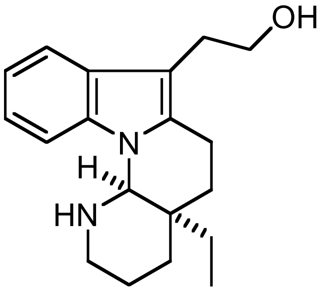
Total Synthesis of (+/-)-Goniomitine via a Formal Nitrile/Donor-Acceptor Cyclopropane [3 + 2] Cyclization

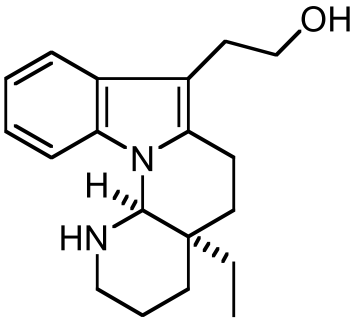


(-)-Goniomitine

Christian L. Morales and Brian Pagenkopf*
Organic Letters, ASAP

Current Literature
Jennifer Davoren
January 5, 2008

Background

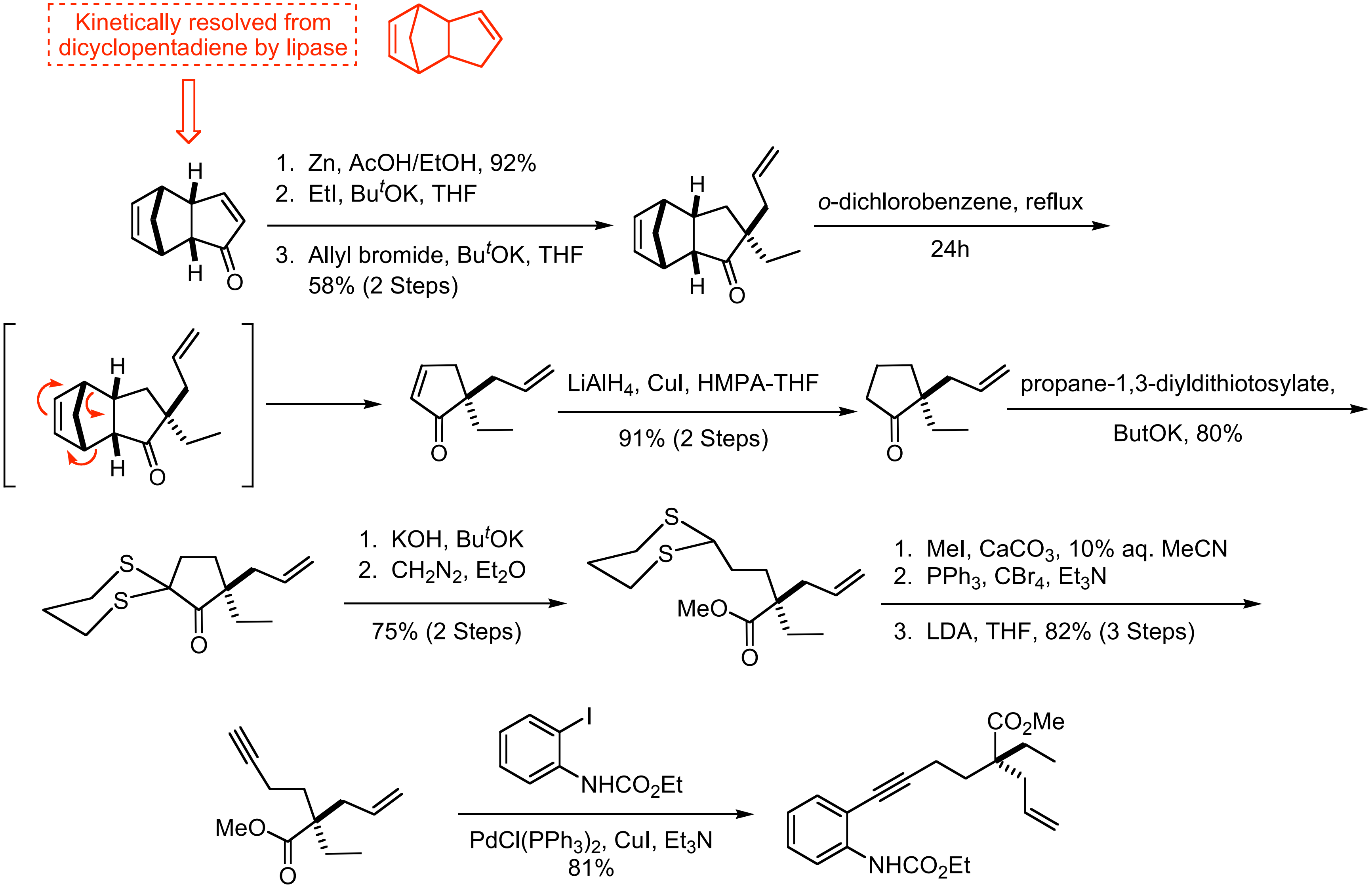


(-)-Goniomitine

- Isolated in 1987 from the root bark of *Gonioma malagasy*
- Molecular formula determined by HRMS
- λ_{max} (EtOH) 228 and 291 nm were consistent with an indolinic chromophore
- OH and NH groups present were determined by IR 3200 and 3450 cm^{-1} respectively
- Remainder of the structure was elucidated by NMR and partial synthesis
- Absolute stereochemistry was unknown, but tentatively assigned based on analogy with similar natural products within the class
- No known biological activity, but some analogs have demonstrated weak cytotoxicity toward L1210 leukemia cells

