I. INTRODUCTION

I.1. Alkaloid:

I.1.1. Definition

The whole word alkaloid is made up of the words 'alkali' and Greek word 'ε ι δ ο σ' ('type', 'similarity') or 'ε ι δ ω' ('to see', 'to appear'). The root 'alkali' originated from the Arabic word 'al-qualja', meaning 'plant ashes'. Essentially, alkaloids mean a substance with an alkali-like character.

The actual word 'alkaloid' itself was first introduced by W. Meissner[1] in 1819, during his investigation of *Veratrum.* In his paper titled 'Ueber ein neues Pflanzenalkali (Alkaloid)', he defined 'alkaloid' simply as plant-derived substances that react like alkalis. It took several decades before this term established itself, when O. Jacobsen[2] wrote a detailed review article about alkaloids for *A. Ladenburg's Handworterbuch der Chemie.* Jacobsen more or less defined it as 'nitrogen-containing organic bases that originated from the plant kingdom or animal'.

The definition evolved further as E. Winterstein and G. Trier[3] wrote in 'Die Alkaloide' in 1910 as:

'compound with nitrogen atoms bound in heterocyclic fashion, with a greater or lesser degree of basic character; marked physiological effects, complicated molecular structure, which are found in plants, and, with a few exceptions, are characteristics for

particular plant families, genera or species'.

Another definition was also provided by A. Stoll[4] in 1953:

'Nitrogen-containing based of vegetable origin'.

P. Karrer[5] classified alkaloids in his 'Lehrbuch der Organischen Chemie' as 'nitrogen-containing, basic compounds found in plants in general'.

W.S. Pelletier[6] also added a 'modern definition' in his first volume of the series 'Alkaloids' which he edited. He explicitly pointed out that the origin of these compounds shoud not be restricted to plants.

'An alkaloid is a cyclic organic compound containing nitrogen in a negative oxidation state which is of limited distribution among living organism'.

In view of the fact that pure amino acids, peptides, nucleic acids, and synthetic organic nitrogen bases such as aniline are not counted among the alkaloids, Hesse[7] put forward the following definition in 2002:

'Alkaloids are nitrogen-containing substances of natural origin with a greater or lesser degree of basic character'.

I.1.2. Classification

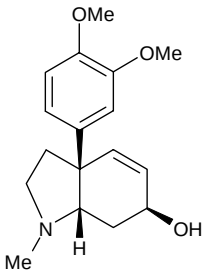
Nowadays, the total number of alkaloids so far isolated from (or detected in) plant and animal organisms, fungi, or natural folk medicines (calabash curare, tubocurare,

opium, etc) is enormous. By rough estimate, around 10,000 different alkaloids exist. Several criteria have been proposed to classify these types of compounds, among others: biogenesis, structural relationship, biological origin, and spectroscopic/spectrometric properties (chromophores in UV spectroscopy, ring systems in mass spectrometry).

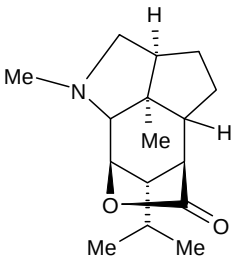
Despite the several proposed classifications, often we still find in exceptions that are grouped under 'Miscellaneous' or 'Unclassified Alkaloids'. The situation clearly reflects the limitations of the classifications now being applied to these compounds.

Recently, Hesse[7] has proposed another kind of classification, based on the position of the N-atom in the main structural element:

- Heterocyclic alkaloids
  - Pyrrolidine Alkaloids, such as Mesembrenol, Dendrobine, etc.

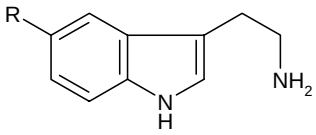


Mesembrenol

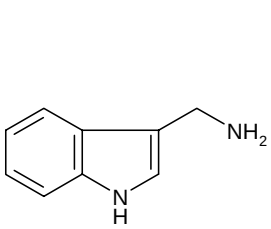


(-)-Dendrobine

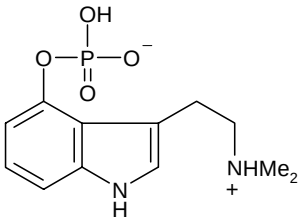
  - Indole Alkaloids, with further classifications as:
    - Simple indole bases, like tryptamine, serotonin, gramine, psilocybine, etc.



R = H : Tryptamine
R = OH : Serotonin

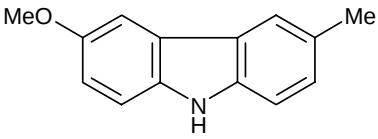


Gramine

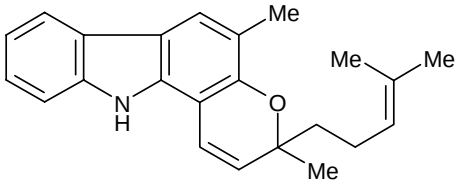


Psilocybine

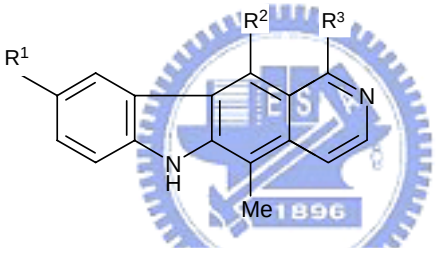
- Alkaloids with carbazole skeletons, such as glycozoline, mahanimbine, olivacine, ellipticine, etc.



Glycozoline

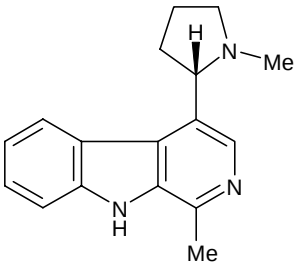


Mahanimbine



$R^1 = R^2 = H, R^3 = Me$: Olivacine
$R^1 = OMe, R^2 = Me, R^3 = H$: Ellipticine

- Alkaloids with the β-carboline skeleton, such as brevicolline, alkaloids of the Canthine type, eburnamine alkaloids, heteroyohimban alkaloids, yohimban alkaloids etc.



(-)-Brevicolline
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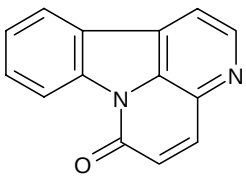
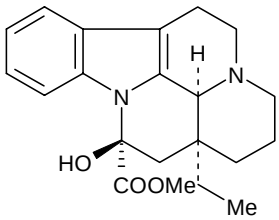


Canthinone



(+)-Vincamine
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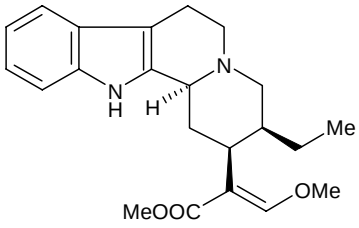
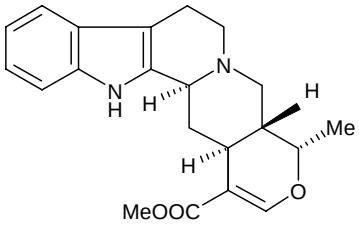


(-)-Corynantheidine
(abs. config.)



(-)-Ajmalicine
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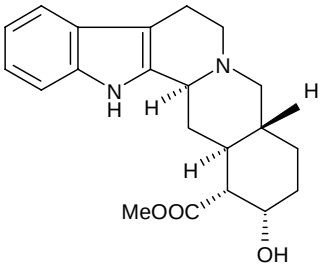
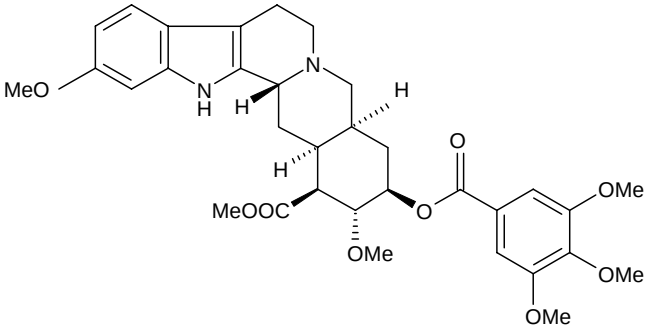
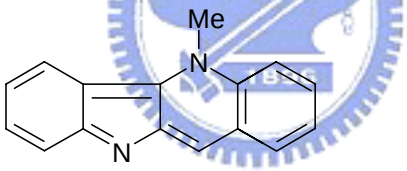


(+)-Yohimbine
(abs. config.)



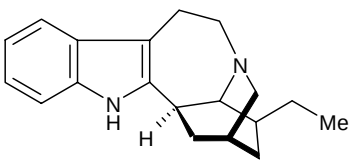
(-)-Reserpine
(abs. config.)

- Alkaloids with the γ-carboline skeleton, such as cryptolepine.



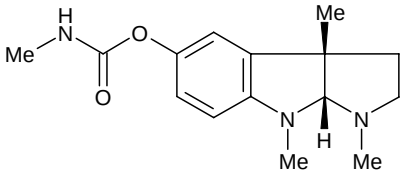
Cryptolepine

- Iboga alkaloids, such as ibogamine, etc.



(-)-Ibogamine
(abs. config.)

- Indole alkaloids with the pyrrolo-indole skeleton.



(-)-Physostigmine (= Eserine)
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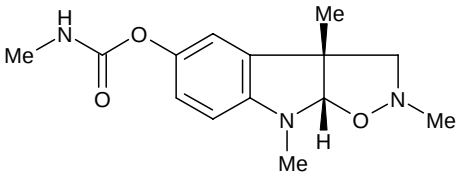

(-)-Geneserine
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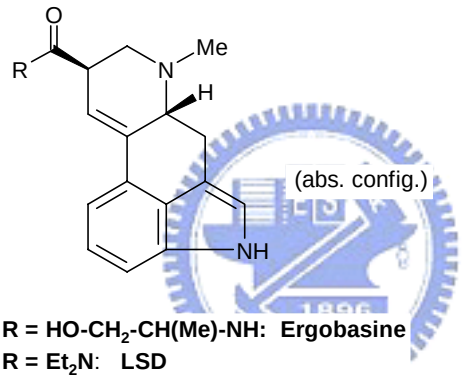
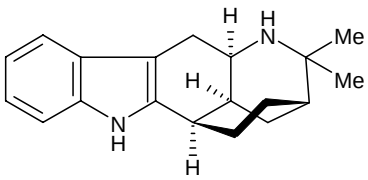
- Ergot alkaloids, such as amides of lysergic acid.



R = HO-CH_2-CH(Me)-NH: Ergobasine
R = Et_2N: LSD

- Alkaloids of the Evodiamine Type.

- Aristotelia Alkaloids.



(+)-Aristoteline
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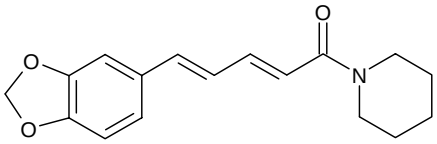
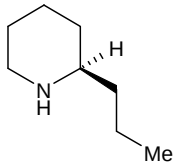
➢ Piperidine Alkaloids, such as piperine, coniine, etc. The pyridine

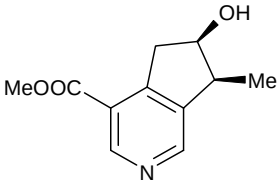
alkaloids are also included in this type.



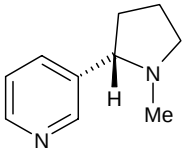
Piperine



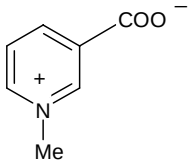
(+)-Coniine
(abs. config.)



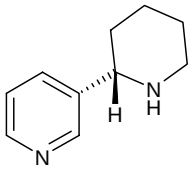
(-)-Cantleyine



(-)-Nicotine



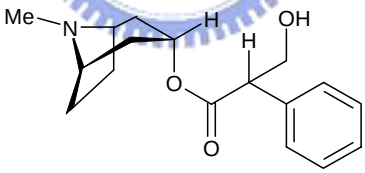
Trigonelline



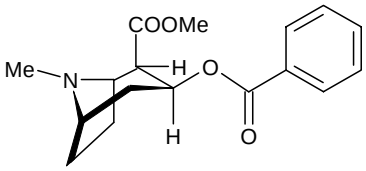
(-)-Anabasine
(abs. config.)

- Tropane and related bases.

Ψ–Pelletierine



(±)-Atropine



(-)-Cocaine
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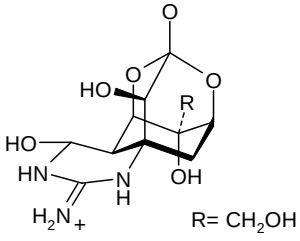
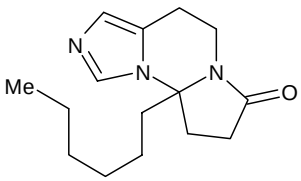
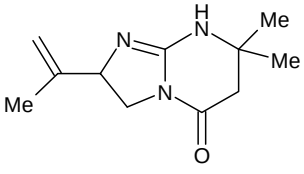
- Histamine, Imidazole and Guanidine Alkaloids.



(-)-Tetrodoxin

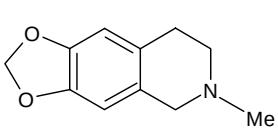


(±)-Glochidine

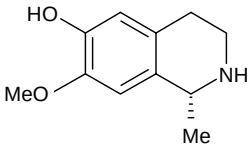


Alchornine

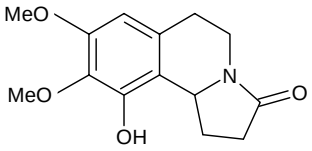
- Isoquinoline Alkaloids, such as salsoline, peyoglutam, lophocerine, morphine alkaloids, etc.



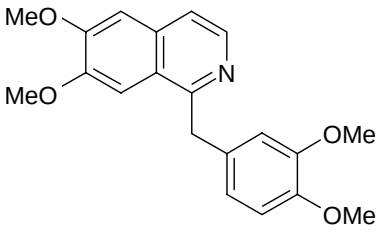
Hydrohydrastinine



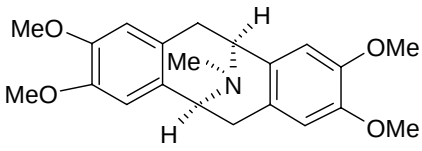
(+)-Salsoline



Peyoglutam



Papaverine



(-)-Argemonine
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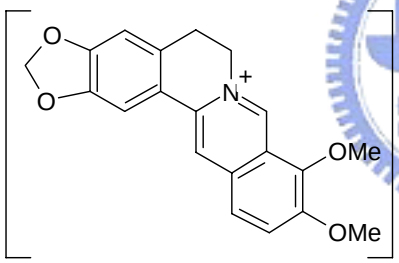
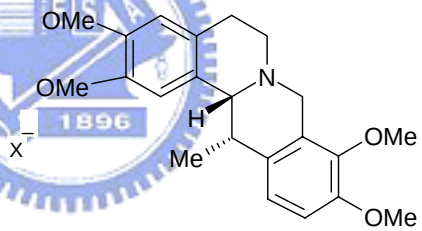


Berberine



(+)-Corydaline
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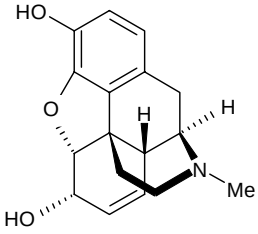
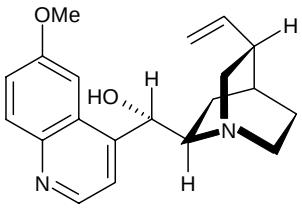


(-)-Morphine
(abs. config.)

- Quinoline Alkaloids, such as quinine alkaloids, melodinus alkaloids, campotheca bases, acridine alkaloids, etc.



(-)-Quinine
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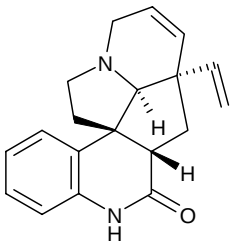

(+)-Meloscine
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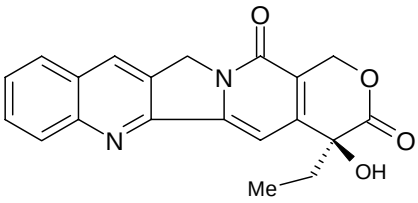

(+)-Camptothecin
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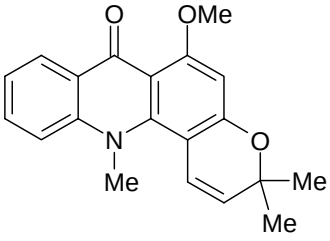
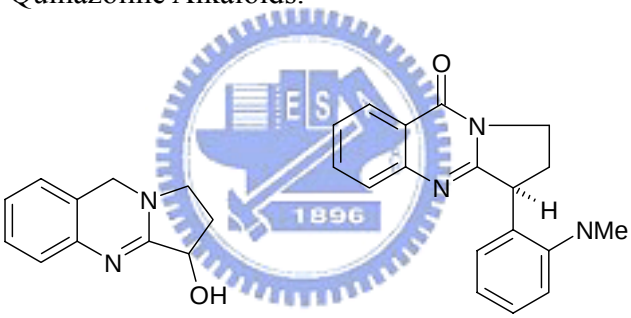


Acronycine

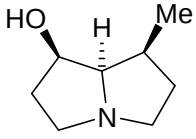
- Quinazoline Alkaloids.



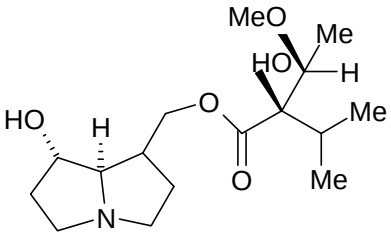
Vasicine **Vasicolinone**

- Benzoxazines and Benzoxazoles.

- Pyrrolizidine Alkaloids (Senecio Alkaloids).



(-)-Retronecanol

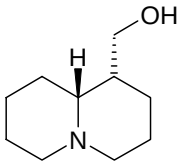


(+)-Heliotrine
(abs. config.)

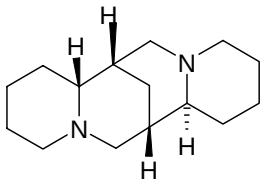
-

- Indolizidine Alkaloids

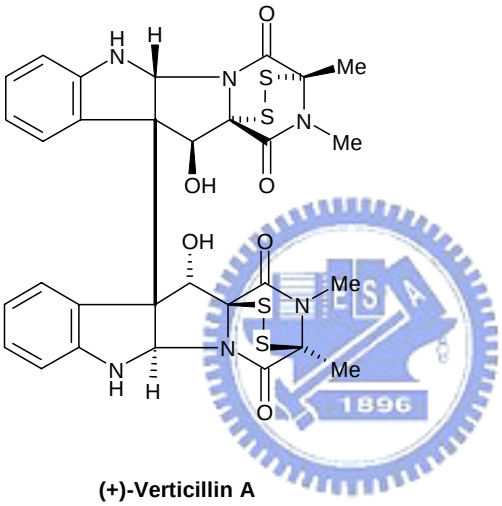
- Quinolizidine Alkaloids such as lupine alkaloids, nuphar alkaloids, etc.



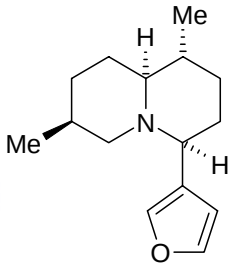
(-)-Lupinine
(abs. config.)



(+)-Sparteine
(abs. config.)



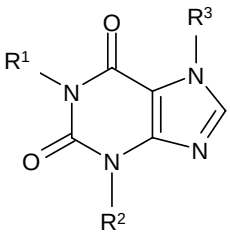
(+)-Verticillin A



(-)-Deoxynupharidine
(abs. config.)

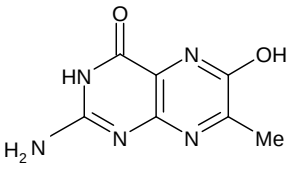
- Pyrazine Alkaloids

- Purine Bases.

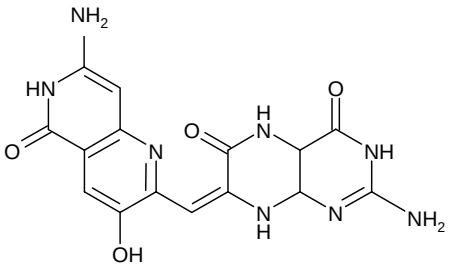


$R^1 = R^2 = Me,\ R^3 = H$: **Theophylline**
$R^1 = H,\ R^2 = R^3 = Me$: **Theobromine**
$R^1 = R^3 = Me,\ R^2 = H$: **Paraxanthine**
$R^1 = R^2 = R^3 = Me$: **Caffeine**

- Pteridines.



Pterin

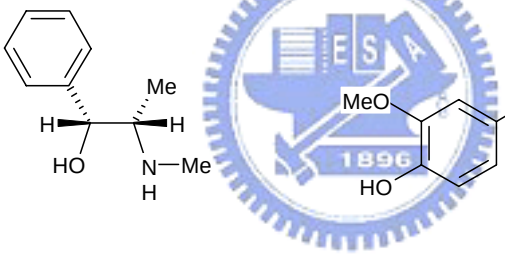


Pterorhodine

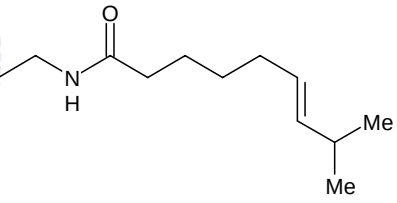
◆ Alkaloids with N-atoms in the exocyclic position including aliphatic amines

- Erytrophleum Alkaloids.

- Phenylalkylamine Derivatives, such as ephedrine, capsaicine, etc



(-)-Ephedrine
(abs. config.)

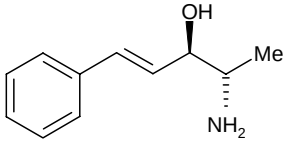


Capsaicine

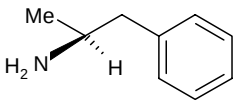
- Benzylamine-Type Alkaloids

- Colchicines.

- Khat.



Merucathine

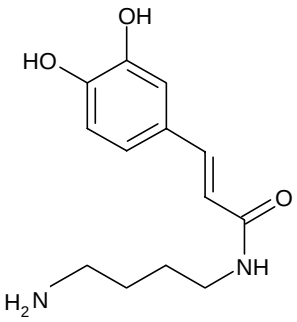


(+)-S-Amphetamine

- Muscarines.

◆ Putrescine, spermidine, and spermine alkaloids

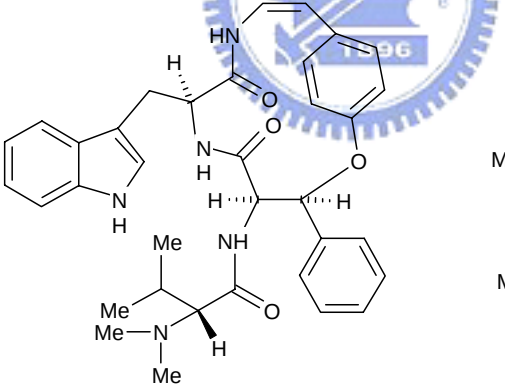
- included in this type: paucine, inandenin-12-one, lunarine, etc.



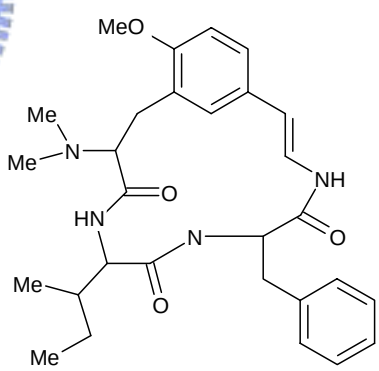
Paucine

◆ Peptide alkaloids

- included in this type: integerrine, mucronine A, etc.



Integerrine
(abs. config.)



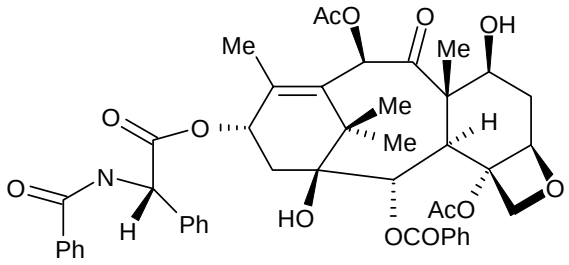
Mucronine A

◆ Terpene and steroid alkaloids

➢ Diterpene Alkaloids.

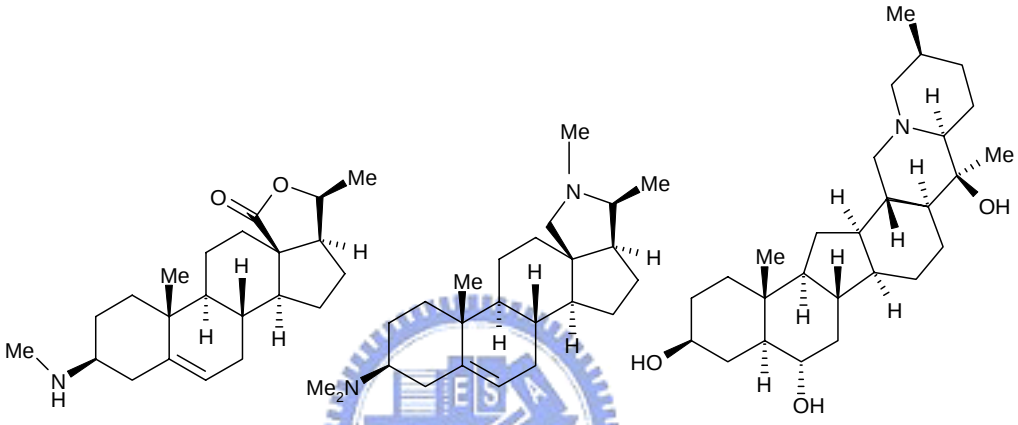
➢ Daphniphyllum Alkaloids

➢ Taxus Alkaloids.



Taxol

- Steroid Alkaloids.

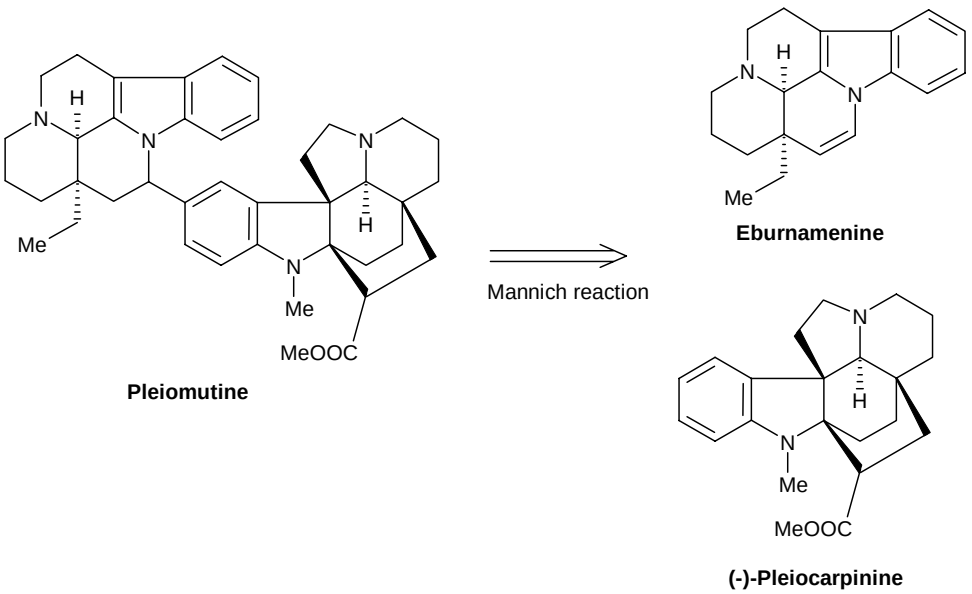


(-)-Paravallarine
(abs. config.)

(+)-Conessine
(abs. config.)

(-)-Verticine
(abs. config.)

In addition to the monomeric alkaloids as illustrated above, dimeric, trimeric, tetrameric alkaloids are also found in nature.

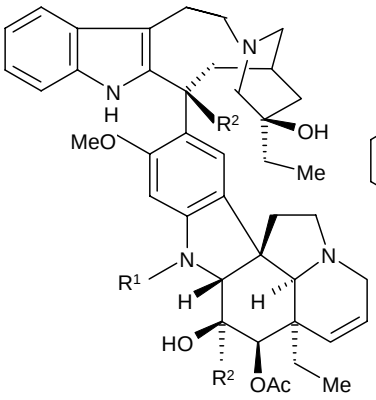


Pleiomutine

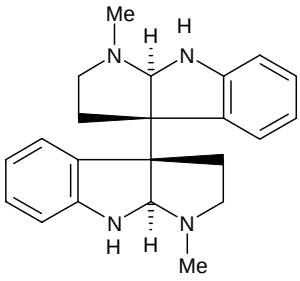
Mannich reaction

Eburnamenine

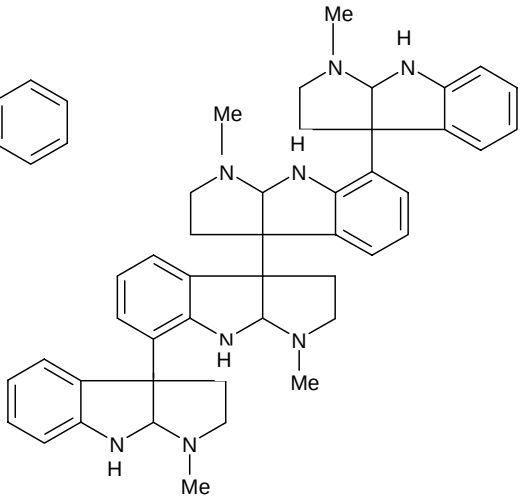
(-)-Pleiocarpinine



R^1 = Me, R^2 = COOMe : Vinblastine
R^1 = CHO, R^2 = COOMe : Vincristine



Chimonanthine



Quadrigemine A

Further discussion on the structure variation of those types of alkaloids is unfortunately out of the scope of this manuscript. But, we still could appreciate the design power of the Mother Nature creating so many diverse structures.

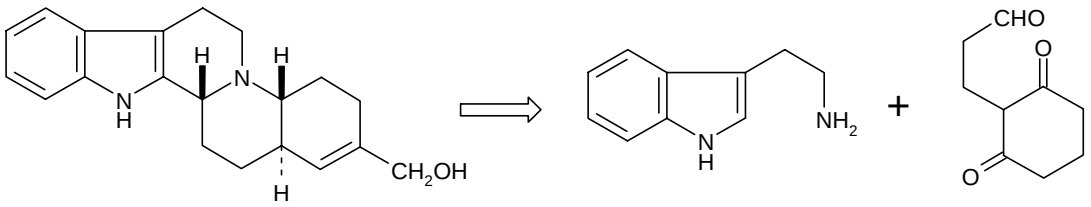
I.2. Molecular Symmetry in Organic Syntheses[8]

During the past several years, our laboratory has been pursuing syntheses of natural products using hidden molecular symmetry as guide for the synthesis design. From our experiences, we have learnt that identification of appropriate building blocks possessing certain symmetry element(s) could enormously simplify the otherwise complicated reaction pathways.

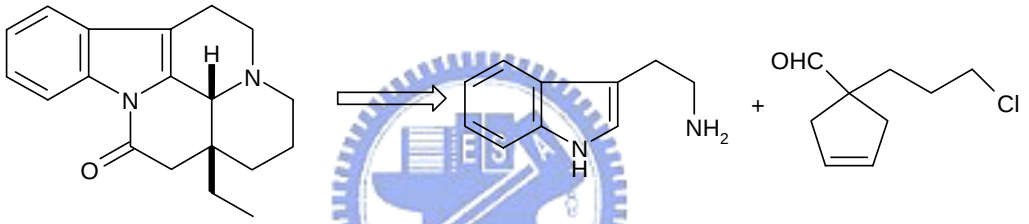
Previous achievement[9] on this context includes: the total syntheses of α-cuparenone[9a], tavacpallescensin[9b], occidol[9b], platyphyllide[9c], cuparene[9d], herbertene[9d],

9-isocyanonepupukeanane[9e], 3-epitacamonine[9f], 14-epitacamonine[9f], cryptolepine[9g], cryptotackiene[9g], tacamonine[9h], nicotyrine[9i].

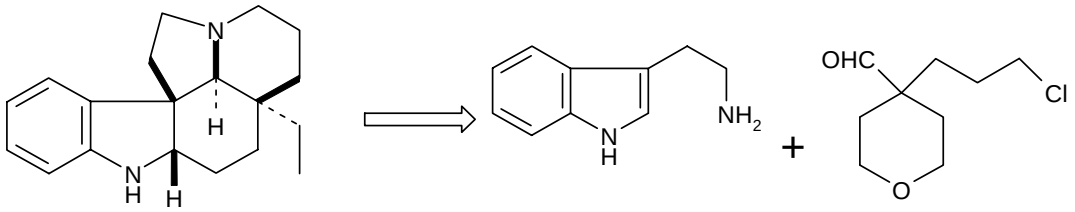
In this dissertation, efforts toward the syntheses of following indole alkaloids will be discussed.



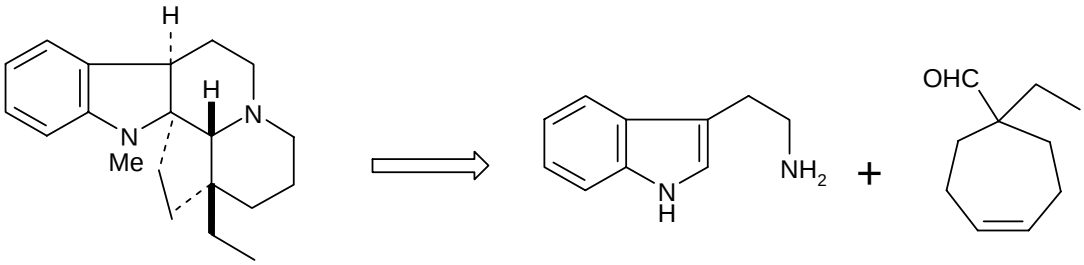
1
Tangutorine



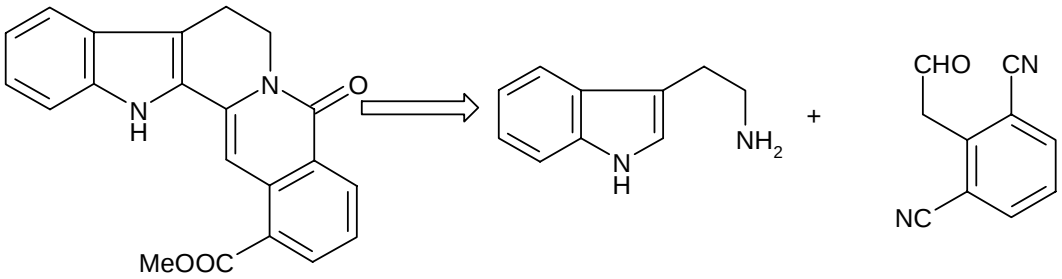
7
Eburnamonine



39
Aspidospermidine



20
Vallesamidine



40
Oxogambirtannine

In each case above, we could see that in our original plans we envisage the reaction of tryptamine with another subunit possessing (hidden) symmetry element.

I.3. Formation of Tetrahydro-β-Carboline

Formation of tetrahydro-β-carboline can be accomplished by several methods, such as:

- Bischler-Napieralski reaction: treatment of an amide – derived from tryptamine with an acid *via* its acid chloride or mixed anhydride derivative - with $POCl_3$, followed by reduction (generally with $NaBH_4$) of the resulting imine/iminium ion;

- Acid-induced Pictet-Spengler[10] reaction of tryptamine and and aldehyde;
- from an imide by treating with trifluoromethanesulfonic anhydride followed by reduction[11];
- from an imide by first converting it to an amide, then proceeds with Bischler-Napieralski reaction[12];
- by reacting a tryptophyl bromide with a pyridine derivative[13], followed by the reductive cyclization of the resulting N-alkylpyridinium salts, etc.

In our synthetic studies here, we use Pictet-Spengler reaction for the construction of the tetrahydro-β-carboline intermediates in all of our reaction plan. The mechanism of the reaction is depicted below (figure 1). Tryptamine reacts with an aldehyde to form a Schiff base, which under the influence of acid, it further reacts to give a tetrahydro-β- carboline *via* a spirocyclic intermediate.

