Chiral tricyclic lactams as versatile scaffolds for alkaloid synthesis

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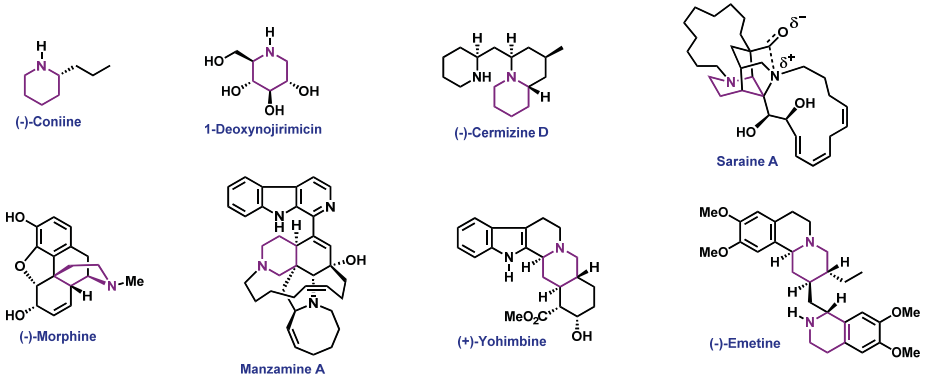
SINTEFARMA

I → B = U → B

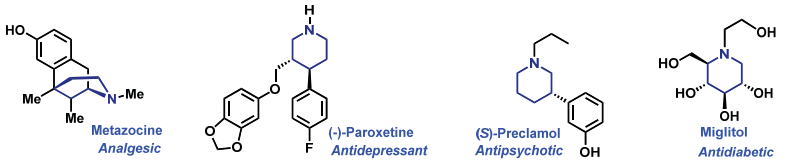
Natural Products

More than half of the known alkaloids contain piperidine rings



Bioactive compounds

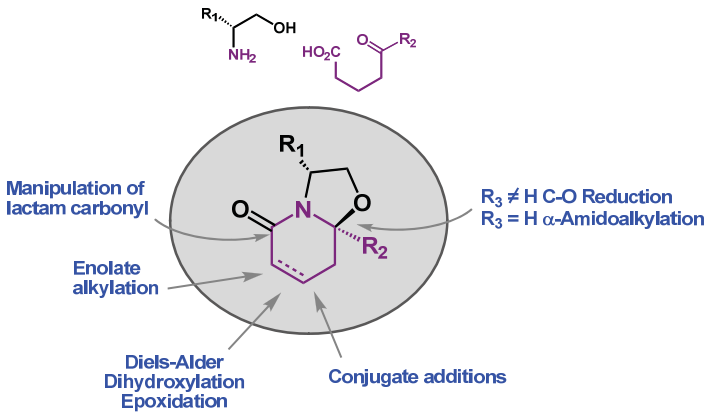
Thousands of references in chemical and patent literature to piperidine derivatives in clinical and preclinical research



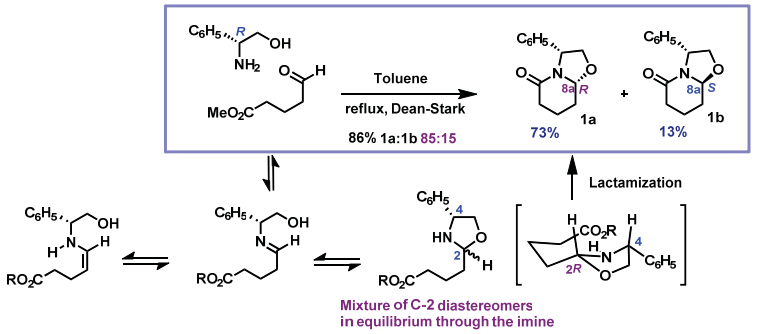
Chiral aminoalcohol derived bicyclic lactams
Enantiomeric scaffolds for the synthesis of piperidine derivatives

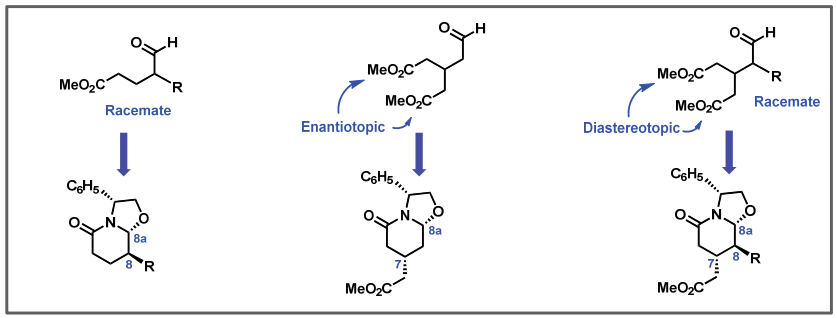
Lanny S. Liebeskind
J. Org. Chem. 2008, *73*, 882-888

In the **enantiomeric scaffolding strategy**, a conceptually simple core molecule of high enantiopurity that bears tactically versatile functionality is constructed. The resident functionality enables the general elaboration of the core molecule in ways that allow access to diverse families of important molecules.

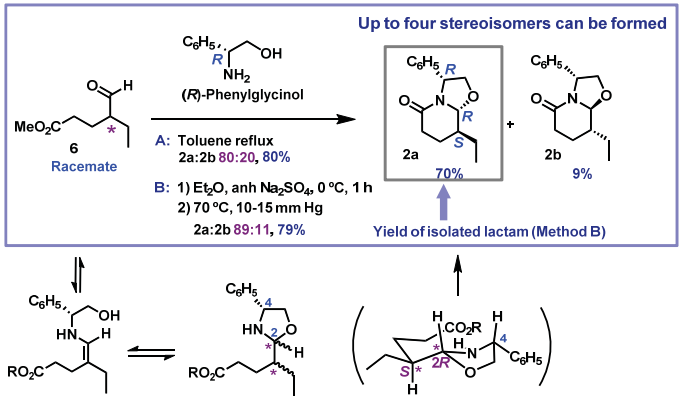


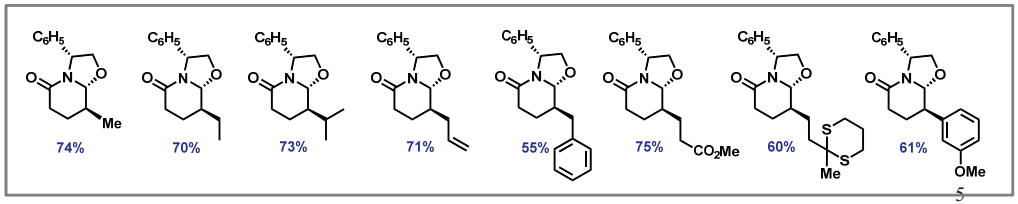
Chiral aminoalcohol derived lactams. The cyclocondensation reaction



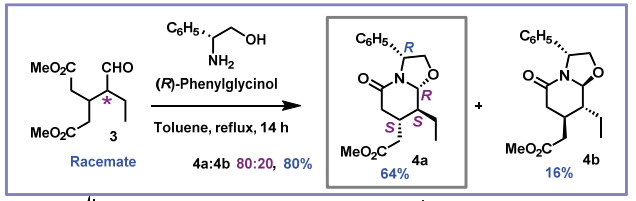


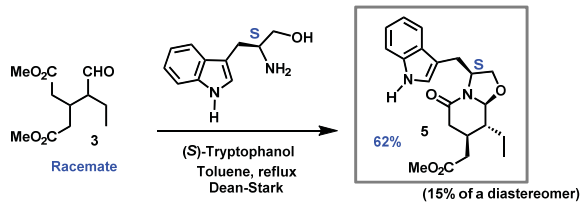
Cyclocondensation reactions of racemic aldehyde-esters



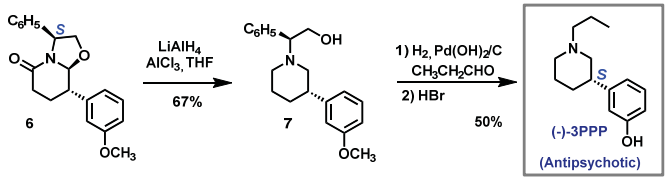


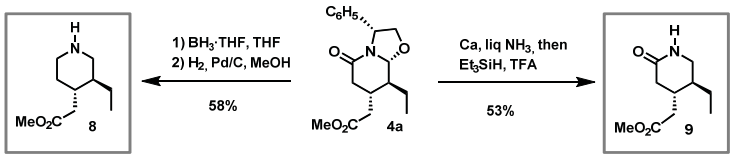
Cyclocondensation reactions of racemic aldehyde-diesters





