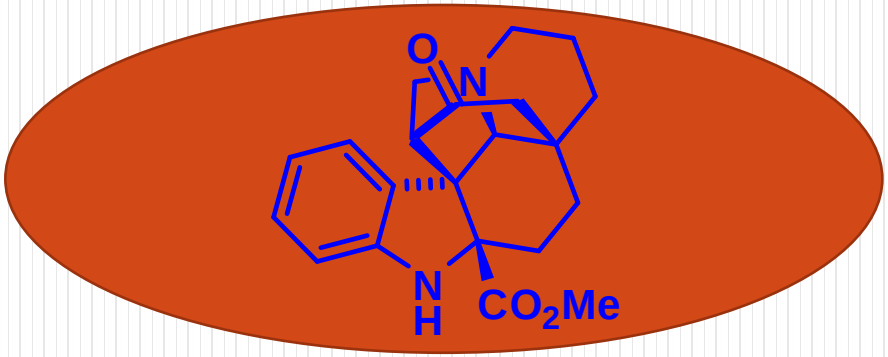
Angewandte Communications

Natural Product Synthesis

Total Synthesis of the Indole Alkaloid (±)-and (+)- Methyl *N*- Decarbomethoxychanofruticosinate

Sankar Rao Suravarapu

Prof. Dr. Philippe Renaud
University of Bern, Departement of Chemistry and Biochemistry



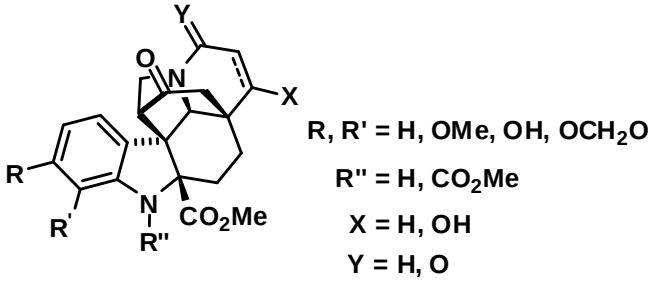
Angew. Chem. Int. Ed. **2013**, *52*, 12988

Introduction

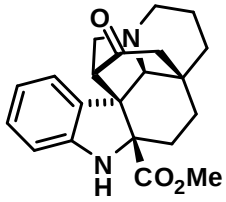
- Methyl chanofruticosinates belongs to growing family of indole alkaloids

- Theses alkaloids have been isolated from *Kopsia* (Apocynaceae)

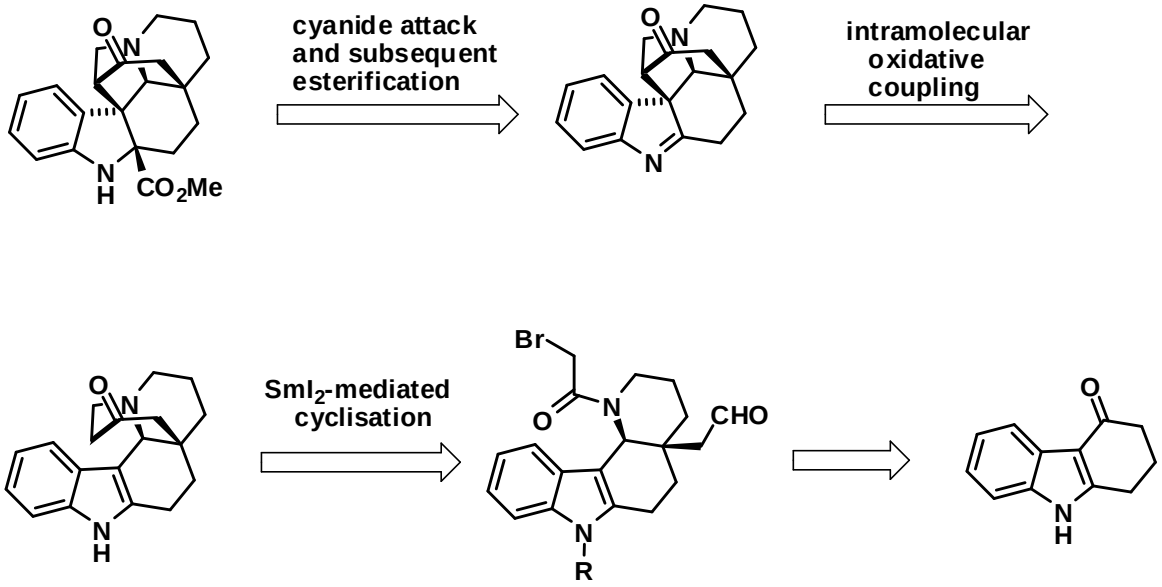
- widely distributed in tropical Asia and they have been historically used for the treatment of rheumatoid arthritis