Isolation paper: Husson, H.P; *Tetrahedron Lett,* **1987**, 2123-2126

First Total Synthesis of (-)-Goniomitine



Kinetically resolved from dicyclopentadiene by lipase

1. Zn, AcOH/EtOH, 92%
2. EtI, Bu^{t}OK, THF
3. Allyl bromide, Bu^{t}OK, THF 58% (2 Steps)

o-dichlorobenzene, reflux

24h

LiAlH$_4$, CuI, HMPA-THF

91% (2 Steps)

propane-1,3-diyldithiotosylate,

ButOK, 80%

1. KOH, Bu^{t}OK
2. CH_2N_2, Et_2O

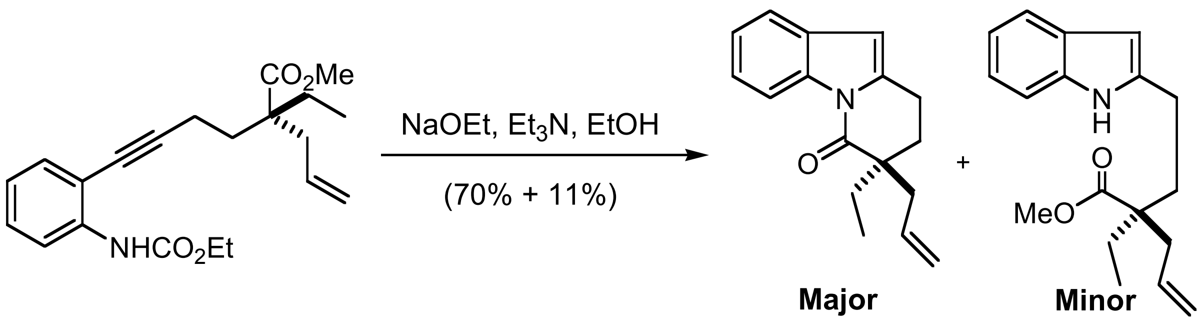
75% (2 Steps)

1. MeI, $CaCO_3$, 10% aq. MeCN
2. PPh_3, CBr_4, Et_3N
3. LDA, THF, 82% (3 Steps)

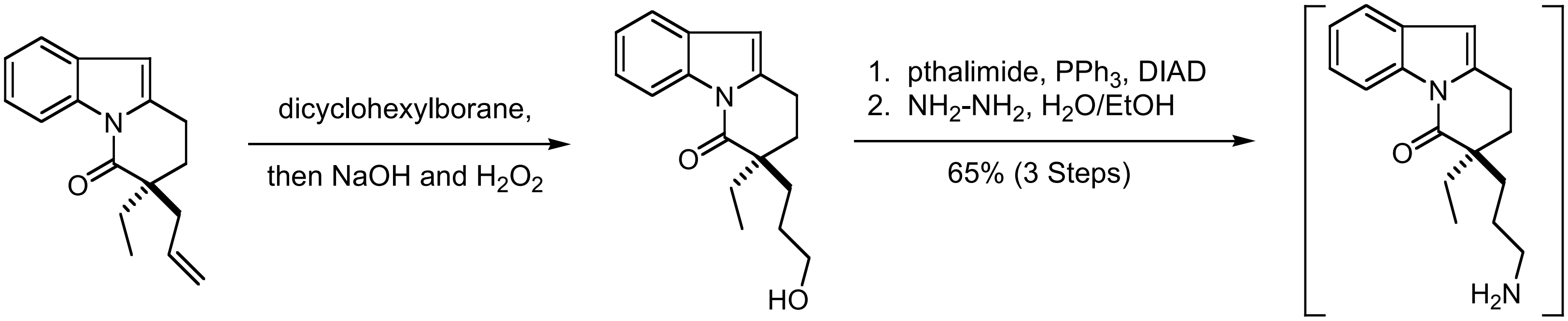
$PdCl(PPh_3)_2$, CuI, Et_3N
81%

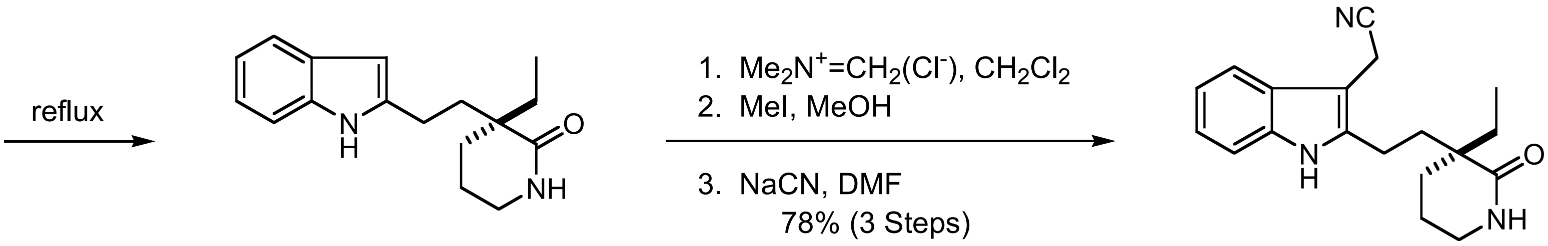
Takano, S.; *J. Chem. Soc., Chem. Comm,* **1991**, 462-464

