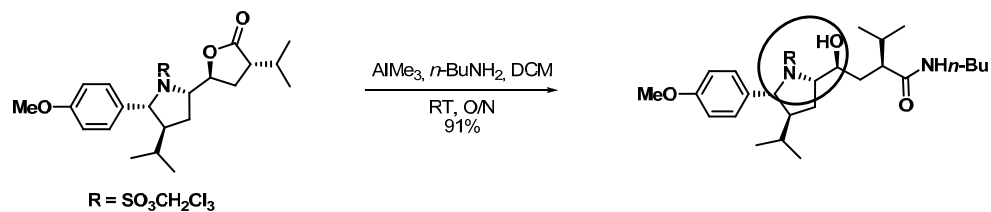
One-step ring contraction !!!



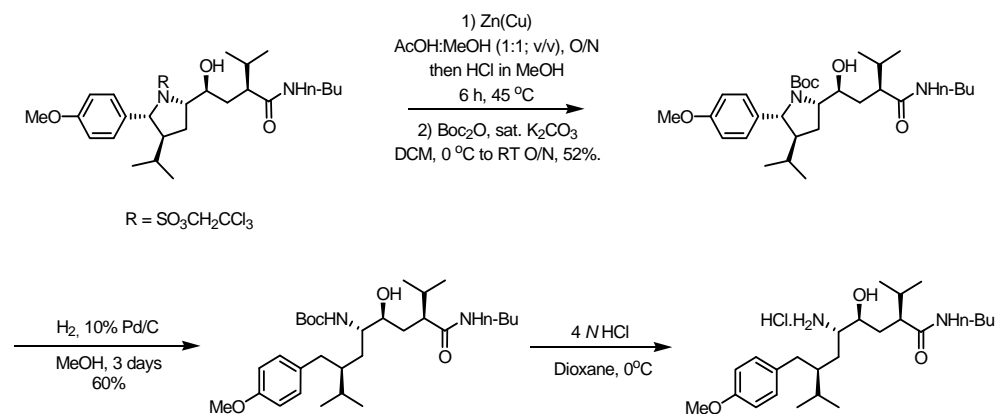
Proposed Mechanism for Ring Contraction



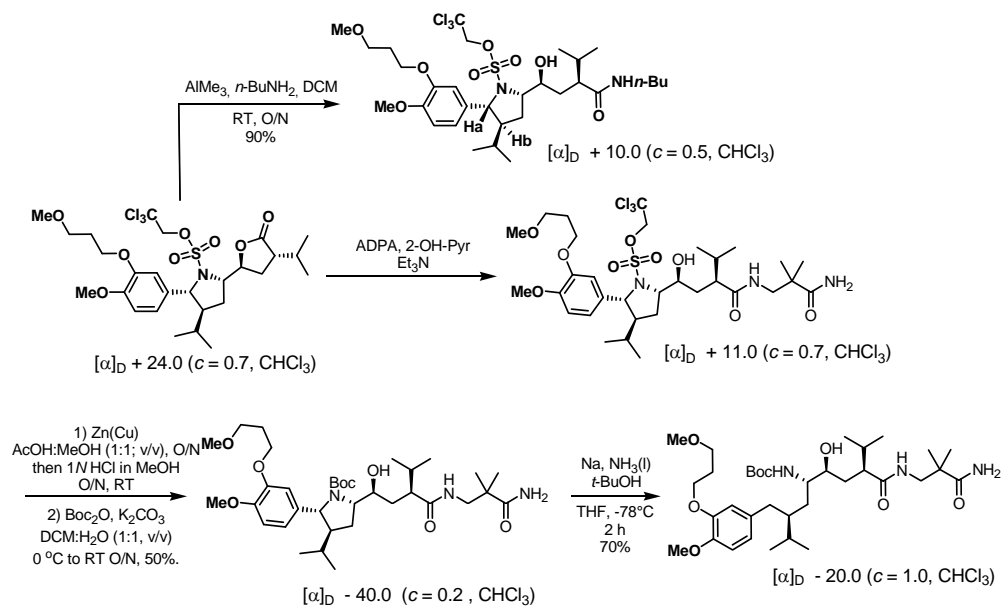
Amide formation: lactone opening and confirmation of the stereochemistry



A bioactive Tektura prototype

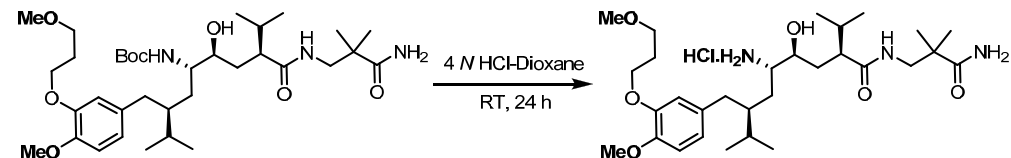


Onward to Tekturna



Completion of the total synthesis of Tekturna

(The Montreal route)



Tekturna

Less than 12 steps, 10 overall yield

with Guesné, S.; Chénard, E. *Org.Lett.* **2010**, *12*, 1816