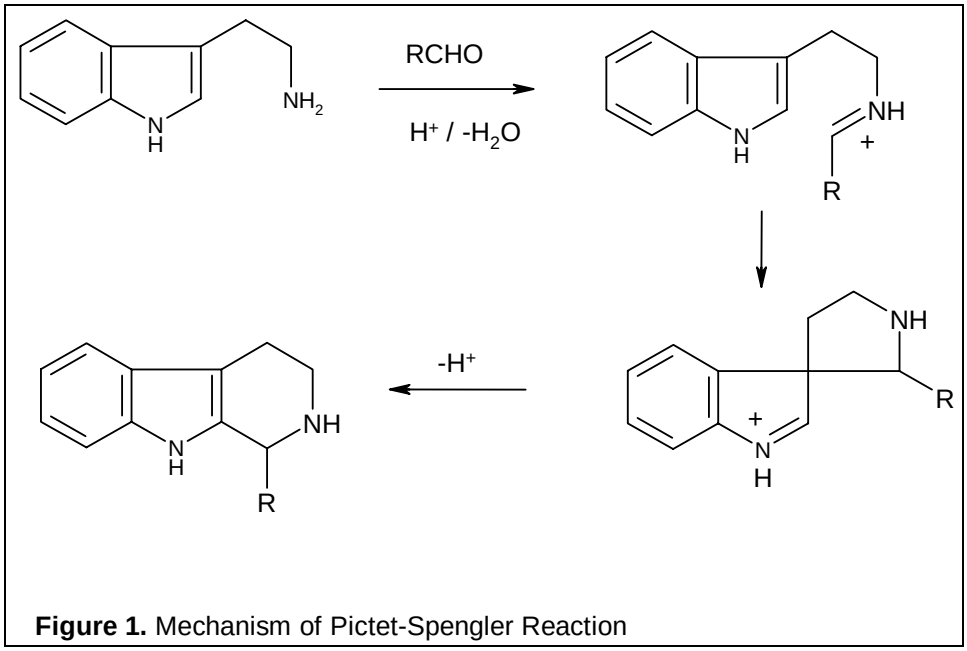


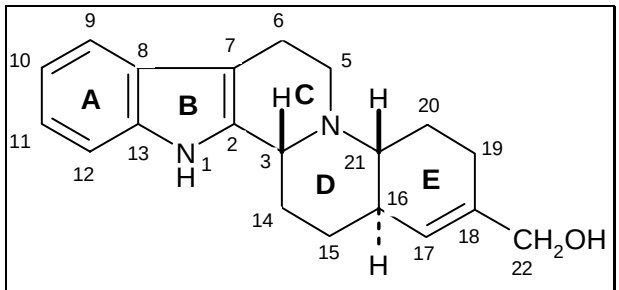
Figure 1. Mechanism of Pictet-Spengler Reaction

Recent development[14] on this reaction has been focusing on performing an asymmetric version of the reaction.

II. Indole Alkaloids Syntheses

II.1. Tangutorine

II.1.1. Introduction



1

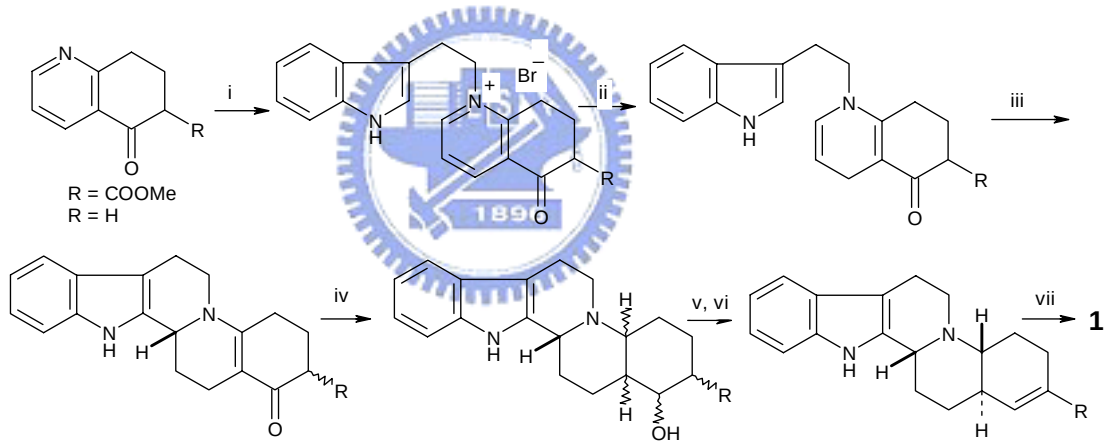
Tangutorine

In 1999, Duan et al[15] reported the isolation of racemic pentacyclic alkaloid, tangutorine **1** from the leaves of Chinese medicinal plant, *Nitraria tangutorum*. Recent study[16] on its potential anti-proliferation activity reveals that this compound induces a p21 suppression of all cyclins and their associated kinases, such as the topoisomerase II, and thus inhibited normal DNA replication and mitosis. Up to now, it is the only known natural product bearing the benz[*f*]indolo[2,3-*a*]-quinolizidine unit[17] .

Its synthesis was subsequently reported by Jokela (2001) and Hsung (2003)[18]. Scheme 1 depicts Jokela's total synthesis of tangutorine **1**. Jokela's synthesis suffered low yield of vinylogous amide reduction using $NaBH_4$/AcOH. Scheme 2 depicts R.P. Hsung's total synthesis of tangutorine **1**, the reduction was modified using dissolving

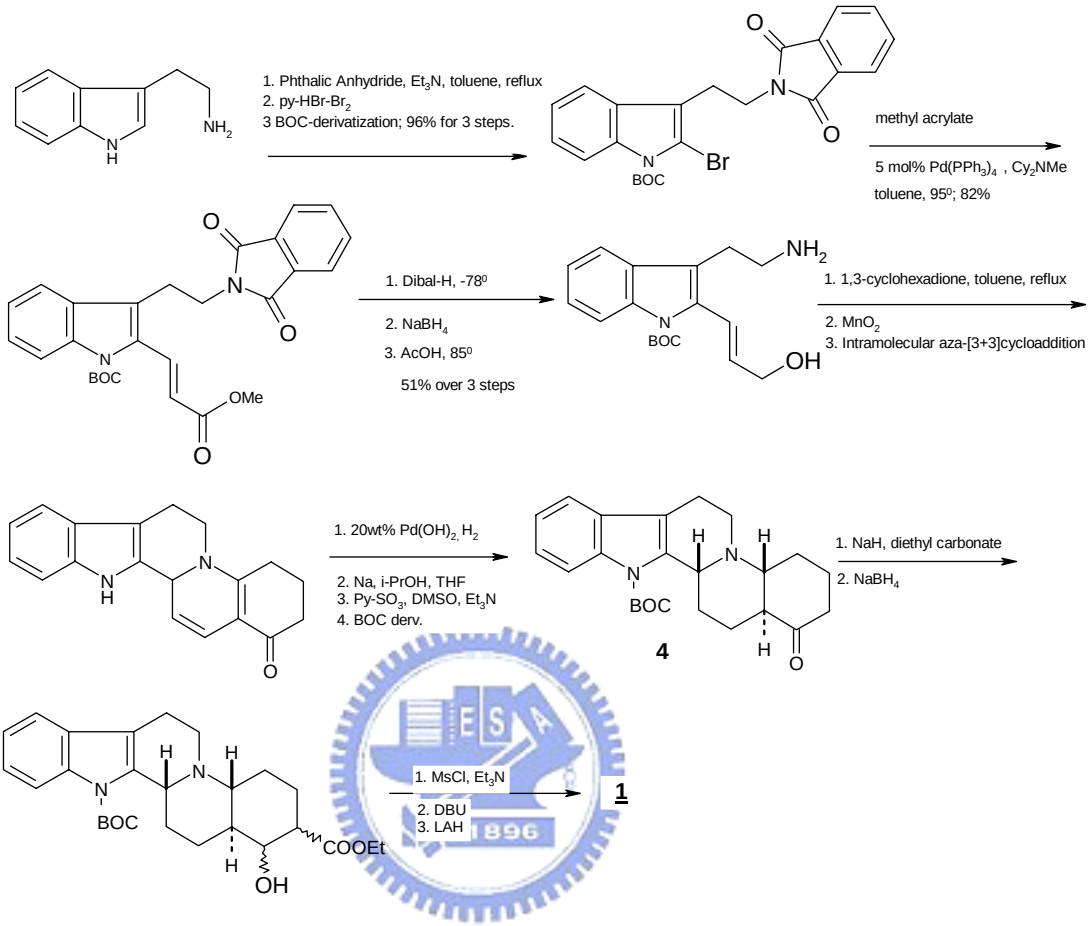
metal reduction. This reduction protocol also reduced the ketone functional group, so Parikh-Doering oxidation, followed by BOC-protection were conducted to form a single product, ketone **4**. NOE spectroscopy on ketone **4** revealed the stereochemistry of ketone **4** on its 3 stereocenters is exactly the same as that of tangutorine **1** (figure 2).

Scheme 1



Scheme 1: Jokela's Synthesis of Tangutorine. (i). Tryptophyl bromide, heat, 90%; (ii). $Na_2S_2O_4$, $NaHCO_3$, MeOH, H_2O, rt, 18h, 95%; (iii). HCl-MeOH, rt, 65h, 85%; (iv). $NaBH_4$, HOAc, rt; (v). MsCl, Et_3N, CH_2Cl_2, 0^0; (vi). DBU, 100^0, 6% over 3 steps; (vii). LAH, THF, rt, 90%.

Scheme 2



Scheme 2. R.P. Hsung's synthesis of tangutorine.

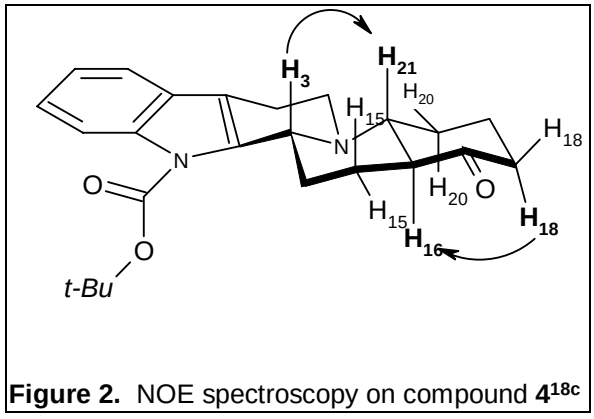
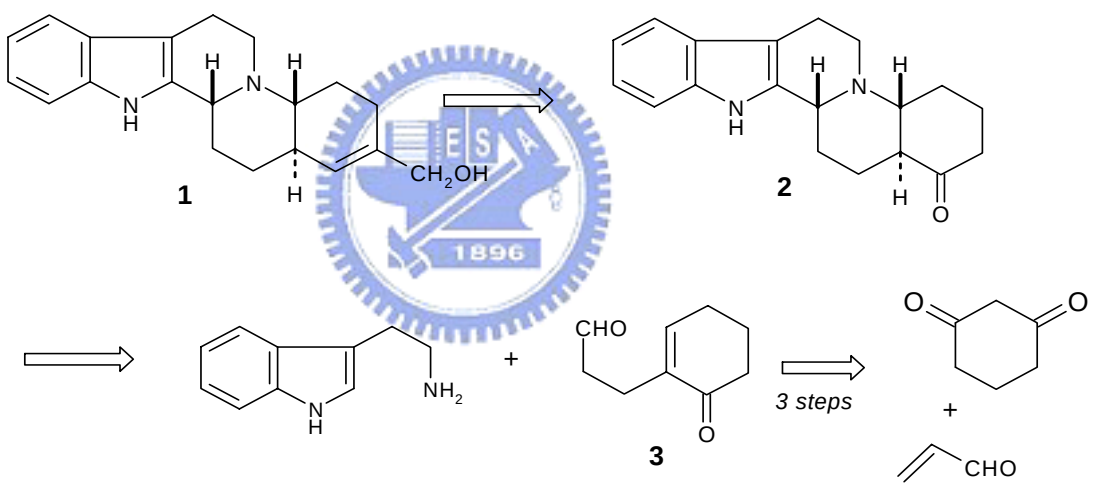


Figure 2. NOE spectroscopy on compound **4**[18c]

Scheme 3 depicts our retrosynthetic analysis of this target compound. We planned to construct the basic skeleton of **1** from an advanced intermediate **2**; intermediate **2** itself could be derived from Pictet-Spengler reaction followed by intramolecular ring closure of tryptamine with known aldehyde **3**, available from the reaction of symmetrical 1,3-cyclohexadione with acrolein in 3 steps[19] .

Scheme 3



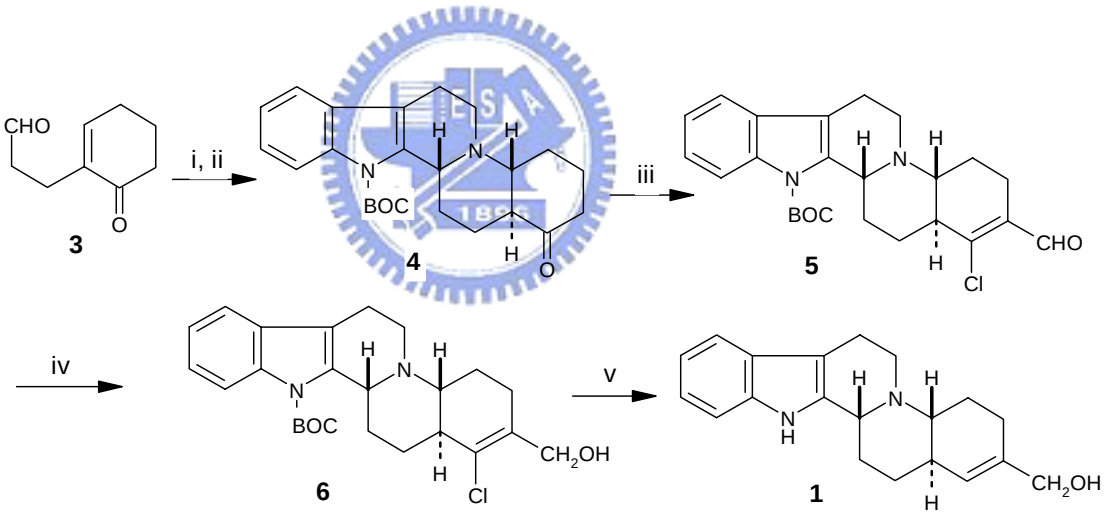
Scheme 3. Retrosynthetic Analysis on Tangutorine

II. 1. 2. Results and Discussions

In realization of our synthetic plan, tryptamine and aldehyde **3** were submitted to a Pictet-Spengler reaction, intramolecular 1,4-addition to the 2-cyclohexen-1-one subunit took place in situ to give a single compound. The product was not easy to purify, so a

BOC derivative was made to give **4**[18c] (31% yield over 2 steps). Thus at this point, we have intercepted the same intermediate **4** reported by Hsung[20]. The introduction of the alcohol side chain, following a previous work conducted in our lab (*vide infra*), involved treatment of **4** with Vilsmeier-Haack reagent ($POCl_3$/DMF) to generate vinylic chloride aldehyde **5**[21], borohydride reduction and simultaneous dechlorination and deprotection with sodium naphthalenide[22,23] to give tangutorine **1** (Scheme 4)**.**

Scheme 4



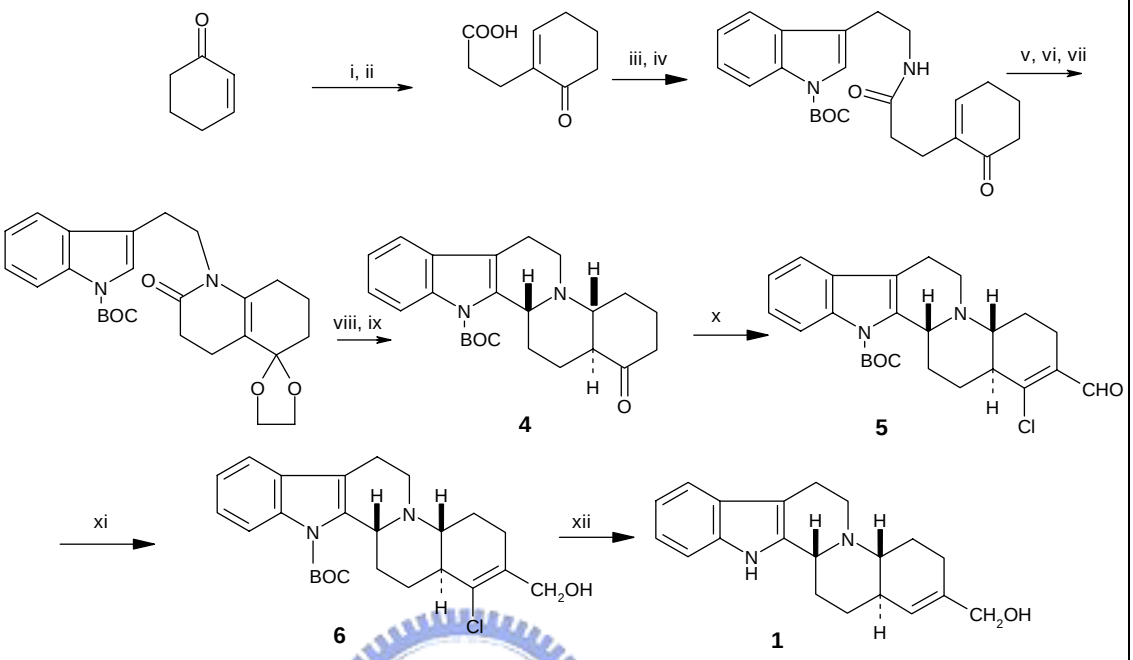
Scheme 4. Total Synthesis of Tangutorine (i). Tryptamine, TFA, CH_2Cl_2, 0^0-r.t. overnight; (ii). $(BOC)_2O$, DMAP (cat.), CH_2Cl_2, r.t. overnight, 31% for 2 steps; (iii). $POCl_3$, DMF, $CHCl_3$, r.t. 2 days, 47%; (iv). $NaBH_4$, EtOH, r.t. 15 min., 93%; (v). Na-naphthalenide, THF, 0^0C, 2 h., 52%.

Actually, the total synthesis of this target molecule has been accomplished in mid 2002 by a post-doctoral research fellow in our lab, Dr. E. Gorobets (Scheme 5)[24].

Tryptamine was condensed with an acid derived from cyclohex-2-enone, the resulting amide was BOC-protected at its indole portion, treated with NaH to induce intramolecular 1,4-addition to form the D-ring of tangutorine **1**. It was found that indole and ketone protection were necessary before proceeding to construct the C-ring (formation of tetrahydro-β-carboline) *via* Bischler-Napieralski reaction. Subsequent deprotection of the ketal generates compound **4.** The conversion from **4** to tangutorine **1** has been described above. It was erroneously concluded at that time that the resulting final product had different stereochemistry with **1**, as different NMR spectroscopic data were obtained due to different solvents used. (d_6-DMSO being used, whereas Duan used mixture of $CD_3OD/CDCl_3$).

Noteworthy to mention, it was later found that although the last reduction step could be conducted both with Li-naphthalenide or Na-naphthalenide, the use of Na-naphthalenide gave cleaner result.

Scheme 5

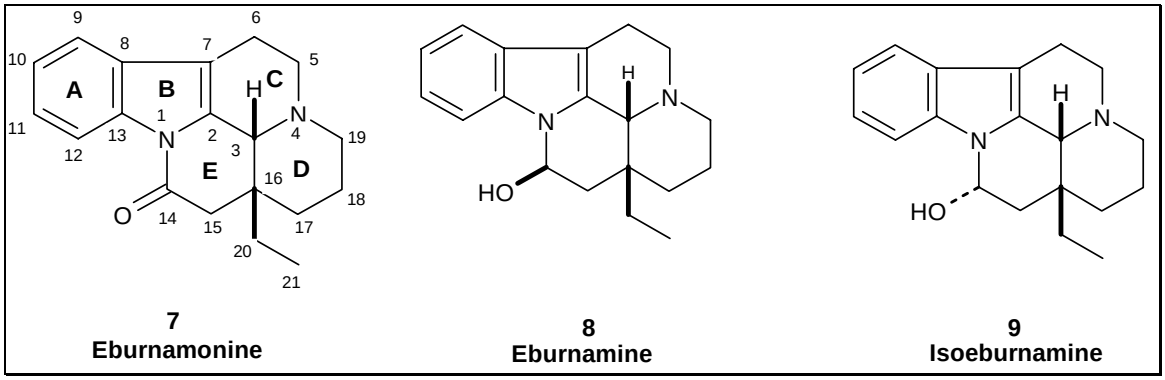


Scheme 5. Ho and Gorobets' Total Synthesis of Tangutorine. (i). DBU, methyl acrylate; (ii). KOH (aq); (iii). $ClCO_2Et$, Et_3N, Tryptamine, THF; (iv). $(BOC)_2O$, DMAP (cat.), CH_2Cl_2; (v).NaH; (vi). $(BOC)_2O$, DMAP (cat), CH_2Cl_2; (vii).ethylene glycol, PPTS, benzene, reflux; (viii). Bischler-Napieralski reaction:$POCl_3$, benzene, reflux; (ix). 1N HCl, *t*-BuOH, acetone; (x). $POCl_3$, DMF, $CHCl_3$, rt; (xi). $NaBH_4$, EtOH, r.t.; (xii). Li-naphthalenide, THF.

To summarize, by identification of appropriate building block that possesses the right symmetry element, we have accomplished the synthesis of tangutorine 1 in 5 steps with 7% overall yield.

II.2. Eburnamonine

II.2.1. Introduction



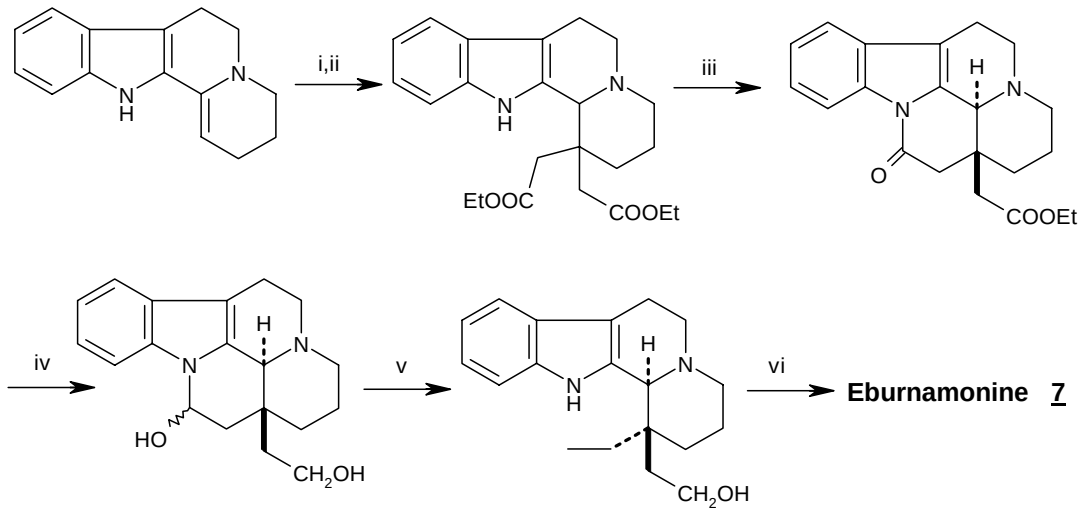
7
Eburnamonine

8
Eburnamine

9
Isoeburnamine

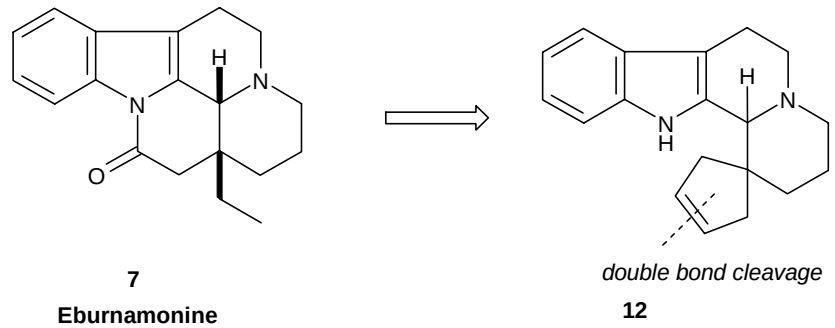
The pentacyclic indole alkaloids represented by eburnamonine (**7**), eburnamine (**8**) and isoeburnamine (**9**) have been isolated from numerous species of the plant family Apocyanaceae[25]. Interestingly, dextrarotatory, levorotatory, and racemic forms of eburnamonine exist in nature. The (-)-form, also known as vincamone (isolated from *Vinca minor*), is a drug that possesses stimulating activity for muscle and used as cerebrotonic, whereas both enantiomers have hypotensive effects. The profound pharmacological activities serve to elicit much effort for the synthesis of this type of compounds[26,27,28]. It is the synthetic work of Wenkert and Wickberg[29] that established the cis D/E-ring junction of the *Eburna* alkaloids. Other synthetic route that is relevant to ours is depicted in Scheme 6 (Lounasmaa and Karvinen's)[27b]

Scheme 6



Scheme 6. Lounasmaa and Karvinen's synthesis of Eburnamonine.(i). DIEA, ICH_2CO_2Et; (ii). $NaBH_4$, EtOH;(iii). NaOEt, EtOH; (iv). LAH, THF; (v). KOH, $H_2NNH_2.H_2O$, $(CH_2OH)_2$, 130^0C; (vi). $BF_3.OEt_2$, PCC, CH_2Cl_2.

With molecular symmetry or hidden symmetry as a guide for synthetic design for natural products, our attention was turned to the possibility of elaborating these substances from a precursor with local symmetry. Our analysis focused on a spirocyclic intermediate which on oxidative cleavage (at the isolated double bond) would release two functionalized carbon chains necessary for completing the ring system as well as erection of the angular ethyl group (figure 3). As stereochemical issue is concerned we believed that adjustment is possible even if the E-ring formation led to the epimeric series.



7
Eburnamonine

12

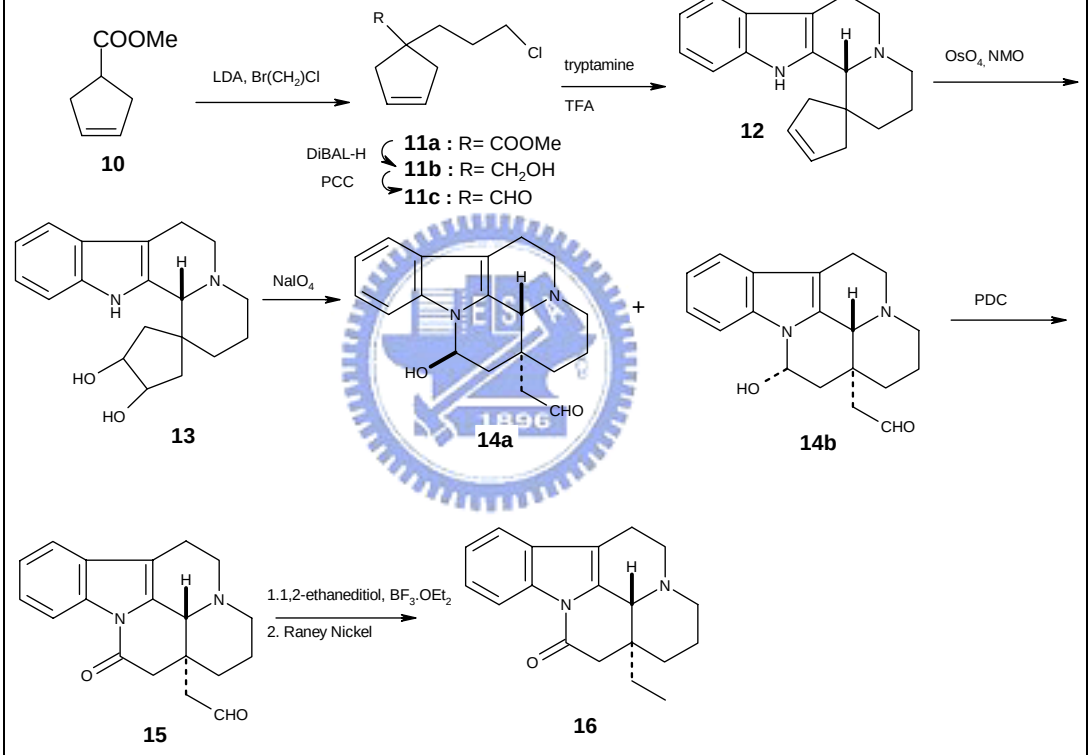
Figure 3. Synthetic Design for Eburnamonine

II. 2. 2. Results and Discussions

Aldehyde **11c** was identified as a component for combining with tryptamine by a *Pictet-Spengler* reaction. Access to **11c** from methyl 3-cyclopentenecarboxylate[30] in 3 steps was straightforward: alkylation with 1-bromo-3-chloropropane, reduction with Dibal-H, and PCC oxidation. Initially, we attempted to convert the ester group into a formyl group with Dibal-H but only the alcohol was obtained. Probably due to the steric hindrance of **11c,** we observed its optimal transformation into **12** by a TFA-promoted *Pictet-Spengler* reaction to the extent of only 50% completion. In any event, we next carried out a *vic*-dihydroxylaton with catalytic amount of OsO_4 and *N*-methylmorpoline *N*-oxide as the reoxidant. Only one product (**13**) was isolated (66% yield). On treatment of the diol with $NaIO_4$ a mixture of pentacyclic aldehydes (later identified as **14a** and **14b** which are epimeric at the carbinol center) was isolated. In order to establish the identity of these aldehydes, particularly the nature of the ring junction, the mixture was

oxidized with PDC. Production of a single product confirmed the notion and it showed that the cyclization was selective. Dithioacetalization of the aldehyde mixture followed by desulfurization with *Raney* nickel led to 3-epi-eburnamonine **16**[27g,29]. Therefore, our objective was yet to be reached (Scheme 7).

Scheme 7

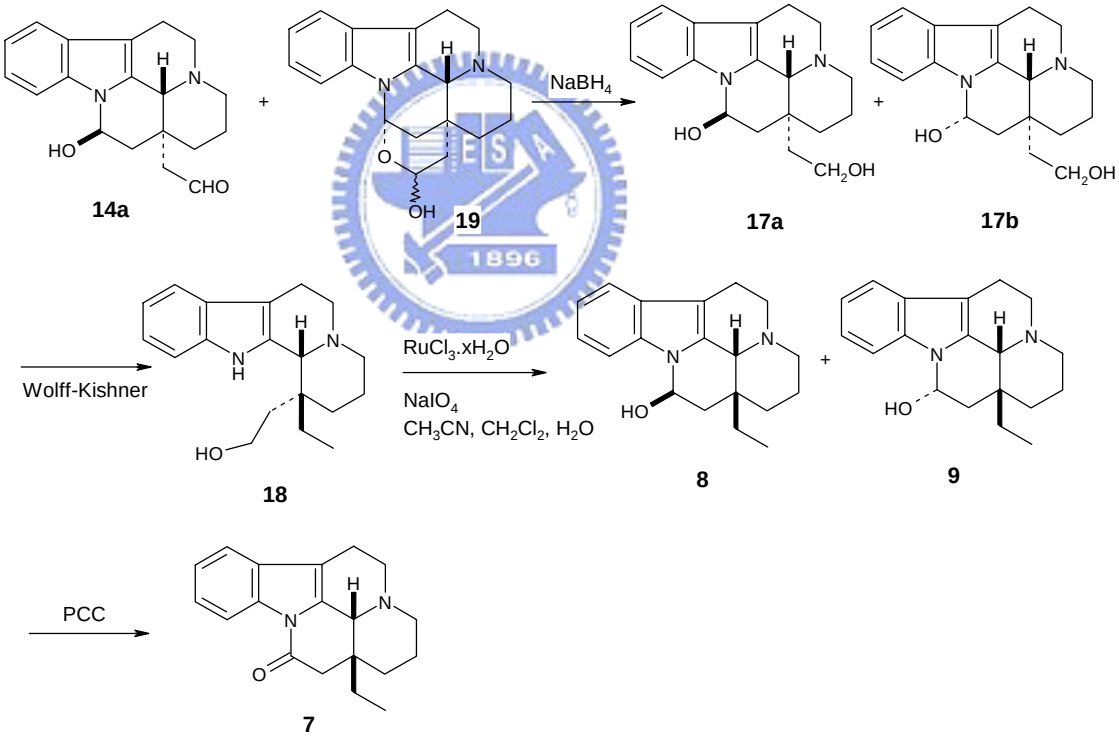


Scheme 7. Elaboration of the Spirocyclic Intermediate **12**, Formation of Epi-eburnamonine

Further identification of the pentacyclic aldehydes proved rather trivial since **14b** readily underwent cyclization to lactol **19** upon column chromatography. Exposure of **14a** and **19** to $NaBH_4$ delivered **17a** and **17b**[27b], respectively. Deoxygenation of **17a/17b** to **18** by a *Wolff-Kishner* reduction under the *Huang-Minlon* conditions proceeded

smoothly. Alcohol **18** is a known compound and its conversion to eburnamonine has been described[27b,31]. However, we were not able to repeat the transformation, using either $BF_3.OEt_2$/PCC[27b,31] or the perrhenate protocols[27d,27g]. We had to carry out a $RuCl_3$-catalyzed periodate oxidation[32] to yield a 1:1 mixture of eburnamine **2** and isoeburnamine **3**[33], before treatment with PCC to afford eburnamonine **7**[33b]. (Scheme 8)

Scheme 8

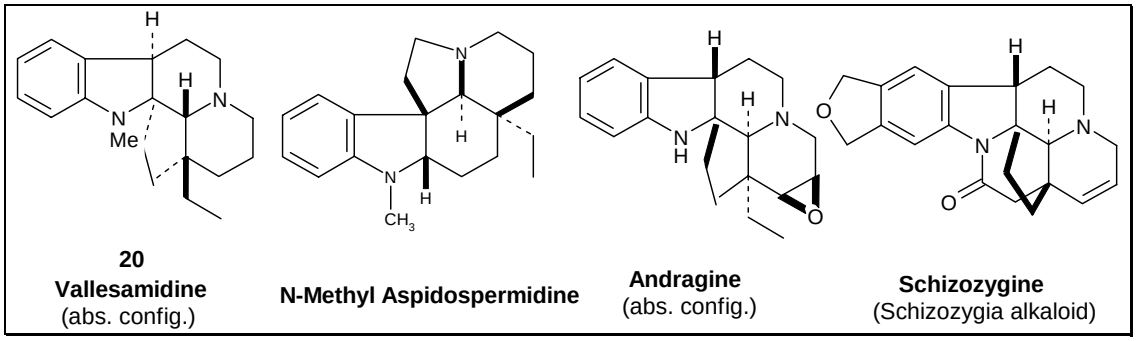


Scheme 8. Total Synthesis of Eburnamonine **7.**

II.3. Vallesamidine

II.3.1. Introduction

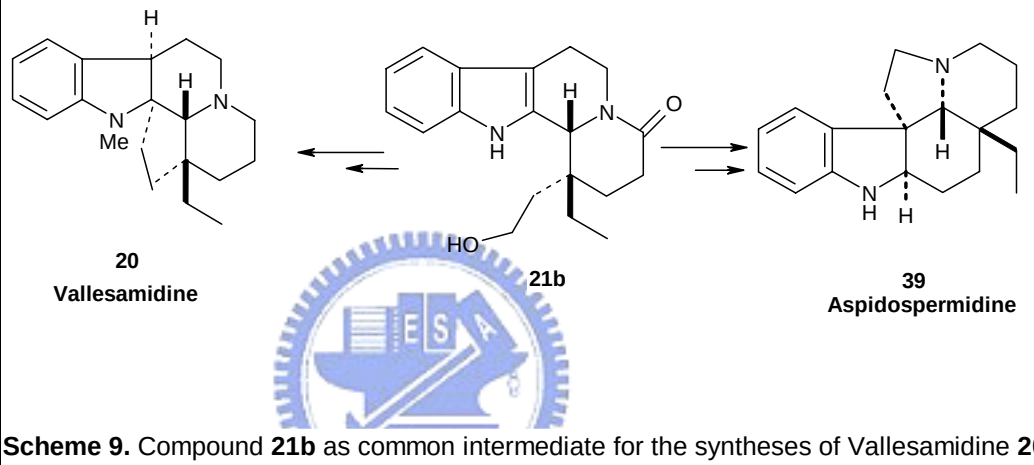
Vallesamidine **20** possesses a unique 2,2,3-trialkylindoline structure. This substance was isolated in 1965 from *Vallesia dichotoma* (Ruiz et Pav)[34]. Due to its scarce amount, it was originally thought to be isomeric with N-methyl aspidospermidine, that possesses typical 2,3,3-trialklyindoline structure. Later on, Djerassi et al[35] determined its molecular structure and absolute configuration by X-ray diffraction. The occurrence of alkaloids possessing 2,2,3-trialkylindoline structure is very rare. Up until now, the only other compound isolated so far is andragine. It should be noted that as vallesamidine and andragine have different absolute configuration, rationally they are considered to be generated from different biosynthetic pathways. Schizozygine, a schizozygia alkaloid have both a 2,2,3-trialkylindoline structure and eburna skeleton.



Total syntheses of this compound have been reported by several groups; Heathcock[36] being succeeded in achieving its first total synthesis. Levy[37], meanwhile, achieved its synthesis by treatment of tabersonine with Zn powder in acetic acid.