First Total Synthesis of (-)-Goniomitine



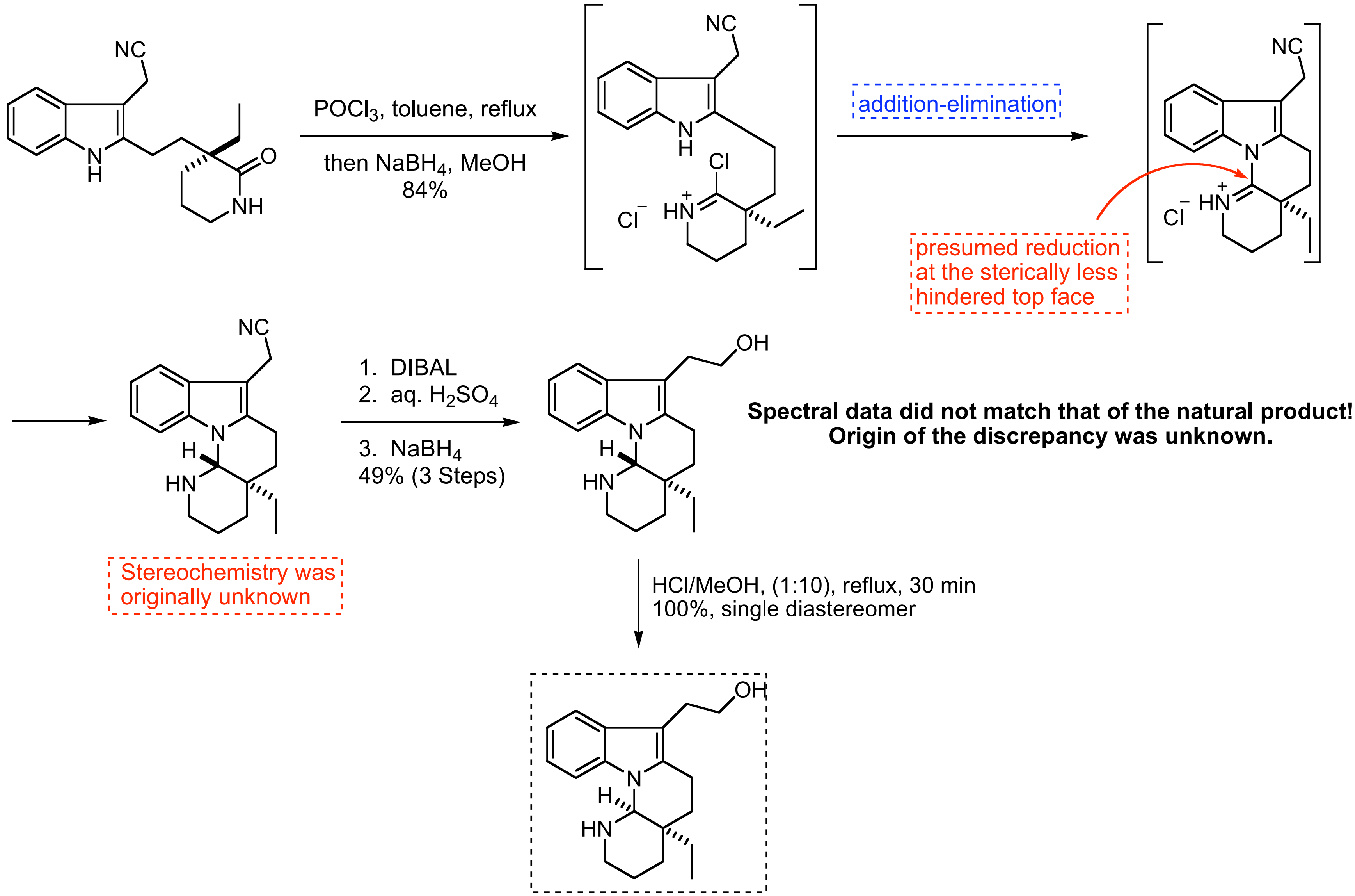
Minor product from indole formation was also transformed to the lactam in 44% overall yield *via* sequential hydroboration-oxidation, Mitsonubu reaction and deacylation