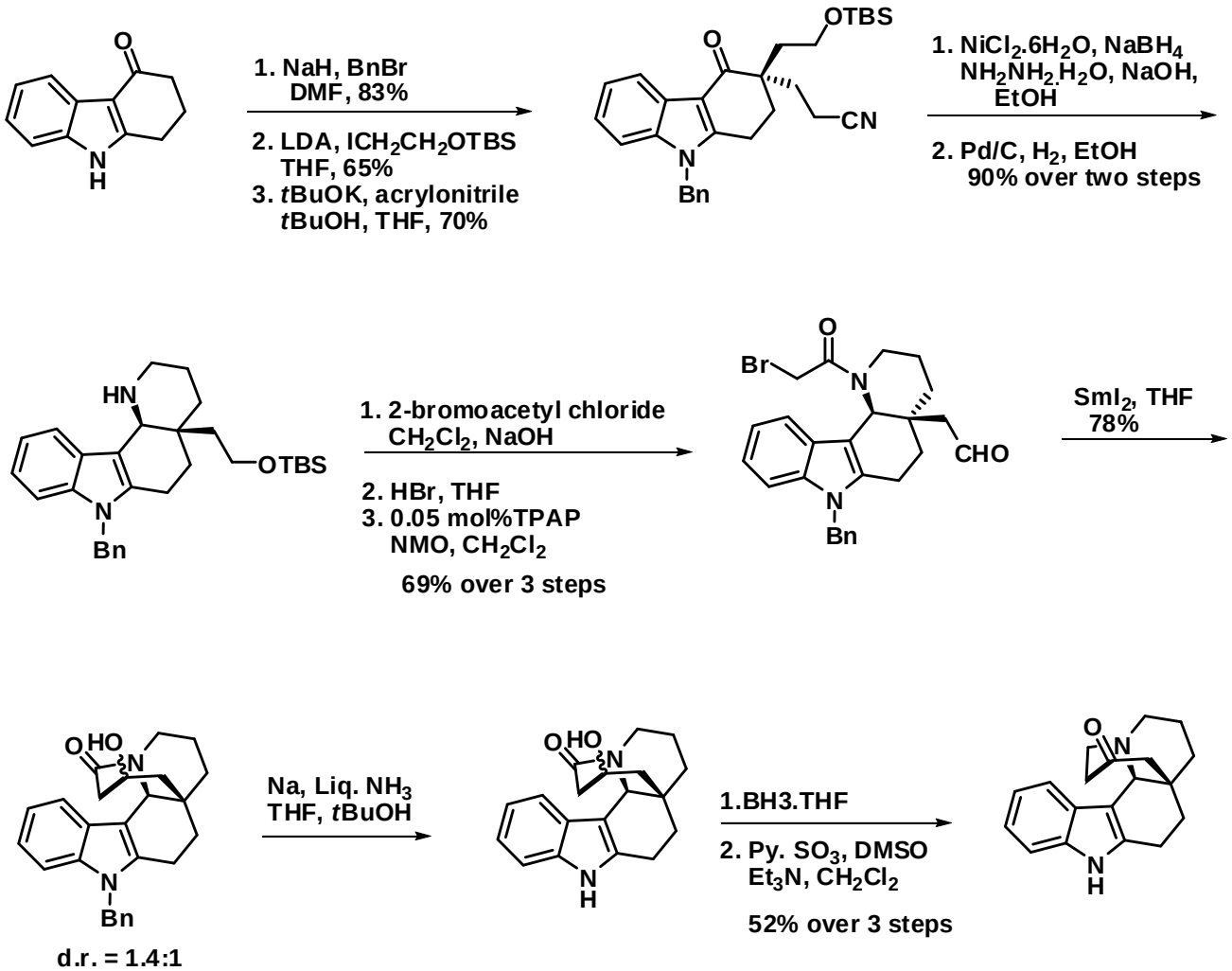
- In particular, Methyl *N*- decarbomethoxychanofruticosinte displays antitussive activity in a citric acid induced guinea pig cough model and also shows relaxation activity against phenylephrine-induced contractions of rat aortas