Recently, Okada[38] also succeeded in constructing this structure by reductive cyclization reaction from a 2,3-dialkylindole derivative, which has been known as an intermediate for the synthesis of aspidospermidine. (Scheme 9)

Scheme 9



20
Vallesamidine

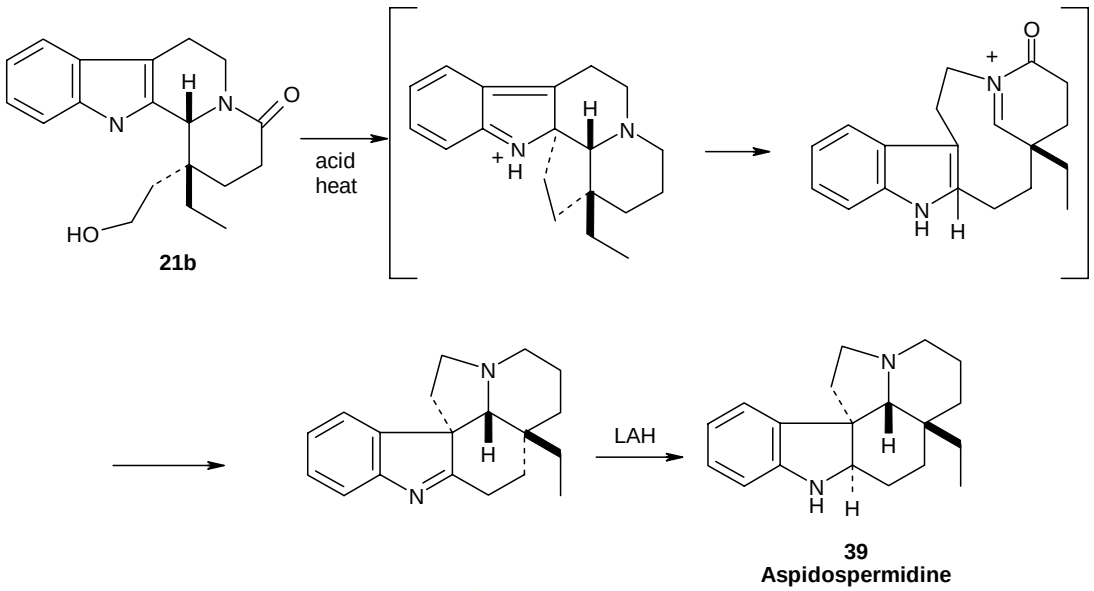
21b

39
Aspidospermidine

Scheme 9. Compound **21b** as common intermediate for the syntheses of Vallesamidine **20** and Aspidospermidine **39.**

The conversion of compound **21b** to aspidospermidine **39** under acidic condition (H_2SO_4) has been known due to pioneering work of Harley-Mason[39]. Later on, Fuji[31] used Lewis acid ($BF_3.OEt_2$) to achieve the same conversion. An ionic mechanism[36] was proposed for the rearrangement as depicted below. Thus, under the influence of acid, compound **21b** is thought to form an structure similar to 2,2,3-trialkylindoline, which rearranged to quebrachamine-type structure, and further to a 2,3,3-trialkylindolenine structure. LAH treatment on this indolenine intermediate would generate aspidospermidine **39** (Scheme 10).

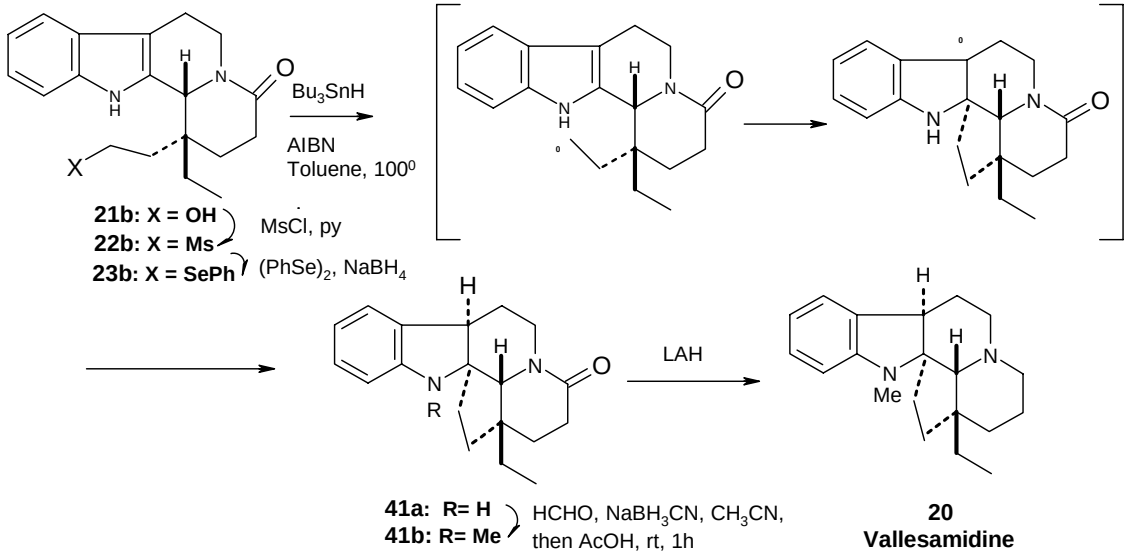
Scheme 10



Scheme 10. Mechanism for the acid-induced rearrangement of **21a** to Aspidospermidine **39**

The same compound **21b** was converted by Okada[38] to vallesamidine **20** *via* a selenide derivative **23b**. Thus, treatment of the *cis* selenide **23b** under radical reaction condition gave a compound possessing the desired 2,2,3-trialkylindoline structure. (Scheme 11). Methylation of the indolinine nitrogen and LAH reduction of the amide functionality gave the target molecule, vallesamidine **39**.

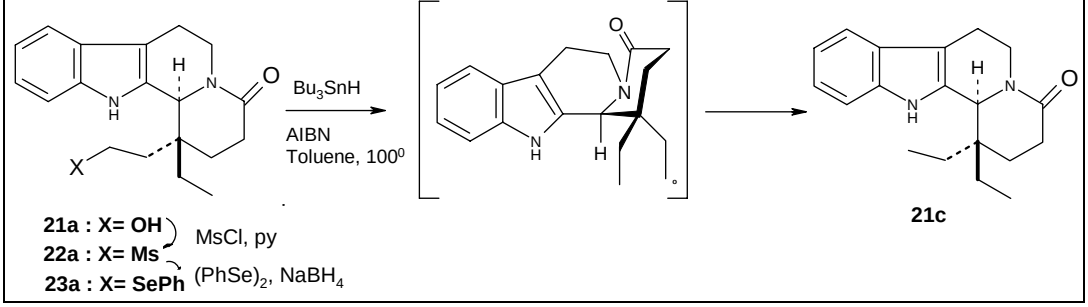
Scheme 11



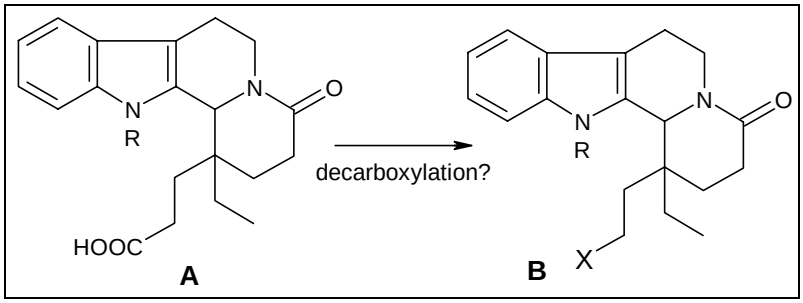
Scheme 11. Conversion of **23b** via a radical reaction mechanism to 2,2,3-trialkylindoline structure **41a**, an advanced intermediate for the synthesis of Vallesamidine **20**

The epimeric selenide *trans* **23a**, on the other hand was converted to compound **21c** under the same reaction condition. Okada reasoned that on **23a**, the radical formed was located away from the indolic subunit causing the radical reduction pathway predominated over the cyclization process to form 2,2,3-trialkyl indoline structure (scheme 12).

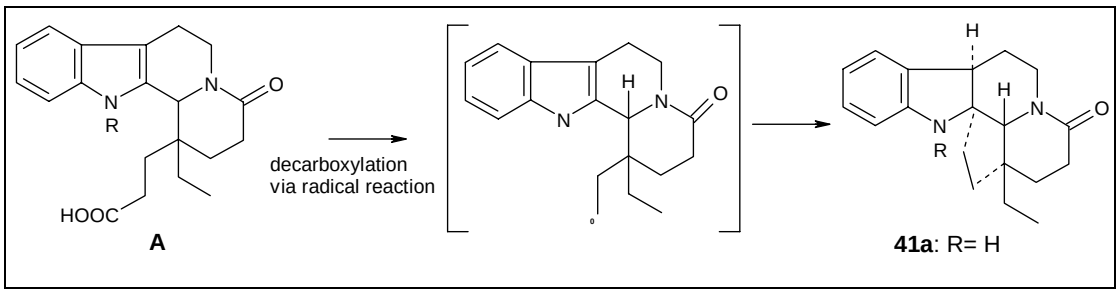
Scheme 12



We have been interested in pursuing the possibility of decarboxylation of structure **A** to **B**, in which the carboxylic acid is replaced by other functionality, such as halide(s).

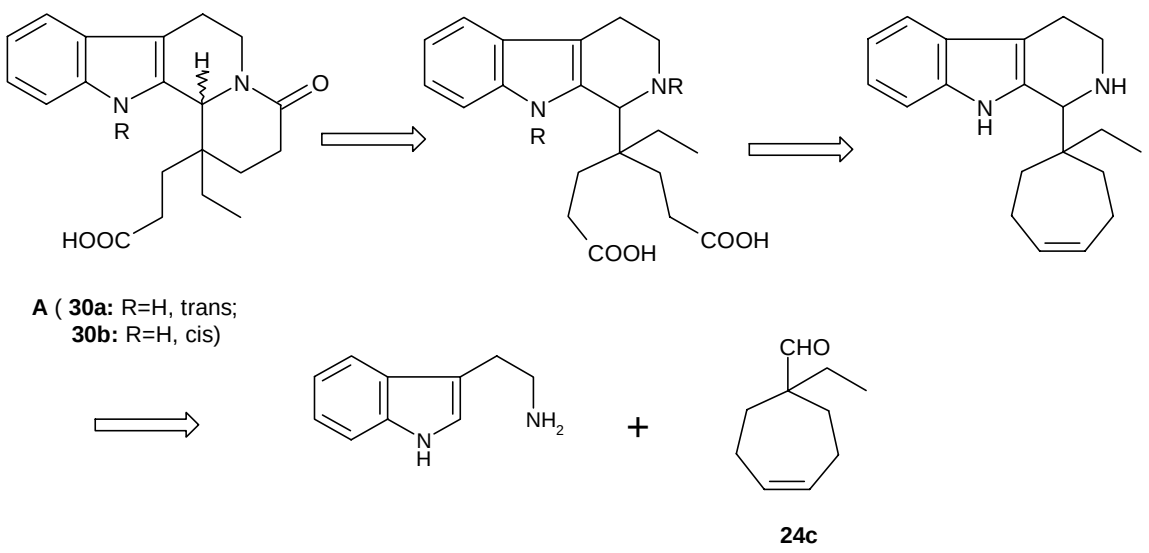


According to literature, several methods existed for achieving this type of reaction, namely the Hunsdiecker-Borodin reaction[40], and its modification[41], treatment with lead tetraacetate[42], with iodosobenzene diacetate[43], Barton decarboxylation[44] reaction, etc. As they normally proceed through radical type reaction, it is then possible to arrive at a structure **41a** during the course of decarboxylation; elaboration of **41a** to Vallesamidine **20** has been reported (see scheme 11).



In our original plan, we hope to construct structure A as depicted in scheme 13, using symmetrical aldehyde **24c.**

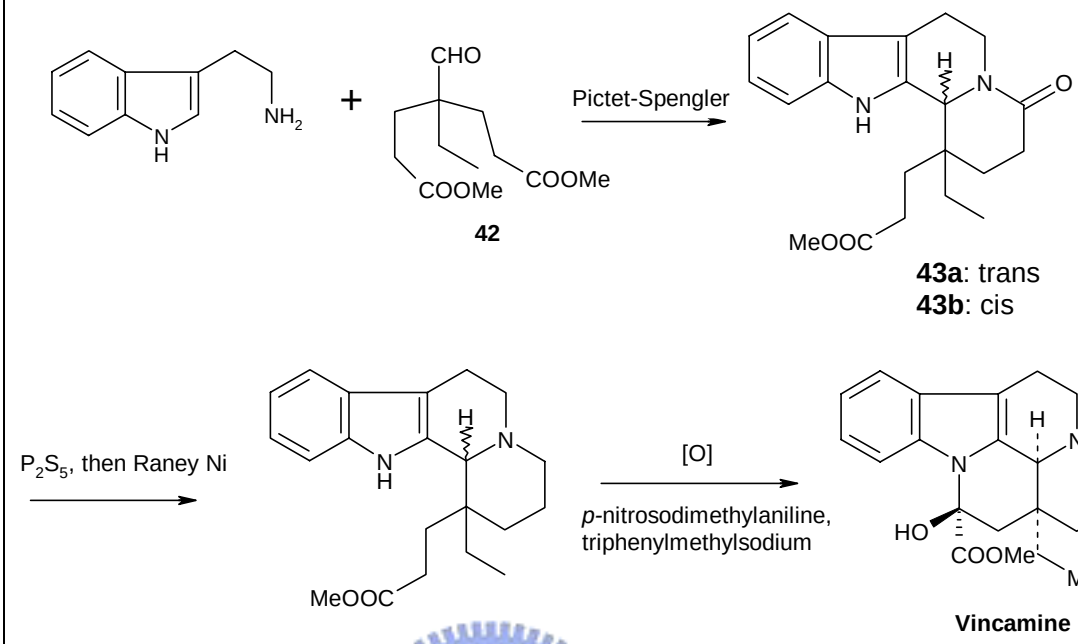
Scheme 13



Scheme 13. Retrosynthetic Analysis for preparation of structure **A**

Compounds **43a/43b,** methyl esters of acids **30a/30b** were already prepared by M. E. Kuehne early in 1964 during his synthesis of vincamine[45] (scheme 14).

Scheme 14



Scheme 14. Kuehne's Synthesis of Vincamine.

II. 3. 2. Results and Discussion

Aldehyde **24c** was prepared from ethyl ester of known compound cyclohept-4-enyl carboxylic acid[46]. Alkylation of the mono ester, and reduction of the ester functionality to formyl group was achieved via its alcohol derivative. Pictet-Spengler reaction of tryptamine and aldehyde **24c** proceeded uneventful providing the tetrahydro β-carboline derivative **25** (scheme 15). Before cleaving the double bond protection of both nitrogens with BOC group was necessary.

The attachment of a carbonyl (forming an amide[47]) or a carboxyl (forming a carbamate[48]) functional groups to the non-indolic nitrogen in tetrahydro-β-carbolines is

known to generate conformational isomers which are revealed in NMR spectra (figure 4). This phenomenon was also found with compound **26**, as shown in both of its ^{1}H- and ^{13}C-NMR, two conformational isomers were observed in ratio 1.7: 1.0 (figure 5).

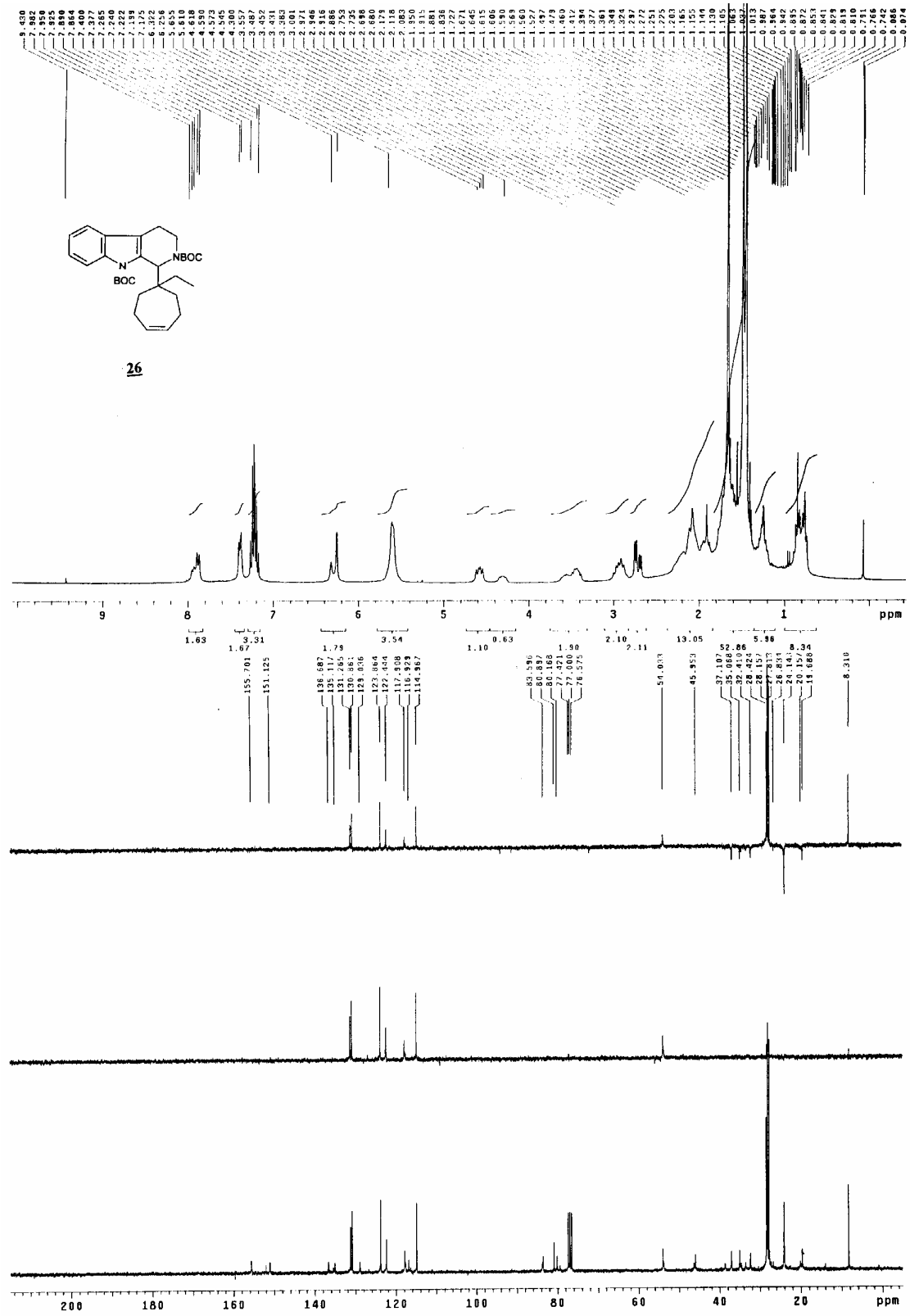
2 Amide conformational isomers of (6:1) ratio

2 carbamate conformational isomers

Figure 4. Attachment of carbonyl or carboxyl to non indolic nitrogen of tetrahydro-β-carbolines generate conformational isomers.

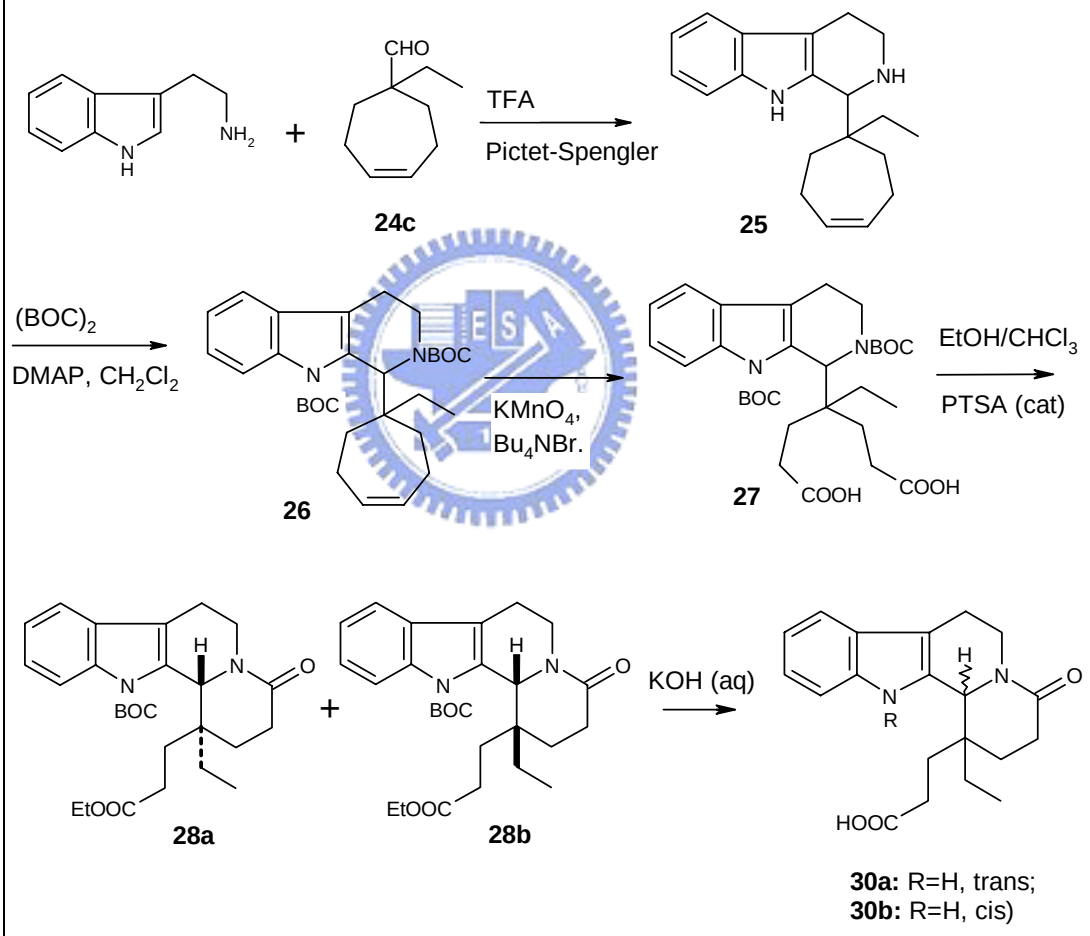
With compound **26** on hand, we then proceeded with the cleavage of the olefin to diacids. After some failure with several reaction conditions, such as ruthenium-catalyzed periodate oxidation, we finally managed to cleave the double bond to diacid in one step using phase transfer catalysis promoted permanganate oxidation[49]. As the high polar diacid was difficult to handle, we decided to proceed with esterification. To our delight, the esterification proceeded smoothly providing a mixture of trans **28a** and cis **28b**.

Figure 5. NMR of Compound **26:** presence of 2 conformational isomers.



(**28a**:**28b** = 1.3: 1). Treatment of this mixture of **28a/28b** with aqueous KOH in methanolic solution hydrolyzed both the BOC protecting group and the ester functionality giving a mixture of acids **30a/30b.**

Scheme 15

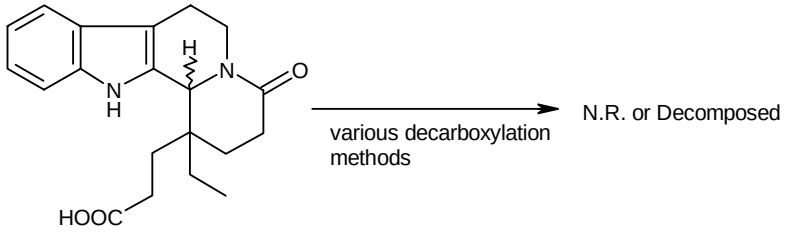


Scheme 12. Preparation of Acids **30a/30b**

With acid **30a/30b** smoothly prepared, the crucial decarboxylation step could be attempted. Treatment of acids **30a/30b** with several reagents: lead

tetraacetate/$Cu(OAc)_2$, lead tetraacetate/LiCl, iodosobenzene diacetate and red HgO did not give the desired 2,2,3-trialkylindoline nor 2,3,3-trialkylindoline product (scheme 16).

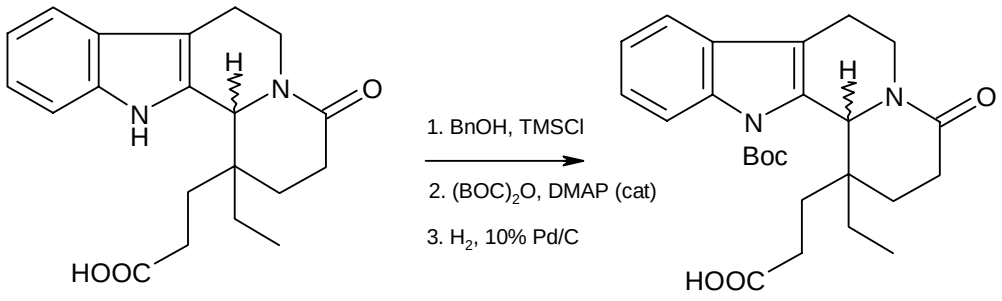
Scheme 16



30a/30b

As we believed all these reagents are perhaps too drastic for the indole bases, we prepared BOC protected acids **33a/33b** as depicted in scheme 17.

Scheme 17



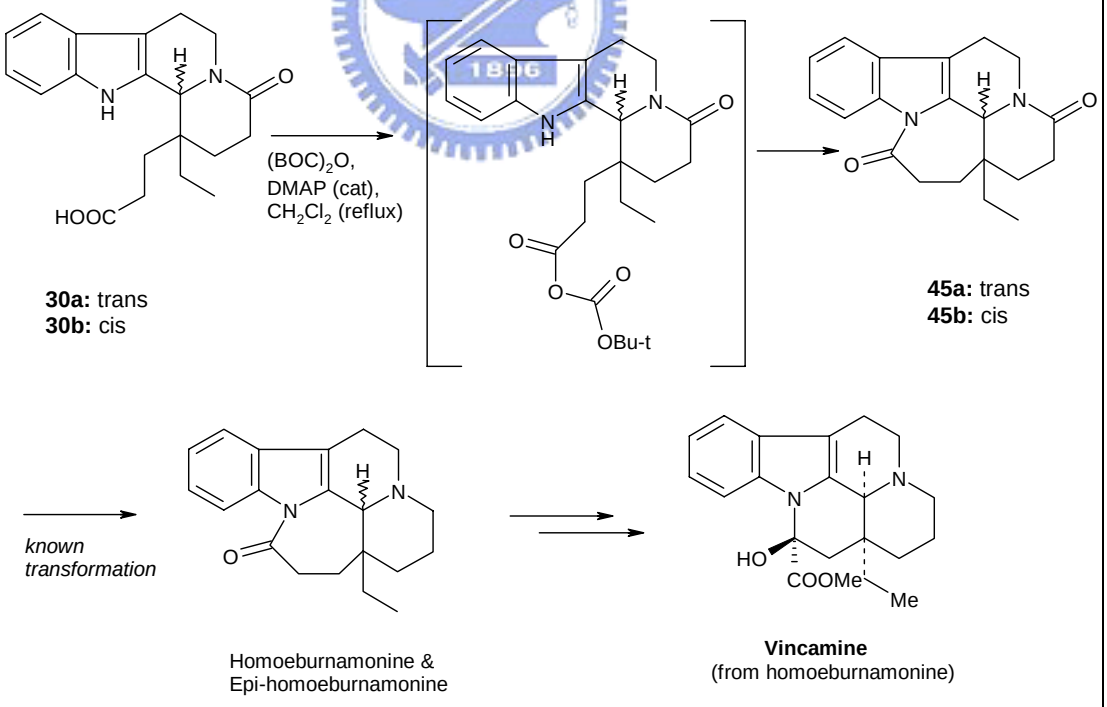
30a: trans
30b: cis

33a: trans
33b: cis

Scheme 17. Preparation of BOC-protected acids **33a/33b.**

Attempt to protect acids **30a/30b** with $(BOC)_2O$/DMAP(cat) directly did not give the desired **33a/33b**, instead epi-19-oxo-homoeburnamonine **45a** and 19-oxo-homoeburnamonine **45b** were formed. Their formation could be explained by activation of the acid functionality to 'mixed carbonate' intermediates, which then undergo an intramolecular cyclization forming **45a/45b**. Redox protocol on **45b** (LAH, then CrO_3/pyridine) has been described in the literature to give homoeburnamonine[60], another advanced intermediate in the synthesis of vincamine (scheme 18).

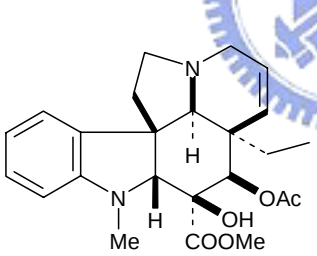
Scheme 18



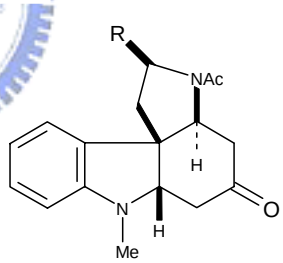
Scheme 18. Direct protection of acids **30a/30b** gave homoeburnamonine/epi-homoeburnamonine **45b/45a;** the cis epimer **45b** can be converted to Homoeburnamonine, an advanced intermediate for the synthesis of Vincamine

Indole nucleus does not interfere with the Barton decarboxylation reaction. Literature examples include tryptophan-like structures: J. D. Winkler's synthetic study on vindorosine (scheme 19); P. Magnus' synthetic study on vinblastine (scheme 20); D. Crich's synthetic studies on ent-debromoflustramine B and flustramine B (scheme 21). S. F. Martin's synthetic study on tetrahydroalstonine (scheme 22) in which the carboxylic acid functionality has been replaced by hydrogen derived by trapping of the intermediate radicals with *t*-BuSH. In addition, bromodecarboxylation on indole bases was also provided by Ziegler (scheme 23), selenodecarboxylation by D. Crich (scheme 24).

Scheme 19



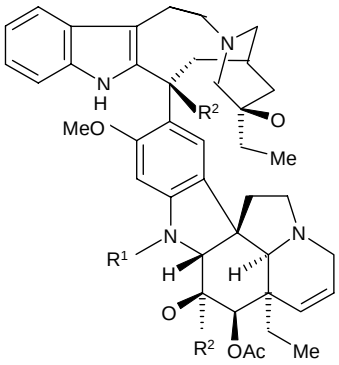
Vindorosine



Barton decarboxylation:
R= -COOH to R= -H (73%)

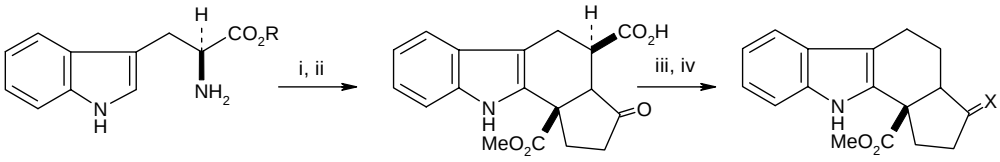
J.D. Winkler; R.D. Scott; P.G. Williard, *J. Am. Chem. Soc.* **1990**, *112*, 8971.
(Formal Synthesis of vindorosine)

Scheme 20



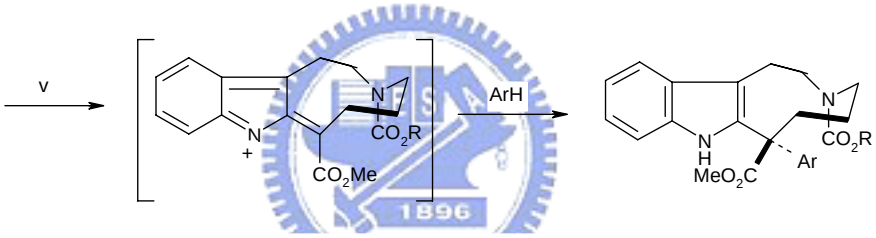
P. Magnus, M. Ladlow, C.S. Kim and P. Boniface
Heterocyles, **1989**, *28*(2), 951.

R^1 = Me, R^2 = COOMe : Vinblastine



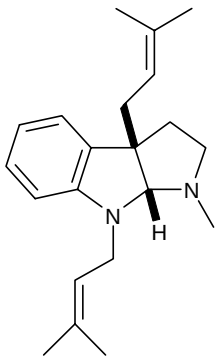
R= -CH_2Ph, TsOH salt
R= -H, L-Tryptophan

major

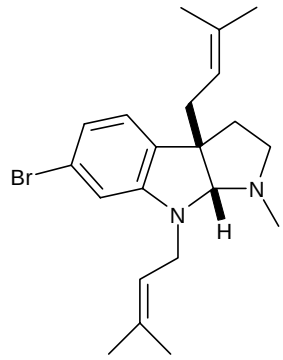


i. dimethyl α-ketoglutarate, THF, heat; ii. hydrogenolysis; iii. Barton decarboxylation: a. *i*-BuOCOCl, NMM, -15^0, b, Et_3N, N-hydroxy-2-thiopyridone, c. *t*-BuSH (10 eq.), hv; iv. Belleau's reagent, then Raney Ni desulfurization; v. chloroformates, ROCOCl

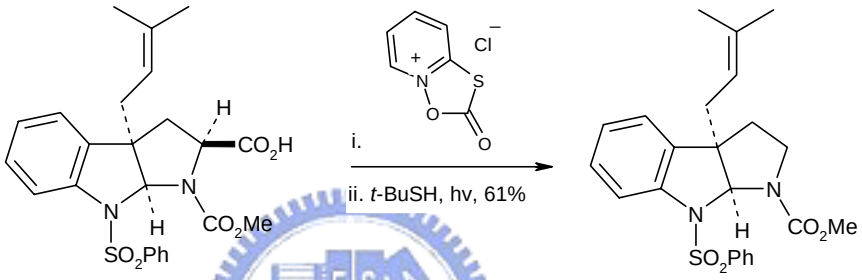
Scheme 21



(+)-ent-Debromoflustramine B

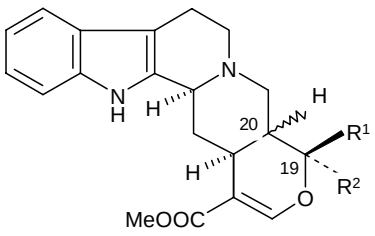


Flustramine B

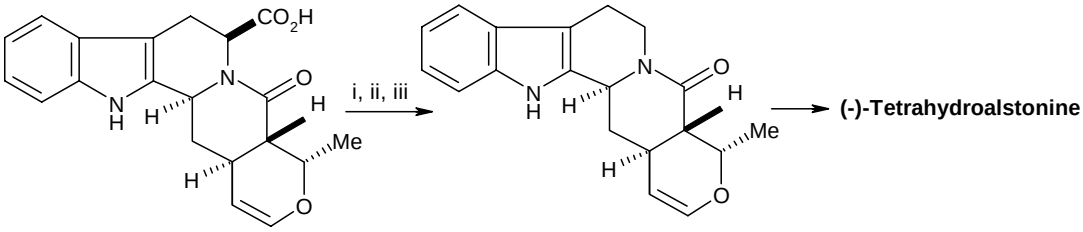


M. Bruncko; D. Crich; R. Samy, *J. Org. Chem.* **1994**, *59*, 5543.

Scheme 22



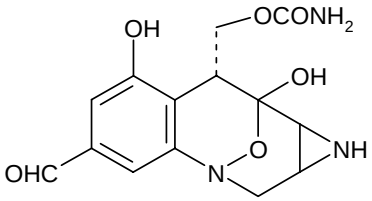
α-H_{20}: R^1 = H; R^2 = Me : **(-)-Tetrahydroalstonine**
β-H_{20}: R^1 = H; R^2 = Me : **(-)-Ajmalicine**
β-H_{20}: R^1 = Me; R^2 = H : **(-)-19-epi-ajmalicine**



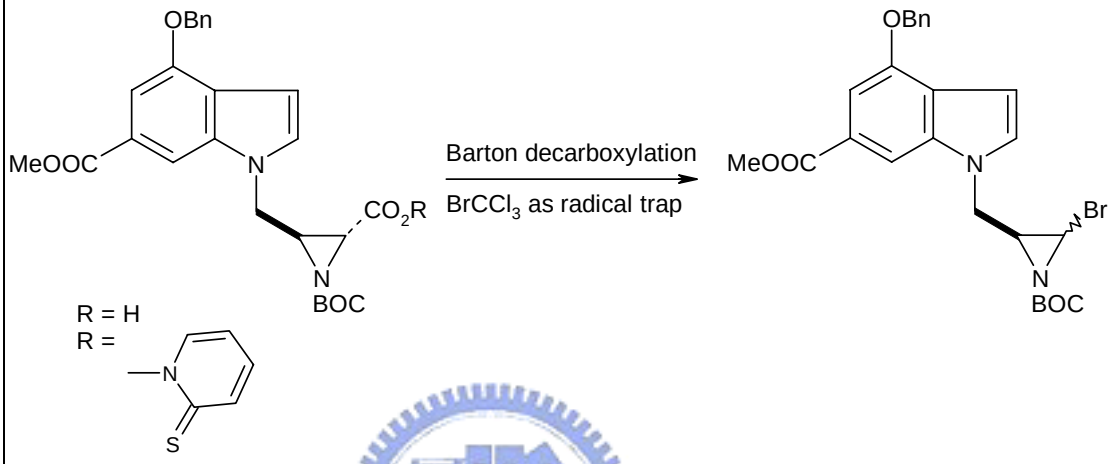
(i). *i*-BuOCOCl, NMM; (ii). C6H4NaNOS, TEA; (iii). t-BuSH, hv.