Takano, S.; *J. Chem. Soc., Chem. Comm,* **1991**, 462-464

First Total Synthesis of (-)-Goniomitine



POCl$_3$, toluene, reflux

then NaBH$_4$, MeOH
84%

addition-elimination

presumed reduction at the sterically less hindered top face

1. DIBAL
2. aq. H$_2$SO$_4$
3. NaBH$_4$
49% (3 Steps)

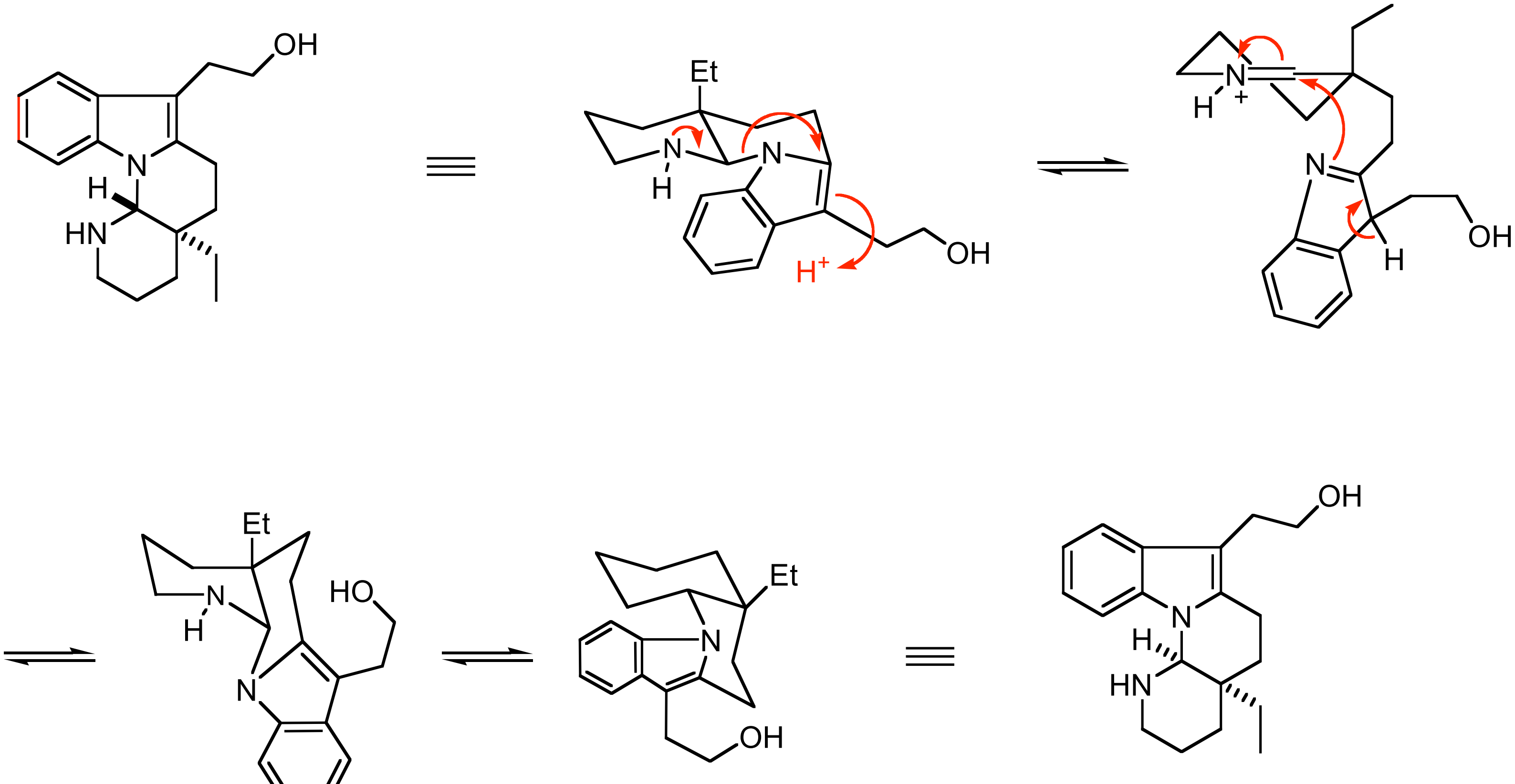
Stereochemistry was originally unknown

Spectral data did not match that of the natural product!
Origin of the discrepancy was unknown.

HCl/MeOH, (1:10), reflux, 30 min
100%, single diastereomer

Takano, S.; *J. Chem. Soc., Chem. Comm,* **1991**, 462-464

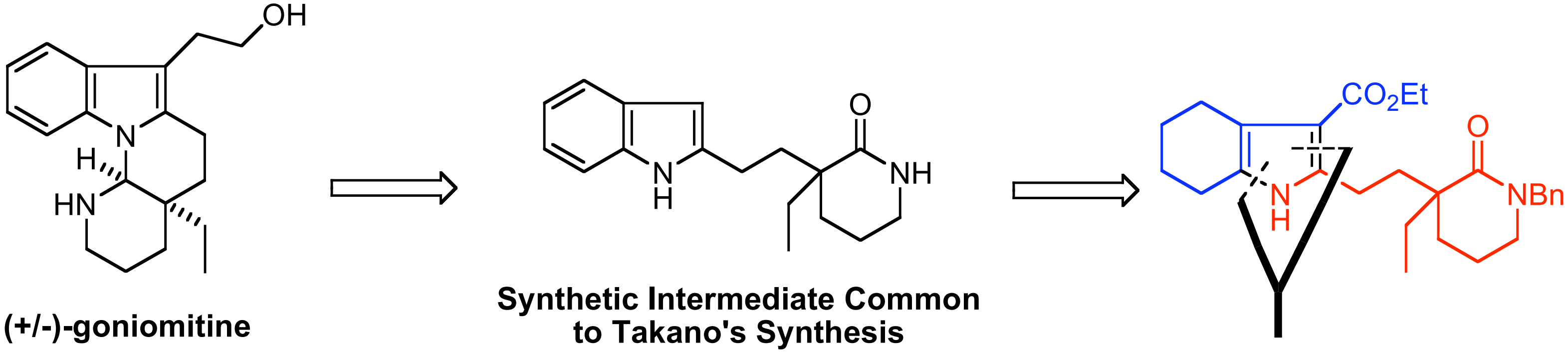
First Total Synthesis of (-)-Goniomitine