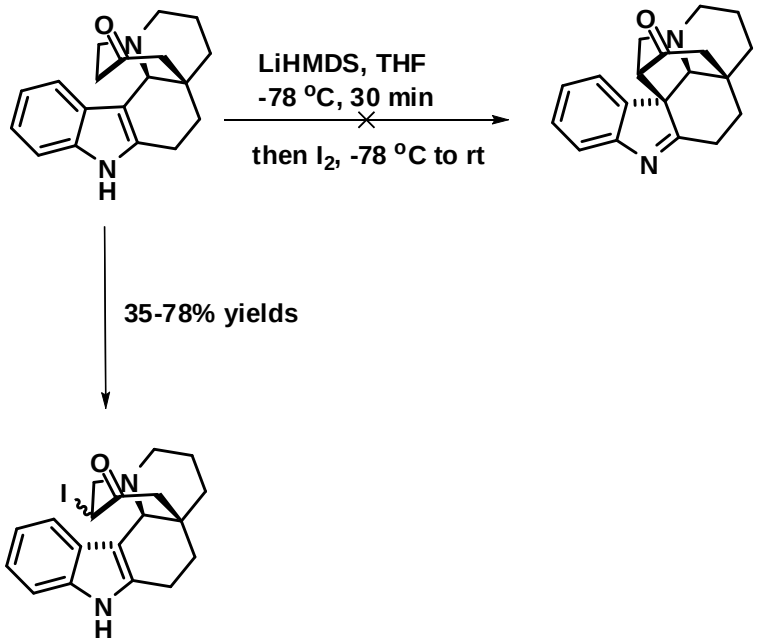
Retrosynthetic analysis

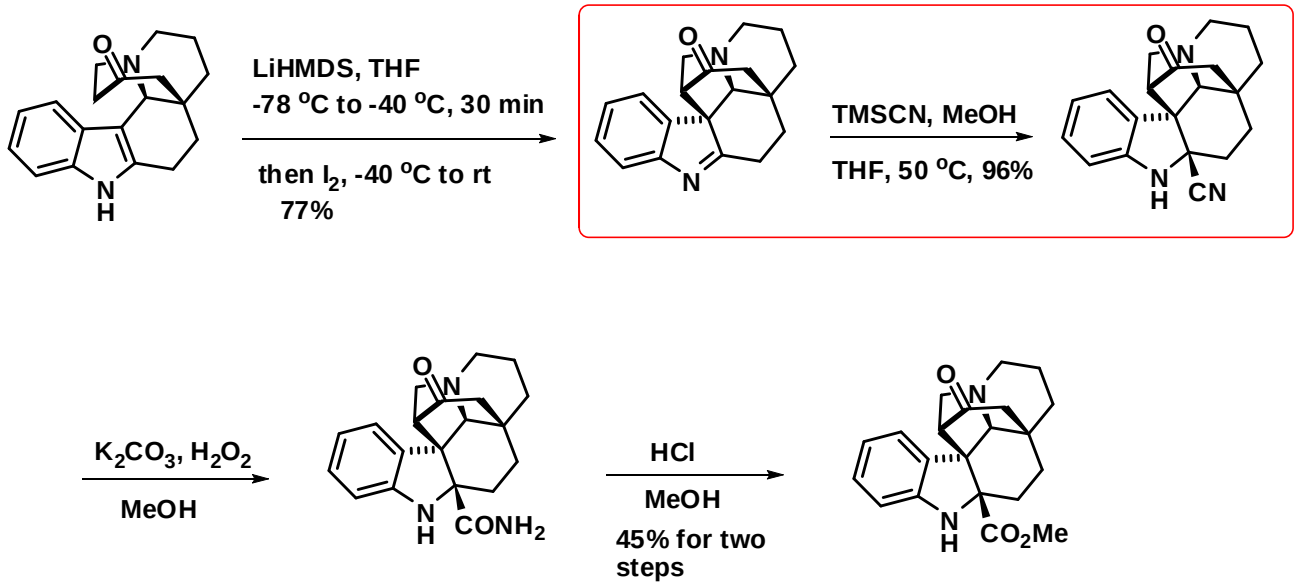


Racemic Synthesis