S.F. Martin; C.W. Clark; J.W. Corbett, *J. Org. Chem.* **1995**, *60*, 3236.

Scheme 23

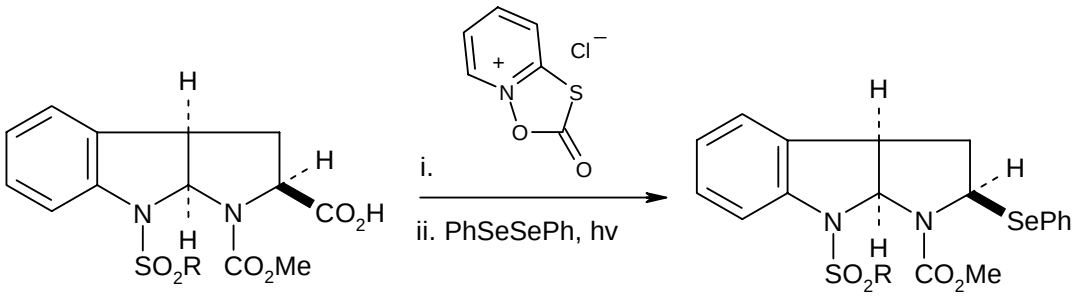


FR-900482



F.E. Ziegler; M. Belema, *J. Org. Chem.* **1997**, *62*, 1083.
Synthesis of core nucleus of FR-900482.

Scheme 24



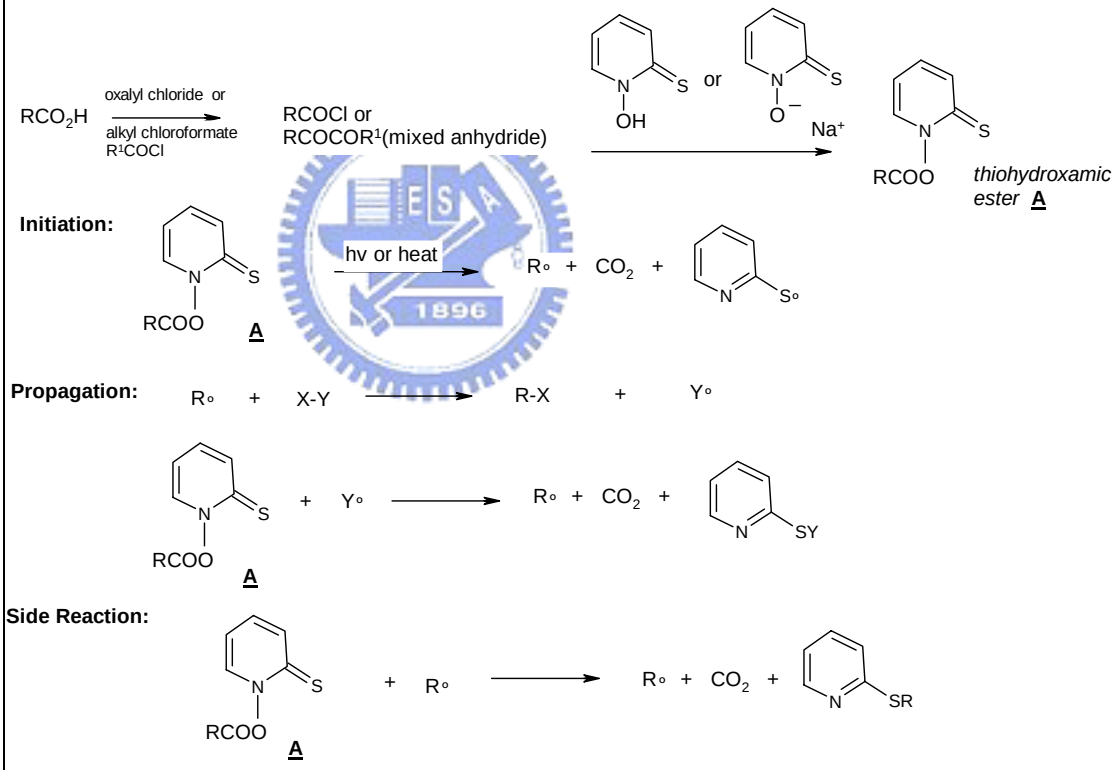
R = Ph or *p*-Tol

R = Ph or *p*-Tol
endo : exo = 19 : 1
80-90%

R.L. Meza-Leon; D.Crich; S.Bernes; L.Quintero, *J. Org. Chem.* **2004**, *69*, 3976.

The mechanism for Barton decarboxylation reaction can be described as in scheme 25. The radical formed by dissociation of thiohydroxamic ester **A** (by light irradiation or heating) in the presence of suitable trapping reagents could be converted to halides, sulfides, selenides, tellurides, alcohols or just replacing the carboxylic acid functionality with hydrogen.

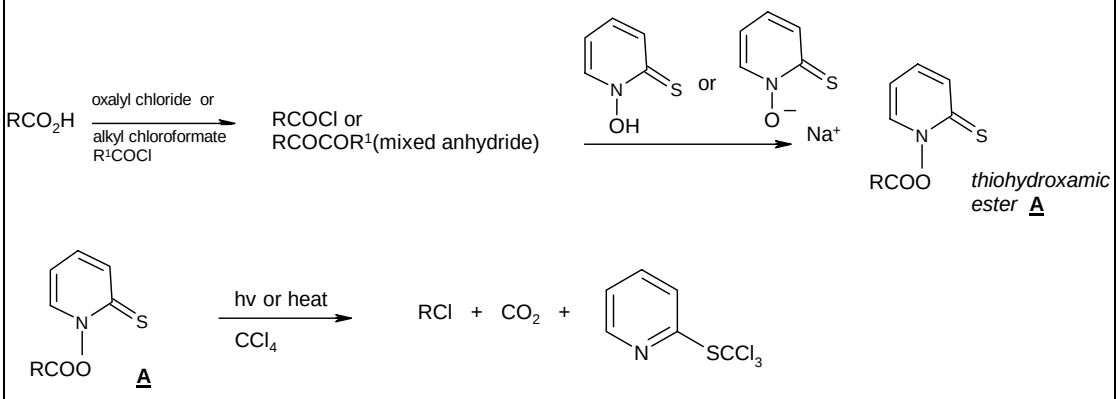
Scheme 25



Scheme 25. Mechanism of Barton Decarboxylation Reaction.

Example for chloro-decarboxylation is provided in scheme 26.

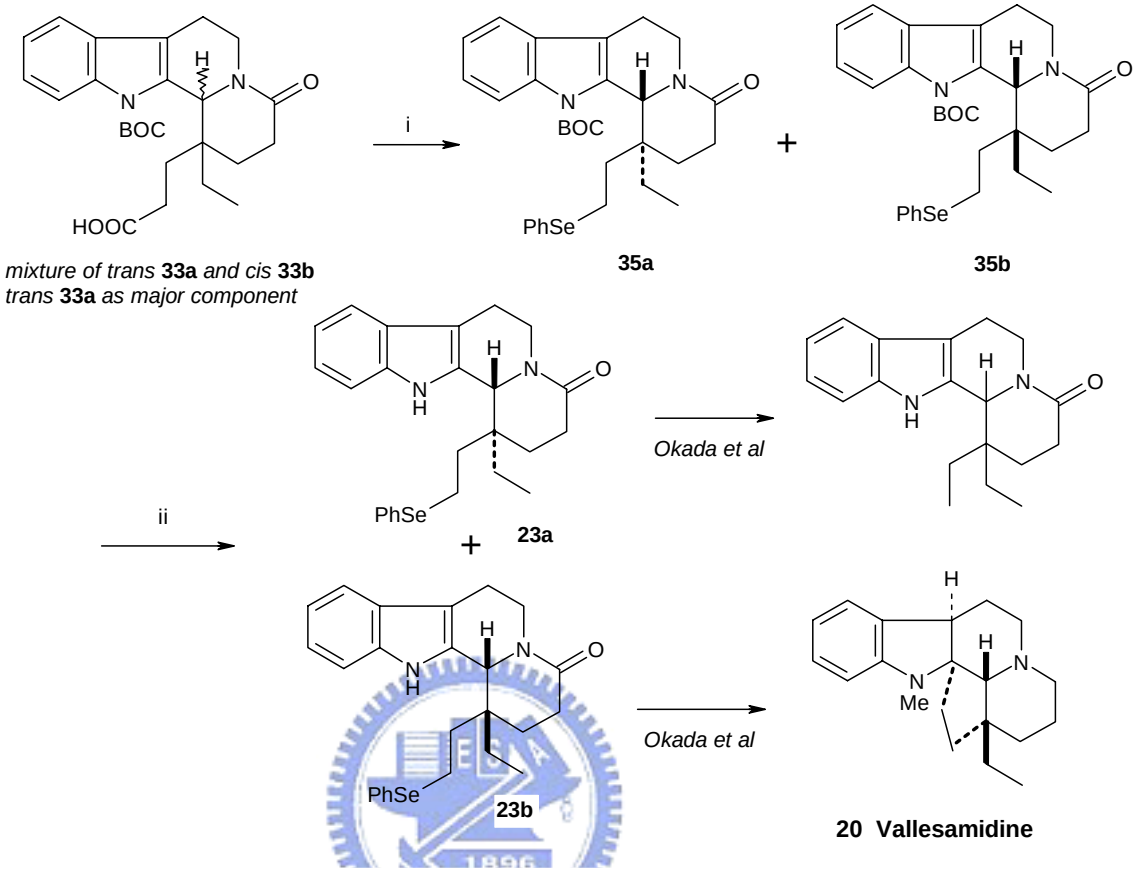
Scheme 26



Scheme 26. Barton Decarboxylation Reaction: trapping the radical intermediate with CCl_4.

The BOC-protected acids **33a**/**33b** reacted smoothly under Barton decarboxylation reaction with diphenyl diselenide as trapping agent to form the BOC-protected selenides **35a/35b.** Deprotection of **35a/35b** under basic condition provide **23a/23b**, whose physical and spectroscopic data are in accordance with Okada's report[38]. As described above, Okada has converted compound **23b** under radical condition to vallesamidine **20**, our result constitutes a formal synthesis of vallesamidine **20** (scheme 27).

Scheme 27

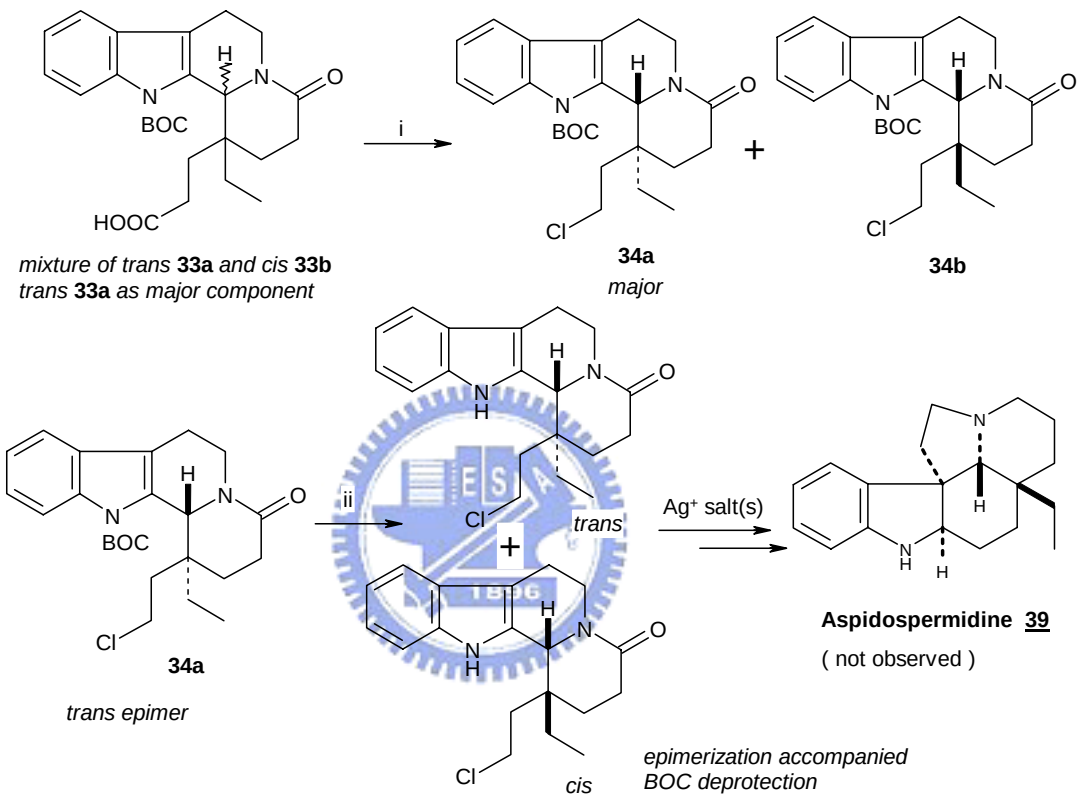


Scheme 27. Selenodecarboxylation of acids **33a/33b:**
i. Barton decarboxylation reaction, trapping with PhSeSePh; ii. Deprotection: KOH(aq), MeOH, rt, 1d.

In addition to selenodecarboxylation of compounds **33a/33b**, we also succeeded in performing chlorodecarboxylation reaction by trapping the intermediate radicals with CCl_4. As small scale reaction was conducted, only the trans epimer **34a** could be purely isolated, the cis epimer **34b** was always found to be mixed with other side products. Deprotection of the trans epimer **34a** under acidic condition (TFA/CH_2Cl_2, rt overnight) proceeded with epimerization[50] on C-3. Treatment of the mixtures with silver salts potentially could induce an ionic reaction, similar to treatment of compound **21a** under

acidic condition (see scheme 10), leading eventually to synthesis of aspidospermidine **39.** Our attempts with several silver salts ($AgNO_3$, AgOAc) unfortunately did not indicate the desired rearrangement took place (scheme 28).

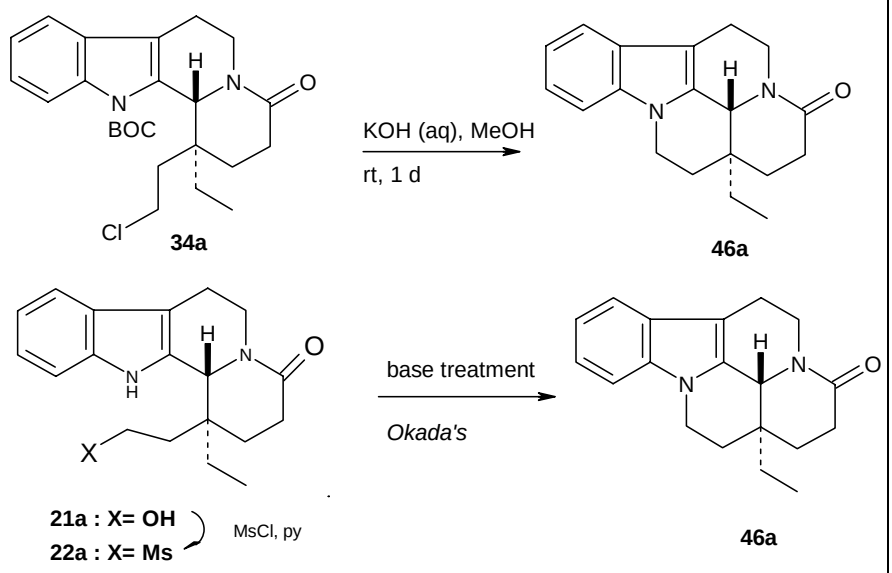
Scheme 28



Scheme 28. Attempt rearrangement to Aspidospermidine **39**:
i. (a). $ClCO_2Et$, NMM, THF, 0^0, 30 min.; (b). Et_3N, N-hydroxy-2-thiopyridone, CCl_4, 0^0, 30 min.; (c) hv (300 nm), 0^0, 1 h; ii. Deprotection: TFA, CH_2Cl_2, rt, 1d.

Base treatment of the trans epimer **34a** gave epi-14,15-dihydroeburnamenin-19-one **46a** (scheme 29) . Okada also obtained the same compound **46a** on treatment of the mesylate **22a** under basic conditions. Physical and spectroscopic data of our product are in accordance with those reported by Okada[38].

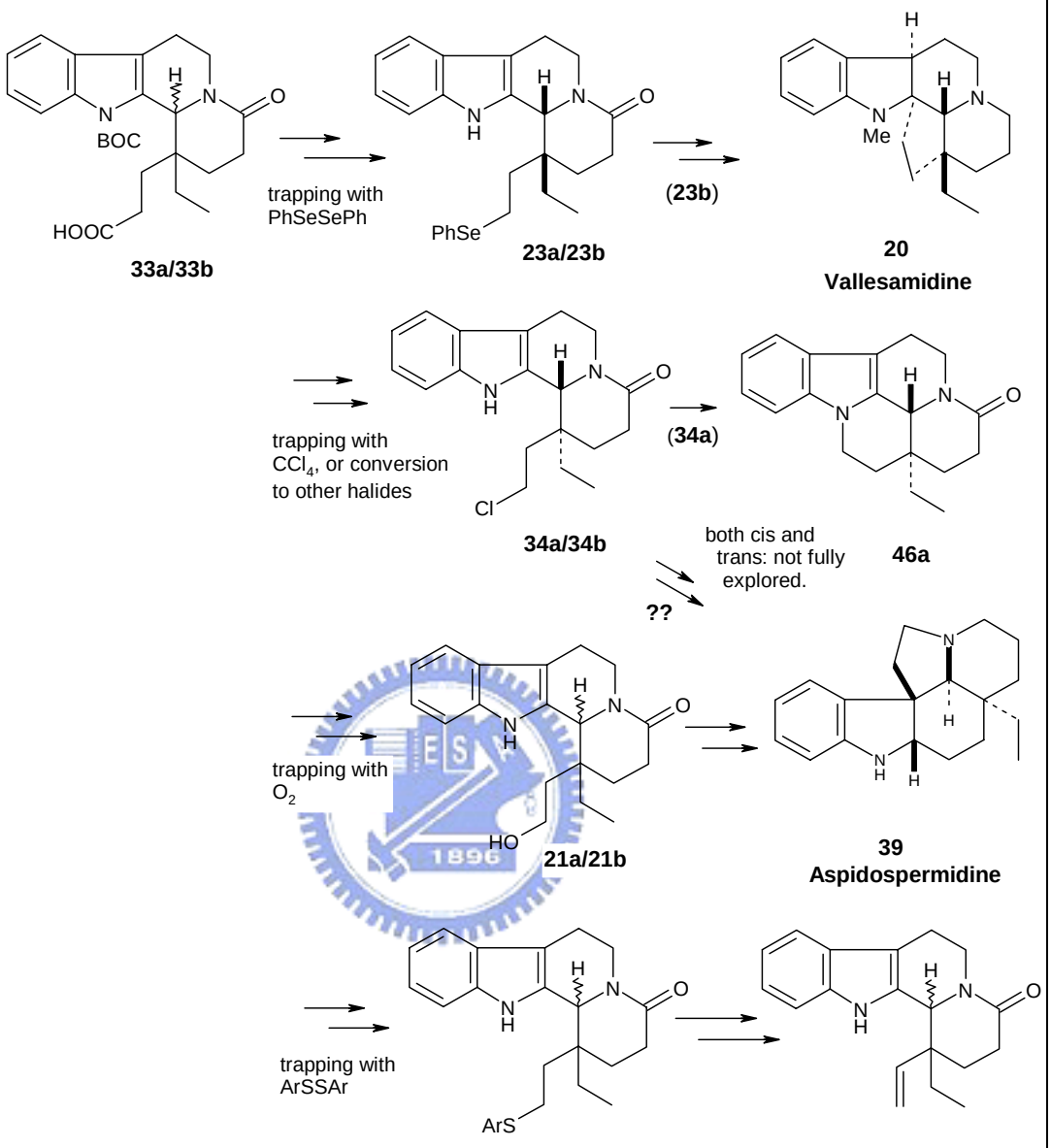
Scheme 29



Scheme 29. Formation of epi-14,15-dihydroeburnamenin-19-one.

To summarize, treatment of BOC-protected acid **33** under Barton reaction condition generates radicals that react with PhSeSePh to give selenides **35a/35b.** Deprotection of **35b** generated the selenide **23b** that has been reported as an intermediate in the synthesis of vallesamidine. Chlorodecarboxylation on acids **33a/33b** also went smoothly, but we fail to induce rearrangement of the deprotected chloride to aspidospermidine **39.** Trapping of the radicals with oxygen should theoretically generate the alcohols **21a/21b**; **21b** is a known intermediate for the synthesis of aspidospermidine **39**, or they could also be trapped with PhSSPh to generate sulfides that could potentially undergo elimination giving olefin. These last two possibilities have not been examined due to lack of time (scheme 30).

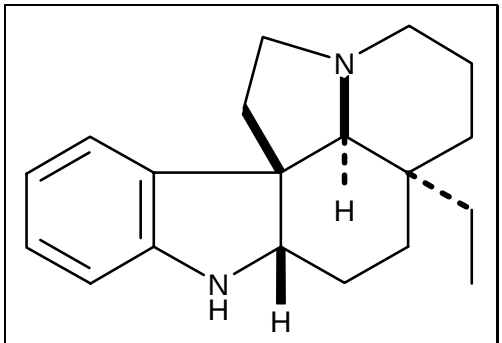
Scheme 30



Scheme 30. Elaboration of BOC-protected acids **33a/33b** for some indole alkaloids syntheses, including possibilities not yet explored.

II.4. Aspidospermidine

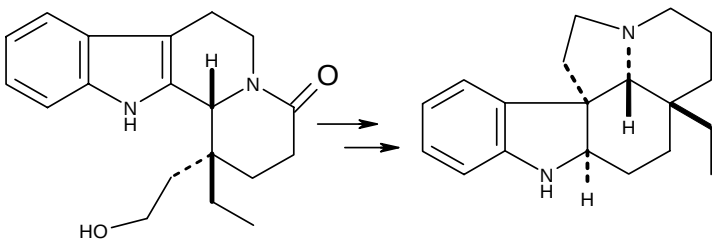
II.4.1. Introduction



39
Aspidospermidine

We are also interested to explore the possibility of constructing aspidospermidine **39** using hidden molecular symmetry as guide for the synthetic design. Our work was inspired by the publication of Harley-Mason[39]. He succeeded in the synthesis using rearrangement of compound **21b** as intermediate to the 2,3,3-trialkylindoline structure of **39**. (Scheme 31)

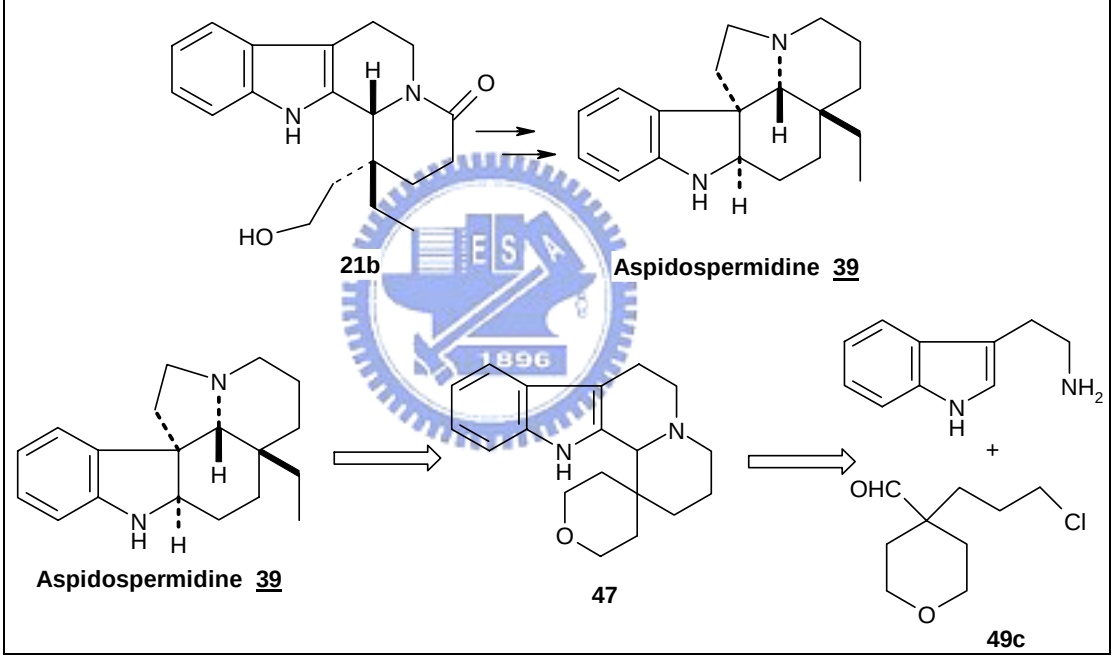
Scheme 31



21b **39**
Aspidospermidine

Our plan was to use compound **47** for the rearrangement to construct the skeleton of the aspidospermidine **39**. Compound **47** itself, in our plan, could be constructed from the Pictet-Spengler reaction of tryptamine with symmetrical aldehyde **49c**. (Scheme 32).

Scheme 32

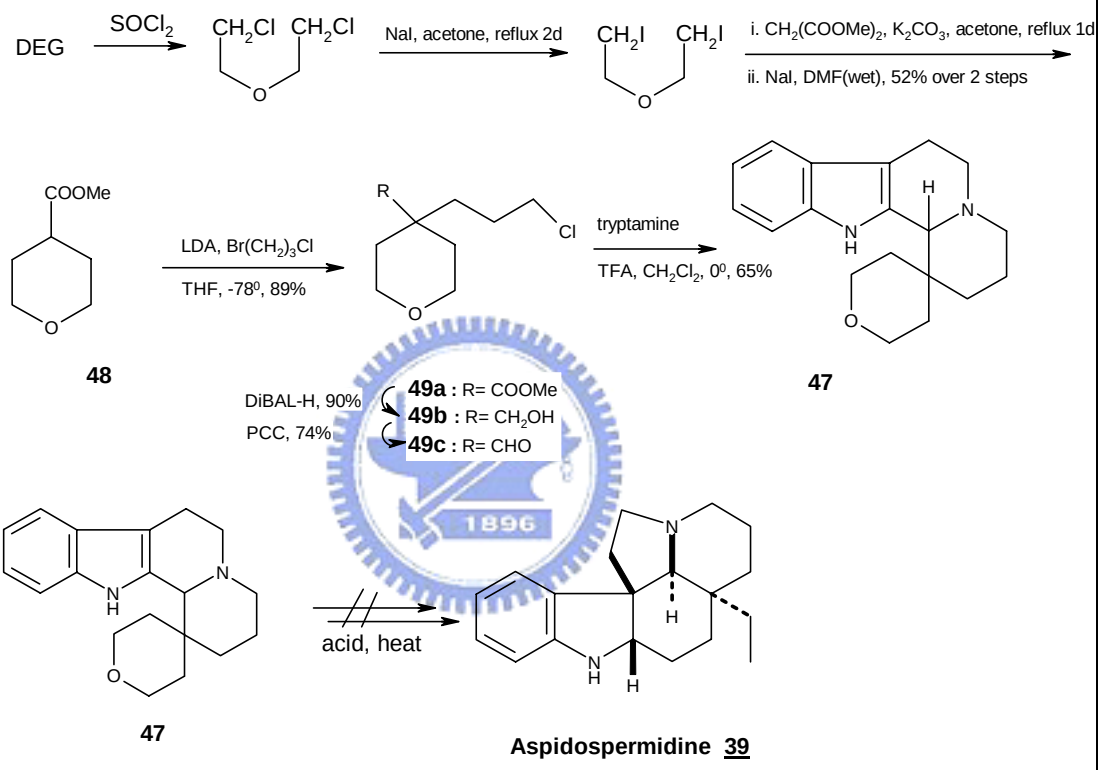


II.4.2. Results and Discussion

Our synthesis of the intermediate **47** was depicted in scheme 33. Access to **49c** from the methyl ester **48** in 3 steps was similar to our construction of **11c** from **10** in the eburnamonine synthesis (see scheme 7): alkylation with 1-bromo-3-chloropropane, reduction with Dibal-H, and PCC oxidation. Compound **47** was then constructed with

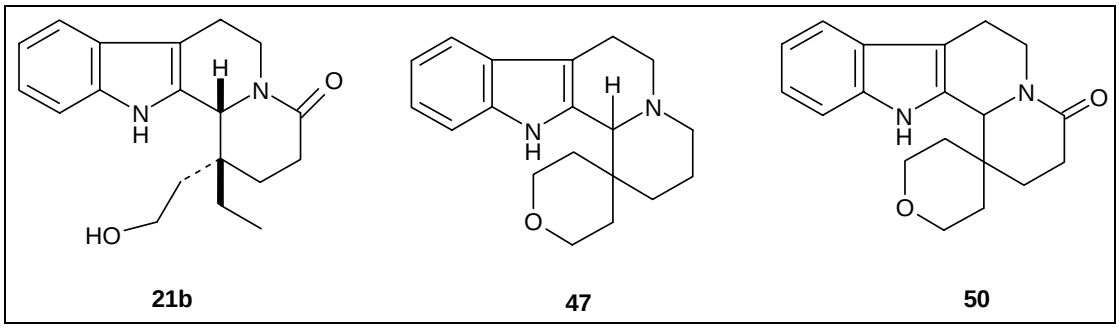
Pictet-Spengler reaction of tryptamine with **49c**. Unfortunately, attempts to convert **47** to 2,3,3-trialkylindoline structure of aspidospermidine **39** was not successful.

Scheme 33



Scheme 33. Preparation of compound **47** and attempt rearrangement to aspidospermidine skeleton.

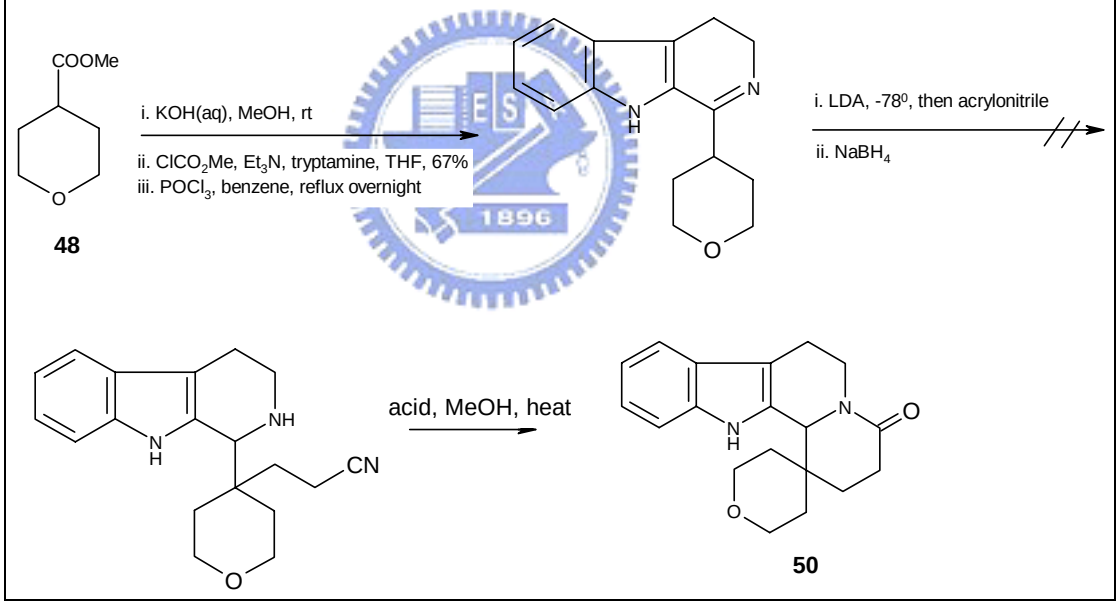
We ascribed this failure due to slight different structure element in **47** compared to **21b**. It is a lactam functionality in **21b**, whereas it is not in **47**. So we changed our plan to construct lactam **50** hoping to be able to induce its rearrangement under acidic condition to the aspidospermidine skeletal.



21b **47** **50**

Our attempt to construct lactam **50** unfortunately has not been fruitful (Scheme 34).

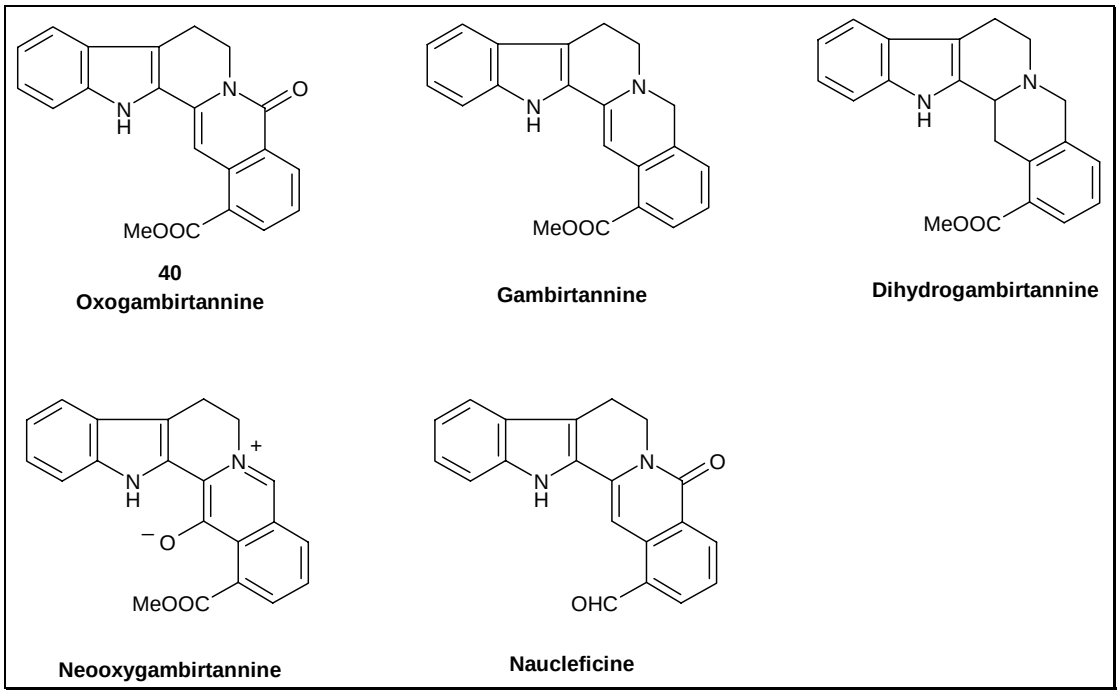
Scheme 34



II.5. Oxogambirtannine

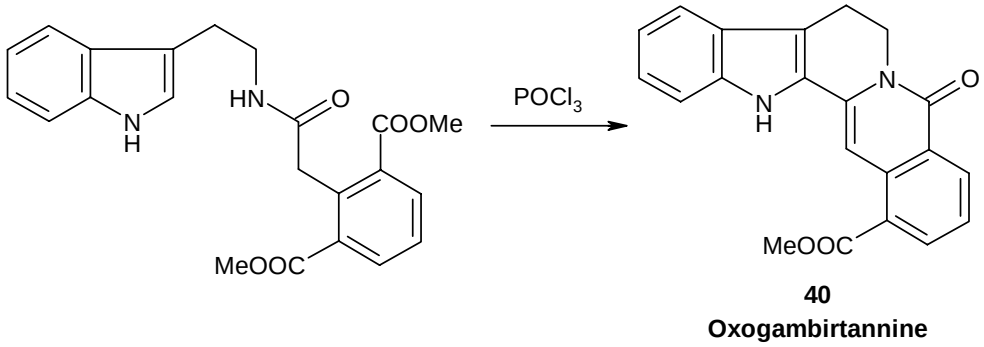
II.5.1. Introduction

Oxogambirtannine **40**[51] was isolated from gambir, a tanning material used in leather industry, produced by evaporation of the aqueous extract of leaves and stems of the Rubiacea *Uncaria gambier* Roxb. (*Ourouparia gambir* Baillon), widely growing in South-East Asia. Together with oxogambirtannine **40**, gambirtannine, dihydrogambirtannine and neooxygambirtannine were also isolated from the same source. As neooxygambirtannine was not found in the crude extract, it is considered as an artifact. Gambirtannine decomposes, even in the solid state, on standing in the air, giving rise to a small amount of **40**. A solution of gambirtannine in many solvents rapidly gives a mixture, from which, gambirtannine, oxogambirtannine **40** and neooxygambirtannine could be isolated[51a]. The aldehyde derivative of **40** was also an alkaloid isolated from the stems of *Nauclea officinalis* (Rubiaceae) which is an anti-inflammatory and anti-bacterial herb in Chinese folk medicine[52].