(-)-goniomitine

Takano, S.; *J. Chem. Soc., Chem. Comm,* **1991**, 462-464

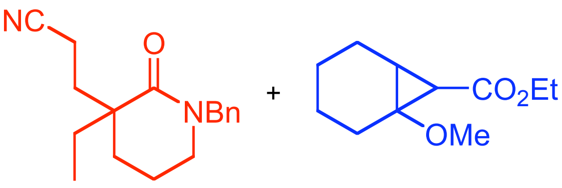
Pagenkopf’s Total Synthesis of (+/-)-Goniomitine



(+/-)-goniomitine

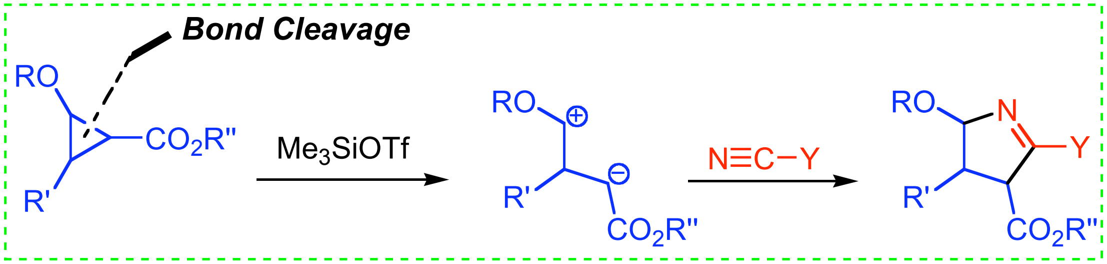
Synthetic Intermediate Common to Takano's Synthesis

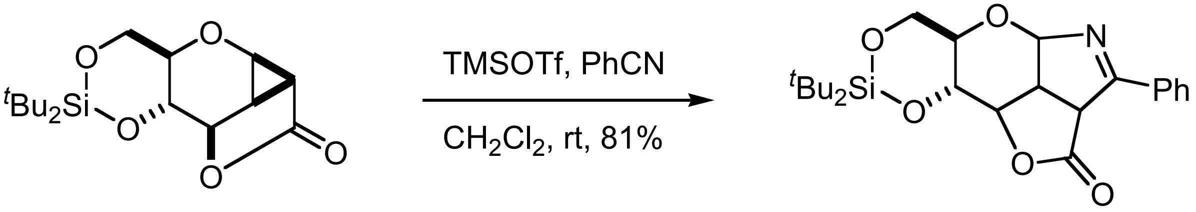
Formal 3 + 2 Cycloaddition reaction



Nitrile

Donor-Acceptor Cyclopropane

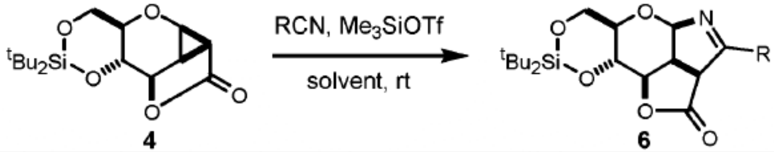


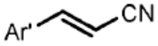
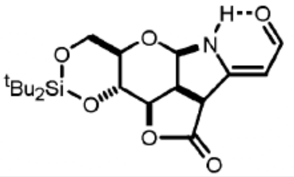


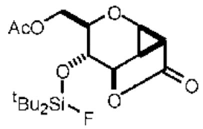
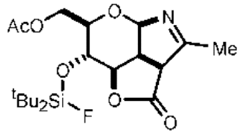
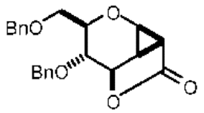
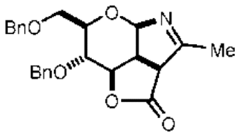
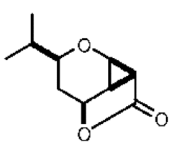
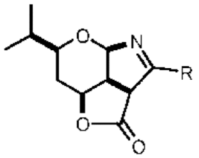
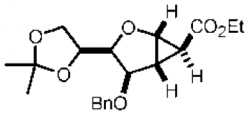
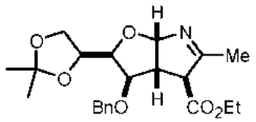
Pagenkopf, B. L; *Org. Lett, ASAP*

For seminal publication see: Pagenkopf, B. L.; *J. Am. Chem. Soc.* **2003**, *125*, 8122-

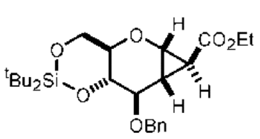
Formal [3 + 2] Cycloadditions of Donor-Acceptor Cyclopropanes and Nitriles

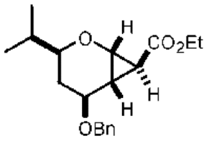


Entry	Nitrile	Solvent	Cycloaddition Product	Yield[a]
1	PhCN	CH_2Cl_2	**6a**, R = Ph	81%
2	MeCN	MeCN	**6b**, R = Me	96%
3	MeCN	CH_2Cl_2	**6b**, R = Me	84%
4	PrCN	CH_2Cl_2	**6c**, R = Pr	95%
5	^tBuCN	CH_2Cl_2	**6d**, R = ^tBu	79%
6	$Cl(CH_2)_3CN$	CH_2Cl_2	**6e**, R = $(CH_2)_3Cl$	87%
7[b]		$MeNO_2$	**6f**, R = CHCHAr, X = H	60%
8[b]		$MeNO_2$	**6g**, R = CHCHAr, X = OMe	75%
9		CH_2Cl_2	**6h**, 	78%

Entry	Substrate	Nitrile	Cycloaddition Product	Yield[a]
1[b]		MeCN		92%
2		MeCN		90%
3	 7	MeCN	 **8a**, R = Me	96%
4[b]	"	PhCN	**8b**, R = Ph	92%
5		MeCN		43%

[a] Isolated yields. [b] Reaction solvent = CH_2Cl_2.