Enantiopure piperidines from chiral substituted bicyclic lactams





Racemic or prochiral δ-oxo-acids

Two synthetic manipulations:

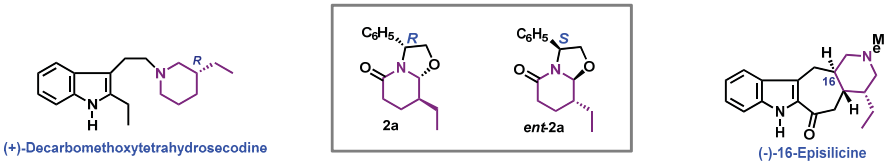
Cyclocondensation

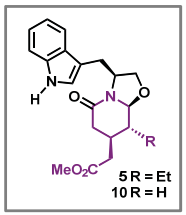
Removal of chiral inductor { **Reduction** / **Debenzylation**

Enantiopure piperidine derivatives

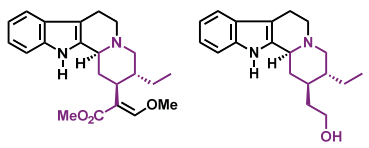
For reviews, see:
Chem.-Eur. J. **2006**, 12, 8198
Synlett **2011**, 143
Nat. Prod. Commun. **2011**, 6, 515
Chem.-Eur. J. **2011**, 17, 7724

Indole alkaloids from chiral substituted bicyclic lactams

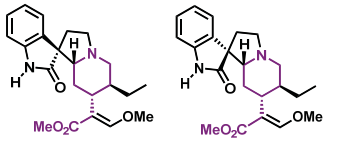




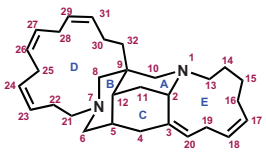
Corynanthe alkaloids



Oxindole alkaloids



Marine alkaloids: madangamines

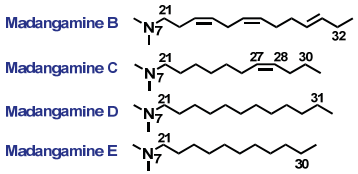


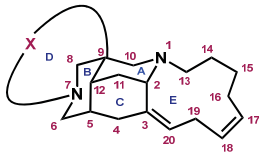
Madangamine A

Xestospongia
(Common name: barrel sponge)

Isolated by Andersen in 1994 from the marine sponge *Xestospongia ingens*
Cytotoxic alkaloid that exhibits inhibitory activity against a number different tumor cell lines
Andersen et al. *J. Am. Chem. Soc.* **1994**, *116*, 6007-6008

Madangamines B-E

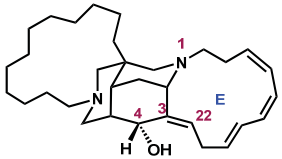




- **1998: Isolation of Madangamines B-E from the same sponge (*Xestospongia ingens*)**
- **No biological data have been reported**

Andersen et al. *J. Nat. Prod.* **1998**, *61*, 267-271

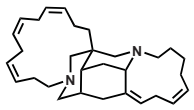
Madangamine F



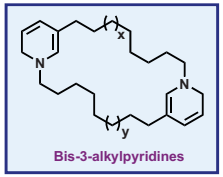
- **2007: Isolation of Madangamine F from the marine sponge *Pachychalina alcaloidifera***
- **Cytotoxic activity against a number different tumor cell lines**

Berlinck et al. *J. Nat. Prod.* **2007**, *70*, 538-543

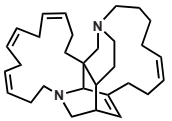
3-Alkylpyridine alkaloids isolated from marine sponges in the Order Haplosclerida



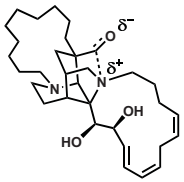
Madangamine A



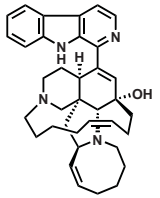
Bis-3-alkylpyridines



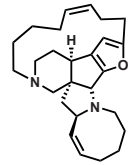
Ingenamine F



Saraine A



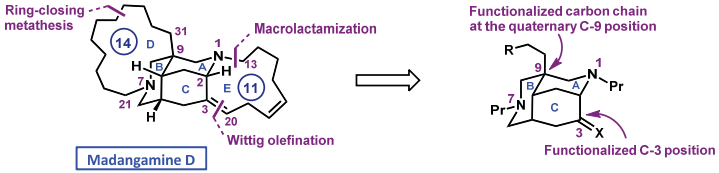
Manzamine A



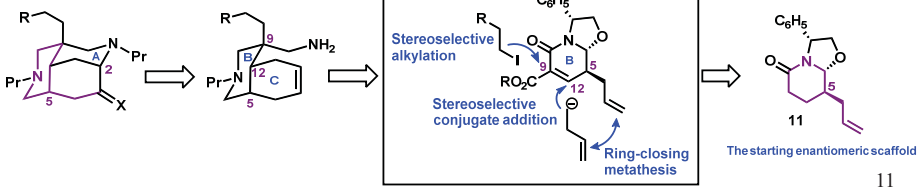
Nakadomarin A

Total synthesis of madangamine D. Synthetic strategy

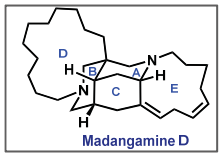
Assembly of the madangamine macrocyclic rings D and E

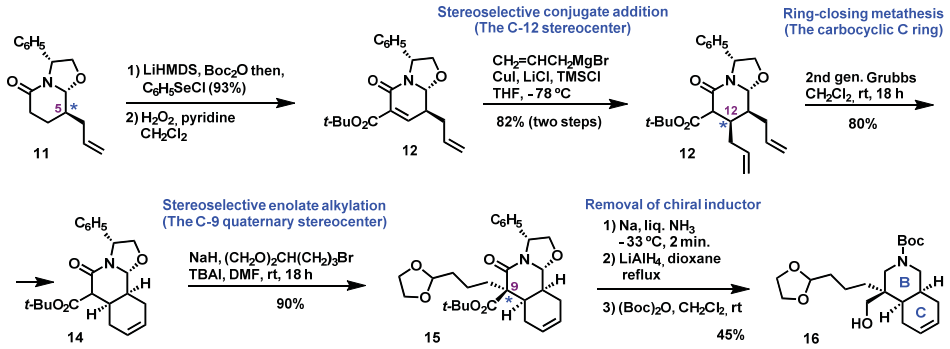


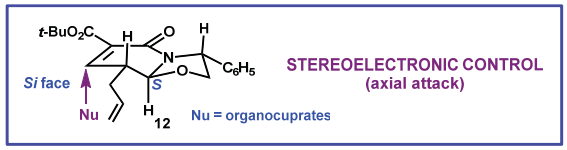
Construction of the diazatricyclic core



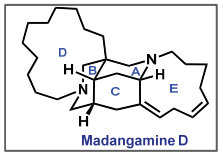
Madangamine D
Construction of the diazatricyclic core

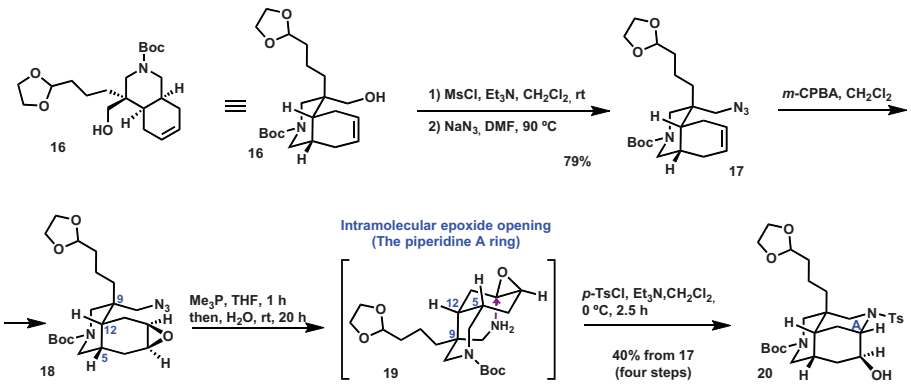




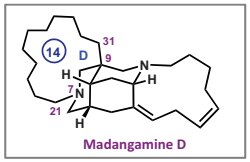


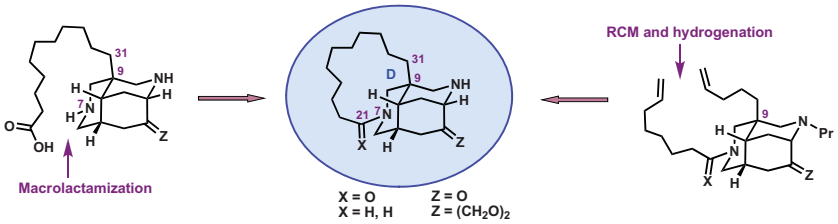
Madangamine D
Construction of the diazatricyclic core