Several synthetic routes to compound **40** have been accomplished. Merlini and Nasini[53] transformed an amide to **40** in one step with $POCl_3$ (scheme 35), more details of their work are not available. J. A. Beisler[54] reported the peroxide (H_2O_2) oxidation of solution of ourouparine iodide in dioxane to **40.** The ourouparine iodide was formed by aromatization of dihydrogambirtannine using Elderfield's aromatization method[55] (scheme 36).

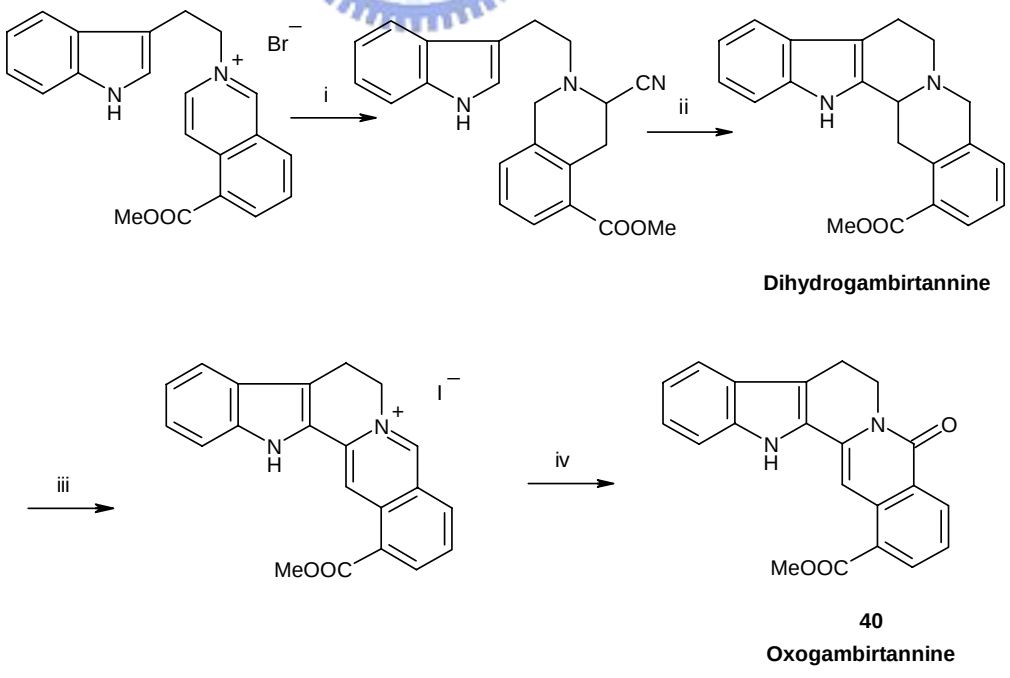
Scheme 35



40
Oxogambirtannine

Scheme 35. Merlini and Nasini synthesis of oxogambirtannine.

Scheme 36



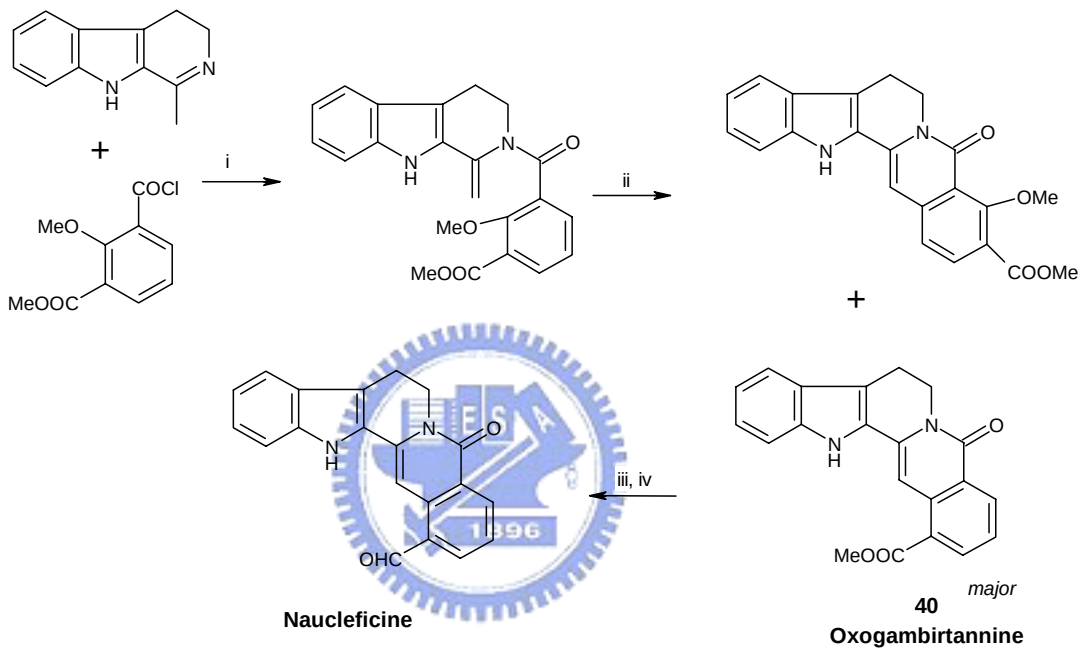
Dihydrogambirtannine

40
Oxogambirtannine

Scheme 36. Beisler's synthesis of oxogambirtannine. i. $NaBH_4$, NaCN; ii. HCl; iii. I_2, KOAc; iv. H_2O_2, dioxane.

Ninomiya[56] also succeeded in preparing compound **40** and naucleficine using enamide photocyclization (scheme 37).

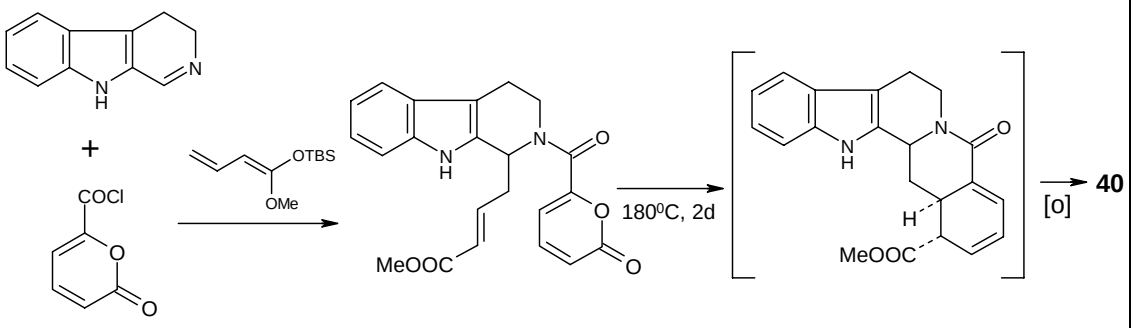
Scheme 37



Scheme 37. Ninomiya's synthesis of oxogambirtannine and naucleficine. i. acylation; ii. irradiation; iii. $NaBH_4$, MeOH/THF, reflux; iv. MnO_2, $CHCl_3$.

In addition to that, Martin[57] developed an ABC → ABCD(E) strategy to synthesize **40** in 2 steps, using Diels-Alder reaction to construct the D/E ring subunits (scheme 38).

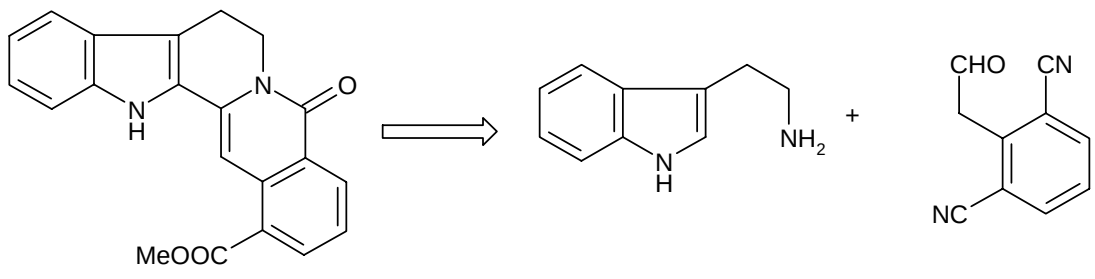
Scheme 38



Scheme 38. Martin's synthesis of oxogambirtannine **40**

Our plan to construct this target molecule is described below. As in other syntheses described earlier, we plan to apply a Pictet-Spengler reaction on tryptamine and a symmetrical 2-aryl substituted acetaldehyde **51** or its derivative. D-ring formation followed by dehydrogenation should then provide **40** (scheme 39)

Scheme 39



40
Oxogambirtannine

51

Scheme 39. Synthetic plan for oxogambirtannine **40.**

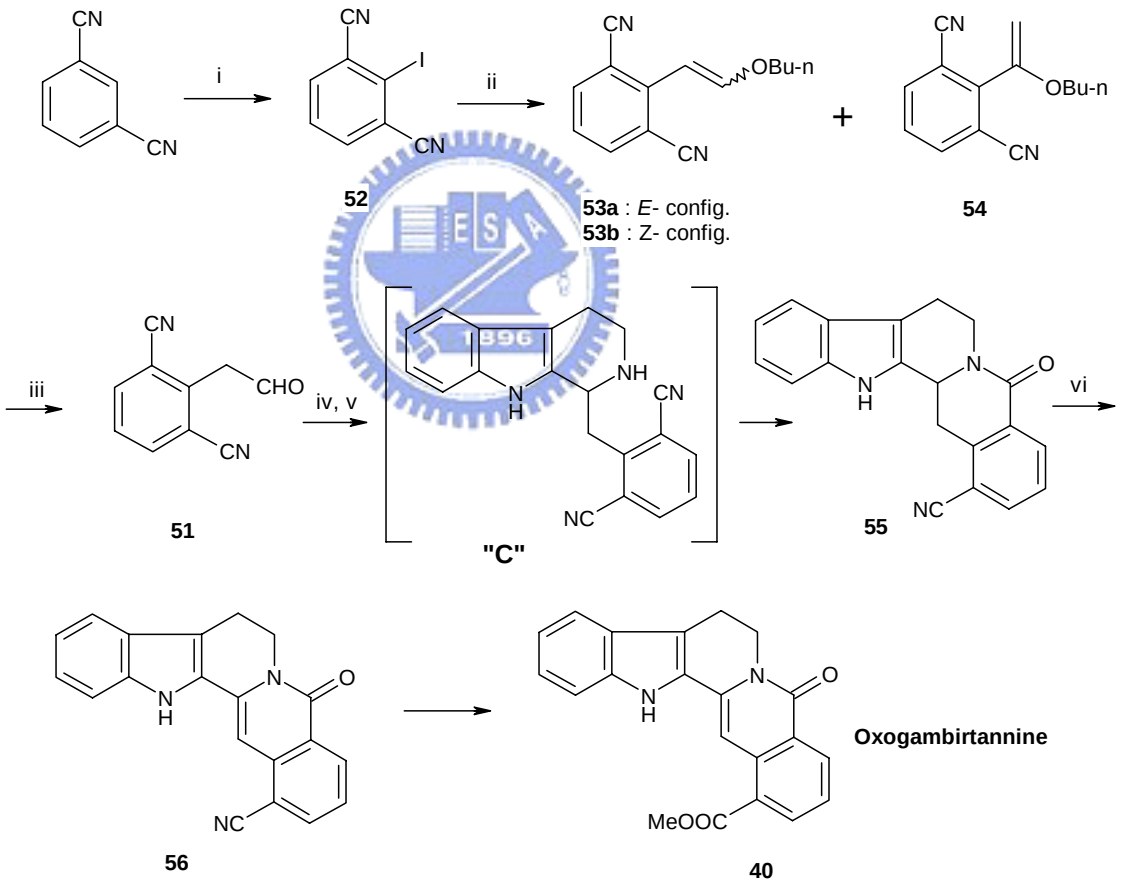
II.5.2. Results and Discussions

The preparation of aldehyde **51** is described in scheme 40. Starting from 1,3-dicyanotoluene, metalation with LDA followed by trapping with I_2 provided 2-iodoisophthalonitrile **52**[58]. Heck reaction[59] of **52** with n-butyl vinyl ether provided inseparable mixture of products consisting of **53a**, **53b**, and **54**. Compounds **53a** and **53b ,** resulting from β-addition to n-butyl vinyl ether, predominate over α-addition product **54** (ratio based on ^{1}H NMR, 5 : 1 using toluene as solvent; lower regioselectivity 3 : 1 using acetonitrile). Acidic treatment on this mixture with 6N HCl provided the required **51.** As **51** is somewhat unstable, decomposed upon chromatography, a Pictet-Spengler reaction was immediately done on crude **51** with tryptamine to generate the tetrahydro β-carboline **C.** However, the crude product mixture of the Pictet-Spengler reaction displayed high polar components on TLC, so it was directly subjected to a nitrile-to-ester reaction condition (conc. H_2SO_4/MeOH/reflux), hoping to induce the D-ring cyclization and at the same time providing a product with moderate polarity. Chromatography on the reaction mixture gave nitrile **55** (15% over 2 steps). Dehydrogenation of **55** under mild reaction condition (I_2/MeOH/reflux)[63] gave **56**, a nitrile analog of oxogambirtannine **40.** Conversion of **56** to oxogambirtannine **40**, due to lack of time was not fully explored, although we observed some promising result on preliminary attempt (2 steps conversion

of nitrile to ester: base hydrolysis, followed by esterification).

In conclusion, upon completion of this dissertation, we succeeded in obtaining **56**, a nitrile analog of oxogambirtannine **40**, but the whole project is not yet finished (scheme 40).

Scheme 40



i. LDA, -100^0, then I_2, 85%; ii. n-butyl vinyl ether, $Pd(OAc)_2$ (cat), Et_3N, toluene, heat, 54%; iii. 6N HCl, rt.
iv. Tryptamine, CH_2Cl_2, TFA, 0^0 to rt; v. H_2SO_4, MeOH, reflux 2d; vi. I_2/MeOH/reflux 2d

III. Experimental Part

General

All reactions were conducted under N_2. For drying organic solutions during workup of reactions, Na_2SO_4 was used.

Solvents

Solvents used in the reactions were dried under N_2 using standard procedures: THF and Ether were distilled from Na and benzophenone ketyl. Toluene, benzene and EtOH were distilled from Na. CH_2Cl_2, Et_3N, MeOH and DMF were distilled from CaH_2.

Column chromatography (CC): *Merck* silica-gel (70-230 mesh).

TLC: *Merck* silica-gel *60 F 254* plates.

M.p.: uncorrected; *Laboratory Devices.*

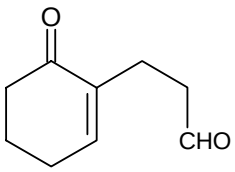
IR Spectroscopy: *Bio-Rad FTS 165 and Digilab FTS 3100* ; ν in cm^{-1}.

NMR Spectroscopy: *Varian Unity-300 and Inova-500*; $CDCl_3$ unless otherwise indicated; δin ppm, J in Hz.

EI-MS: *Trio-2000* and *Jeol SX-102A*; ionization potential 70 eV unless otherwise indicated.

Photochemical Apparatus: *Rayonet.*

3-(6-oxo-1-cyclohexenyl)propanal **3**



Prepared according to literature[19] from 1,3-cyclohexadione and acrolein in about 50% yield.

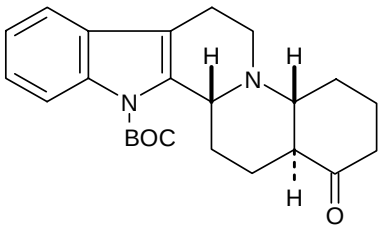
Physical Property: colorless liquid.

IR: 1670, 1720 (C=O).

^{1}H-NMR (300 MHz): 1.86-1.93 (*m*, 2 H); 2.24- 2.35 (*m*, 4 H); 2.41-2.52 (*m*, 4 H); 6.71 (*t*, *J*= 3.9, 1 H), 9.65 (*t*, *J*= 1.5, 1 H).

^{13}C- NMR (75 MHz): 22.71 (*t*), 22.79 (*t*), 25.83 (*t*), 38.22 (*t*), 42.56 (*t*), 137.73 (*s*), 146.62 (*d*), 199.12 (*s*), 201.86 (*d*).

***tert-butyl(4aRS,12bRS,14aRS)-1-oxo-1,2,3,4,4a,6,7,12,12b,13,14,14a-dodeca-hydroquino[2,1-a]ß-carboline-12-carboxylate* 4**



To an ice-cooled soln. of aldehyde **2** (0.30 g, 1.97 mmol) in anh. CH_2Cl_2 (5 ml) was added a soln. of tryptamine (0.32 g, 2.18 mmol) in CH_2Cl_2 (10 ml) dropwise during 10 min. A soln. of TFA (0.52 g, 4.53 mmol) in CH_2Cl_2 (5 ml) was then added during 10 min. The reaction mixture was kept stirred at ice-cooled temperature for 1 hour, allowed to gradually warm up to r.t. overnight and poured into an ice-cold aq. $NaHCO_3$ (5%, 50 ml). Workup involved layer separation, extraction with CH_2Cl_2, rewashing with $NaHCO_3$(aq) and brine, dried, concentrated *in vacuo* to give crude of compound **3**, which was directly protected. Thus the resulting crude **2** was mixed with $(BOC)_2O$ (0.50 g, 2.29 mmol), DMAP (0.02 g, 0.02 mmol) in CH_2Cl_2 (10 ml) and stirred at r.t. overnight. Workup involved washing with brine, dried, concentrated *in vacuo* and chromatography (eluent gradient: 50-50 AcOEt/hexane) to give **4** (0.31 g, 31%) as light reddish-brown solid. R_f= 0.15 (1:1 AcOEt/hexane).

Physical property: light reddish-brown solid, m.p.: 108-110^0.

IR: 2977, 2933, 2862 (C-H), 1723, 1701 (C=O), 1450, 1351, 1314.

^{1}H-NMR (500 MHz): 1.54-1.75 (*m*, 3 H); 1.61 (*s*, 9 H); 1.88-2.11 (*m*, 5 H); 2.22-2.43 (*m*, 3 H), 2.72-2.76 (*m*, 2 H), 2.95 (*dt*, *J*= 11.1, 3.3, 1 H), 2.96-3.04 (*m*, 2 H), 4.32 (*d*, *J*= 9, 1 H), 7.14-7.24 (*m*, 2 H), 7.50 (*d*, *J*= 7.5, 1 H), 8.11 (*d*, *J*= 7.5, 1 H).

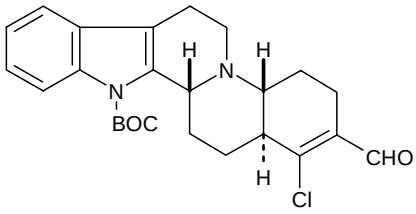
^{13}C- NMR (75 MHz): 21.92 (*t*), 23.30 (*t*), 24.37 (*t*), 25.14 (*t*), 28.15 (*q*), 29.78 (*t*), 36.80 (*t*),

41.38 (*t*), 47.80 (*d*), 58.21 (*d*), 66.95 (*d*), 83.62 (*s*), 114.60 (*s*), 115.64 (*d*), 117.69 (*d*), 122.49 (*d*), 123.81 (*d*), 128.95 (*s*), 136.39 (*s*), 136.55 (*s*), 149.85 (*s*), 211.12 (*s*).

EI-MS: 395 (3.3), 394 (16.8, $M^{+\circ}$), 339 (5.0), 338 (27.2), 337 (100), 294 (13.5).

HR-MS: 394.2249 ($C_{24}H_{30}N_2O_3^{+\circ}$; calc. 394.2256).

tert-butyl(4aRS,12bRS,14aRS)-1-chloro-2-formyl-3,4,4a,6,7,12,12b,13,14,14a-decahydroquino[2,1-a]ß-carboline-12-carboxylate **5**



To an ice-cooled soln. of anh. DMF (0.56 g, 7.6 mmol) in anh. $CHCl_3$ (2.0 ml) was added freshly-redistilled $POCl_3$ (0.80 g, 5.2 mmol) during 10 min. After the reaction mixture was allowed to stir at r.t. for 3 h., a soln. of **4** (0.31 g, 0.78 mmol) in $CHCl_3$ (6.0 ml) was added dropwise during 30 min. and stirred overnight. Workup involved dilution with CH_2Cl_2 (15 ml), washing with water, aq. $NaHCO_3$ (5%), brine, dried, concentrated *in vacuo* and chromatography (eluent gradient: 10-90 AcOEt/hexane) to give unreacted **4** (0.10 g) and **5** (0.11 g, 47% based on reacted **4**) as thick oil. R_f = 0.6 (1:1 AcOEt/hexane).

Physical Property: thick oil.

IR: 2971, 2932, 2863 (C-H), 1724, 1679 (C=O), 1613, 1454, 1357, 1244, 1154.

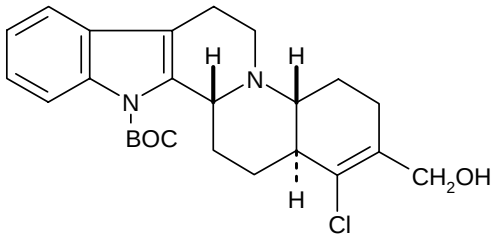
^{1}H-NMR (300 MHz): 1.45-1.84 (*m*, 3 H), 1.65 (*s*, 9 H), 1.98-2.02 (*m*, 1 H), 2.14-2.23 (*m*, 2 H), 2.52-2.76 (*m*, 5 H), 2.95-3.02 (*m*, 3 H), 4.56 (*d*, *J*= 11.1, 1 H), 7.20-7.28 (*m*, 2 H), 7.38-7.40 (*m*, 1 H), 8.11 (*d*, J= 7.8, 1 H), 10.20 (*s*, 1 H).

^{13}C- NMR (75 MHz): 21.91 (*t*), 23.91 (*t*), 25.89 (*t*), 26.15 (*t*), 28.19 (*q*), 29.52 (*t*), 36.39 (*t*), 40.21 (*d*), 58.02 (*d*), 64.73 (*d*), 83.66 (*s*), 114.66 (*s*), 115.76 (*d*), 117.83 (*d*), 122.59 (*d*), 123.93 (*d*), 129.00 (*s*), 133.14 (*s*), 136.21 (*s*), 136.26 (*s*), 149.87 (*s*), 153.44 (*s*), 191.44 (*d*).

EI-MS: 442 (8), 441 (7), 440 (26, $M^{+\circ}$), 412 (5), 383 (58), 356 (23), 339 (15), 214 (70), 170 (78).

HR-MS: 440.1858 ($C_{25}H_{29}ClN_2O_3^{+\circ}$; calc. 440.18687).

tert-butyl(4aRS,12bRS,14aRS)-1-chloro-2-(hydroxymethyl)-3,4,4a,6,7,12,12b,13,14,14a-decahydroquino[2,1-a]ß-carboline-12-carboxylate **6**



To a soln. of **5** (0.10 g, 0.22 mmol) in abs. ethanol (5 ml) was added $NaBH_4$ (0.08 g, 2.2 mmol) portionwise during 10 min. at r.t. The resulting mixture was stirred for 10 min. and a mixture of H_2O (5 ml) and CH_2Cl_2 (25 ml) was added. The organic layer was washed with water, brine, and dried. Evaporation *in vacuo* was followed by chromatography (eluent: 75:25 AcOEt/hexane) to give **6** (0.09 g, 93%) as a light yellow solid. R_f = 0.33 (75:25 AcOEt/hexane).

Physical Property: light yellow solid, m.p.: 178-180^0 (dec.).

IR: 3350 (O-H), 2975, 2931, 2861 (C-H), 1718 (C=O), 1479, 1378, 1249, 1160.

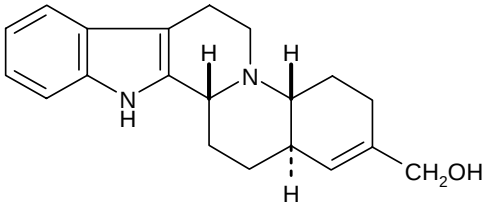
^{1}H-NMR (300 MHz): 1.30-1.93 (*m*, 4 H), 1.64 (*s*, 9 H), 2.08 (*d*, J= 13.6, 1 H), 2.22-2.46 (*m*, 4 H), 2.73-2.78 (*m*, 2 H), 2.89-2.97 (*m*, 3 H), 4.17 (*d*, J= 12.3, 1 H), 4.29 (*d*, J= 12.3, 1 H), 4.50 (*d*, J= 9.6, 1 H), 7.20-7.27 (*m*, 2 H), 7.37-7.40 (*m*, 1 H), 8.14 (*d*, J= 7.8, 1 H).

^{13}C- NMR (75 MHz): 21.92 (*t*), 25.87 (*t*), 27.01 (*t*), 28.04 (*t*), 28.23 (*q*), 30.19 (*t*), 36.42 (*t*), 38.31 (*d*), 58.10 (*d*), 63.10 (*t*), 65.19 (*d*), 83.63 (*s*), 114.62 (*s*), 115.78 (*d*), 117.83 (*d*), 122.57 (*d*), 123.89 (*d*), 129.08 (*s*), 131.70 (*s*), 133.16 (*s*), 136.34 (*s*), 136.49 (*s*), 149.92 (*s*).

EI-MS: 442 (10, $M^{+\circ}$), 385 (51), 341 (21), 305 (3), 270 (5), 241 (4), 214 (58), 170 (41), 168 (64).

HR-MS: 442.2017 ($C_{25}H_{31}ClN_2O_3^{+\circ}$; calc. 442.20253).

Tangutorine 1



To a suspension of Na wire (0.06 g, 2.6 mmol) in anh. THF (3 ml) was added a soln. of naphthalene (0.16 g, 1.25 mmol) in THF (3 ml). The mixture was then subjected to ultrasonification until deep green color persisted (about 10 min.), and stirred at r.t. for 1 h. Upon cooling to 0^0 C, a soln. of **6** (0.06 g, 0.13 mmol) in THF (6 ml) was added at once, and stirred for 2 h. Water (2 ml) was then cautiously added to destroy the unreacted Na. Workup involved dilution with CH_2Cl_2 (15 ml), washing brine, dried, concentrated *in vacuo* and chromatography (eluent gradient: 10:90 MeOH/CH_2Cl_2) to give **1** (0.02 g, 52%) as white solid. R_f = 0.10 (10:90 MeOH /CH_2Cl_2).

Physical Property: white solid, m.p.: 273-275^0 (lit.[15] : m.p. 276-278^0).

IR: 3282 (N-H, O-H), 2924, 2854 (C-H), 1666, 1454, 1051.

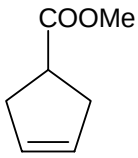
^{1}H-NMR (500 MHz): (5:95 $CD_3OD/CDCl_3$) 1.20-1.29 (*m*, 1 H), 1.40-1.49 (*m*, 1 H), 1.60-1.68 (*dq*, *J*=12.8, 3.5, 1 H),1.81-1.84 (*dd*, *J*=12.8, 2.8, 1 H), 2.05-2.22 (*m*, 6 H), 2.35-2.38 (*m*, 1 H), 2.71 (*br d*, *J*=15, 1H), 2.79-2.85 (*m*, 1 H), 3.46 (*br d*, *J*=11.5, 1 H), 3.55 (*m*, 1 H, buried in d-solvent peaks), 3.83 (*d*, *J*= 13.0, 1 H), 3.87 (*d*, *J*= 13.0, 1 H), 5.26 (*br s*, 1 H), 6.93 (*t*, *J*= 7.5, 1 H), 6.99 (*t*, *J*= 7.5, 1 H), 7.20 (*d*, *J*=7.5, 1 H), 7.34 (*d*, *J*=7.5, 1 H).

^{13}C- NMR (300 MHz): (5:95 $CD_3OD/CDCl_3$) 21.40 (*t*), 25.59 (*t*), 25.90 (*t*), 28.87 (*t*), 30.69 (*t*), 38.62 (*d*), 45.08 (*t*), 60.62 (*d*), 64.99 (*d*), 65.57 (*t*), 106.91 (*s*), 110.73 (*d*), 117.72 (*d*), 118.76 (*d*), 120.92 (*d*), 125.25 (*d*), 126.68 (*s*), 134.78 (*s*), 136.14 (*s*), 136.48 (*s*) .

EI-MS: 309 (3), 308 (23, $M^{+\circ}$), 307 (19), 170 (100), 169 (86), 144 (7).

HR-MS: 308.1883 ($C_{20}H_{24}N_2O^{+\circ}$; calc. 308.18902).

Methyl 3-cyclopentenecarboxylate **10**

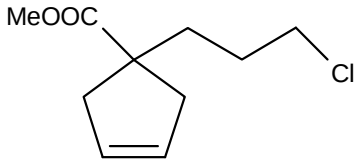


Prepared according to literature[30] from dimethyl malonate and *cis*-1.4-dichloro-2-butene in about 50% yield.

Physical Property: strong odor, colorless oil.

^{1}H-NMR (300 MHz): 2.63 (*d*, *J*= 8.4, 4 H); 3.05-3.15 (*m*, 1 H); 3.68 (*s*, 3 H); 5.64 (*s*, 2 H).

Methyl 1-(3-chloropropyl)-3-cyclopentenecarboxylate **11a**



To a stirred soln. of LDA (28 mmol, prepared from n-BuLi and diisopropylamine in 20 ml anh. THF) was added a soln. of **10** (3.0 g, 23.7 mmol) in THF (5 ml) during 5 min. while temperature was maintained at -78^0. After 30 min. a soln. of 1-bromo-3-chloropropane (3.78 g, 24 mmol) in THF (5 ml) was introduced dropwise. When an additional 1 h elapsed, the mixture was allowed to gradually warm up to room temperature and kept overnight. On quenching with saturated NH_4Cl(aq) (20ml), the product was extracted into ether, and the combined organic solutions were washed with brine, dried, concentrated *in vacuo* and chromatographed (eluent: 1:9 AcOEt/hexane) to give **11a** (4.22 g, 88%). R_f= 0.4 (1:9 AcOEt/hexane).

Physical Property: colorless liquid.

IR: 1723 (C=O).

^{1}H-NMR (300 MHz): 1.67-1.72 (*m*, 2 H); 1.76-1.80 (*m*, 2 H); 2.28 (*d*, *J* = 15, 2 H); 2.88 (*d*, *J* = 15, 2 H), 3.48 (*t*, *J* = 6, 2 H); 3.67 (*s*, 3 H); 5.58 (*s*, 2 H).

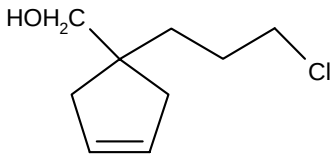
^{13}C- NMR (75 MHz): 28.58 (*t*); 36.55 (*t*); 42.34 (*t*); 45.04 (*t*); 51.83 (*s*); 51.95 (*q*); 128.33 (*d*); 177.59 (*s*).

EI-MS (30 eV): 204 (0.40), 202 (1.05, $M^{+\circ}$), 187 (2.13), 145 (35.95), 143 (100), 125 (16.83).

Elemental Analysis: Anal. calcd for $C_{10}H_{15}ClO_2$: C 59.26, H, 7.46;

found: C 59.12, H 7.86.

[1-(3-Chloropropyl)-3-cyclopentenyl]methanol **<u>11b</u>**



A soln. of **11a** (3.55 g, 17.5 mmol) in anh. THF (25 ml) was cooled to -78^0 and treated with DIBAL-H (38.5 mmol, 32 ml, 20% w/w in PhMe) during 10 min. The resulting soln. was stirred for 30 min. at -78^0, 2 h at 0^0, and cautiously quenched by MeOH (5 ml). After dilution with water (15 ml) while warming up to rt. during an additional 2 h, it was poured into 5% HCl (50 ml). Workup involved ether extraction, rewashing with $NaHCO_3$(aq) and brine, dried, concentrated *in vacuo* and chromatography (eluent: 15:85 AcOEt/hexane) to afford **11b** (2.99 g, 98%). R_f= 0.15 (1:9 AcOEt/hexane).

Property Property: colorless oil.

IR: 3385 (O-H).

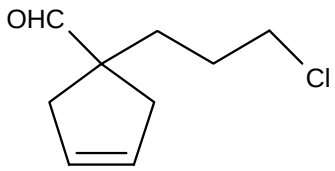
^{1}H-NMR (300 MHz): 1.52-1.58 (*m*, 2 H); 1.67-1.76 (*m*, 2 H); 1.83 (*br*., 1 H); 2.09 (*d*, *J*=15, 2 H); 2.21 (*d*, *J*=15, 2 H); 3.42 (*s*, 2 H); 3.50 (*t*, *J*= 6.6, 2 H); 5.56 (*s*, 2 H).

^{13}C- NMR (75 MHz): 28.07 (*t*); 34.62 (*t*); 41.07 (*t*); 45.69 (*s*); 45.74 (*t*); 69.02 (*t*); 129.12 (*d*).

Elemental Analysis: Anal. calcd for $C_9H_{15}ClO$: C 61.89, H 8.66;

found: C 61.79, H 8.90.

1-(3-Chloropropyl)-3-cyclopentenecarbaldehyde **11c**



PCC (6.47 g, 30 mmol) was added in portions to a mixture of **11b** (2.62 g, 15 mmol), Na_2CO_3 (5.24 g, 49.5 mmol) and powdered 4 Å MS (7.67 g) in anh. CH_2Cl_2 (60 ml) during 10 min. at r.t. After 1 h, the resulting mixture was diluted with ether (25 ml) and passed through a pad of florisil. The florisil bed was thoroughly rinsed with the same solvent and the combined soln was then concentrated *in vacuo*. Chromatography (eluent: 5:95 AcOEt/hexane) gave **11c** (2.04 g, 79%). R_f=0.4 (1:9 AcOEt/ hexane).

Physical Property: colorless oil.

IR: 1724 (C=O).

^{1}H-NMR (300 MHz): 1.64-1.70 (*m*, 2 H); 1.77-1.83 (*m*, 2 H); 2.23 (*d*, *J* =15, 2 H); 2.71 (*d*, *J* = 15, 2 H); 3.51 (*t*, *J* = 6.3, 2 H); 5.61 (*s*, 2 H); 9.49 (*s*, 1 H).

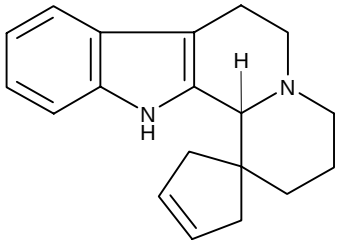
^{13}C- NMR (75 MHz): 28.24 (*t*); 32.66 (*t*); 38.82 (*t*); 45.11 (*t*); 56.05 (*s*); 128.68 (*d*); 203.42 (*d*).

EI-MS (30 eV): 174 (0.91), 172 (2.29, $M^{+\cdot}$), 145 (2.48), 143 (9.28).

Elemental Analysis: Anal. calcd for $C_9H_{13}ClO$: C 62.61, H 7.59;

found: C 62.75, H 7.88.

1',2',3',4',6',7',12',12'b-Octahydro-spirocyclopent-3-ene-1,1'-indolo[2,3-a] quinolizine **12**



A soln. of **11c** (1.85 g, 10.7 mmol) in anh. CH_2Cl_2 (30 ml) was mixed with a soln. of tryptamine (1.88 g, 11.8 mmol) in CH_2Cl_2 (30 ml) at r.t. and stirred for 2 h. On cooling to 0^0 it was treated with a soln. of TFA (45.0 mmol, 3.45 ml) in CH_2Cl_2 (5 ml) during 10 min. After 1 h the ice bath was removed, the reaction mixture was kept overnight, and poured into an ice-cold aq. $NaHCO_3$ (5%, 50 ml). Workup involved layer separation, extraction with CH_2Cl_2, rewashing with $NaHCO_3$(aq) and brine, dried, concentrated *in vacuo* and chromatography (eluent gradient: 10-50:90-50 AcOEt/hexane) to give unreacted **11c** (0.68 g, 3.94 mmol) and compound **12** (0.68 g, 2.45 mmol, 36% based on reacted **11c**). R_f = 0.25 (1:1 AcOEt/hexane).

Physical Property: light yellow solid, m.p.: 101-103^0.

IR: 2803, 2849, 2919 (C-H), 3439 (N-H).

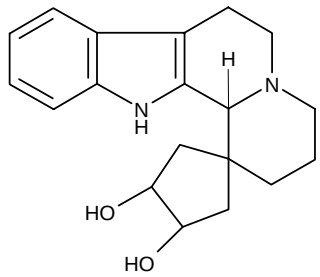
^{1}H-NMR (300 MHz): 1.47- 1.69 (*m*, 2H); 1.79-1.93 (*m*, 2H); 2.16-2.45 (*m*, 4H); 2.62-2.73 (*m*, 2H); 2.98-3.13 (*m*, 4H); 3.34 (*s*, 1H); 5.71-5.74 (*m*, 1H); 5.80-5.84 (*m*, 1H); 7.04-7.15 (*m*, 2H); 7.24 (*d*, *J*= 7.2, 1H); 7.46 (*d*, *J*= 7.2, 1H); 7.90 (*s*, 1H).