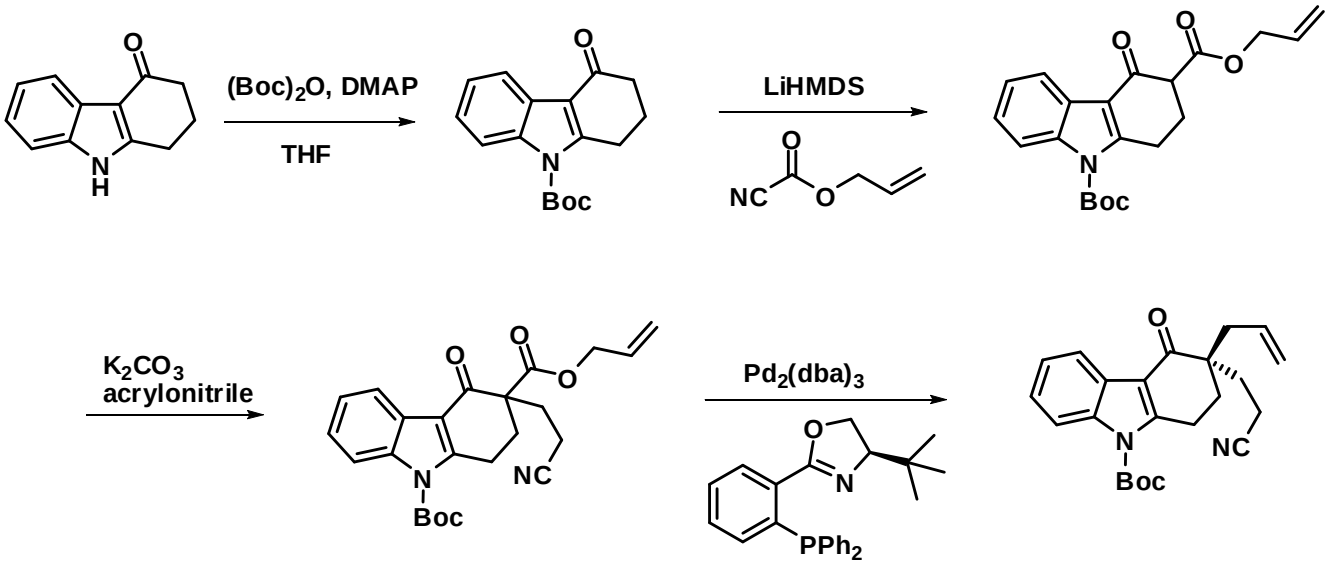


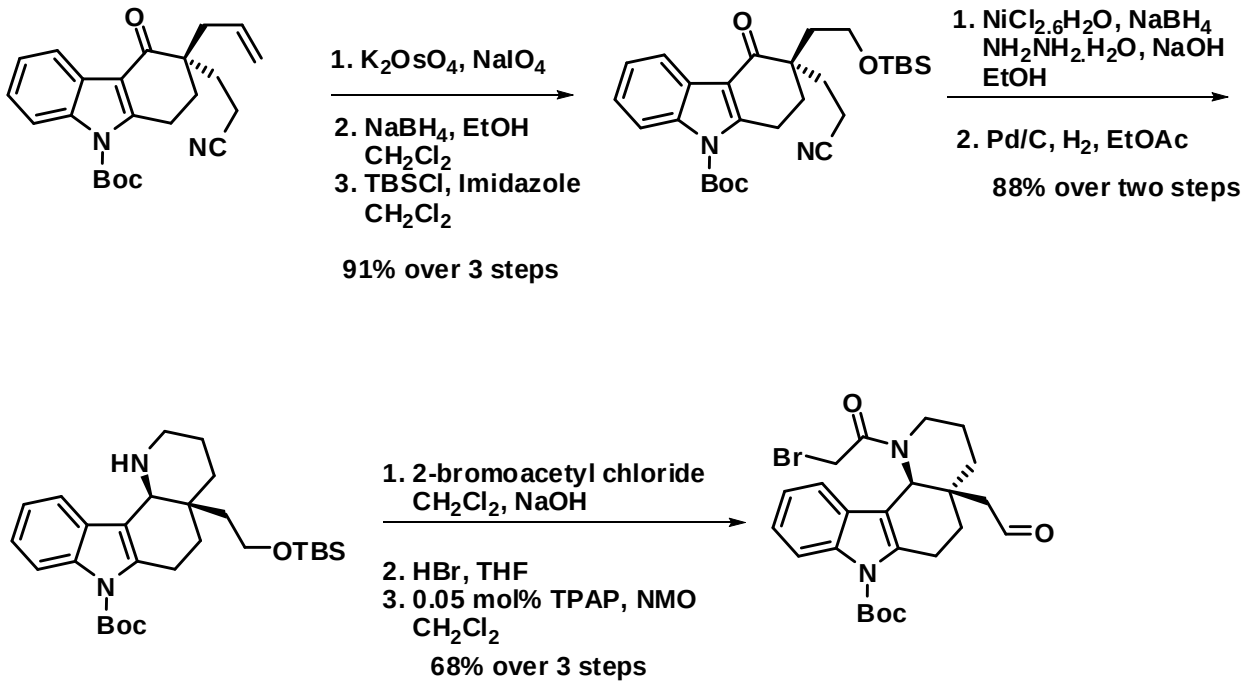
Iodination is much faster than Oxidation of enolate?