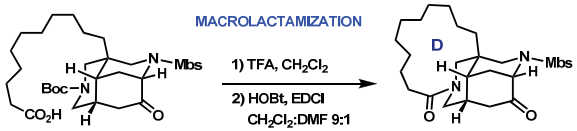




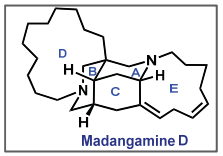
The D ring of madangamine D

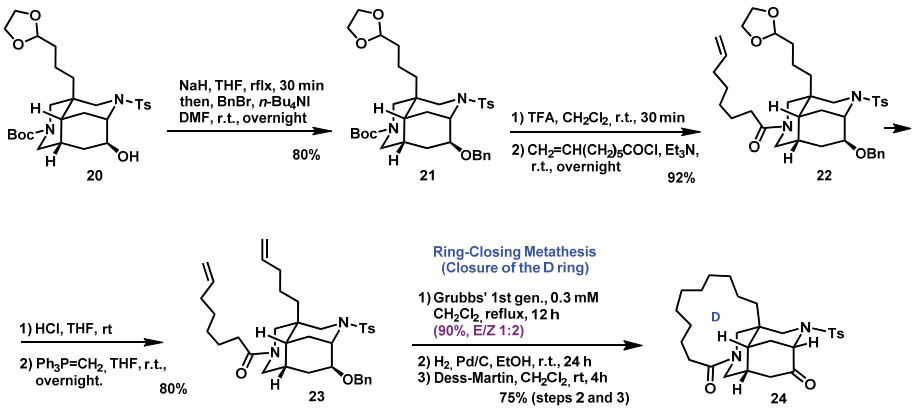




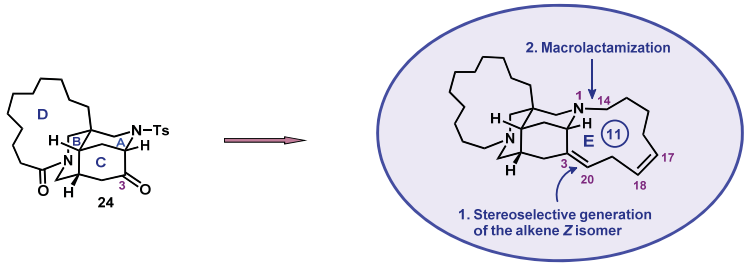


Closure of the macrocycle D of madangamine D

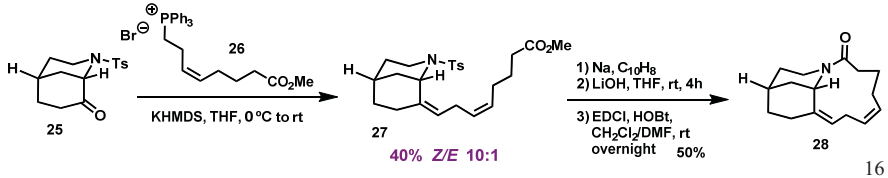




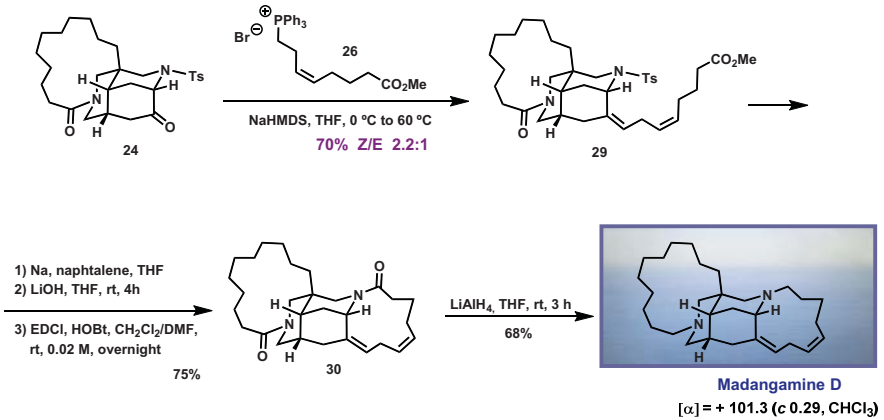
Closure of the macrocycle E of madangamines



Model studies
Stereoselective Wittig (Z)-olefination



The E ring of madangamines
Total synthesis of Madangamine D



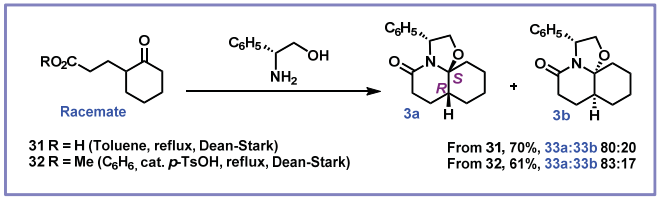
Angew. Chem.-Int.Ed. **2014**, *53*, 6202

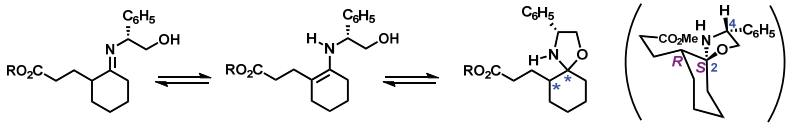
Pharma Mar — Grupo Zeltia

In vitro* cytotoxic inhibitory activity against *tumor cell lines

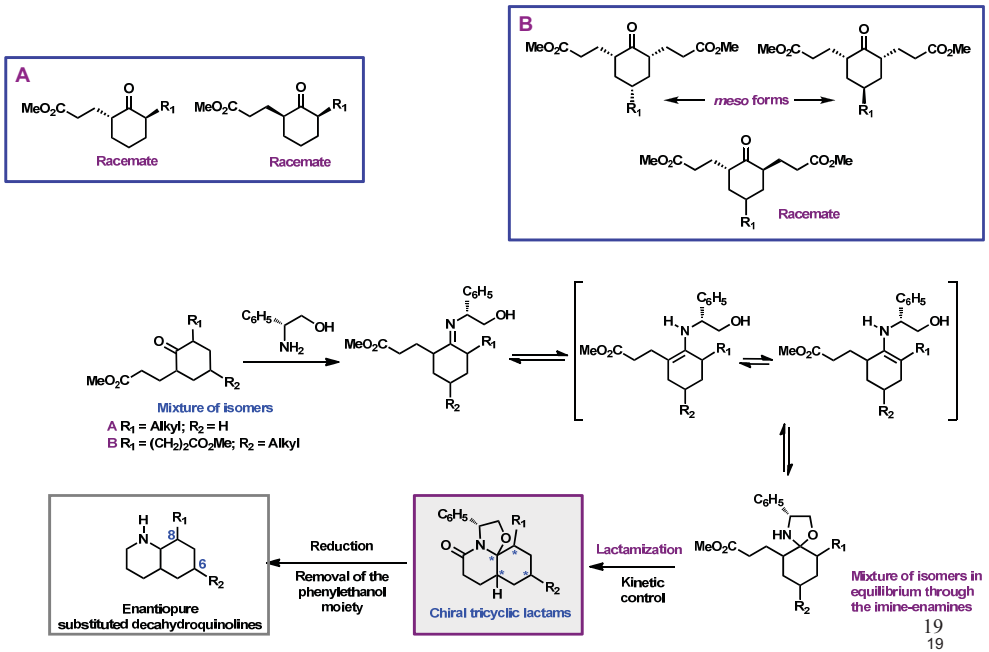
- COLON HT29 (GI_{50} 4.4 µg/mL)
- PANCREAS PSN1 (GI_{50} 7.4 µg/mL)
- LUNG NSCLC (GI_{50} >10 µg/mL)
- BREAST MDA-MB-231 (GI_{50} >10 µg/mL)

Chiral aminoalcohol-derived tricyclic lactams
Cyclocondensation of 2-cyclohexanonepropionate with (*R*)-phenylglycinol