^{13}C- NMR (75 MHz): 21.38 (*t*); 22.60 (*t*); 40.05 (*t*); 40.83 (*t*); 43.14 (*s*); 47.94 (*t*); 54.56 (*t*); 56.10 (*t*); 69.15 (*d*); 110.63 (*s*); 110.78 (*d*); 117.74 (*d*); 119.08 (*d*); 121.31 (*d*); 126.69 (*d*); 126.86 (*s*); 134.07(*d*); 134.58(*s*); 136.02 (*s*).

EI-MS: 279 (5.88), 278 (31.66, $M^{+\circ}$), 211 (2.79), 198 (5.37), 197 (4.11), 184 (3.19), 171 (6.25), 170 (14.95), 168 (10.60).

HR-MS: 278.1777 ($C_{19}H_{22}N_2^{+\circ}$; calc. 278.1785).

3,4-Dihydroxy-1',2',3',4',6',7',12',12'b-Octahydro-spirocyclopentane-1,1'-indolo[2,3-a]quinolizine **13**



Compound **12** (0.38g, 1.37 mmol), OsO_4 (2.5% in *t*-BuOH, 2 drops), and *N*-methylmorpholine *N*-oxide monohydrate (NMO) (0.54 g, 4.0 mmol) were dissolved in a mixed solvent (THF 9.0 ml, H_2O 0.45 ml, *t*-BuOH 0.90 ml) and stirred at r.t. overnight. Addition of CH_2Cl_2 (25 ml) was followed by washing with water and brine. The organic solution was dried, concentrated *in vacuo* and chromatographed (eluent: AcOEt) to give **13** (0.28 g, 66%). R_f= 0.15 (AcOEt).

Physical Property: light yellow solid, m.p.: 122-124^0.

IR: 2807, 2850, 2931 (C-H), 3342 (N-H, O-H).

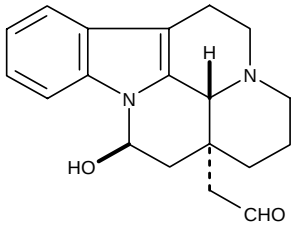
^{1}H-NMR (300 MHz): 1.53-1.79 (*m*, 4H); 1.93-2.03 (*m*, 1H); 2.34-2.64 (*m*, 6H); 2.85-2.92 (*m*, 3H); 3.32 (br., 1H); 3.78 (br., 1H); 4.12 (br., 1H); 7.02-7.12 (*m*, 2H); 7.31 (*d*, *J*= 7.8, 1H); 7.42 (*d*, *J*= 7.8, 1H); 8.29 (*s*, 1H).

^{13}C- NMR (75 MHz): (2:8 d_6-acetone/$CDCl_3$) 21.07 (*t*); 22.20 (*t*); 36.00 (*t*); 40.78 (*t*); 42.81 (*t*); 43.30 (*s*); 52.23 (*t*); 55.43 (*t*); 68.16(*d*); 72.59 (*d*); 72.76 (*d*); 110.32 (*d*); 110.93 (*s*); 116.50 (*d*); 117.90 (*d*); 120.11 (*d*); 125.94 (*s*); 132.79 (*s*); 135.89 (*s*).

EI-MS: 312 (39, $M^{+\circ}$), 311 (100), 310 (79), 295 (3), 185 (4), 170 (15).

HR-MS: 312.1833 ($C_{19}H_{24}N_2O_2^{+\circ}$; calc. 312.1839).

***2-((12SR,13aSR,13bRS)-12-Hydroxy-2,3,5,6,12,13,13a,13b-octahydro-1H-[1,7] naphthridino[7,8,1-lma]β-carbolin-13-yl)acetaldehyde* <u>14a</u>**



To a soln. of **13** (0.30 g, 0.97 mmol) in a 50% aq. THF (16.0 ml) was added $NaIO_4$ (1.28 g, 5.98 mmol). The mixture was stirred for 30 min at r.t., then CH_2Cl_2 (50 ml) was added. The organic layer was washed with water, brine, dried, and evaporated *in vacuo*. ^{1}H-NMR of the crude product indicated the presence of two aldehydes in a ratio of *ca* 2.5 : 1.0. Chromatography (eluent: AcOEt/hexane gradient 10% to 100% AcOEt) gave aldehyde **14a** (0.18 g, 0.58 mmol, whereas the minor product **14b** was converted to lactol **15** (80 mg, 0.26 mmol) during the course of chromatography (combined yield: 87%). Attempt to purify compound **14b** failed, and the identity of which was confirmed by $NaBH_4$ reduction to **17b** (*vide infra*). R_f = 0.50 (100% EA).

Physical Property: light yellow amorphous solid.

IR: 1711 (C=O), 2806, 2852, 2940 (C-H), 3363 (N-H, O-H).

^{1}H-NMR (300 MHz): 1.08-1.20 (*m*, 1H); 1.43 (*ddd*, *J*= 13.8, 9.0, 1.2, 1H); 1.49-1.59 (*m*, 2H); 1.80-1.92 (*m*, 2H); 2.14 (*dt*, *J*= 11.1, 3.3, 1H); 2.38 (*dt*, *J*= 11.1, 4.2, 1H); 2.53 (*dd*, J= 13.8, 5.7, 1H); 2.57-2.64 (*m*, 2H); 2.74-2.88 (*m*, 2H); 2.92-2.98 (*m*, 2H); 3.60 (br., 1H); 5.53 (*dd*, *J*= 9.0, 6.0, 1H); 7.09-7.18 (*m*, 2H); 7.40-7.46 (*m*, 1H); 7.57-7.60 (*m*, 1H); 9.56 (*t*, *J*= 2.4, 1H).

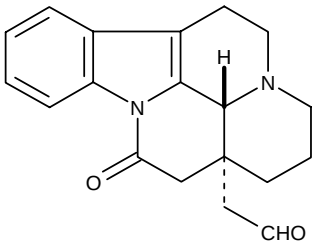
^{13}C- NMR (75 MHz): 21.22 (*t*); 32.79 (*t*); 37.75 (*s*); 42.10 (*t*); 43.00 (*t*); 52.14 (*t*); 55.17 (*t*); 66.40 (*d*); 76.44 (*d*); 106.79 (*s*); 111.76 (*d*); 118.28 (*d*); 120.30 (*d*); 121.51

(*d*); 128.29 (*s*); 133.07 (*s*); 137.61 (*s*); 202.61 (*d*).

EI-MS: 310 (20, $M^{+\cdot}$), 309 (30), 308 (16), 282 (72), 281 (100), 280 (52), 266 (20), 248 (14), 238 (63).

HR-MS: 310.1676 ($C_{19}H_{22}N_2O_2^{+\cdot}$; calc. 310.1683).

***2-((13aSR,13bRS)-12-Oxo-2,3,5,6,12,13,13a,13b-octahydro-1H-[1,7]naphthridino [7,8,1-lma]β-carbolin-13-yl)acetaldehyde* <u>15</u>**



PDC (0.11 g, 0.29mmol) was added to a mixture of **14a** and **14b** (70 mg, 0.23 mmol) in anh. CH_2Cl_2 (5ml), and the mixture was stirred at r.t. overnight. The oxidation product was diluted with AcOEt (20 ml) and passed through celite. The celite pad was further rinsed, filtrates were combined, evaporated *in vacuo*, and the residue chromatographed (eluent: 1:1 AcOEt/hexane) to furnish **15** (30 mg, 43%). R_f = 0.50 (3:1 AcOEt/hexane).

Physical Property: thick oil.

IR: 1656, 1707 (C=O), 2943 (C-H).

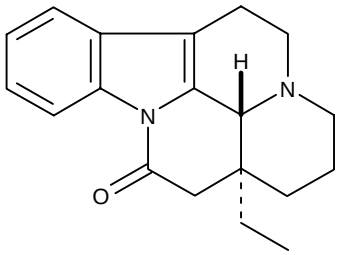
^{1}H-NMR (300 MHz): 1.31 (*ddt*, *J*= 13.5, 4.3, 1.5, 1H); 1.59-1.70 (*m*, 1H); 1.79-1.93 (*m*, 3H); 2.11 (*td*, *J*= 13.5, 3.3, 1H); 2.28 (*dt*, *J*= 11.7, 3.6, 1H); 2.44-2.53 (*m*, 2H); 2.56-2.64 (*m*, 1H); 2.74-2.86 (*m*, 1H); 2.92 (*td*, *J*= 14.1, 2.4, 1H); 2.98-3.08 (*m*, 3H); 7.20-7.28 (*m*, 2H); 7.35-7.38 (*m*, 1H); 8.26-8.29 (*m*, 1H); 9.66 (*t*, *J*= 2.1, 1H).

^{13}C- NMR (75 MHz): 21.08 (*t*); 21.43 (*t*); 32.92 (*t*); 39.12 (*s*); 43.16 (*t*); 44.62 (*t*); 51.86 (*t*); 55.00 (*t*); 65.07 (*d*); 113.72 (*s*); 116.27 (*d*); 118.27 (*d*); 124.04 (*d*); 124.45 (*d*); 129.62 (*s*); 131.92 (*s*); 134.96(*s*); 166.52(*s*); 200.99 (*d*).

EI-MS: 308 (3.53, $M^{+\circ}$), 307 (14.73), 282 (10.45), 281 (56.79), 279 (100), 263 (15.54), 237 (22.77).

HR-MS: 308.1529 ($C_{19}H_{20}N_2O_2^{+\circ}$; calc. 308.1526).

3-Epi-eburnamonine **16**



A mixture of **15** (30 mg, 0.098 mmol), ethanedithiol (0.03 ml, 0.35 mmol) and boron trifluoride etherate (0.02 ml, 0.16 mmol) in CH_2Cl_2 (5 ml) was stirred at 0^0 for 1 h, then at r.t. for 8 h. It was diluted with CH_2Cl_2 (15 ml), washed with 5% $NaHCO_3$ (aq), brine, dried and evaporated *in vacuo*. The residue was dissolved in ethanol (8ml), treated with Raney nickel (50% aq. slurry, *ca*. 0.5 ml) and refluxed for 8 hrs. The cooled reaction mixture was filtered through celite, washed with CH_2Cl_2 (15 ml), and the filtrate was concentrated *in vacuo*. Chromatography (eluent: 1:1 AcOEt/hexane) gave **16** (20 mg, 69%) as a white solid. R_f = 0.40 (1:1 AcOEt/hexane).

Physical Property: white solid, m.p.: 135-137^0 (lit.[29]: m.p. 138-139^0).

IR: 1654, 1708 (C=O), 2854, 2926 (C-H).

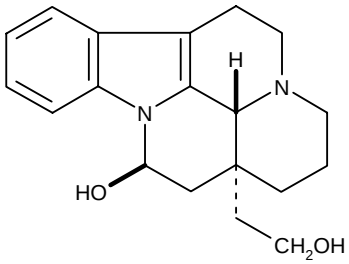
^{1}H-NMR (300 MHz): 0.73-0.87 (*m*, 4H); 1.12-1.23 (*m*, 2H); 1.57-1.63 (*m*, 2H); 1.79-1.86 (*m*, 2H); 2.29 (*dt*, *J* = 14.4, 3.3, 1H); 2.33 (*dd*, *J* = 16.8, 1.8, 1H); 2.54 (*dt*, *J* = 11.2, 4.2, 1H); 2.58-2.68 (*m*, 1H); 2.78 (*d*, *J* = 17.1, 1H); 2.78-2.92 (*m*, 1H); 3.01-3.11 (*m*, 2H); 7.22-7.30 (*m*, 2H); 7.37-7.40 (*m*, 1H); 8.29-8.32 (*m*, 1H).

^{13}C- NMR (75 MHz): 7.36 (*q*); 20.66 (*t*); 20.95 (*t*); 21.25 (*t*); 31.51 (*t*); 39.42 (*s*); 44.09 (*t*); 52.30 (*t*); 55.22 (*t*); 65.71 (*d*); 112.95 (*s*); 116.12 (*d*); 118.20 (*d*); 123.86 (*d*); 124.22 (*d*); 129.69 (*s*); 133.60 (*s*); 135.00(*s*); 167.34(*s*).

EI-MS: 294 (64.6, $M^{+\cdot}$), 293 (100), 265 (12.94), 237 (32.96).

HR-MS: 294.1729 ($C_{19}H_{22}N_2O^{+\cdot}$; calc. 294.17336).

(12SR,13aSR,13bRS)-13a-(2-Hydroxyethyl)-2,3,5,6,12,13,13a,13b-octahydro-1H-[1,7]naphthridino[7,8,1-lma]β-carbolin-12-ol **17a**



To a soln. of **14a** (0.12 g, 0.39 mmol) in ethanol (5 ml) was added $NaBH_4$ (0.10 g, 2.64 mmol) in portions during 5 min. at r.t. The resulting mixture was stirred for 1 h. and a mixture of H_2O (5 ml) and CH_2Cl_2 (25 ml) was added. The organic layer was washed with water and brine, and dried. Evaporation *in vacuo* was followed by chromatography (eluent: 5:95 MeOH/CH_2Cl_2) to give **17a** (0.10 g, 82%). R_f= 0.15 (5:95 MeOH /CH_2Cl_2).

Physical Property: white solid, m.p.: 100-102^0 (lit.[27b]: m.p. 102-103^0).

IR: 2809, 2852, 2928 (C-H), 3303 (O-H).

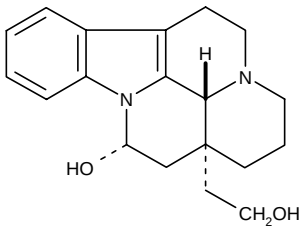
^{1}H-NMR (300 MHz): 0.96-1.04 (*m*, 1H); 1.12-1.24 (*m*, 1H); 1.41-1.60 (*m*, 3H); 1.74 (*d*, *J*= 13.5, 1H); 1.85-2.04 (*m*, 1H); 2.15-2.27 (*m*, 2H); 2.44 (*dt*, J= 11.1, 4.2, 1H); 2.63 (*dd*, *J*= 14.4, 2.4, 1H); 2.81 (*s*, 1H); 2.81-3.00 (*m*, 3H); 3.22-3.30 (*m*, 1H); 3.52- 3.60 (*m*, 1H); 5.58 (*dd*, *J*= 9.0, 5.7, 1H); 7.08-7.15 (*m*, 2H); 7.40-7.43 (*m*, 1H); 7.55-7.58 (*m*, 1H).

^{13}C- NMR (75 MHz): 21.06 (*t*); 21.97 (*t*); 33.29 (*t*); 33.55 (*t*); 38.26 (*s*); 47.03 (*t*); 52.29 (*t*); 55.22 (*t*); 58.41 (*t*); 66.08 (*d*); 76.84 (*d*); 106.31 (*s*); 111.54 (*d*); 118.31 (*d*); 120.23 (*d*); 121.40 (*d*); 128.32 (*s*); 133.05 (*s*); 137.59 (*s*).

EI-MS: 312 (80, $M^{+\circ}$), 311 (100), 294 (44), 293 (67), 267 (34), 249 (21), 237 (14).

HR-MS: 312.1840 ($C_{19}H_{24}N_2O_2^{+\circ}$; calc. 312.1839).

(12RS,13aSR,13bRS)-13a-(2-Hydroxyethyl)-2,3,5,6,12,13,13a,13b-octahydro-1H-[1,7]naphthridino[7,8,1-lma]β-carbolin-12-ol **17b**



To a stirred solution of **15** (70 mg, 0.23 mmol) in ethanol (5ml) was added $NaBH_4$ (70 mg, 2.59 mmol) in portions during 5 min at r.t. After 1 h. H_2O (5 ml) and CH_2Cl_2 (25 ml) were added. Layers were separated and the organic layer was washed with water, brine and dried. Evaporation *in vacuo* was followed by chromatography (eluent: 5:95 MeOH/ CH_2Cl_2) to give **17b** (60 mg, 83%). R_f = 0.33 (5% MeOH/CH_2Cl_2).

Physical Property: white solid, m.p.: 168-170^0 (lit.[27b]: m.p.172-174^0).

IR: 2803, 2852, 2935 (C-H), 3292 (O-H).

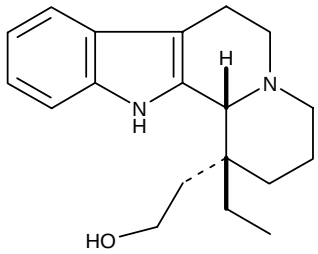
^{1}H-NMR (300 MHz): 1.08-1.16 (*m*, 1H); 1.44-1.58 (*m*, 2H); 1.78-1.89 (*m*, 3H); 2.07 (*d*, *J*= 16.5, 1H); 2.20 (*dt*, *J*= 16.5, 3.3, 1H); 2.35 (*d*, *J*= 15, 1H); 2.43 (*dt*, *J*= 11.1, 4.5, 1H); 2.67 (*dd*, J= 15, 4.2, 1H); 2.77 (*s*, 1H); 2.86-2.92 (*m*, 1H); 2.99-3.08 (*m*, 2H); 3.60-3.70 (*m*, 2H); 5.84 (*d*, J= 5.1, 1H); 7.05- 7.15 (*m*, 2H); 7.45 (*dd*, J= 10.5, 7.5, 2H).

^{13}C- NMR (75 MHz): 21.18 (*t*); 21.23 (*t*); 29.97 (*t*); 32.39 (*t*); 34.14 (*s*); 41.82 (*t*); 53.32 (*t*); 55.85 (*t*); 58.96 (*t*); 67.83 (*d*); 74.88 (*d*); 105.30 (*s*); 111.07 (*d*); 118.13 (*d*); 119.63 (*d*); 120.87 (*d*); 128.26 (*s*); 131.34 (*s*); 135.75 (*s*).

EI-MS: 312 (18, $M^{+\circ}$), 311 (33), 310 (22), 294 (29), 293 (100), 265 (8), 249 (7).

HR-MS: 312.1836 ($C_{19}H_{24}N_2O_2^{+\circ}$;calc. 312.1839).

***2-[(1SR,12bRS)-1-Ethyl-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]β-carbolin-1-yl] -1-ethanol* <u>18</u>**



Compound **18** was prepared according to modified literature procedure[27b]. A mixture of **17a** and **17b** (60 mg, 0.19 mmol), KOH (30 mg, 0.52 mmol) and hydrazine hydrate (0.32 ml, 6.6 mmol) in ethylene glycol (1.0 ml) was heated at 130^0 for 2 h, then refluxed for 8 h. After cooling to r.t., it was diluted with water, and extracted with CH_2Cl_2. The organic solution was washed with water, brine, dried, evaporated *in vacuo*, and the residue was chromatographed (eluent: 5:95 MeOH/ CH_2Cl_2) to give **18** (30 mg, 53%).

Physical Property: light yellow solid, m.p.: $168\text{-}170^0$ (lit.[31]: $173.5\text{-}175^0$).

IR: 2758, 2808, 2852, 2929 (C-H), 3317, 3480 (N-H, O-H).

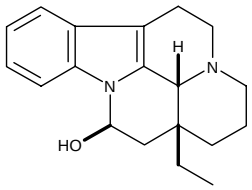
^{1}H-NMR (300 MHz): 1.08 (*t*, *J*= 7.5, 3H); 1.29 (*td*, *J*= 14.7, 3.3, 1H); 1.55-1.82 (*m*, 6H); 2.00-2.12 (*m*, 1H), 2.41 (*dt*, J= 12.0, 3.0, 1H); 2.60-2.70 (*m*, 1H); 2.66 (*d*, *J*= 12.6, 1H); 2.94-3.08 (*m*, 3H); 3.32 (*s*, 1H); 3.41 (*td*, J= 11.7, 4.5, 1H); 3.73 (*dt*, J= 11.7, 3.0, 1H); 7.04-7.15 (*m*, 2H); 7.29 (*d*, *J*= 7.5, 1H); 7.45 (*d*, J= 7.5, 1H); 7.89 (*s*, 1H).

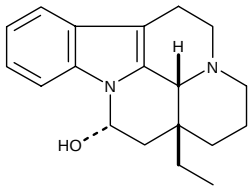
^{13}C- NMR (75 MHz): 8.43 (*q*); 21.27 (*t*); 22.91 (*t*); 32.22 (*t*); 35.46 (*t*); 38.58 (*t*); 40.73 (*s*); 53.94 (*t*); 56.24 (*t*); 58.56 (*t*); 67.10 (*d*); 110.61 (*d*); 111.71 (*s*); 118.06 (*d*); 119.33 (*d*); 121.62 (*d*); 126.61 (*s*); 132.19 (*s*); 136.04 (*s*).

EI-MS: 299 (8), 298 (100, $M^{+\circ}$), 297 (48), 283 (6), 267 (19), 253 (10), 237 (9).

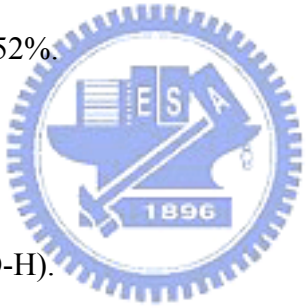
HR-MS: 298.2048 ($C_{19}H_{26}N_2O^{+\circ}$; calc. 298.20468).

Eburnamine 8 and *Isoeburnamine* 9





Alcohol **18** (40mg, 0.13 mmol), $RuCl_3.xH_2O$ (5 mg, 0.02 mmol), $NaIO_4$ (80 mg, 0.37 mmol) were stirred into a mixture of CH_2Cl_2 (1.0 ml), MeCN (1.0 ml) and H_2O (1.5 ml) at 0^0C for 6 h. The mixture was diluted with CH_2Cl_2 (15 ml), washed with water, brine, dried, evaporated *in vacuo*, and chromatographed (eluent: MeOH/CH_2Cl_2 1% to 5% gradient containing 0.25% Et_3N) to give **8**[33] (10 mg, 0.034 mmol) and **9**[33] (10 mg, 0.034 mmol). Combined yield: 52%.



Eburnamine 8

IR: 2933 (C-H), 3346 (O-H).

^{1}H-NMR (300 MHz): 0.80-0.94 (*m*, 4H); 1.23- 1.70 (*m*, 5H); 1.95-2.06 (*m*, 1H); 2.26-2.39(*m*, 2H); 2.45-2.67 (*m*, 2H); 2.88-3.10 (*m*, 2H); 3.15-3.25 (*m*, 2H); 3.76 (*s*, 1H); 5.53 (*m*, 1H); 7.06-7.19 (*m*, 2H); 7.43(*d*, *J*= 6.9, 1H); 7.72 (*d*, *J*= 6.9, 1H).

^{13}C- NMR (75 MHz): 7.5 (*q*); 16.7 (*t*); 20.4 (*t*); 25.0 (*t*); 28.5 (*t*); 36.8 (*s*); 43.4 (*t*); 44.3 (*t*); 50.8 (*t*); 58.7 (*d*); 76.7 (*d*); 105.5 (*s*); 112.2 (*d*); 118.0 (*d*); 120.0 (*d*); 121.2 (*d*); 128.6 (*s*); 132.6 (*s*); 136.6 (*s*).

EI-MS: 296 (40, $M^{+\circ}$), 295 (31), 278 (25), 249 (90), 208 (100).

HR-MS: 296,1886 ($C_{19}H_{24}N_2O^{+\circ}$; calc. 296.1890).

Isoeburnamine **9**

IR: 2929 (C-H), 3310 (O-H).

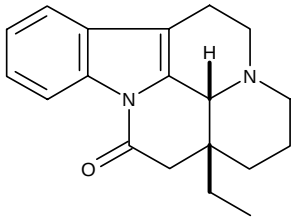
^{1}H-NMR (300 MHz): 0.91 (*t*, *J*= 7.5, 3H); 1.40-1.83 (*m*, 5H); 1.99 (*d*, *J*= 7.8, 1H); 2.17-2.25(*m*, 2H); 2.57-2.75 (*m*, 3H); 2.98-3.03 (*m*, 1H); 3.25-3.38 (*m*, 2H); 3.91 (*s*, 1H); 6.06 (*d*, *J*=3.9, 1H); 7.13-7.23 (*m*, 2H); 7.43 (*d*, *J*= 7.8, 1H); 7.48 (d, *J*= 7.8, 1H).

^{13}C- NMR (75 MHz): 7.5 (*q*); 16.5 (*t*); 20.2 (*t*); 25.8 (*t*); 29.0 (*t*); 34.8 (*s*); 39.7 (*t*); 44.8 (*t*); 51.4 (*t*); 59.5 (*d*); 74.3 (*d*); 105.2 (*s*); 110.1 (*d*); 118.5 (*d*); 120.4 (*d*); 121.7 (*d*); 128.4 (*s*); 129.3 (*s*); 135.0 (*s*).

EI-MS: 296 (81, $M^{+\circ}$), 295 (100), 278 (20), 267 (38), 249 (50), 208 (36).

HR-MS: 296.1888 ($C_{19}H_{24}N_2O^{+\circ}$; calc. 296.1890).

Eburnamonine 7



A mixture of eburnamine and isoeburnamine (35 mg, 0.12 mmol) was dissolved in anh. CH_2Cl_2 (4 ml) and treated with PDC (60 mg, 0.16 mmol), and stirred at room temperature. After 3 h, the mixture was diluted with AcOEt (20 ml), and passed through a short column of celite. The filtrate was evaporated *in vacuo*, and the residue was chromatographed (eluent: 1:1 AcOEt/hexane) to afford **7** (15 mg, 42%). Rf = 0.40 (1:1 AcOEt/hexane).

Physical Property: white solid, m.p.: 195-197^0 (lit.[29]: m.p. 199.5-200.5^0).

IR: 1703 (C=O), 2855, 2931 (C-H).

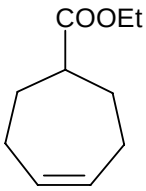
^{1}H-NMR (300 MHz): 0.91 (*t*, J= 7.5, 3H); 1.01 (*dt*, J= 13.8, 3.9, 1H); 1.39-1.49 (*m*, 1H); 1.58-1.80 (*m*, 3H); 2.02 (*m*, 1H); 2.35-2.71 (*m*, 5H); 2.80-3.00 (*m*, 1H); 3.18-3.35 (*m*, 2H); 3.96 (*s*, 1H); 7.24-7.32 (*m*, 2H); 7.40-7.43 (*m*, 1H); 8.33-8.36 (*m*, 1H).

^{13}C- NMR (75 MHz): 7.63 (*q*); 16.52 (*t*); 20.59 (*t*); 26.91 (*t*); 28.32 (*t*); 38.43 (*s*); 44.29 (*t*); 44.33 (*t*); 50.62 (*t*); 57.67 (*d*); 112.59 (*s*); 116.23 (*d*); 118.07 (*d*); 123.82 (*d*); 124.31 (*d*); 130.07 (*s*); 131.95 (s); 134.18 (*s*); 167.64(*s*).

EI-MS: 294(100, $M^{+\circ}$), 293 (64), 278 (3), 265 (57), 237 (67), 224 (21).

HR-MS: 294.1722 ($C_{19}H_{22}N_2O^{+\circ}$; calc. 294.17336).

Ethyl 4-cycloheptene-1-carboxylate **37**



Ester **37** was prepared from esterification of the corresponding acid **36** according to literature procedure[61]. Acid **36** was also prepared according to literature procedure[46].

Acid **36:**

^{1}H-NMR (300 MHz): 1.58-1.70 (*m*, 2 H); 1.94-2.15 (*m*, 4 H); 2.24-2.33 (*m*, 2 H); 2.54-2.63 (*m*, 1 H); 5.74-5.77 (*m*, 2 H).

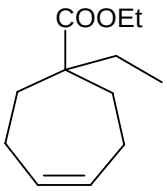
^{13}C- NMR (75 MHz): 26.60 (*t*); 29.05 (*t*); 46.98 (*d*); 131.66 (*d*); 182.30 (*s*).

Ester **37:**

^{1}H-NMR (300 MHz): 1.23 (*t*, *J* = 7.2, 3 H); 1.53-1.66 (*m*, 2 H); 1.89-1.98 (*m*, 2 H); 2.01-2.10 (*m*, 2 H); 2.22-2.31 (*m*, 2 H); 2.47-2.56 (*m*, 1 H); 4.09 (*q*, *J* = 7.2, 2 H); 5.27-5.76 (*m*, 2 H).

^{13}C- NMR (75 MHz): 14.20 (*q*); 26.72 (*t*); 29.31 (*t*); 47.45 (*d*); 60.14 (*t*); 131.71 (*d*); 176.21 (*s*).

Ethyl 1-ethyl-4-cycloheptene-1-carboxylate **<u>24a</u>**



To a stirred soln. of LDA (16 mmol, prepared from n-BuLi and diisopropylamine in 20 ml anh. THF) was added a soln. of **37** (2.0 g, 11.9 mmol) in THF (5 ml) during 5 min. while temperature was maintained at -78^0. After 30 min. a soln. of bromoethane (1.63 g, 15 mmol) in THF (5 ml) was introduced dropwise in 5 min. When an additional 1 h elapsed, the mixture was allowed to gradually warm up to room temperature and kept overnight. On quenching with saturated NH_4Cl(aq) (20ml), the product was extracted into ether, and the combined organic solutions were washed with brine, dried, concentrated *in vacuo* and chromatographed (eluent: 1:19 AcOEt/hexane) to give **24a** (2.21 g, 95%).

Physical Property: colorless liquid.

IR: 1725 (C=O).

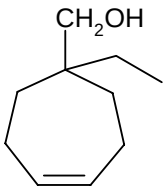
^{1}H-NMR (300 MHz): 0.78 (*t*, *J* = 7.5, 3 H); 1.23 (*t*, *J* = 7.5, 3 H); 1.52-1.58 (*m*, 4 H); 2.08-2.14 (*m*, 6 H); 4.13 (*q*, *J* = 7.5, 2 H); 5.64-5.66 (*t*, *J* = 2.7, 2 H).

^{13}C- NMR (75 MHz): 8.98 (*q*); 14.32 (*q*); 24.43 (*t*); 32.14 (*t*); 33.81 (*t*); 50.40 (*s*); 60.08 (*t*); 131.23 (*d*); 177.20 (*s*).

EI-MS (30eV)**:** 197 (11, $M+1^{+\circ}$), 195 (18, $M-1^{+\circ}$), 167 (9), 123 (71).

HR-MS: 196.1477 ($C_{12}H_{20}O_2^{+\circ}$; calc. 196.1464).

(1-ethyl-4-cycloheptenyl)methanol **<u>24b</u>**



To an ice-cooled suspension of LAH (0.45g, 11.28 mmol) in THF (15 ml) was added a soln. of **24a** (2.21 g, 11.3 mmol) in anh. THF (10 ml) dropwise during 10 min. The resulting soln. was stirred for 30 min. at 0^0 and allowed to gradually warm up to rt overnight. Work up involved cautiously quenching the reaction with EtOH (5 ml), followed by 3N NaOH (aq) (15 ml), ether extraction, washing with brine, dried, concentrated *in vacuo* and chromatography (eluent: 15:85 AcOEt/hexane) to afford **24b** (1.60 g, 92%).

Physical Property: colorless liquid.

IR: 3358 (O-H).

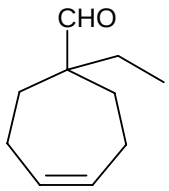
^{1}H-NMR (300 MHz): 0.81 (*t*, *J* = 7.5, 3 H); 1.35-1.48 (*m*, 6 H); 2.08-2.10 (*m*, 4 H); 3.40 (*s*, 2 H); 5.62 (*t*, J = 2.7, 2 H).

^{13}C- NMR (75 MHz): 7.81 (*q*); 23.71 (*t*); 27.12 (*t*); 32.98 (*t*); 40.06 (*s*); 67.16 (*t*); 130.99 (*d*).

EI-MS: 154 (3, $M^{+\cdot}$), 137 (3), 123 (43), 107 (58).

HR-MS: 154.1358 ($C_{10}H_{18}O^{+\cdot}$; calc. 154.1358).

1-ethyl-4-cycloheptene-1-carbaldehyde **<u>24c</u>**



PCC (5.09 g, 23.6 mmol) was added in portions to a mixture of **24b** (1.55 g, 10.1 mmol), Na_2CO_3 (4.30 g, 40.6 mmol) and powdered 4 Å MS (5.60 g) in anh. CH_2Cl_2 (40 ml) during 10 min. at r.t. After 1 h, the resulting mixture was diluted with ether (25 ml) and passed through a pad of florisil. The florisil bed was thoroughly rinsed with the same solvent and the combined soln was then concentrated *in vacuo*. Chromatography (eluent: 5:95 AcOEt/hexane) gave **24c** (1.20 g, 78%).

Physical Property: colorless liquid.

IR: 1722 (C=O).

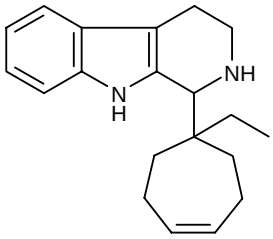
^{1}H-NMR (300 MHz): 0.77 (*t*, *J* = 7.5, 3 H); 1.49-1.58 (*m*, 4 H); 1.88-1.96 (*m*, 2 H); 2.06-2.10 (*m*, 4 H); 5.62 (*t*, *J* = 3.0, 2 H); 9.41 (*s*, 1 H).

^{13}C- NMR (75 MHz): 8.41 (*q*); 23.69 (*t*); 28.04 (*t*); 30.47 (*t*); 52.78 (*s*); 130.87 (*t*); 206.60 (*d*).

EI-MS (30 eV): 153 (3, $M+1^{+\circ}$), 151 (3, $M-1^{+\circ}$), 123 (21), 109 (48).

HR-MS: 153.1294 [(M+1) $C_{10}H_{17}O^{+\circ}$; calc. 153.1280).

1-(1-ethyl-4-cycloheptenyl)-2,3,4,9-tetrahydro-1H-β-carboline **25**



A soln. of **24c** (0.15 g, 1.0 mmol) in anh. CH_2Cl_2 (3 ml) was mixed with a soln. of tryptamine (0.18 g, 1.1 mmol) in CH_2Cl_2 (3 ml) at r.t. and stirred for 2 h. On cooling to 0^0 it was treated with a soln. of TFA (3.0 mmol, 0.25 ml) in CH_2Cl_2 (2 ml) during 10 min. After 1 h the ice bath was removed, the reaction mixture was kept overnight, and poured into an ice-cold aq. $NaHCO_3$ (5%, 50 ml). Workup involved layer separation, extraction with CH_2Cl_2, rewashing with $NaHCO_3$(aq) and brine, dried, concentrated *in vacuo* and chromatography (eluent gradient: 10-50:90-50 AcOEt/hexane) to give compound **25** (0.10 g, 51%).

Physical Property: light brown thick oil.

IR: 3482 (N-H); 3012, 2924, 2843 (C-H).

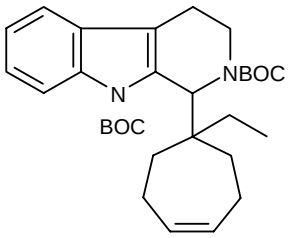
^{1}H-NMR (300 MHz): 0.71 (*t*, *J* = 7.5, 3 H); 1,37-1,64 (*m*, 2 H); 1.66-1.93 (*m*, 4 H); 2.12-2.33 (m, 4 H); 2.70-2,74 (*m*, 2 H); 2.81-2.89 (*m*, 1 H); 3.35 (*dt*, *J* = 11.7, 3.6, 1 H); 4.21 (*s*, 1 H); 5.68 (*s*, 1 H); 7.08-7.19 (*m*, 2 H); 7.34 (*d*, *J* = 7.5, 1 H); 7.51 (*d*, *J* = 7.5, 1 H); 7.89 (*s*, 1 H).

^{13}C- NMR (75 MHz): 8.03 (*q*); 23.18 (*t*); 24.65 (*t*); 24.70 (*t*); 27.51 (*t*); 33.42 (*t*); 35.57 (*t*); 43.20 (*s*); 43.78 (*t*); 58.58 (*d*); 110.48 (*d*); 112.04 (*s*); 117.69 (*d*); 119.13 (*d*); 121.34 (*d*); 127.11 (*s*); 130.34 (*d*); 130.65 (*d*); 134.56 (*s*); 135.44 (*s*).

EI-MS: 294 (5, $M^{+\circ}$), 225 (2), 186 (10), 171 (100).

HR-MS: 294.2116 ($C_{20}H_{26}N_2^{+\circ}$; calc. 294.2098).