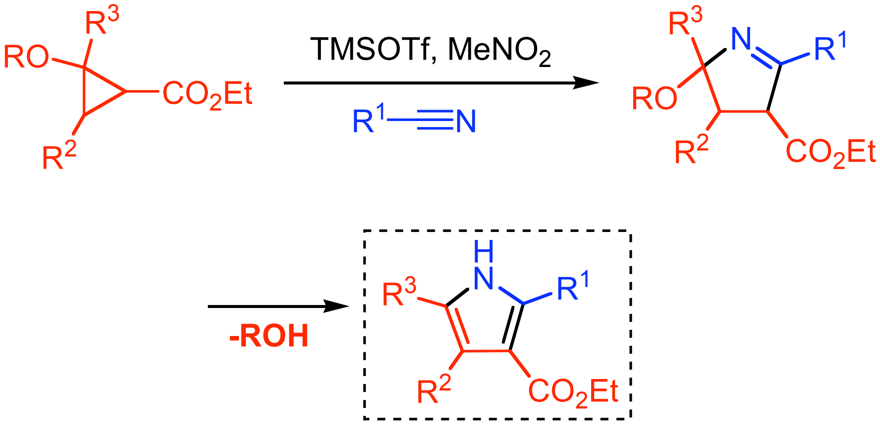


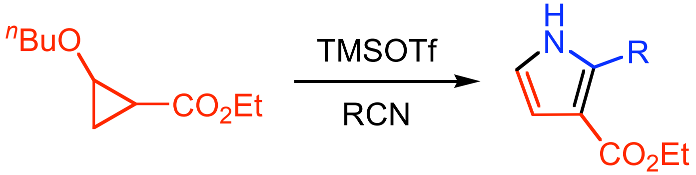
Provide Complex Mixtures

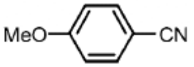
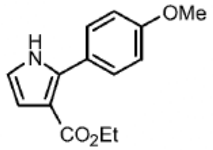
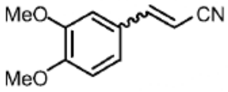
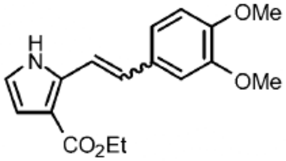
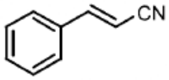
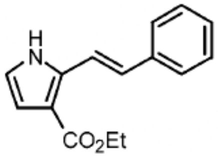
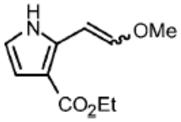
For seminal publication see: Pagenkopf, B. L.; *J. Am. Chem. Soc.* **2003**, *125*, 8122-8123

Formal [3 + 2] Cycloadditions to Form Pyrroles

Synthesis of substituted Pyrroles from DA cyclopropanes via a domino cycloaddition, dehydration, and tautomerization strategy

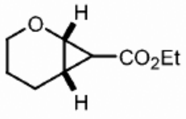
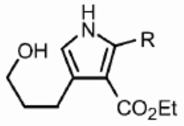
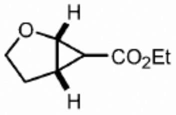
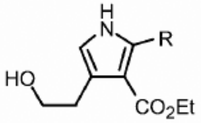
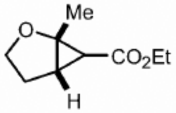
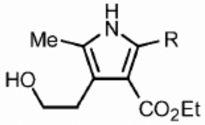
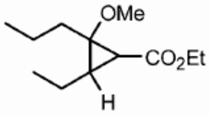
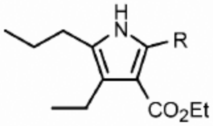
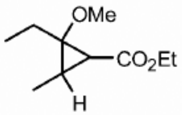
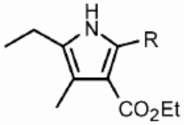
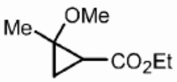
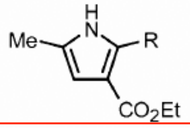
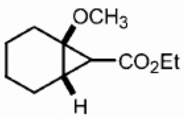
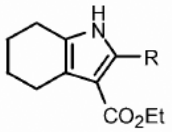


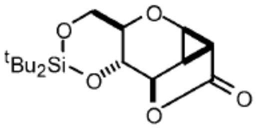
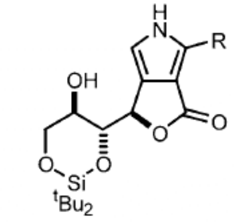
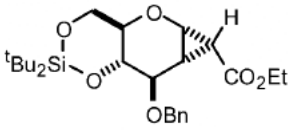
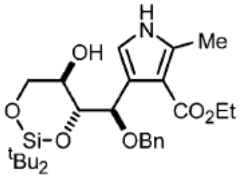
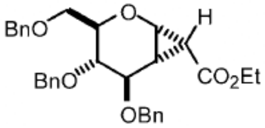
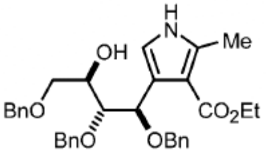
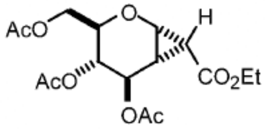
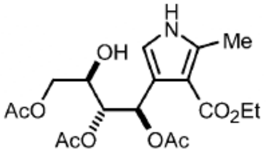
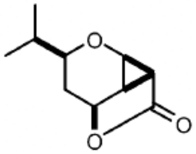
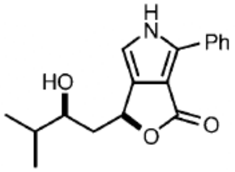