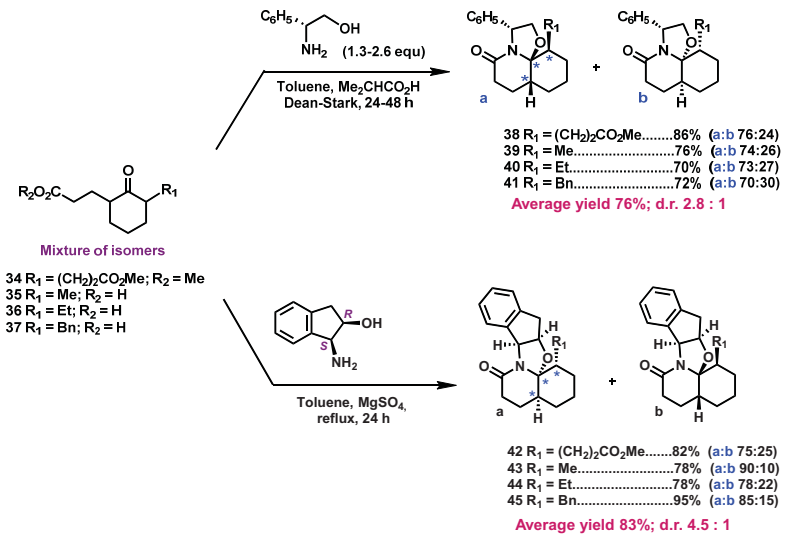




Chiral aminoalcohol derived tricyclic lactams

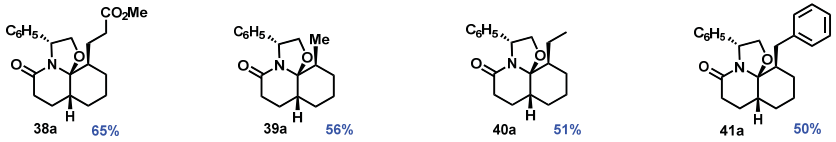


Chiral aminoalcohol derived tricyclic lactams
Results

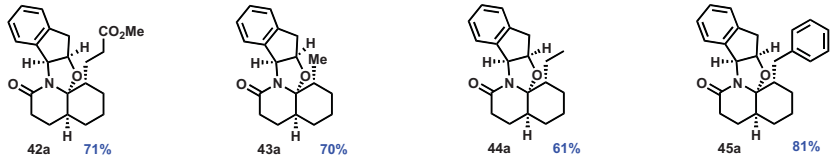


Chiral aminoalcohol derived tricyclic lactams
Results

Yield of isolated product after column chromatography

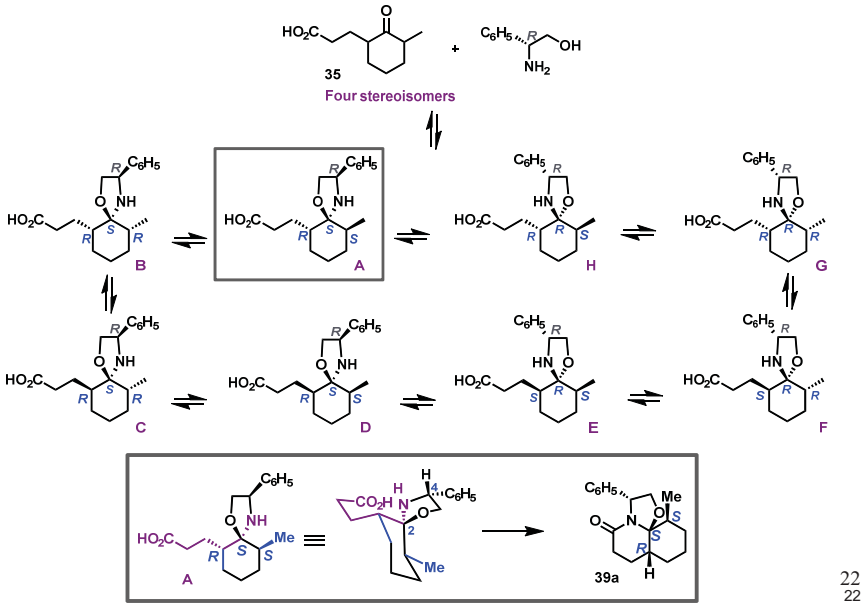


Calculated yield of major isomer (ratio of isomers a:b determined by ^{1}H-NMR)

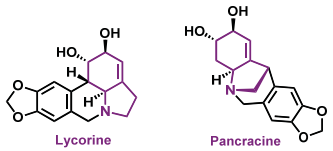


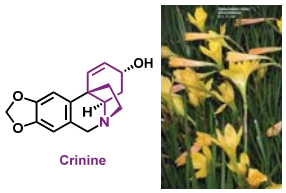
Chem.-Eur. J. **2013**, *19*, 16044

Chiral aminoalcohol derived tricyclic lactams
Mechanistic considerations

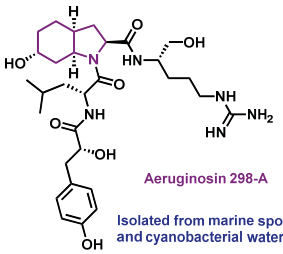


Amaryllidaceae alkaloids

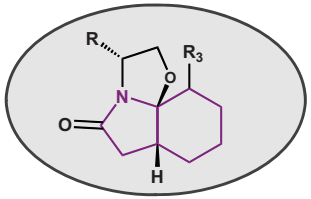


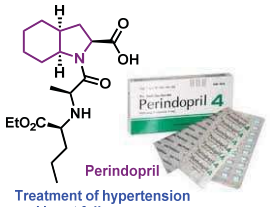


Aeruginosins



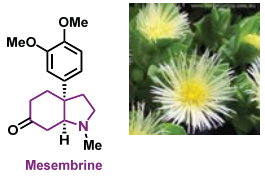
Isolated from marine sponges and cyanobacterial waterblooms



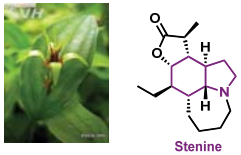


Treatment of hypertension and heart failure

Scelentium alkaloids

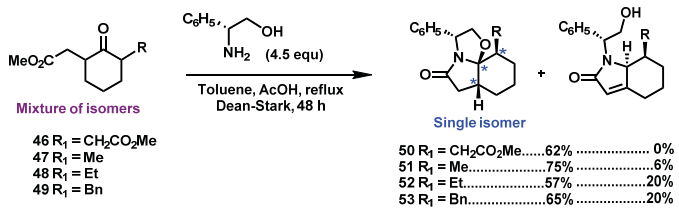


Stemona alkaloids



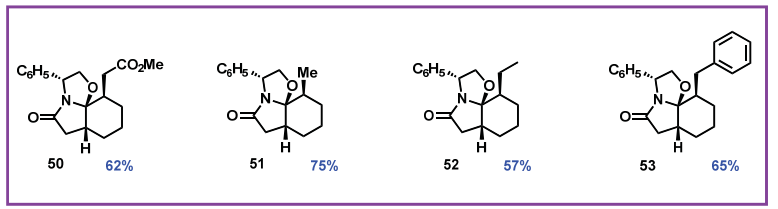
Erythrina alkaloids

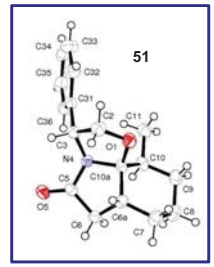
Chiral aminoalcohol derived tricyclic lactams
Results



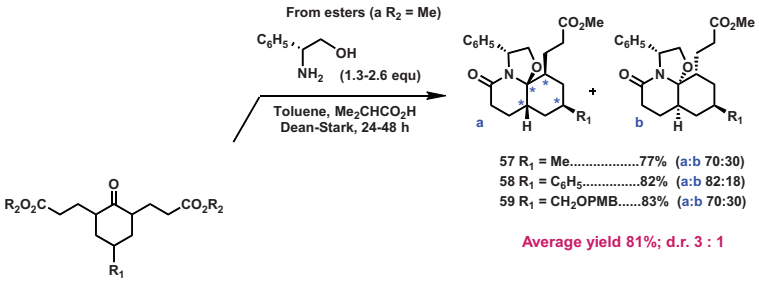
46 R_1 = CH_2CO_2Me
47 R_1 = Me
48 R_1 = Et
49 R_1 = Bn