***Di(t-butyl)1-(1-ethyl-4-cycloheptenyl)-2,3,4,9-tetrahydro-1H-β-carboline-2,9-dicarboxylate* 26**



Compound **25** (0.10 g, 0.34 mmol) was mixed with $(BOC)_2O$ (0.25 g, 1.18 mmol), DMAP (0.01 g, 0.02 mmol) in CH_2Cl_2 (5 ml) and stirred at 50^0 overnight. Workup involved diluting with CH_2Cl_2 (5 ml), washing with brine, dried, concentrated *in vacuo* and chromatography (eluent: 50:50 AcOEt/hexane) to give **26** (80 mg, 48%).

Physical Property: colorless thick oil.

IR: 3007, 2977, 2932 (C-H); 1734, 1691 (C=O).

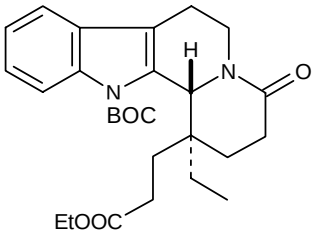
^{1}H-NMR (300 MHz): existed as 2 conformational isomers: 0.81-0.89 (*m*, 3 H); 1.41-1.80 (*m*, 24 H); 1.83-2.34 (*m*, 4 H); 2.74 (major conformer) and 2.69 (minor conformer) (*d*, *J* = 5.4, 1 H); 2.88-3.00 (*m*, 1 H); 3.38-3.60 (*m*, 1 H); 4.27-4.35 (minor conformer) and 4.58 (major conformer) (*dd*, *J* = 13.5, 8.4, 1 H); 5.61 (*br s*, 2 H); 6.26 (major conformer) and 6.32 (minor conformer) (*s*, 1 H); 7.17-7.27 (*m*, 2 H); 7.39 (*d*, *J* = 7.5, 1 H); 7.88 (major conformer) and 7.94 (minor conformer) (*d*, *J* = 7.5, 1 H).

^{13}C- NMR (75 MHz): major conformational isomer: 8.31 (*q*); 19.69 (*t*); 24.14 (*t*); 27.81 (*q*); 28.16 (*t*); 32.41 (*t*); 35.07 (*t*); 37.11 (*t*); 45.95 (*s*); 54.03 (*d*); 80.17 (*s*); 83.60 (*s*); 114.97 (*d*); 116.93 (*s*); 117.91 (*d*); 122.44 (*d*); 123.86 (*d*); 129.04 (*s*); 130.86 (*d*); 131.27 (*d*); 135.12 (*s*); 136.69 (*s*); 151.13 (*s*); 155.70 (*s*).

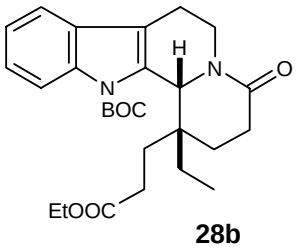
EI-MS: 494 (1, $M^{+\circ}$), 371 (35), 315 (29), 294 (13), 259 (78), 215 (81), 171(42).

HR-MS: 494.3118 ($C_{30}H_{42}N_2O_4^{+\circ}$; calc. 494.3147).

***tert-Butyl (1RS,12bSR)-1-ethyl-1-(3-ethoxy-3-oxopropyl)-4-oxo-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]β-carboline-12-carboxylate* <u>28a</u> and *tert-Butyl (1SR,12bSR)-1-ethyl-1-(3-ethoxy-3-oxopropyl)-4-oxo-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]β-carboline-12-carboxylate* <u>28b</u>**



28a



28b

To an ice-cooled mixture of di-BOC compound **26** (200 mg, 0.40 mmol), n-Bu_4NBr (20 mg, 0.06 mmol) in THF (2.0 ml) and water (12.0 ml) was added $KMnO_4$ (320 mg, 2.0 mmol) portionwise during 30 min. Additional water (3.0 ml) was then added and the mixture was allowed to warm up to r.t. with stirring. Excess oxidant was quenched by addition of Na_2SO_3 (250 mg, 2.0 mmol). The resulting mixture was stirred at r.t. for 30 min. Work up involved dilution with CH_2Cl_2 (15 ml), filtration through a pad of celite, washing the solid residue with additional CH_2Cl_2 (15 ml), washing the combined organic layer with brine, drying (Na_2SO_4) and concentration *in vacuo* to afford diacid **27.** Immediate esterification was performed by refluxing with TsOH (10 mg, 0.05 mmol), $CHCl_3$ (7.5 ml), and EtOH (5.0 ml) for 18 h. Workup involved dilution with CH_2Cl_2 (15 ml), layer separation, washing with brine, drying, concentration *in vacuo* and chromatography (eluent gradient: 10-50:90-50) to give **28a** (40 mg, 21%) and **28b** (30 mg, 16%).

28a:

Physical Property: light yellow amorphous solid.

IR: 3052, 2977, 2936, 2881 (C-H); 1732, 1665 (C=O).

^{1}H-NMR (300 MHz): 0.50 (*t*, J= 7.5 Hz, 3 H); 0.89-1.04 (*m*, 1 H); 1.06-1.18 (*m*, 1 H); 1.23 (*t*, J= 7.2 Hz, 3 H); 1.47-1.57 (*m*, 1 H); 1.63 (*s*, 9 H); 1.69-1.84 (*m*, 2 H); 1.94-2.04 (*m*, 1 H); 2.21 (*ddd*, J= 4.5, 12, 14 Hz, 1 H); 2.42-2.50 (*m*, 2 H); 2.54-2.71 (*m*, 2 H); 2.80-2.90 (*m*, 2 H); 4.03-4.14 (*m*, 2 H); 4.80-4.85 (*m*, 1 H); 5.57 (*s*, 1 H); 7.21-7.32 (*m*, 2 H); 7.44 (*d*, J= 1.5, 7.8 Hz, 1 H); 7.94 (*d*, J= 7.8 Hz, 1 H).

^{13}C- NMR (75 MHz): 7.65 (*q*); 14.13 (*q*); 20.97 (*t*); 26.61 (*t*); 28.11 (*q*); 29.30 (*t*); 29.68 (*t*); 30.31 (*t*); 30.75 (*t*); 39.03 (*t*); 42.93 (*s*); 58.41 (*d*); 60.22 (*t*); 84.63 (*s*); 115.85 (*d*); 118.15 (*d*); 122.80 (*s*); 123.02 (*d*); 124.69 (*d*); 128.20 (*s*); 132.81 (*s*); 137.23 (*s*); 151.20 (*s*); 172.93 (*s*); 173.56 (*s*).

EI-MS: 468 (66), 368 (62), 339 (19), 323 (25), 256 (63), 214 (88), 169 (100).

HR-MS: 468.2620 ($C_{27}H_{36}N_2O_5^{+\circ}$; calc. 468.2626).

28b:

Physical Property: colorless thick oil.

IR: 3052, 2978, 2935, 2882 (C-H), 1732, 1665 (C=O).

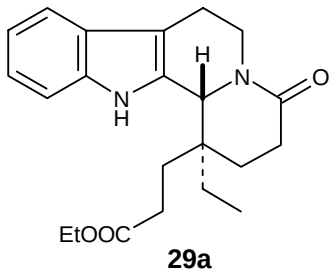
^{1}H-NMR (300 MHz): 0.93 (*t*, J= 7.5 Hz, 3 H), 1.07 (*t*, J= 7.2 Hz, 3 H),1.31-1.43 (*m*, 2 H), 1.45.-1.64 (*m*, 4 H), 1.66 (*s*, 9 H), 1.72-1.95 (*m*, 2 H), 2.46-2.53 (*m*, 2 H), 2.70-2.88 (*m*, 3 H), 3.91 (*q*, J=7.2 Hz, 2 H), 4.82-4.87 (*m*, 1 H), 5.54 (*s*, 1 H), 7.20-7.32 (*m*, 2 H), 7.45 (*d*, J= 1.5, 7.8 Hz, 1 H), 7.92 (*d*, J= 7.8 Hz, 1 H).

^{13}C- NMR (75 MHz): 8.63 (*q*), 13.97 (*q*), 20.89 (*t*), 27.56 (*t*), 28.14 (*q*), 28.82 (*t*), 28.92 (*t*), 30.16 (*t*), 31.04 (*t*), 39.16 (*t*), 43.14 (*s*), 58.33 (*d*), 60.18 (*t*), 84.49 (*s*), 115.28 (*d*), 118.37 (*d*), 122.69 (*s*), 122.99 (*d*), 124.77 (*d*), 127.95 (*s*), 132.34 (*s*), 136.95 (*s*), 151.09 (*s*), 173.05 (*s*), 173.36 (*s*).

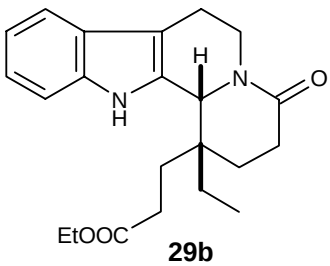
EI-MS: 468 (40), 368 (41), 339 (10), 323 (15), 256 (28), 214 (61), 169 (100).

HR-MS: 468.2608 ($C_{27}H_{36}N_2O_5^{+\circ}$; calc. 468.2626).

Ethyl 3-[(1RS,12bSR)-1-ethyl-4-oxo-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a] ß-carbolin-1-yl]propanoate **29a** **and** ***Ethyl 3-[(1SR,12bSR)-1-ethyl-4-oxo-1,2,3,4,6,7,12,12b- octahydropyrido[2,1-a]ß-carbolin-1-yl]propanoate*** **29b**



29a



29b

To a soln. of compound **28a** (60 mg, 0.13 mmol) in CH_2Cl_2 (5 ml) was added TFA (1.0 ml). The resulting soln. was refluxed overnight, then diluted with CH_2Cl_2 (15 ml), poured into an ice-cold 5% $NaHCO_3$ (15 ml). Workup involved layer separation, extraction with CH_2Cl_2, rewashing with $NaHCO_3$(aq) and brine, drying, concentration *in vacuo* and chromatography (eluent gradient: 10-50:90-50 AcOEt/hexane) to give **29a** (20 mg, 42%) and **29b** (15 mg, 31%).

29a:

Physical Property: white solid, m.p.: 199-201^{0}C.

IR: 3317 (N-H), 3058, 2966, 2938, 2883 (C-H), 1730, 1621 (C=O).

^{1}H-NMR (300 MHz): 0.69 (*t*, *J*= 7.5, 3 H), 0.80-1.09 (*m*, 2 H), 1.31 (*t*, *J* = 7.2., 3 H), 1.38-1.48 (*m*, 1H), 1.54-1.62 (*m*, 1 H), 1.68-1.78 (*m*, 1 H), 1.98-2.08 (*m*, 1 H), 2.21-2.29 (*m*, 1 H), 2.38-2.47 (*m*, 2 H), 2.52-2.58 (*m*, 2 H), 2.64-2.75 (*m*, 2 H), 4.22 (*q*, *J* = 7.2, 2 H), 4.72 (*s*, 1 H), 5.05-5.10 (*m*, 1 H), 7.05-7.18 (*m*, 2 H), 7,39 (*d*, *J* = 7.8, 1 H), 7.47 (*d*, *J* = 7.8, 1H), 9.35 (*br s*, 1 H).

0.69 (*t*, *J* = 7.5, 3 H); 0.80-1.09 (*m*, 2 H); 1.31 (*t*, *J* = 7.2., 3 H); 1.38-1.48 (*m*, 1H); 1.54-1.62 (*m*, 1 H); 1.68-1.78 (*m*, 1 H); 1.98-2.08 (*m*, 1 H); 2.21-2.29 (*m*, 1 H); 2.38-2.47 (*m*, 2 H); 2.52-2.58 (*m*, 2 H); 2.64-2.75 (*m*, 2 H); 4.22 (*q*, *J* = 7.2, 2 H); 4.72 (*s*, 1H); 5.05-5.10 (*m*, 1 H); 7.05-7.18 (*m*, 2 H); 7,39 (*d*, *J* = 7.8, 1 H); 7.47 (*d*, *J* = 7.8, 1H); 9.35 (*br s*, 1 H).

^{13}C- NMR (75 MHz): 6.92 (*q*), 14.07(*q*), 20.99 (*t*), 23.91 (*t*), 26.66 (*t*), 28.10 (*t*), 28.78 (*t*), 30.80 (*t*), 39.09 (*s*), 40.80 (*t*), 60.08 (*d*), 61.33 (*t*), 111.12 (*d*), 112.94 (s), 117.84 (*d*), 119.36 (*d*), 121.86 (*d*), 126.17 (*s*), 130.35 (*s*), 136.39 (*s*), 169.92 (*s*), 175.00 (*s*).

EI-MS: 368 (66), 339 (11), 323 (11), 251 (21), 211 (66), 169 (100).

HR-MS: 368.2101 ($C_{22}H_{28}N_2O_3^{+\circ}$; calc. 368.2101).

29b:

Physical Property: colorless oil.

IR: 3317 (N-H), 3057, 2966, 2939, 2884 (C-H), 1731, 1622 (C=O).

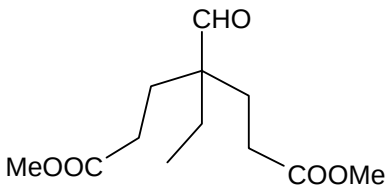
^{1}H-NMR (300 MHz): 1.12-1.18 (*m*, 6 H), 1.39-1.46 (*m*, 1 H), 1.49-1.57 (*m*,1 H); 1.67-1.89 (*m*, 2 H), 1.90-1.96 (*m*, 2 H), 2.04-2.13 (*m*, 2 H), 2.45-2.56 (*m*, 2 H), 2.67-2.78 (*m*, 3 H), 4.01 (*q*, *J*= 7.2, 2 H), 4.80 (*s*, 1H); 5.10-5.14 (*m*, 1 H), 7.08-7.19 (*m*, 2 H), 7,34 (*d*, *J* = 7.8, 1 H), 7.49 (*d*, *J* = 7.8, 1H), 8.16 (*br s*, 1 H).

^{13}C- NMR (75 MHz): 8.07 (*q*), 14.06 (*q*), 20.99 (*t*), 27.24 (*t*), 27.30 (*t*), 28.46 (*t*), 28.85 (*t*), 29.73 (*t*), 39.03 (*s*), 41.11 (*t*), 60.46 (*d*), 60.58 (*t*), 110.97 (*d*), 113.40 (s), 118.22 (*d*), 119.79 (*d*), 122.30 (*d*), 126.42 (*s*), 130.40 (*d*), 136.26(*s*), 169.90 (*s*), 173.37 (*s*).

EI-MS: 368 (91), 323 (14), 251 (8), 211 (56), 170 (79), 169 (100).

HR-MS: 368.2102 ($C_{22}H_{28}N_2O_3^{+\circ}$; calc. 368.2101).

***Aldehyde* <u>42</u>**

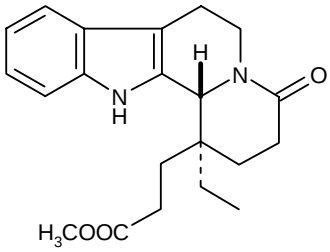


Prepared according to literature procedure[45] from pyrollidine enamine of n-butyraldehyde and methyl acrylate.

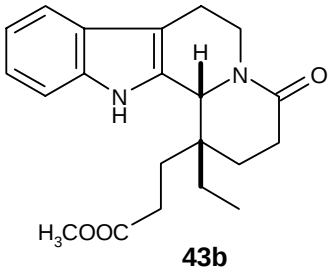
^{1}H-NMR (300 MHz): 0.80 (*t*, J= 7.5 Hz, 3 H); 1.54 (*q*, J= 7.5 Hz, 2 H); 1.79-1.84 (*m*, 4 H); 2.15-2.20 (*m*, 4 H), 3.63 (*s*, 6 H), 9.38 (*s*, 1 H).

^{13}C- NMR (75 MHz): 7.65, 24.39, 26.07, 28.33, 51.06, 51.72, 173.34, 205.03.

***Methyl 3-[(1RS,12bSR)-1-ethyl-4-oxo-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a] β-carbolin-1-yl]propanoate* 43a and *methyl 3-[(1SR,12bSR)-1-ethyl-4-oxo-1,2,3,4,6,7,12,12b- octahydropyrido[2,1-a] β-carbolin-1-yl]propanoate* 43b**



43a



43b

Tryptamine (180 mg, 1.1 mmol), aldehyde **42** (340 mg, 1.0 mmol) and anh. $MgSO_4$ (300 mg) were mixed in CH_2Cl_2 (5 ml) and stirred overnight at r.t. The resulting mixture was then filtered, additional CH_2Cl_2 (5 ml) was used to wash the solid. The combined filtrate was then cooled to 0^0 and added dropwise with a soln. of TFA (0.35 ml, 4.5 mmol) in CH_2Cl_2 (1 ml) during 5 min. After additional stirring at 0^0 for 1 h, it was allowed to warm up to r.t. overnight and poured into an ice-cold aq. $NaHCO_3$ (5%, 15 ml). Workup involved layer separation, extraction with CH_2Cl_2, rewashing with $NaHCO_3$(aq) and brine, dried, concentrated *in vacuo* and chromatography (eluent gradient: 10-70:90-30 AcOEt/hexane) to give **43a** (0.16 g, 0.45 mmol) and **43b** (0.12 g, 0.34 mmol). Yield: 79%.

43a:

Physical Property: white solid, m.p.: 190-192^{0}C. [lit.[60]: 193-195^{0}C].

IR: 3317 (N-H), 3057, 2951, 2882 (C-H), 1737, 1621 (C=O).

^{1}**H-NMR** (300 MHz): 0.70 (*t*, *J*= 7.5 Hz., 3 H), 0.79-1.02 (*m*, 2 H), 1.39-1.51 (*m*, 1H), 1.57-1.65 (*m*, 1 H), 1.74-1.82 (*m*, 1 H), 2.04-2.10 (*m*, 1 H),

2.20-2.30 (*m*, 1 H), 2.41-2.49 (*m*, 2 H), 2.55-2.61 (*m*, 2 H), 2.62-2.76 (*m*, 2 H), 3.78 (*s*, 3 H), 4.74 (*s*, 1H), 5.08-5.12 (*m*, 1 H), 7.06-7.20 (*m*, 2 H), 7.39 (*d*, *J*= 7.8 Hz, 1 H), 7.48 (*d*, *J*= 7.8 Hz, 1H), 9.33 (*br s*, 1 H).

^{13}C- NMR: (75 MHz): 6.95 (*q*), 20.99 (*t*), 23.91 (*t*), 26.65 (*t*), 27.85 (*t*), 28.76 (*t*), 30.81 (*t*), 39.05 (*s*), 40.83 (*t*), 52.33 (*q*), 60.12 (*d*), 111.14 (*d*), 112.96 (s), 117.86 (*d*), 119.39 (*d*), 121.89 (*d*), 126.16 (*s*), 130.31 (*s*), 136.38 (*s*), 169.93 (*s*), 175.42 (*s*).

EI-MS: 354 (100), 323 (8), 251 (11), 211 (45), 169 (91).

43b:

Physical Property: white solid, m.p.: 188-190^{0}C. [lit.[60]: 189-191^{0}C].

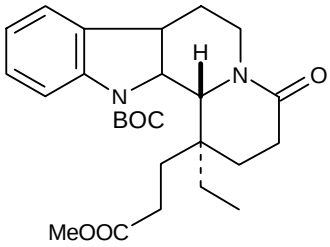
IR: 3349 (N-H), 3056, 3034, 2949, 2882, 2851 (C-H), 1734, 1622 (C=O).

^{1}H-NMR (300 MHz): 1.15 (*t*, *J*= 7.5 Hz., 3 H), 1.39-1.46 (*m*, 1 H), 1.49-1.57 (*m*, 1H), 1.67-1.89 (*m*, 2 H), 1.90-1.96 (*m*, 2 H), 2.07-2.13 (*m*, 2 H), 2.43-2.56 (*m*, 2 H), 2.67-2.76 (*m*, 3 H), 3.55 (*s*, 3 H), 4.81 (*s*, 1H), 5.11-5.15 (*m*, 1 H), 7.10-7.18 (*m*, 2 H), 7.34 (*d*, *J*= 7.8 Hz, 1 H), 7.49 (*d*, *J*= 7.8 Hz, 1H), 8.06 (*br s*, 1 H).

^{13}C- NMR (75 MHz): 7.96 (*q*), 20.83 (*t*), 27.08 (*t*), 27.12 (*t*), 28.08 (*t*), 28.61 (*t*), 29.45 (*t*), 38.83 (*s*), 40.93 (*t*), 51.53 (*q*), 60.26 (*d*), 110.99 (*d*), 112.93 (s), 117.98 (*d*), 119.51 (*d*), 122.03 (*d*), 126.21 (*s*), 130.19 (*s*), 136.28 (*s*), 170.02 (*s*), 173.63 (*s*).

EI-MS: 354 (100), 323 (12), 251 (7), 211 (55), 170 (78), 169 (34).

***tert-Butyl (1RS,12bSR)-1-ethyl-1-(3-methoxy-3-oxopropyl)-4-oxo-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]β-carboline-12-carboxylate* <u>44a</u>**



Compound **43a** (150 mg, 0.42 mmol) was mixed with $(BOC)_2O$ (0.18 g, 0.84 mmol), DMAP (0.02 g, 0.02 mmol) in CH_2Cl_2 (5 ml) and stirred at r.t. overnight. Workup involved diluting with CH_2Cl_2 (5 ml), washing with brine, dried, concentrated *in vacuo* and chromatography (eluent: 50:50 AcOEt/hexane) to give **44a** (150 mg, 79%).

Physical Property: white solid m.p.: 158-160^{0}C.

IR: 3051, 2975, 2947 (C-H), 1733, 1664 (C=O).

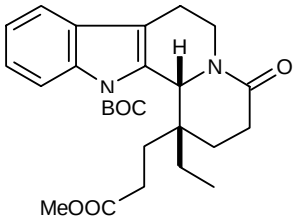
^{1}H-NMR (300 MHz): 0.49 (*t*, J= 7.5 Hz, 3 H), 0.85-1.00 (*m*, 1 H), 1.05-1.17 (*m*, 1 H), 1.47-1.57 (*m*, 1 H), 1.63 (*s*, 9 H), 1.69-1.84 (*m*, 2 H), 1.97-2.03 (*m*, 1 H), 2.22 (*ddd*, J= 4.5, 12, 14 Hz, 1 H), 2.44-2.50 (*m*, 2 H), 2.56-2.71 (*m*, 2 H), 2.80-2.90 (*m*, 2 H), 3.63 (*s*, 3 H), 4.79-4.84 (*m*, 1 H), 5.56 (*s*, 1 H), 7.22-7.31 (*m*, 2 H), 7.44 (*dd*, J= 1.5, 7.8 Hz, 1 H), 7.94 (*d*, J= 7.8 Hz, 1 H).

^{13}C- NMR: 7.66 (*q*), 20.97 (*t*), 26.62 (*t*), 28.08 (*q*), 29.12 (*t*), 29.73 (*t*), 30.29 (*t*), 30.75 (*t*), 39.07 (*t*), 42.90 (*s*), 51.43 (*q*), 58.40 (*d*), 84.68 (*s*), 115.88 (*d*), 118.18 (*d*), 122.83 (*s*), 123.06 (*d*), 124.73 (*d*), 128.21 (*s*), 132.78 (*s*), 137.21 (*s*), 151.23 (*s*), 173.00 (*s*), 174.00 (*s*).

EI-MS: 454 (53), 398 (37), 354 (50), 323 (11), 256 (40), 214 (55), 170 (100).

HR-MS: 454.2470 ($C_{26}H_{34}N_2O_5^{+\circ}$; calc. 454.2469).

***tert-Butyl (1SR,12bSR)-1-ethyl-1-(3-methoxy-3-oxopropyl)-4-oxo-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]β-carboline-12-carboxylate* <u>44b</u>**



Compound **43b** (110 mg, 0.31 mmol) was mixed with $(BOC)_2O$ (135 mg, 0.62 mmol), DMAP (0.01 g, 0.01 mmol) in CH_2Cl_2 (5 ml) and stirred at r.t. overnight. Workup involved diluting with CH_2Cl_2 (5 ml), washing with brine, dried, concentrated *in vacuo* and chromatography (eluent: 50:50 AcOEt/hexane) to give **44b** (110 mg, 78%).

Physical Property: white amorphous solid.

IR: 3052, 2976, 2936, 2882 (C-H), 1733, 1665 (C=O).

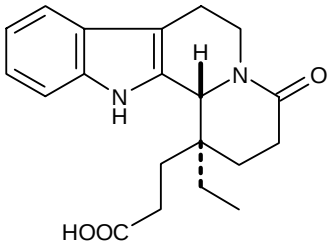
^{1}H-NMR (300 MHz): 0.89 (*t*, J= 7.5 Hz, 3 H), 1.34-1.41 (*m*, 2 H), 1.42.-1.64 (*m*, 4 H), 1.64 (*s*, 9 H), 1.72-1.95 (*m*, 2 H), 2.37-2.56 (*m*, 2 H), 2.70-2.88 (*m*, 3 H), 3.43 (*s*, 3 H), 4.80-4.85 (*m*, 1 H), 5.51 (*s*, 1 H), 7.19-7.29 (*m*, 2 H), 7.43 (*d*, J= 1.5, 7.8 Hz, 1 H), 7.90 (*d*, J= 7.8 Hz, 1 H).

^{13}C- NMR: 8.55 (*q*), 20.87 (*t*), 27.48 (*t*), 28.10 (*q*), 28.46 (*t*), 28.76 (*t*), 30.08 (*t*), 31.03 (*t*), 39.11 (*t*), 43.09 (*s*), 51.39 (*q*), 58.31 (*d*), 84.45 (*s*), 115.22 (*d*), 118.35 (*d*), 122.61 (*s*), 122.95 (*d*), 124.74 (*d*), 127.91 (*d*), 132.33 (*s*), 136.92 (*s*), 151.05 (*s*), 172.85 (*s*), 173.76 (*s*).

EI-MS: 454 (53), 398 (37), 354 (50), 323 (11), 256 (40), 214 (55), 170 (100).

HR-MS: 454.2466 ($C_{26}H_{34}N_2O_5^{+\circ}$; calc. 454.2469).

3-[(1RS,12bSR)-1-ethyl-4-oxo-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a] β-carbolin-1-yl]propanoic acid **30a**



To a soln. of **28a** (30 mg, 0.064 mmol) in EtOH (5.0 ml) was added 50% KOH(aq) (0.80 g), the resulting soln. was stirred at r.t. overnight. Water (10 ml) was added, and the soln. was carefully acidified with conc. HCl, extracted with CH_2Cl_2 (25 ml), washing with brine, dried, concentrated *in vacuo* to give **30a** (15 mg, 0.044 mmol) sufficiently pure for the next step. Yield: 69%.

Physical Property: light yellow solid, m.p.: 220-224^{0}C.

IR: 3296 (N-H, O-H); 1721, 1672 (C=O).

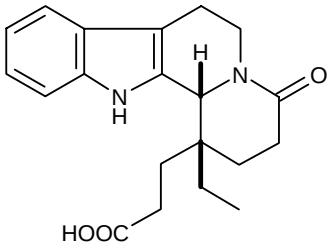
^{1}H-NMR (300 MHz): 0.58 (*t*, *J* = 7.5, 3 H); 0.82-1.00 (*m*, 1 H); 1.20-1.30 (*m*, 1 H); 1.47-1.80 (*m*, 2 H); 1.90-2.14 (*m*, 2 H); 2.24-2.47 (*m*, 4 H); 2.58-2.67 (*m*, 2 H); 4.66 (*s*, 1H); 4.95 (*d*, *J* = 6.6, 1 H); 6.98 (*d*, *J* = 7.5, 1 H); 7.05 (*d*, *J* = 7.5, 1H); 7.30 (*d*, *J* = 7.5, 1 H); 7.38 (*d*, *J* = 7.5, 1 H); 9.62 (*br s*, 1 H).

^{13}C- NMR (75 MHz): 6.81 (*q*); 20.78 (*t*); 23.84 (*t*); 26.42 (*t*); 27.96 (*t*); 28.44 (*t*); 30.75 (*t*); 38.84 (*s*); 41.03 (*t*); 60.60 (*d*); 111.07 (*d*); 112.36(s); 117.60 (*d*); 119.09 (*d*); 121.66 (*d*); 125.92 (*s*); 130.09 (*s*); 136.45 (*s*); 171.02 (*s*); 176.97(*s*).

EI-MS: 340 (43), 322 (14), 293 (11), 251 (9), 211 (46), 169 (100).

HR-MS: 340.1767 ($C_{20}H_{24}N_2O_3^{+\circ}$; calc. 340.1788).

3-[(1SR,12bSR)-1-ethyl-4-oxo-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a] β-carbolin-1-yl]propanoic acid **30b**



To a soln. of **28b** (20 mg, 0.043 mmol) in EtOH (5.0 ml) was added 50% KOH(aq) (0.80 g), the resulting soln. was stirred at r.t. overnight. Water (10 ml) was added, and the soln. was carefully acidified with conc. HCl, extracted with CH_2Cl_2 (25 ml), washing with brine, dried, concentrated *in vacuo* to give **30b** (10 mg, 0.029 mmol) sufficiently pure for the next step. Yield: 67%.

Physical Property: light yellow solid, m.p.: 235-238^{0}C.

IR: 3259(N-H, O-H), 1728, 1672 (C=O).

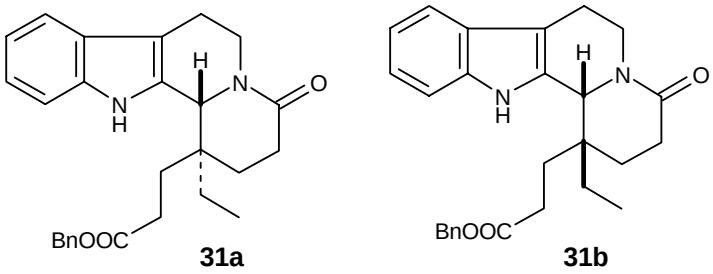
^{1}H-NMR (300 MHz): 1.10 (*m*, 3 H); 1.24-1.49 (*m*, 2 H); 1.66-1.89 (*m*, 4 H); 1.97-2.11 (*m*, 2 H); 2.38-2.56 (*m*, 2 H); 2.60-2.72 (*m*, 3 H); 4.75 (*s*, 1H); 5.04-5.06 (*m*, 1 H); 7.05-7.18 (*m*, 2 H); 7.33 (*d*, *J*= 7.8, 1 H); 7.43 (*d*, *J* = 7.8, 1H); 8.20 (*br* s, 1 H).

^{13}C- NMR (75 MHz): 8.00 (*q*); 20.87 (*t*); 26.75 (*t*); 26.99 (*t*); 28.08 (*t*); 28.49 (*t*); 29.59 (*t*); 38.80 (*s*); 41.38 (*t*); 60.55 (*d*); 111.12 (*d*); 112.95 (s); 118.08 (*d*); 119.66 (*d*); 122.20 (*d*); 126.24 (*s*); 130.12 (*d*); 136.33 (*s*); 170.89 (*s*); 176.71 (*s*).

EI-MS: 340 (43), 211 (46), 169 (100).

HR-MS: 340.1787 ($C_{20}H_{24}N_2O_3^{+\circ}$; calc. 340.1788).

Benzyl 3-[(1RS,12bSR)-1-ethyl-4-oxo-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a] β-carbolin-1-yl]propanoate **31a** **and** ***Benzyl 3-[(1SR,12bSR)-1-ethyl-4-oxo-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]β-carbolin-1-yl]propanoate*** **31b**



31a **31b**

To a mixture of acid **30a** and **30b** (210 mg, 0.62 mmol), benzyl alcohol (1.35g, 12.5 mmol) in THF (12.5 ml) was added TMSCl (0.75 ml, 6 mmol) during 3 min. at r.t. The resulting soln. was refluxed for 18 h, cooled, diluted with CH_2Cl_2 (30 ml), and poured into an ice-cold 5% $NaHCO_3$ (15 ml). Workup involved layer separation, extraction with CH_2Cl_2, rewashing with $NaHCO_3$ and brine, drying, concentration *in vacuo* and chromatography (eluent gradient: 10-70:90-30 AcOEt/hexane) to give **31a** (120 mg, 45%) and **31b** (90 mg, 34% mmol).

31a:

Physical Property: light brown oil.

IR: 3318 (N-H), 3060, 3034, 2957, 2931, 2879 (C-H), 1734, 1621 (C=O).

^{1}H-NMR (300 MHz): 0.69 (*t*, *J*= 7.5 Hz., 3 H); 0.82-1.02 (*m*, 2 H); 1.39-1.49 (*m*, 1H); 1.55-1.63 (*m*, 1 H); 1.69-1.80 (*m*, 1 H); 2.03-2.11 (*m*, 1 H); 2.21-2.31 (*m*, 1 H); 2.40-2.49 (*m*, 2 H); 2.59-2.67 (*m*, 2 H); 2.69-2.75 (*m*, 2 H); 4.68 (*s*, 1H); 5.05-5.10 (*m*, 1 H); 5.20 (*dd*, J= 15, 12 Hz, 2 H); 7.09 (*dt*, *J* = 1.2, 7.2, 1 H); 7.16 (*dt*, *J*= 1.2, 7.2, 1 H); 7.29-7.37 (*m*, 6 H); 7.48 (*d*, *J* = 7.2, 1H); 9.15 (*br s*, 1 H).

^{13}C- NMR (75 MHz): 7.01 (*q*), 21.06 (*t*), 24.05 (*t*), 26.82 (*t*), 28.34 (*t*), 28.92 (*t*), 31.01 (*t*), 39.23 (*s*), 40.84 (*t*), 60.15 (*d*), 67.30 (*t*), 111.20 (*d*), 113.15(s), 117.94 (*d*), 119.49 (*d*), 121.98 (*d*), 126.27 (*s*), 128.46 (*d*), 128.58 (*d*), 128.68 (*d*), 130.37 (*s*), 135.16 (*s*), 136.44 (*s*), 169.93 (*s*), 174.88 (*s*).

EI-MS: 430 (26), 339 (24), 251 (11), 211 (48), 170 (100), 169 (97).

HR-MS: 430.2260 ($C_{27}H_{30}N_2O_3^{+\circ}$; calc. 430.2258).

31b:

Physical Property: light brown amorphous solid.

IR: 3318 (N-H), 3060, 3034, 2957, 2931, 2879 (C-H), 1734, 1621 (C=O).

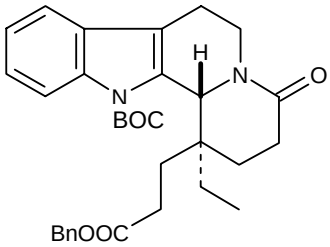
^{1}H-NMR (300 MHz): 1.12 (*t*, *J*= 7.5, 3 H), 1.39-1.46 (*m*, 1 H), 1.49-1.56 (*m*, 1H), 1.67-1.94 (*m*, 4 H), 2.08-2.19 (*m*, 2 H), 2.43-2.54 (*m*, 2 H), 2.67-2.80 (*m*, 3 H), 4.79 (*s*, 1H), 4.99 (*s*, 2 H), 5.08-5.13 (*m*, 1 H), 7.09-7.37 (*m*, 7 H), 7.36 (*d*, *J*= 5.7 Hz, 1 H), 7.49 (*d*, *J*= 7.5 Hz, 1H), 8.22 (*br s*, 1 H).

^{13}C- NMR (75 MHz): 8.06 (*q*), 20.95 (*t*), 27.17 (*t*), 27.26 (*t*), 28.36 (*t*), 28.82 (*t*), 29.70 (*t*), 38.96 (*s*), 41.01 (*t*), 60.28 (*d*), 66.33 (*t*), 110.97 (*d*), 113.30(s), 118.18 (*d*), 119.74 (*d*), 122.25 (*d*), 126.34 (*s*), 128.12 (*d*), 128.17 (*d*), 128.46 (*d*), 130.29 (*s*), 135.59 (*s*), 136.22 (*s*), 169.86 (*s*), 173.06 (*s*).

EI-MS: 430 (68), 339 (39), 251 (15), 211 (70), 170 (100), 169 (80).

HR-MS: 430.2261 ($C_{27}H_{30}N_2O_3^{+\circ}$; calc. 430.2258).

tert-Butyl (1RS,12bSR)-1-ethyl-1-(3-benzyloxy-3-oxopropyl)-4-oxo-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]β-carboline-12-carboxylate **32a**



Compound **31a** (150 mg, 0.35 mmol) was mixed with $(BOC)_2O$ (150 mg, 0.71 mmol), DMAP (0.02 g, 0.02 mmol) in CH_2Cl_2 (5 ml) and stirred at 50^0 overnight. Workup involved diluting with CH_2Cl_2 (5 ml), washing with brine, dried, concentrated *in vacuo* and chromatography (eluent: 50:50 AcOEt/hexane) to give **32a** (150 mg, 80%).

Physical Property: colorless oil.

IR: 3054, 2974, 2935, 2881 (C-H), 1732, 1660, 1646 (C=O).