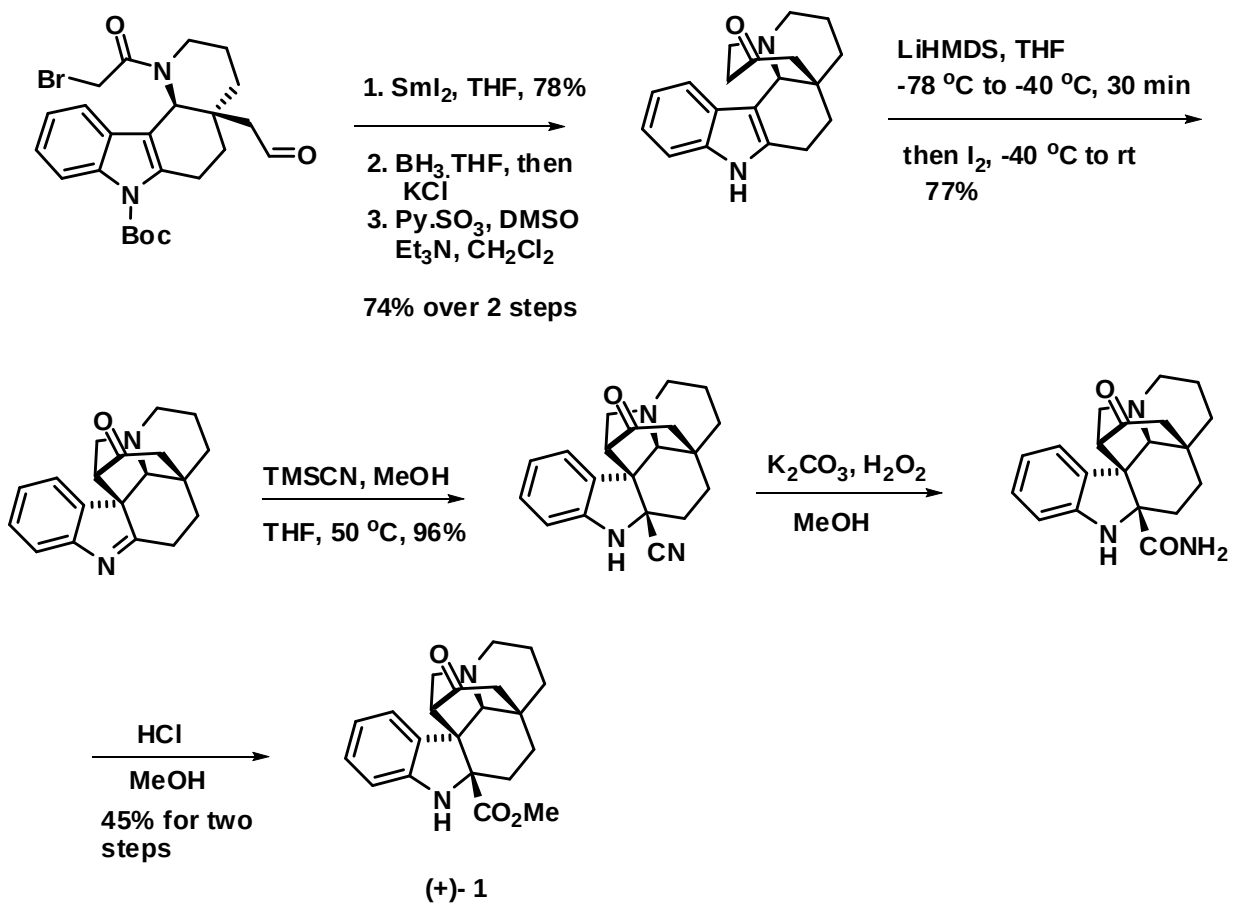



LiHMDS, THF
-78 °C to -40 °C, 30 min
then I_2, -40 °C to rt
77%
TMSCN, MeOH
THF, 50 °C, 96%
K_2CO_3, H_2O_2
MeOH
HCl
MeOH
45% for two steps
favoured approach
unfavoured approach
1, 3-diaxial interaction

Preparation Starting material for enantioselective Synthesis




O
N
Boc
NC
1. K_2OsO_4, $NaIO_4$
2. $NaBH_4$, EtOH
CH_2Cl_2
3. TBSCl, Imidazole
CH_2Cl_2
91% over 3 steps
OTBS
1. $NiCl_{2.6}H_2O$, $NaBH_4$
$NH_2NH_2.H_2O$, NaOH
EtOH
2. Pd/C, H_2, EtOAc
88% over two steps
HN
1. 2-bromoacetyl chloride
CH_2Cl_2, NaOH
2. HBr, THF
3. 0.05 mol% TPAP, NMO
CH_2Cl_2
68% over 3 steps
Br


Br
O
N
O
N
Boc
1. SmI2, THF, 78%
2. BH3.THF, then KCl
3. Py.SO3, DMSO
Et3N, CH2Cl2
74% over 2 steps
O
N
N
H
LiHMDS, THF
-78 °C to -40 °C, 30 min
then I2, -40 °C to rt
77%
O
N
N
TMSCN, MeOH
THF, 50 °C, 96%
O
N
N
H
CN
K2CO3, H2O2
MeOH
O
N
N
H
CONH2
HCl
MeOH
45% for two steps
O
N
N
H
CO2Me
(+)- 1

Conclusion and key features

- achieved the total synthesis of Methyl N- Decarbomethoxychanofruticosinate in both racemic and enantioselective forms for the first time
- racemic synthesis- 16 linear steps and enantioselective synthesis- 19 linear steps
- SmI2-mediated intramolecular Reformatsky-like reaction to create seven- membered ring and Intramolecular oxidative coupling to install caged and strained ring system

Thank you
For your attention