50 R_1 = CH_2CO_2Me.....62% 0%
51 R_1 = Me.....75% 6%
52 R_1 = Et.....57% 20%
53 R_1 = Bn.....65% 20%





Chiral aminoalcohol derived tricyclic lactams
Results



57 R_1 = Me.....77% (a:b 70:30)
58 R_1 = C_6H_5.....82% (a:b 82:18)
59 R_1 = CH_2OPMB.....83% (a:b 70:30)

Average yield 81%; d.r. 3 : 1

60 R_1 = Me.....84% (a:b 70:30)
61 R_1 = C_6H_5.....95% (a:b 86:14)

Average yield 89%; d.r. 3.5 : 1

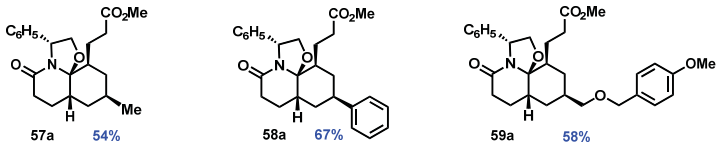
(1*S*,2*R*)-(-)-*cis*-1-Amino-2-indanol *versus* (*R*)-phenylglycinol

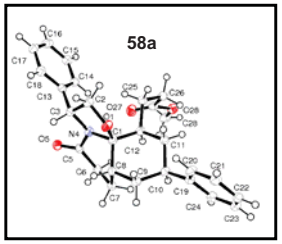
Better yields and stereoselectivity.

Difficult separation of diastereomeric tricyclic lactams by column chromatography.

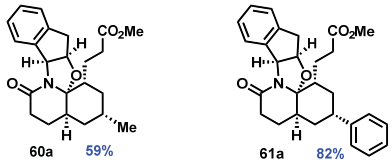
Chiral aminoalcohol derived tricyclic lactams
Results

Yield of isolated product after column chromatography



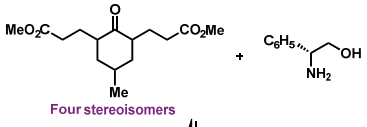


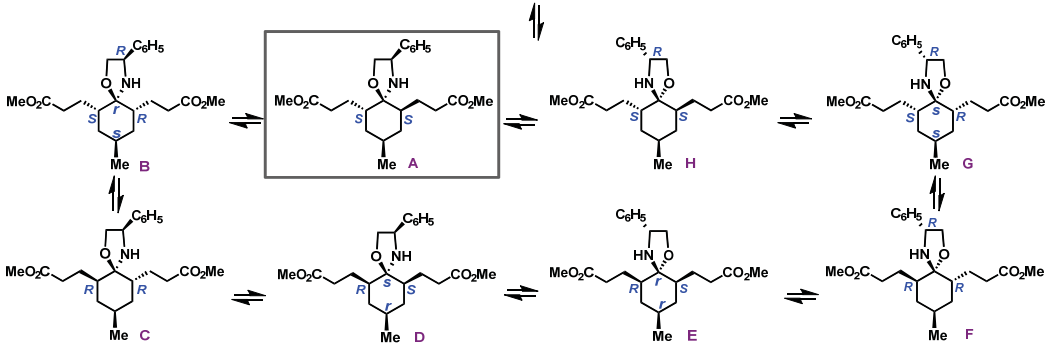
Calculated yield of major isomer (ratio of isomers a:b determined by ^{1}H-NMR)

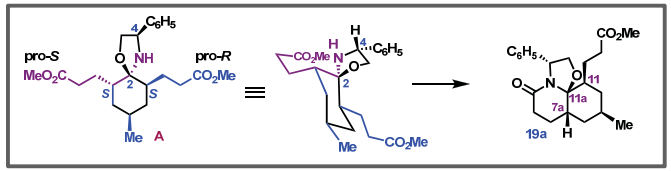


Chem.-Eur. J. **2013**, *19*, 16044

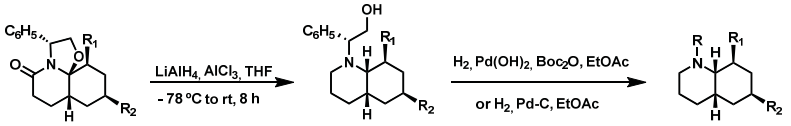
Chiral aminoalcohol derived tricyclic lactams
Mechanistic considerations



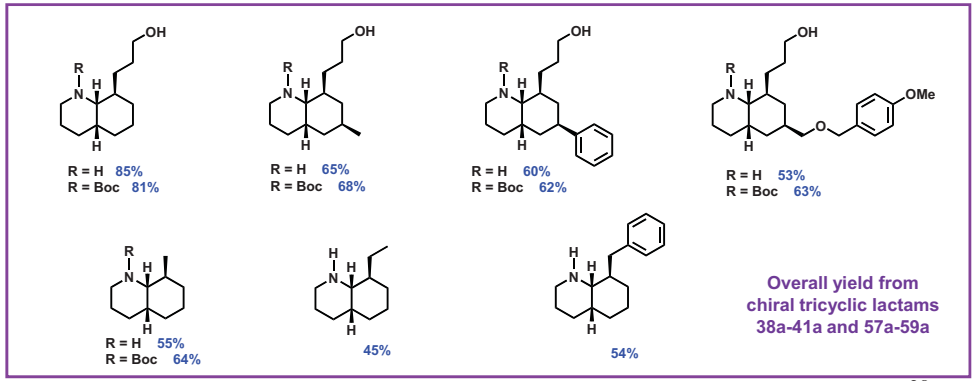




cis-Decahydroquinolines from chiral aminoalcohol derived tricyclic lactams



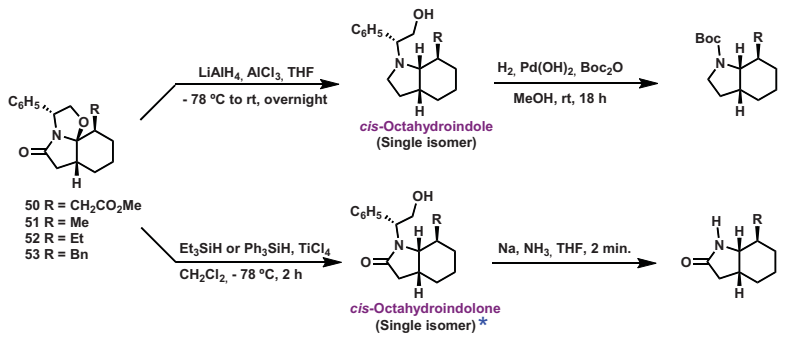
39a R_1 = Me, R_2 = H
40a R_1 = Et, R_2 = H
41a R_1 = Bn, R_2 = H
38a R_1 = $(CH_2)_2CO_2Me$, R_2 = H
57a R_1 = $(CH_2)_2CO_2Me$, R_2 = Me
58a R_1 = $(CH_2)_2CO_2Me$, R_2 = C_6H_5
59a R_1 = $(CH_2)_2CO_2Me$, R_2 = CH_2OPMB