MeCN	R = Me	80%
PrCN	R = Pr	77%
PhCN	R = Ph	35%
		55%
		85%
		39%
		91%

Pagenkopf, B. L.; *Org. Lett.* **2003**, *5*, 5099-5101

Formal [3 + 2] Cycloadditions to Form Pyrroles: Scope

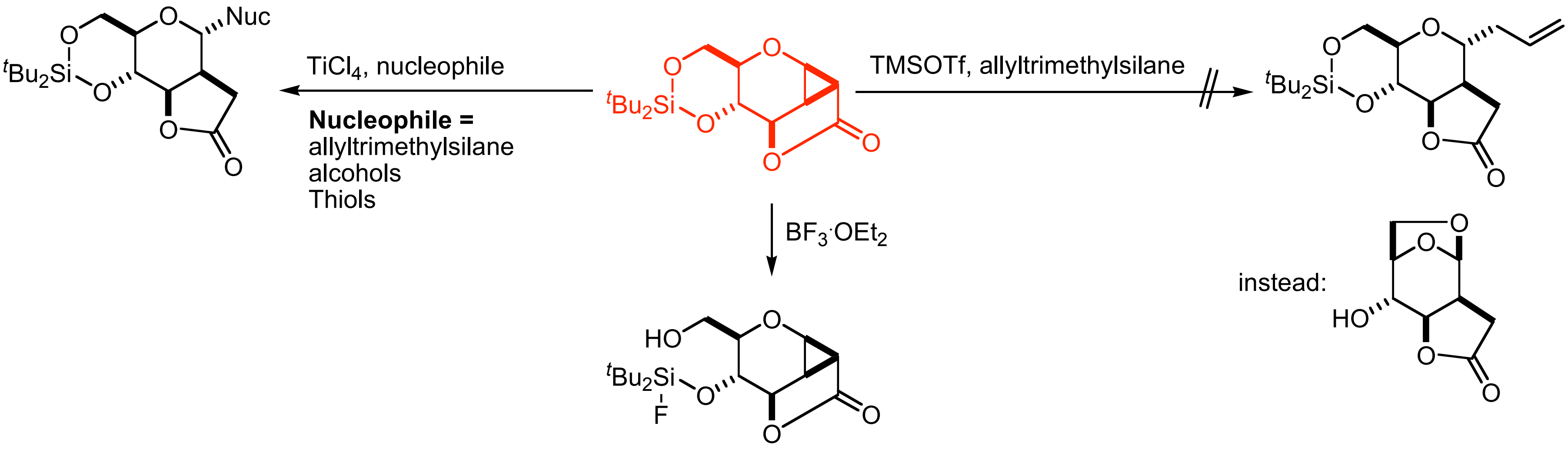
substrate	nitrile	pyrrole	isolated yield
	MeCN PrCN PhCN Cl(CH$_2$)$_3$CN		72% 78% 58% 61%
	MeCN PrCN MeOC$_2$H$_2$CN		52% 58% 81%
	MeCN PrCN		31% 25%
	MeCN PrCN PhCN		93% 82% 76%
	MeCN PrCN		98% 85%
	MeCN PrCN		62% 55%
	MeCN PrCN		72% 75%

substrate	nitrile	pyrrole	isolated yield
	^{t}BuCN PhCN ArCN		87% 85% 93%
	MeCN		87%
	MeCN		77%
	MeCN		58%
	PhCN		82%

Pagenkopf, B. L.; *Org. Lett.* **2003**, *5*, 5099-5101

Formal [3 + 2] Cycloaddition Methodology

Successfully revealing the dipolar nature of the cyclopropane is highly dependent upon the LA and solvent used
Ideal conditions are DA cyclopropane (1 eq), TMSOTf (1 eq), RCN (5-10 eq), $MeNO_2$ or CH_2Cl_2 (solvent)



$TiCl_4$, nucleophile

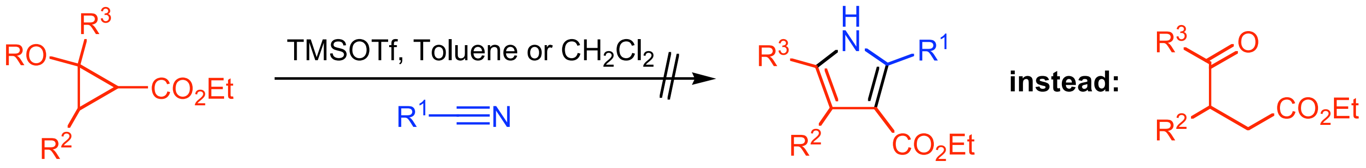
Nucleophile =
allyltrimethylsilane
alcohols
Thiols

TMSOTf, allyltrimethylsilane

$BF_3{\cdot}OEt_2$

instead:

$MeNO_2$ must be used as solvent when forming pyrroles

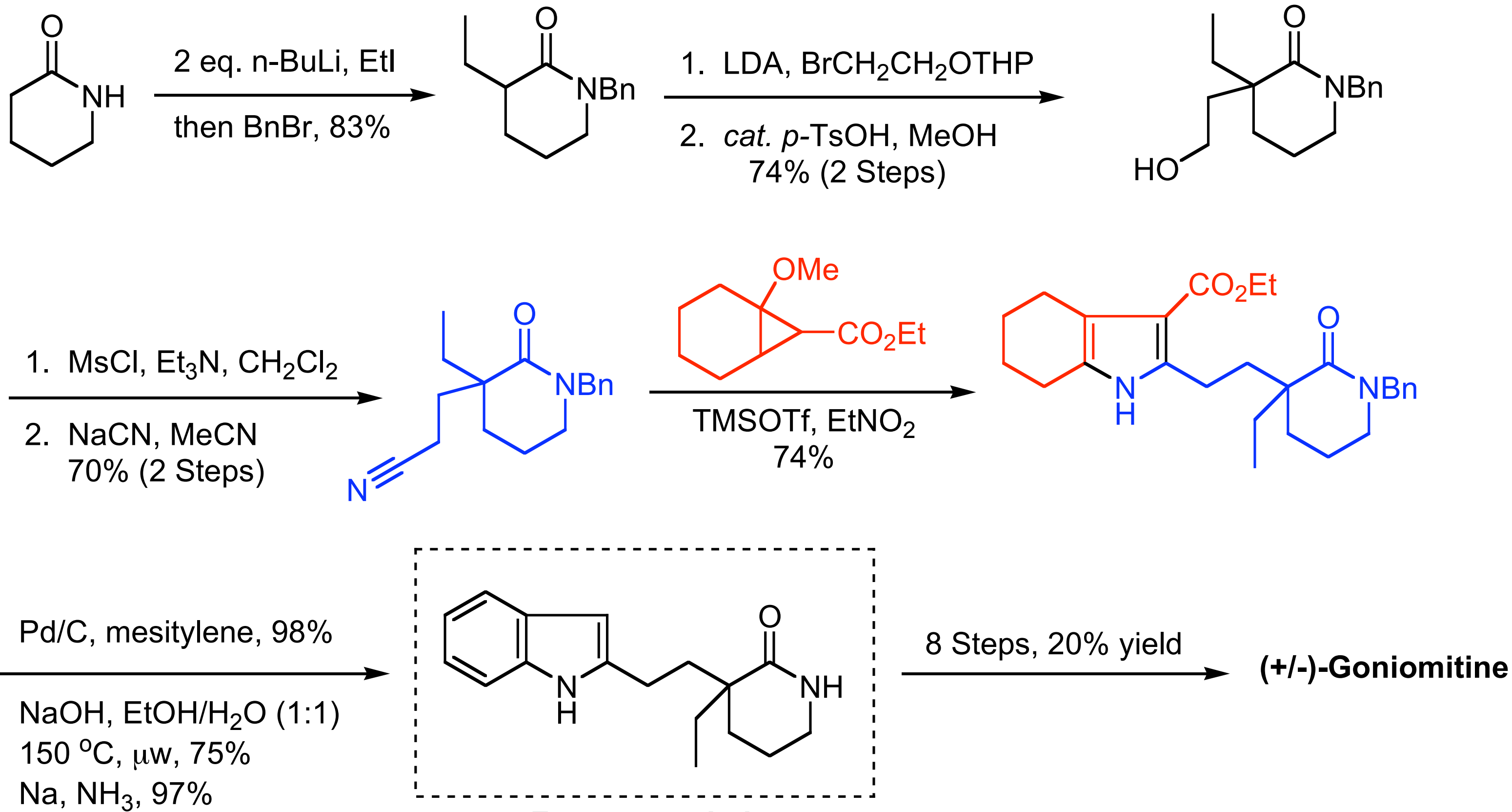


TMSOTf, Toluene or CH_2Cl_2

$R^1—≡N$

instead:

Pagenkopf's Total Synthesis of (+/-)-Goniomitine



2 eq. n-BuLi, EtI

then BnBr, 83%

1. LDA, $BrCH_2CH_2OTHP$
2. *cat. p*-TsOH, MeOH
   74% (2 Steps)

1. MsCl, Et_3N, CH_2Cl_2
2. NaCN, MeCN
   70% (2 Steps)

TMSOTf, $EtNO_2$
74%

1. Pd/C, mesitylene, 98%
2. NaOH, EtOH/H_2O (1:1)
   150 ^{o}C, µw, 75%
3. Na, NH_3, 97%

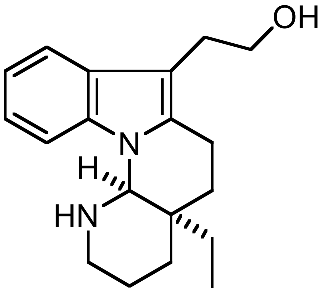
Formal syntheis

8 Steps, 20% yield

(+/-)-Goniomitine

Pagenkopf, B. L; *Org. Lett, ASAP*

Conclusions



(-)-Goniomitine

Pagenkopf's Synthesis:

- 17 Linear Steps, 5% overall yield
- Racemic
- First "practical" application" of his formal [3 +2] nitrile/donor-acceptor cyclopropane cyclization

Takano's Synthesis:

- 24 Linear Steps, 2.8% (1.4) overall yield
- Asymmetric