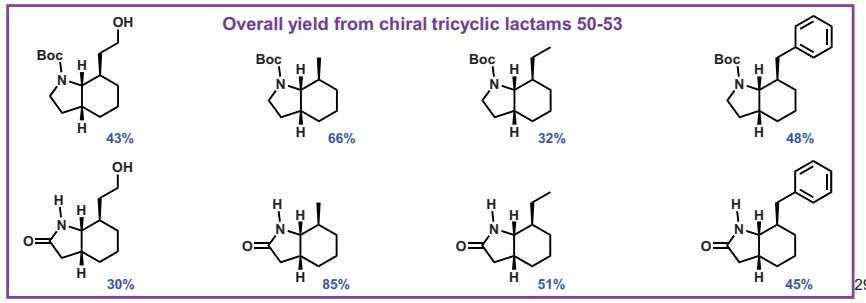


Overall yield from chiral tricyclic lactams 38a-41a and 57a-59a

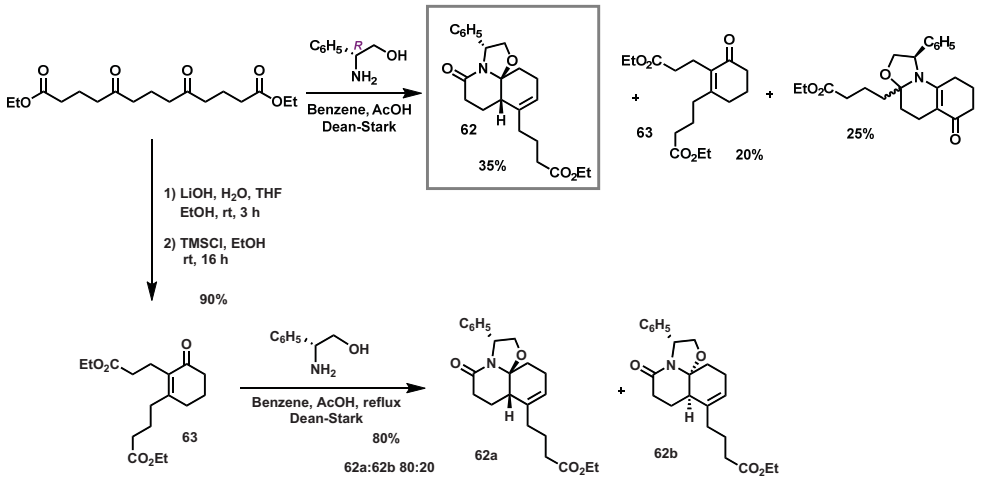
Chem.-Eur. J. **2013**, *19*, 16044

cis-Octahydroindoles from chiral aminoalcohol derived tricyclic lactams

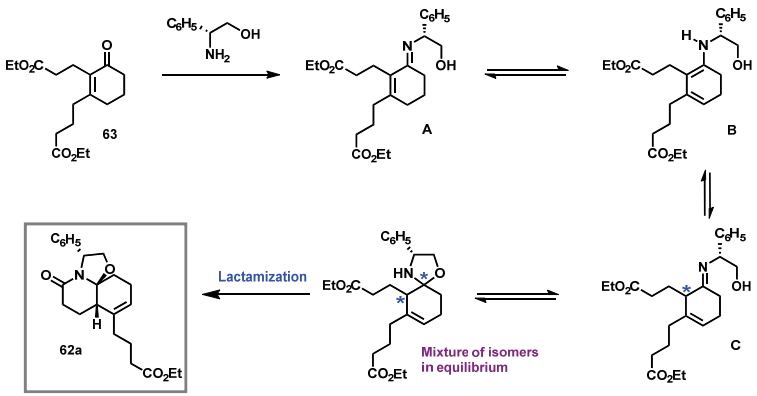


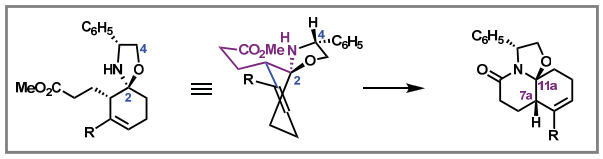


Unsaturated chiral tricyclic lactams. Preliminary studies

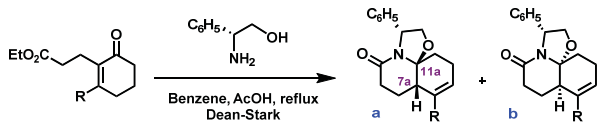


Chiral aminoalcohol derived tricyclic lactams
Mechanistic considerations





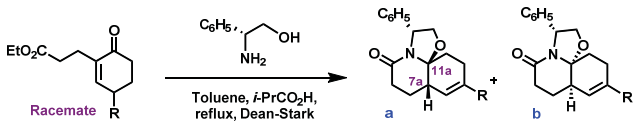
Chiral aminoalcohol derived tricyclic lactams
Results



64 R = Me
65 R = $(CH_2)_3CH_3$
63 R = $(CH_2)_3CO_2Me$
66 R = $(CH_2)_2CH(O_2C_2H_4)$
67 R = $(CH_2)_5OTBDPS$
68 R = C_6H_4-*p*-OMe

69 R = Me.....89% (a:b 80:20)
70 R = $(CH_2)_3CH_3$.....76% (a:b 80:20)
62 R = $(CH_2)_3CO_2Me$.....80% (a:b 80:20)
71 R = $(CH_2)_2CH(O_2C_2H_4)$.....77% (a:b 85:15)
72 R = $(CH_2)_5OTBDPS$.....51% (a:b 78:22)
73 R = C_6H_4-*p*-OMe.....77% (a:b 78:22)

Average yield 75%; d.r. 4 : 1



74 R = Me
75 R = $(CH_2)_2CH_3$
76 R = CO_2Et
77 R = CH_2OPMB

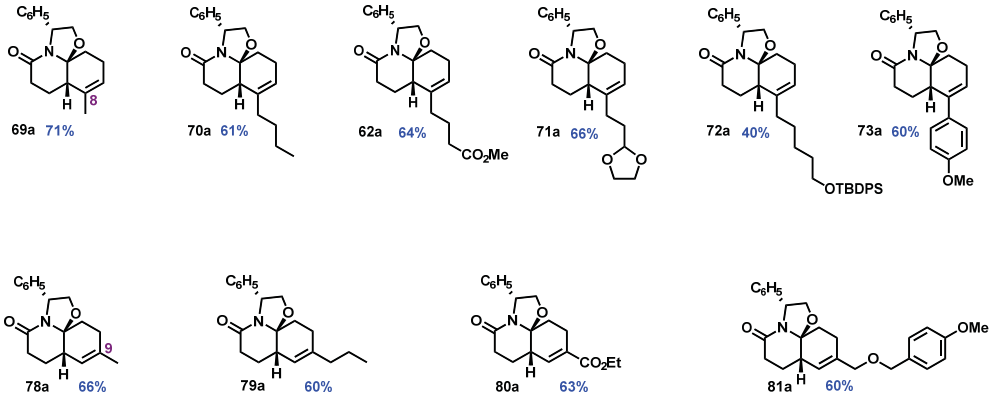
78 R = Me.....82% (a:b 80:20)
79 R = $(CH_2)_2CH_3$.....75% (a:b 80:20)
80 R = CO_2Et.....78% (a:b 81:19)
81 R = CH_2OPMB.....76% (a:b 79:21)

Average yield 77%; d.r. 4 : 1

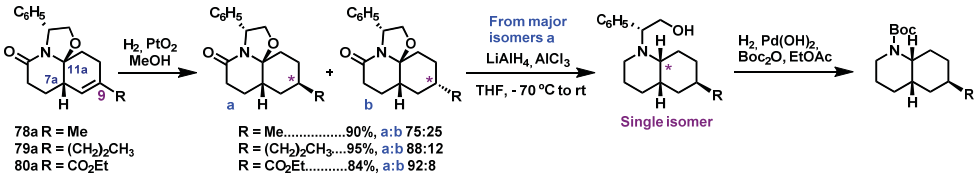
J. Org. Chem. **2009**, *74*, 1794

Chiral aminoalcohol derived tricyclic lactams
Results

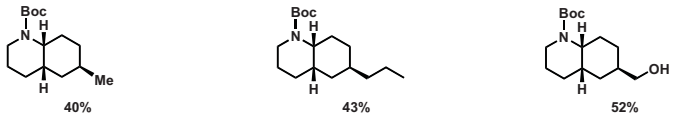
Yield of isolated product after column chromatography



Chiral tricyclic lactams. Synthetic transformations

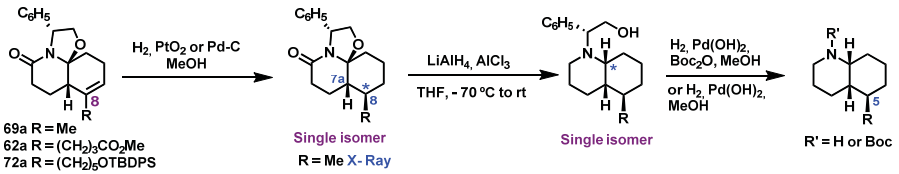


Overall yield from tricyclic lactam (Three steps)



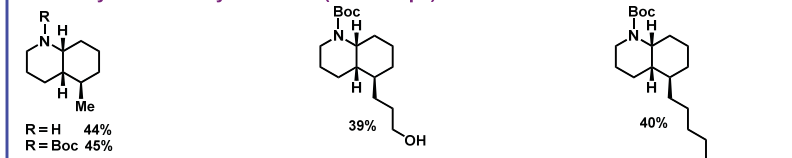
Org. Lett. **2012**, *14*, 210

Chiral tricyclic lactams. Synthetic transformations



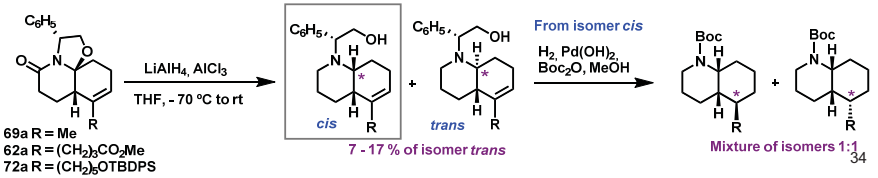
C-5 Substituted *cis*-decahydroquinolines

Overall yield from tricyclic lactam (Three steps)

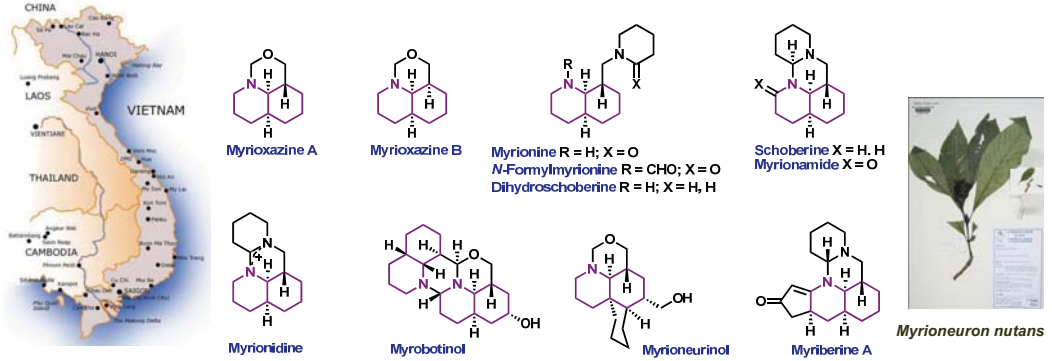


J. Org. Chem. **2009**, *74*, 1794

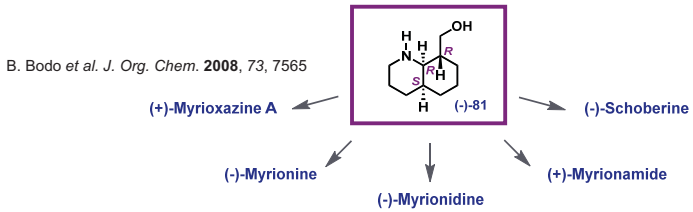
An alternative route shorter but less efficient



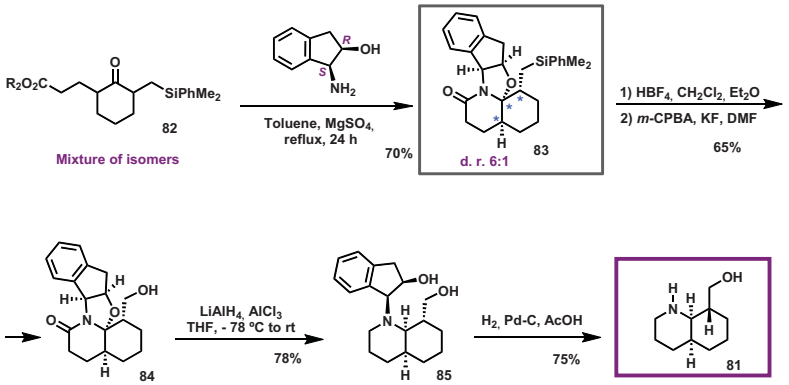
Myrioneuron alkaloids



Isolated from plants of the genus *Myrioneuron* R. Br. (Rubiaceae) in North Vietnam.
Some of them show inhibition on KB cell proliferation and remarkable antimalarial activities



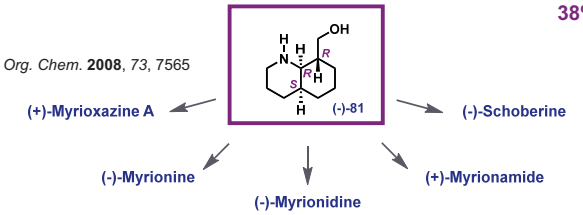
Formal synthesis of *Myrioneuron* alkaloids



Chem.-Eur. J. **2013**, *19*, 16044

Four steps from 83
38% overall yield

B. Bodo *et al. J. Org. Chem.* **2008**, *73*, 7565



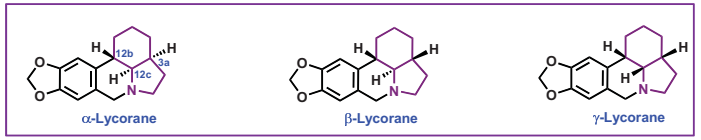
Lycorine alkaloids

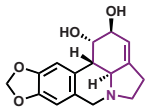
Several members possess potent biological activities:
- Antiviral
- Antineoplastic
- Insect antifeedant activity
- Plant growth inhibition
- Disruption of protein synthesis

Isolated from Amaryllidaceae plant species:
- *Lycoris*
- *Pancratium*
- *Narcissus*
- *Galanthus*
- *Zephyranthes*
- *Haemanthus*

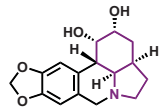
Zephyrantes candida

Narcissus p.





Lycorine
(First isolated in 1877 from *Narcissus pseudonarcissus*)

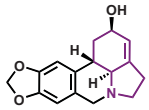


Zephiranthine

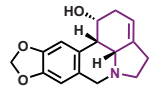
Kirkine

Galanthus nivalis

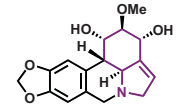
Lycoris radiata



1-Deoxylycorine

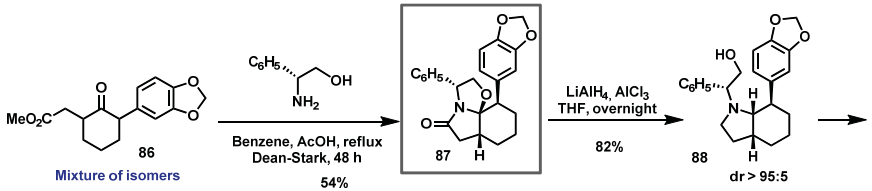


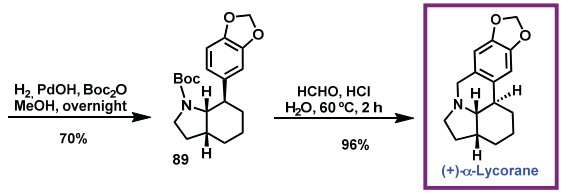
Fortucine



Giminorine

Total synthesis of (+)-α-lycorane

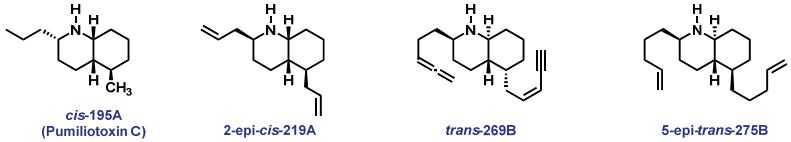




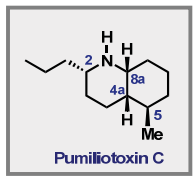
Three steps from 87
30% overall yield

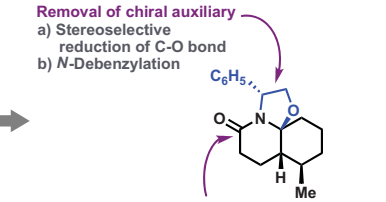
Amphibian alkaloids

Dendrobatidae
(poison arrow frogs)

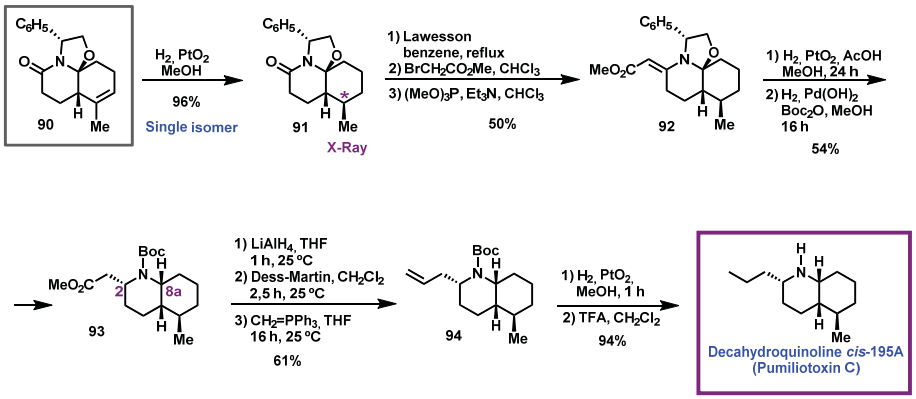


Enantioselective synthesis of Pumiliotoxin C





Synthesis of the amphibian alkaloid pumiliotoxin C

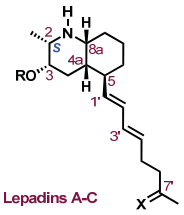


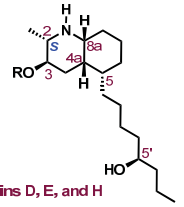
Ten steps from 90
15% overall yield

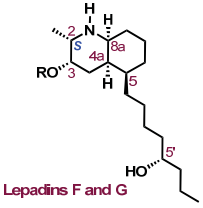
J. Org. Chem. **2010**, *75*, 3794

Marine alkaloids

The lepadins





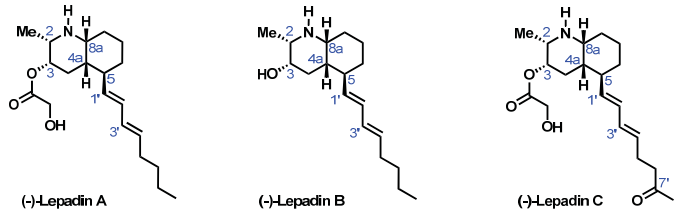


(-)-Lepadin A X = H, H; R =
(-)-Lepadin B X = H, H; R = H
(-)-Lepadin C X = O; R =

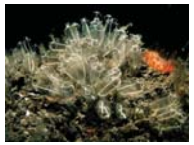
(+)-Lepadin D R = H
(-)-Lepadin E R =
(+)-Lepadin H R =

(+)-Lepadin F R =
(-)-Lepadin G R =

Lepadins A-C



Flatworms
Prostheceraeus vittatus
(Didemnidae)



Tunicates
Clavelina lepadiformis
(Clavelinidae)

Stereochemical pattern of lepadins A-C

cis-Decahydroquinoline

C-2/C-3 *cis*
C-3/C-4a *cis*
C-4a/C-5 *trans*

First isolation

Lepadin A: Bert Steffan (1991) from the tunicate *Clavelina lepadiformis* (North Sea, Helgolan island)

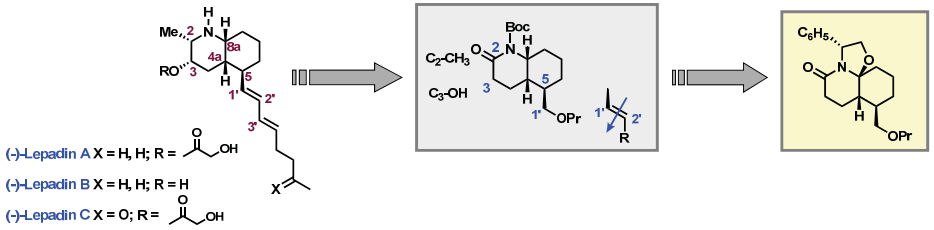
Lepadins B and C: Raymond J. Andersen (1995) from the flatworm *Prostheceraeus vittatus* (North Sea, Bergen, Norway)

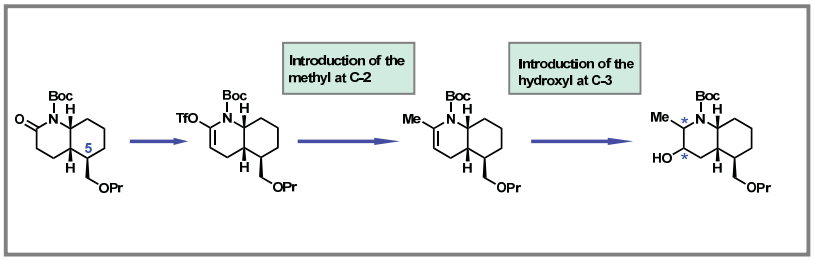
Biological activity

Lepadins A and B exhibit significant *in vitro* cytotoxicity against several human cancer cell lines

Lepadin B is a potent blocker for neuronal nicotinic acetylcholine receptors (nAChR's)

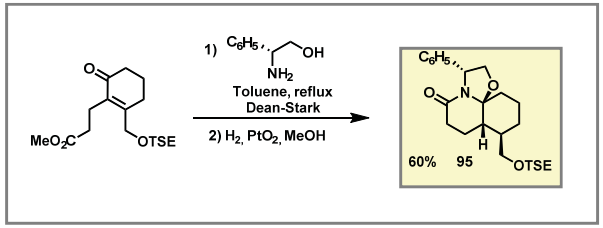
Enantioselective synthesis of lepadins A-C. Synthetic strategy

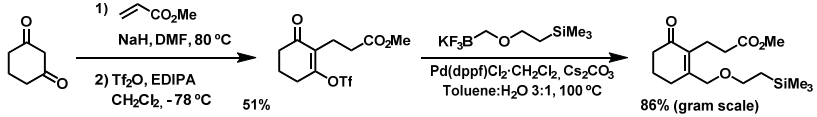




Enantioselective synthesis of lepadins A, B and C

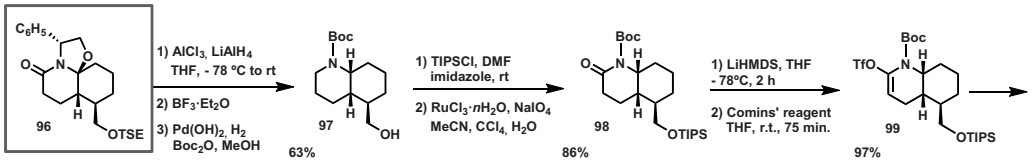
The starting enantiomeric scaffold





Enantioselective synthesis of lepadins A, B and C

Removal of the phenylethanol moiety of chiral inductor

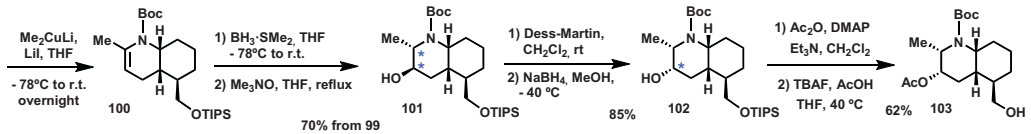


54% overall yield from tricyclic lactam 96

Introduction of the C_2-Me and C_3-OH

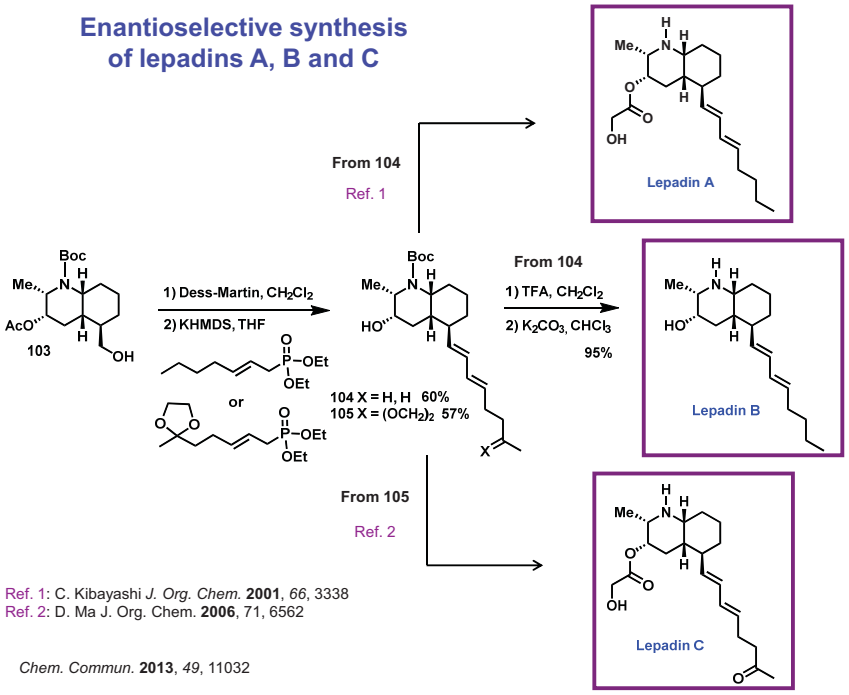
Inversion of the C-3 configuration

Protecting groups



58% overall yield from *cis*-decahydroquinolone 98

Enantioselective synthesis of lepadins A, B and C



Ref. 1: C. Kibayashi *J. Org. Chem.* **2001**, *66*, 3338
Ref. 2: D. Ma J. Org. Chem. **2006**, 71, 6562

Chem. Commun. **2013**, *49*, 11032

Chiral amino-alcohol derived lactams as versatile scaffolds for alkaloid synthesis