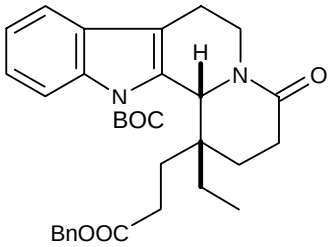
^{1}H-NMR (300 MHz): 0.50 (*t*, J= 7.5 Hz, 3 H), 0.92-1.00 (*m*, 1 H), 1.06-1.16 (*m*, 1 H), 1.47-1.57 (*m*, 1 H), 1.60 (*s*, 9 H), 1.69-1.84 (*m*, 2 H), 1.97-2.06 (*m*, 1 H), 2.28 (*ddd*, J= 4.5, 12, 14, 1 H), 2.43-2.49 (*m*, 2 H), 2.56-2.71 (*m*, 2 H), 2.80-2.90 (*m*, 2 H), 4.81-4.86 (*m*, 1 H), 5.05 (*d*, *J* = 12, 1 H), 5.12 (*d*, *J* = 12, 1 H), 5.58 (*s*, 1 H), 7.22-7.35 (*m*, 7 H), 7.45 (*d*, *J* = 7.5, 1 H), 7.95 (*d*, *J* = 7.5, 1 H).

^{13}C- NMR (75 MHz): 7.67 (*q*), 20.99 (*t*), 26.58 (*t*), 28.10 (*q*), 29.31 (*t*), 29.65 (*t*), 30.27 (*t*), 30.71 (*t*), 39.09 (*t*), 42.93 (*s*), 58.45 (*d*), 66.16 (*t*), 84.70 (*s*), 115.91 (*d*), 118.19 (*d*), 122.85 (*s*), 123.07 (*d*), 124.73 (*d*), 128.13 (*d*) 128.17 (*d*), 128.23 (*s*), 128.49 (*d*), 132.80 (*s*), 135.82 (*s*), 137.23 (*s*), 151.25 (*s*), 172.95 (*s*), 173.40 (*s*).

EI-MS: 530 (9), 430 (22), 339 (19), 251 (36), 211 (86), 169 (100).

HR-MS: 530.2776 ($C_{32}H_{38}N_2O_5^{+\circ}$; calc. 530.2782).

tert-Butyl (1SR,12bSR)-1-ethyl-1-(3-benzyloxy-3-oxopropyl)-4-oxo-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]β-carboline-12-carboxylate **32b**



Compound **31b** (100 mg, 0.23 mmol) was mixed with $(BOC)_2O$ (100 mg, 0.46 mmol), DMAP (0.01 g, 0.01 mmol) in CH_2Cl_2 (5 ml) and stirred at 50^0 overnight. Workup involved diluting with CH_2Cl_2 (5 ml), washing with brine, dried, concentrated *in vacuo* and chromatography (eluent: 50:50 AcOEt/hexane) to give **32b** (100 mg, 82%).

Physical Property: colorless oil.

IR: 3055, 2975, 2936, 2882 (C-H), 1733, 1664 (C=O).

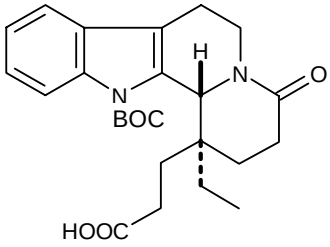
^{1}H-NMR (300 MHz): 0.92 (*t*, J= 7.5, 3 H), 1.32-1.42 (*m*, 2 H), 1.46-1.66 (*m*, 4 H), 1.65 (*s*, 9 H), 1.75-2.03 (*m*, 2 H), 2.40-2.52 (*m*, 2 H), 2.69-2.85 (*m*, 3 H), 4.80-4.85 (*m*, 1 H), 4.85-4.91 (m, 2 H), 5.53 (*s*, 1 H), 7.11-7.14 (*m*, 1 H), 7.20-7.32 (*m*, 6 H), 7.39 (*d*, J= 7.5, 1 H), 7.92 (*d*, J= 7.5, 1 H).

^{13}C- NMR: 8.60 (*q*), 20.81 (*t*), 27.51 (*t*), 28.08 (*q*), 28.76 (*t*), 28.99 (*t*), 30.16 (*t*), 30.99 (*t*), 39.07 (*t*), 43.06 (*s*), 58.18 (*d*), 65.98 (*t*), 84.44 (*s*), 115.25 (*d*), 118.35 (*d*), 122.64 (*s*), 122.95 (*d*), 124.73 (*d*), 127.87 (*d*), 127.92 (*d*), 128.01 (*s*), 128.36 (*d*), 132.27 (*s*), 135.65 (*s*), 136.88 (*s*), 151.02 (*s*), 173.02 (*s*), 173.11 (*s*).

EI-MS: 530 (9), 430 (22), 339 (19), 251 (36), 211 (86), 169 (100).

HR-MS: 530.2808 ($C_{32}H_{38}N_2O_5^{+\circ}$; calc. 530.2782).

***tert-Butyl (1RS,12bSR)-1-ethyl-1-(3-hydroxy-3-oxopropyl)-4-oxo-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]β-carboline-12-carboxylate* <u>33a</u>**



MeOH (2.0 ml) was carefully added to 5% Pd/C (10 mg), followed by $NaHCO_3$ (100 mg) and a soln. of **32a** (180 mg, 0.34 mmol) in MeOH (8.0 ml). The mixture was stirred under H_2 at r.t. for 2 d. Work up involved dilution with CH_2Cl_2 (15 ml) and sat. NH_4Cl (10 ml), filtration, washing with brine, drying and concentration *in vacuo* to give **33a** (125 mg, 85%).

Physical Property: light yellow solid, m.p.: 188-190^{0}C (dec.).

IR: 3435 (O-H), 3053, 2974, 2935, 2883 (C-H), 1731, 1620 (C=O).

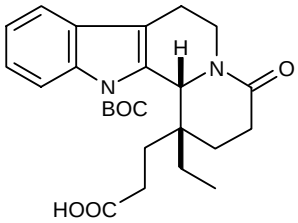
^{1}H-NMR (300 MHz): 0.50 (*t*, *J* = 7.2, 3 H); 0.92-1.17 (*m*, 2 H); 1.46-1.57 (*m*, 1 H); 1.64 (*s*, 9 H); 1.73-1.84 (*m*, 2 H); 1.95-2.04 (*m*, 1 H); 2.21-2.32 (*m*, 1 H); 2.48-2.51 (*m*, 2 H); 2.57-2.72 (*m*, 2 H); 2.81-2.90 (*m*, 2 H); 4.82-4.86 (*m*, 1 H); 5.60 (*s*, 1 H); 7.23-7.32 (*m*, 2 H); 7.50 (*dd*, J= 1.5, 7.8, 1 H); 7.95 (*d*, *J* = 7.8, 1 H).

^{13}C- NMR (75 MHz): 7.77 (*q*); 20.99 (*t*); 26.45 (*t*); 28.19 (*q*); 29.10 (*t*); 29.55 (*t*); 30.07 (*t*); 30.71 (*t*); 39.33 (*t*); 42.95 (*s*); 58.76 (*d*); 84.86 (*s*); 115.99 (*d*); 118.28 (*d*); 122.87 (*s*); 123.14 (*d*); 124.83 (*d*); 128.24 (*s*); 132.70 (*s*); 137.26 (*s*); 151.31 (*s*); 173.36 (*s*); 178.06 (*s*).

EI-MS: 440 (0.4), 340 (6), 211 (29), 169 (100).

HR-MS: 440.2295 ($C_{25}H_{32}N_2O_5^{+\circ}$; calc. 440.2313).

***tert-Butyl (1SR,12bSR)-1-ethyl-1-(3-hydroxy-3-oxopropyl)-4-oxo-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]β-carboline-12-carboxylate* <u>33b</u>**



MeOH (2.0 ml) was carefully added to 5% Pd/C (10 mg), followed by $NaHCO_3$ (100 mg) and a soln. of **32b** (150 mg, 0.28 mmol) in MeOH (8.0 ml). The mixture was then stirred under H_2 at r.t. for 2 d. Work up involved dilution with CH_2Cl_2 (15 ml) and sat. NH_4Cl (10 ml), filtration, washing with brine, drying and concentration *in vacuo* to give **33b** (100 mg, 82%).

Physical Property: white solid, m.p.: 188-190^{0}C (dec.).

IR: 3445 (O-H), 3053, 2970, 2932, 2884 (C-H), 1732, 1645, 1624 (C=O).

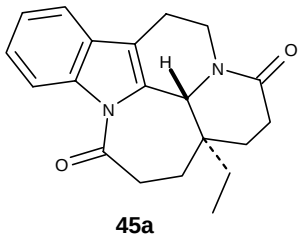
^{1}H-NMR (300 MHz): 0.93 (*t*, *J* = 6.6, 3 H); 1.38-1.44 (*m*, 2 H); 1.48.-1.63 (*m*, 4 H); 1.66 (*s*, 9 H); 1.72-1.95 (*m*, 2 H); 2.32-2.56 (*m*, 2 H); 2.75-2.88 (*m*, 3 H); 4.85 (*br d*, *J* = 9.6, 1 H); 5.54 (*s*, 1 H); 7.23-7.32 (*m*, 2 H); 7.44 (*d*, *J* = 6.0, 1 H); 7.92 (*d*, J= 6.6, 1 H).

^{13}C- NMR (75 MHz): 8.59 (*q*); 20.94 (*t*); 27.63 (*t*); 28.17 (*q*); 28.53 (*t*); 29.63 (*t*); 29.97 (*t*); 30.85 (*t*); 39.39 (*t*); 43.18 (*s*); 58.57 (*d*); 84.60 (*s*); 115.28 (*d*); 118.48 (s); 122.63 (*d*); 123.03 (*d*); 124.82 (*d*); 127.92 (*s*); 132.25 (*s*); 136.95 (*s*); 151.12 (*s*); 173.35 (*s*); 173.85 (*s*).

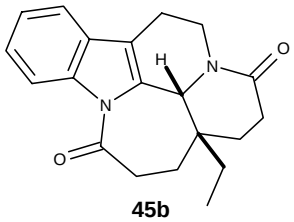
EI-MS: 440 (M^+, 10), 211 (36), 169 (100).

HR-MS: 440.2295 ($C_{25}H_{32}N_2O_5^{+\circ}$; calc. 440.2313).

***Epi 19-oxo-homoeburnamonine* 45a and *19-oxo-homoeburnamonine* 45b**



45a



45b

To a mixture of acid **30a** and **30b** (100 mg, 0.29 mmol) was mixed with $(BOC)_2O$ (130 mg, 0.58 mmol), DMAP (0.01 g, 0.01 mmol) in CH_2Cl_2 (5 ml) and stirred at 50^0 overnight. Workup involved diluting with CH_2Cl_2 (5 ml), washing with brine, drying, concentration *in vacuo* and chromatography (eluent gradient: 20-50:80-50 AcOEt/hexane) to give **45a** (40 mg, 0.12 mmol) and **45b** (30 mg, 0.09 mmol). Yield: 72%.

45a:

Physical Property: white solid, m.p.: 150-152^{0}C. [lit.[60]: 151-153^{0}C].

IR: 1703, 1647 (C=O).

^{1}H-NMR (300 MHz): 0.74 (*t*, *J* = 7.5, 3 H); 0.76-0.96 (*m*, 1 H); 1.29-1.41 (*m*, 1 H); 1.67 (*td*, *J* = 14.7, 4.8, 1 H); 1.74-1.90 (*m*, 3 H); 2.09 (*dt*, *J* = 14.1, 3.6, 1 H); 2.29-2.41 (*m*, 1 H); 2.50 (*ddd*, *J* = 18.3, 6.3, 1.8, 1 H); 2.69-2.84 (*m*, 3 H); 2.97 (*dt*, *J* = 14.1, 4.5, 1 H); 4.92 (*s*, 1 H); 5.10-5.15 (*m*, 1 H); 7.26-7.37 (*m*, 2 H); 7.43 (*d*, *J* = 7.5, 1H); 8.46 (*d*, *J* = 7.5, 1 H).

^{13}C- NMR (75 MHz): 6.57 (*q*); 20.90 (*t*); 22.90 (*t*); 28.74 (*t*); 29.97 (*t*); 31.42 (*t*); 34.40 (*t*); 37.10 (*s*); 39.30 (*t*); 61.67 (*d*); 116.90 (*d*); 117.95 (*d*); 119.82 (*s*); 124.00 (*d*); 125.39 (*d*); 128.42 (*s*); 130.29 (*s*); 135.90 (*s*); 169.15 (*s*); 171.39 (*s*).

EI-MS: 322 (100), 293 (92), 265 (20), 251 (29), 169 (29).

HR-MS: 322.1680 ($C_{20}H_{22}N_2O_2^{+\circ}$; calc. 322.1683).

45b:

Physical Property: white solid, m.p.: 215-217^{0}C. [lit.[60]: 221-223^{0}C].

IR: 1703, 1645 (C=O).

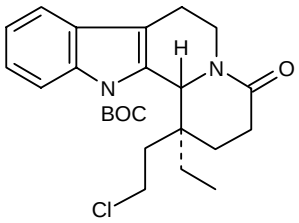
^{1}**H-NMR** (300 MHz): 0.93 (*t*, *J* = 7.5, 3 H); 1.40-1.65 (*m*, 4 H); 1.78-1.96 (*m*, 1 H); 2.12-2.21 (*m*, 1 H); 2.32-2.37 (*m*, 2 H); 2.53-2.64 (*m*, 2 H); 2.71-2.82 (*m*, 2 H); 2.87-3.01 (*m*, 1 H); 4.60 (*s*, 1 H); 4.93-4.99 (*m*, 1 H); 7.22-7.33 (*m*, 2 H); 7.39 (*d*, *J* = 7.5, 1 H); 8.40 (*d*, *J* = 8.1, 1 H).

^{13}**C- NMR** (75 MHz): 7.24 (*q*); 21.88 (*t*); 26.45 (*q*); 27.99 (*t*); 28.62 (*t*); 29.75 (*t*); 31.98 (*t*); 37.05 (*s*); 43.59 (*t*); 64.99 (*d*); 117.40 (*d*); 117.92 (*d*); 121.26 (*s*); 123.89 (*d*); 125.34 (*d*); 129.40 (*s*); 131.28 (*s*); 136.28 (*s*); 170.16 (*s*); 172.07 (*s*).

EI-MS: 322 (100), 293 (68), 265 (13), 251 (9), 169 (37).

HR-MS: 322.1664 ($C_{20}H_{22}N_2O_2^{+\circ}$; calc. 322.1683).

tert-Butyl (1RS,12bSR)-1-(2-chloroethyl)-1-ethyl-4-oxo-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]β-carboline-12-carboxylate **34a**



To an ice-cooled mixture of compounds **33a** (50 mg, 0.113 mmol) in THF (3.0 ml) was added in sequence solns. of N-methyl morpholine (40 mg, 0.40 mmol) in THF (1 ml) and ethyl chloroformate (40 mg, 0.37 mmol) in THF (1 ml). The resulting mixture was kept stirring at ice-bath temperature for 30 min., followed by addition in sequence of soln. of Et_3N (40 mg, 0.40 mmol) in CCl_4 (2 ml) and N-hydoxy thiopyridone (40 mg, 0.31 mmol) in CCl_4 (3 ml). The resulting mixture was kept stirring under ice-bath temperature in the dark for additional 30 min. The yellow-colored mixture was then irradiated (300 nm) in a Rayonet photochemical apparatus at ice-bath temperature for 1 hour. Work up involved dilution with CH_2Cl_2 (10 ml), washing with 5% HCl (aq), brine, drying, concentrating *in vacuo* and chromatography (eluent gradient: 10-50:90-50 AcOEt/hexane) to give **34a** (20 mg, 41%).

Physical Property: colorless oil.

IR: 3052, 2973, 2933, 2879 (C-H), 1730, 1665(C=O).

^{1}H-NMR (300 MHz): 0.53 (*t*, *J* = 7.5, 3 H); 0.86-1.01 (*m*, 1 H); 1.03-1.22 (*m*, 1H); 1.53-1.64 (*m*, 1 H); 1.70 (*s*, 9 H); 1.82-1.91 (*m*, 2 H); 2.01 (*dt*, *J* = 14.0, 5.0, 1H); 2.13 (*dt*, *J* = 14.0, 5.0, 1 H); 2.47 (*t*, *J* = 6.9, 2 H); 2.59-2.70 (*m*, 1 H); 2.80-2.89 (*m*, 2 H); 3.42 (*dt*, *J* = 10.8, 5.0, 1 H); 3.76 (*td*, *J* = 10.8, 5.0, 1

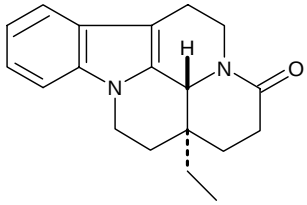
H); 4.84 (*dd*, *J* = 11.7, 4.5, 1 H); 5.61 (*s*, 1 H); 7.24-7.33 (*m*, 2 H); 7.45 (*dd*, *J* = 8.0, 1.2, 1 H); 7.97 (*d*, *J* = 8.0, 1 H).

^{13}C- NMR (75 MHz): 7.89 (*q*); 21.05 (*t*); 26.26 (*t*); 28.40 (*q*); 30.13 (*t*); 30.75 (*t*); 39.09 (*t*); 39.15 (*t*); 41.02 (*t*); 43.93 (*s*); 58.62 (*d*); 85.13 (*s*); 116.01 (*d*); 118.31 (*d*); 123.06 (*s*); 123.21 (*d*); 124.91 (*d*); 128.27 (*s*); 132.59 (*s*); 137.22 (*s*); 151.38 (*s*); 172.66 (*s*).

EI-MS: 432 (8), 430 (24), 376 (8), 374 (24), 255 (33), 211 (20), 169 (100).

HR-MS: 430.2023 ($C_{24}H_{31}N_2O_3Cl^{+\circ}$; calc. 430.2025).

(3RS,16SR)-epi-14,15-Dihydroeburnamenin-19-one **46a**



To a soln. of **34a** (10 mg, 0.023 mmol) in MeOH (5.0 ml) was added 50% KOH (aq) (0.50 g). The resulting soln. was kept stirring at r.t. overnight. Work up involved dilution with water (10 ml) and CH_2Cl_2 (15 ml), layer separation, washing with water, brine, dried, concentrated *in vacuo*, and chromatography (eluent: 50:50 AcOEt/hexane) to give **46a** (5 mg, 0.017 mmol). Yield: 74%.

Physical Property: colorless oil.

IR: 3051, 2962, 2927 (C-H), 1729, 1646 (C=O).

^{1}H-NMR (300 MHz): 0.53-0.66 (*m*, 1 H); 0.77 (*t*, *J* = 7.5, 3 H); 1.23-1.40 (*m*, 1 H); 1.55-1.63 (*m*, 1 H); 1.79-1.88 (*m*, 1 H); 1.96-2.02 (*m*, 1 H); 2.19 (*dd*, *J* = 14.4, 5.4, 1 H); 2.46-2.55 (*m*, 2 H); 2.78-2.82 (*m*, 2 H); 3.00-3.06 (*m*, 1 H); 3.77 (*td*, *J* = 12.0, 6.0, 1 H); 4.20 (*dd*, *J* = 12.0, 6.9, 1 H); 4.42 (*s*, 1 H); 4.85-4.92 (*m*, 1 H); 7.10-7.21 (*m*, 2 H); 7.27 (*d*, *J* = 7.5, 1 H); 7.48 (*d*, *J* = 7.5, 1 H).

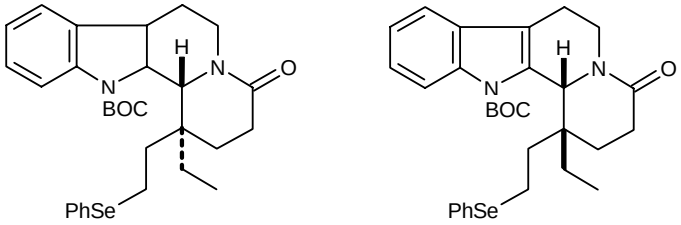
^{13}C- NMR (75 MHz): 7.08 (*q*); 16.92 (*t*); 20.21 (*t*); 28.69 (*t*); 29.25 (*t*); 30.35 (*t*); 35.68 (*s*); 38.88 (*t*); 39.83 (*t*); 59.97 (*d*); 106.51 (*s*); 109.69 (*d*); 118.47 (*d*); 119.90 (*d*); 121.42 (*d*); 127.66 (*s*); 132.10 (*s*); 138.29 (*s*); 169.71 (*s*).

EI-MS: 294 (87), 265 (100), 223 (14), 169 (12).

HR-MS: 294.1716 ($C_{19}H_{22}N_2O^{+\circ}$; calc. 294.1734).

tert-Butyl (1RS,12bSR)-1-ethyl-4-oxo-1-[2-(phenylseleno)ethyl]-1,2,3,4,6,712,12b-octahydropyrido[2,1-a] β-carboline-12-carboxylate **35a**

tert-Butyl (1SR,12bSR)-1-ethyl-4-oxo-1-[2-(phenylseleno)ethyl]-1,2,3,4,6,712,12b-octahydropyrido[2,1-a] β-carboline-12-carboxylate **35b**



To an ice-cooled mixture of compounds **33a** and **33b** (60 mg, 0.136 mmol) in THF (3.0 ml) was added solutions of N-methyl morpholine (50 mg, 0.49 mmol) in THF (1 ml) and ethyl chloroformate (50 mg, 0.46 mmol) in THF (1 ml). After stirring for 0.5 h, solns. of Et_3N (50 mg, 0.49 mmol) in CH_2Cl_2 (2 ml) and N-hydoxy-2-thiopyridone (50 mg, 0.39 mmol) in CH_2Cl_2 (2 ml) were added consecutively. The resulting mixture was kept stirring under ice-bath temperature in the dark for additional 30 min, followed by addition of a soln. of diphenyl diselenide (150 mg, 0.48 mmol) in CH_2Cl_2 (2 ml) in one portion. The yellow-colored mixture was then irradiated (300 nm) in a Rayonet photochemical apparatus at ice-bath temperature for 1 hour. Work up involved dilution with CH_2Cl_2 (10 ml), washing with 5% HCl (aq), brine, drying, concentrating *in vacuo* and chromatography (eluent gradient: 10-50:90-50 AcOEt/hexane) to give **35a** (25 mg, 41%) and **35b** (15 mg, 24%).

35a:

Physical Property: colorless oil.

IR: 3053, 2973, 2933, 2878 (C-H), 1730, 1662 (C=O).

^{1}H-NMR (300 MHz): 0.35 (*t*, *J* = 7.5, 3 H); 1.03-1.16 (*m*, 2 H); 1.52-1.66 (*m*, 1 H); 1.69 (*s*, 9 H); 1.74-1.84 (*m*, 1 H); 1.91 (*td*, *J* = 13.4, 5.1, 1H); 2.07 (*td*, *J* =

13.4, 4.2, 1 H); 2.41-2.53 (*m*, 2 H); 2.59-2.89 (*m*, 4H); 3.04 (*td*, *J* = 12.0, 4.8, 1 H); 4.82-4.87 (*m*, 1 H); 5.60 (*s*, 1 H); 7.16-7.34 (*m*, 5 H); 7.41-7.46 (*m*, 3 H); 7.98 (*d*, *J* = 8.2, 1H).

^{13}C- NMR (75 MHz): 7.84 (*q*); 20.98 (*t*); 23.07 (*t*); 25.78 (*t*); 28.43 (*q*); 30.06 (*t*); 31.02 (*t*); 35.68 (*t*); 39.10 (*t*); 44.67 (*s*); 58.89 (*d*); 84.92 (*s*); 115.92 (*d*); 118.21 (*d*); 122.78 (*s*); 123.08 (*d*); 124.76 (*d*); 126.85 (*d*); 128.22 (*s*); 128.98 (*d*); 130.42 (*s*); 132.54 (*d*); 132.84 (*s*);137.20 (*s*); 151.23 (*s*); 172.67 (*s*).

EI-MS: 552 (M^+, 80), 550 (43), 339 (48), 295 (23), 256 (83), 214 (90), 169 (100).

HR-MS: 552.1864 ($C_{30}H_{36}N_2O_3Se^{+\circ}$; calc. 552.1911).

35b:

Physical Property: colorless oil.

IR: 3053, 2974, 2931, 2878 (C-H), 1732, 1664 (C=O).

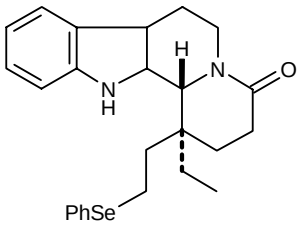
^{1}H-NMR (300 MHz): 0.89 (*t*, *J* = 7.5, 3 H); 1.33-1.91 (*m*, 7 H); 1.65 (*s*, 9 H); 2.36-2.52 (*m*, 4 H); 2.71 (*d*, *J* = 16.2, 1 H); 2.81 (*td*, *J* = 12.3, 3.3, 1 H); 4.76-4.81 (*m*, 1 H); 5.46 (*s*, 1 H); 7.03-7.18 (*m*, 5 H); 7.25-7.36 (*m*, 2 H); 7.45 (*d*, *J* = 7.5, 1 H); 7.92 (*d*, *J* = 7.5, 1 H).

^{13}C- NMR: 8.61 (*q*); 20.84 (*t*); 22.29 (*t*); 27.26 (*t*); 28.16 (*q*); 30.04 (*t*); 31.33 (*t*); 34.89 (*t*); 39.14 (*t*); 44.79 (*s*); 58.63 (*d*); 84.53 (*s*); 115.39 (*d*); 118.53 (*d*); 122.63 (*s*); 123.08 (*d*); 124.87 (*d*); 127.01 (*d*); 127.96 (*s*); 128.86 (*d*); 129.28 (*s*); 132.69 (*s*); 133.43 (*d*); 137.02 (*s*); 151.09 (*s*); 172.86 (*s*).

EI-MS: 552 (M^+, 9), 452 (17), 339 (18), 295 (15), 256 (27), 214 (45), 169 (100).

HR-MS: 552.1906 ($C_{30}H_{36}N_2O_3Se^{+\circ}$; calc. 552.1911).

(1RS,12bSR) -1-ethyl-1-[2-(phenylseleno)ethyl]-1,2,3,4,6,712,12b-octahydropyrido[2,1-a]β-carbolin-4-one **23a**



To a soln. of **35a** (30 mg, 0.054 mmol) in MeOH (5.0 ml) was stirred with 50% KOH (500 mg) at r.t. for 2 d. Dilution with H_2O (10 ml) and CH_2Cl_2 (15 ml), layer separation, washing with H_2O, brine, drying, concentration *in vacuo*, and chromatography (eluent: 50:50 AcOEt/hexane) gave **23a** (20 mg, 81%).

Physical Property: colorless oil.

IR: 3308, 3055, 2958, 2927 (C-H), 1621 (C=O).

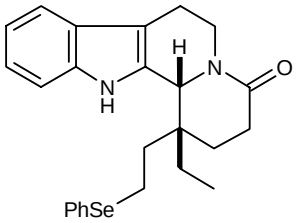
^{1}H-NMR (300 MHz): 0.67 (*t*, *J* = 7.5, 3 H); 0.81-0.91 (*m*, 1 H); 1.32-1.42 (*m*, 1 H); 1.63-1.69 (*m*, 1 H); 1.86-2.08 (*m*, 2 H); 2.16-2.27 (*m*, 1 H); 2.36-2.53 (*m*, 2 H); 2.55-2.74 (*m*, 4 H); 2.99-3.15 (*m*, 2 H); 4.84 (*s*, 1 H); 5.08-5.12 (*m*, 1 H); 7.05-7.15 (*m*, 3 H); 7.32 (*br s*, 1 H); 7.35-7.46 (*m*, 4 H); 7.64-7.67 (*m*, 1 H).

^{13}C- NMR (75 MHz): 7.02 (*q*); 21.04 (*t*); 22.08 (*t*); 24.12 (*t*); 26.87 (*t*); 28.84 (*t*); 38.41 (*t*); 40.47 (*s*); 40.90 (*t*); 60.18 (*d*); 111.01 (*d*); 113.51 (*s*); 118.09 (*d*); 119.79 (*d*); 122.20 (*d*); 126.23 (*s*); 128.18 (*d*); 128.98 (*s*); 129.69 (*d*); 130.42 (*s*); 134.07 (*d*); 135.99 (*s*); 169.86 (*s*).

EI-MS: 452 (M^+, 37), 450 (20), 295 (18), 251 (18), 212 (49), 170 (100), 169 (69)

HR-MS: 452.1386 ($C_{25}H_{28}N_2OSe^{+\circ}$; calc. 452.1386).

***(1SR,12bSR)-1-ethyl-1-[2-(phenylseleno)ethyl]-1,2,3,4,6,712,12b-octahydropyrido[2,1-a]β-carbolin-4-one* 23b**



To a soln. of **35b** (20 mg, 0.036 mmol) in MeOH (5.0 ml) was stirred with 50% KOH (500 mg) at r.t. for 2 d., diluted with H_2O (10 ml) and CH_2Cl_2 (15 ml), separated into layers, washed with H_2O, brine, dried, concentration *in vacuo*, and chromatographed (eluent: 50:50 AcOEt/hexane) to give **23a** (15 mg, 92%).

Physical Property: white solid, m.p.: 177-179^{0}C. [lit.[33]: 180-181^{0}C].

IR: 3308, 3055, 2961, 2928, 2878 (C-H), 1622 (C=O).

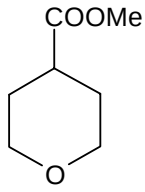
^{1}H-NMR (300 MHz): 1.13 (*t*, *J* = 7.5, 3 H); 1.48 (*dt*, *J* = 13.2, 4.8, 1 H); 1.55-1.94 (m, 5 H); 2.29-2.54 (*m*, 3 H); 2.58-2.74 (*m*, 4 H); 4.75 (*s*, 1 H); 5.02-5.12 (*m*, 1 H); 7.06-7.40 (*m*, 7 H); 7.32 (*d*, *J* = 7.2, 1H); 7.51 (*d*, *J* = 7.2, 1 H); 7.82 (*s*, 1 H).

^{13}C- NMR: 8.14 (*q*); 20.95 (*t*); 21.84 (*t*); 27.76 (*t*); 28.85 (*t*); 29.91 (*t*); 33.04 (*t*); 40.49 (*s*); 40.82 (*t*); 60.34 (*d*); 110.94 (*d*); 113.39 (*s*); 118.29 (*d*); 119.90 (*d*); 122.37 (*d*); 126.37 (*s*); 127.20 (*d*); 128.97 (*d*); 129.42 (*s*); 130.42 (*s*); 133.25 (*d*); 136.09 (*s*); 169.84 (*s*).

EI-MS: 452 (M^+, 31), 450 (19), 294 (42), 251 (19), 212 (46), 170 (100), 169 (92).

HR-MS: 452.1350 ($C_{25}H_{28}N_2OSe^{+\cdot}$; calc. 452.1386).

Methyl tetrahydro-2H-4-pyrancarboxylate **48**



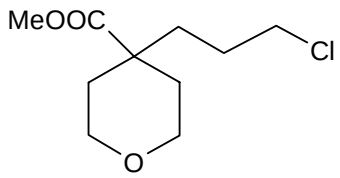
Prepared according to literature[62] from diethyl malonate and di(2-iodoethyl)ether in about 50% yield.

Physical Property: colorless oil.

^{1}H-NMR (300 MHz): 1.72-1.86 (*m*, 4 H); 2.44-2.55 (*m*, 1 H); 3.40 (*td*, *J* = 11.1, 3.6, 2 H); 3.69 (*s*, 3 H); 3.93 (*td*, *J* = 11.1, 3.6, 2 H).

^{13}C- NMR (75 MHz): 28.64 (*t*); 40.12 (*d*); 52.50 (*q*); 67.10 (*t*); 174.51 (*s*).

***Ethyl 4-(3-chloropropyl)tetrahydro-2H-4-pyrancarboxylate* <u>49a</u>**



To a stirred soln. of LDA (12 mmol, prepared from n-BuLi and diisopropylamine in 10 ml anh. THF) was added a soln. of **48** (1.37 g, 9.49 mmol) in THF (5 ml) during 5 min. while temperature was maintained at -78^0. After 30 min. a soln. of 1-bromo-3-chloropropane (1.73 g, 11.0 mmol) in THF (5 ml) was introduced dropwise. When an additional 1 h elapsed, the mixture was allowed to gradually warm up to room temperature and kept overnight. On quenching with saturated NH_4Cl(aq) (10 ml), the product was extracted into ether, and the combined organic solutions were washed with brine, dried, concentrated *in vacuo* and chromatographed (eluent: 1:9 AcOEt/hexane) to give **49a** (1.83 g, 89%).

Physical Property: colorless liquid.

IR: 1723 (C=O).

^{1}H-NMR (300 MHz): 1.43-1.53 (*m*, 2 H); 1.61-1.68 (*m*, 4 H); 2.02-2.09 (*m*, 4 H); 3.37-3.42 (*m*, 2 H); 3.45-3.49 (*m*, 2 H); 3.67 (*s*, 3 H); 3.77-3.84 (*m*, 2 H).

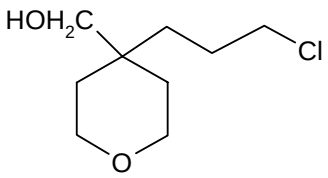
^{13}C- NMR (75 MHz): 26.99 (*t*); 34.15 (*t*); 37.88 (*t*); 44.37 (*s*); 44.95 (*t*); 51.83 (*q*); 65.33 (*t*); 175.31 (*s*).

EI-MS : 220, 205, 176, 161.

Elemental Analysis: Anal. calcd for $C_{10}H_{17}ClO_3$: C 54.42, H, 7.76;

found: C 54.24, H 7.61.

[4-(3-chloropropyl)tetrahydro-2H-4-pyranyl]methanol **49b**



A soln. of **49a** (1.81 g, 8.21 mmol) in anh. THF (10 ml) was cooled to -78^0 and treated with DIBAL-H (20.0 mmol, 16.6 ml, 20% w/w in PhMe) during 10 min. The resulting soln. was stirred for 30 min. at -78^0, 2 h at 0^0, and cautiously quenched by MeOH (5 ml). After dilution with water (15 ml) while warming up to rt. during an additional 2 h, it was poured into 5% HCl (50 ml). Workup involved ether extraction, rewashing with $NaHCO_3$(aq) and brine, dried, concentrated *in vacuo* and chromatography (eluent: 15:85 AcOEt/hexane) to afford **49b** (1.42 g, 90%).

Property Property: colorless oil.

IR: 3385 (O-H).

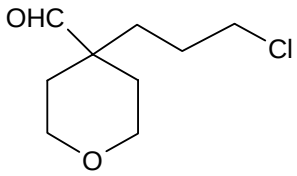
^{1}H-NMR (300 MHz): 1.42-1.58 (*m*, 4 H); 1.70-1.76 (*m*, 4 H); 3.47-3.55 (*m*, 4 H); 3.62-3.67 (*m*, 4 H).

^{13}C- NMR (75 MHz): 26.37 (*t*); 31.69 (*t*); 32.27 (*t*); 34.79 (*s*); 45.68 (*t*); 63.45 (*t*); 67.01 (*t*).

Elemental Analysis: Anal. calcd for $C_9H_{17}ClO_2$: C 56.10, H 8.89;

found: C 55.45, H 8.96.

4-(3-chloropropyl)tetrahydro-2H-4-pyrancarbaldehyde **49c**



PCC (3.51 g, 16.3 mmol) was added in portions to a mixture of **49b** (1.42 g, 7.4 mmol), Na_2CO_3 (2.97 g, 28 mmol) and powdered 4 Å MS (3.86 g) in anh. CH_2Cl_2 (40 ml) during 10 min. at r.t. After 1 h, the resulting mixture was diluted with ether (15 ml) and passed through a pad of florisil. The florisil bed was thoroughly rinsed with the same solvent and the combined soln was then concentrated *in vacuo*. Chromatography (eluent: 5:95 AcOEt/hexane) gave **49c** (1.05 g, 74%).

Physical Property: colorless oil.

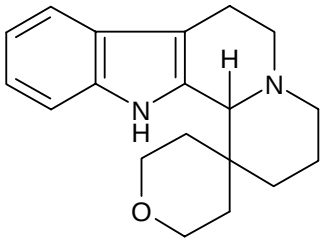
IR: 1724 (C=O).

^{1}H-NMR (300 MHz): 1.51-1.61 (*m*, 6 H); 1.90 (*d*, *J* = 13.7, 2 H); 3.36 (*td*, *J* = 11.7, 2.7, 2 H); 3.43-3.47 (*m*, 2 H); 3.76 (*dt*, *J* = 11.7, 4.2, 2 H); 9.43 (*s*, 1 H).

^{13}C- NMR (75 MHz): 26.20 (*t*); 30.88 (*t*); 33.62 (*t*); 44.77 (*t*); 47.16 (*s*); 64.51 (*t*); 205.00 (*d*).

EI-MS: not detected.

Spirocyclic **47**



A soln. of **49c** (0.19 g, 1.0 mmol) in anh. CH_2Cl_2 (3 ml) was mixed with a soln. of tryptamine (0.18 g, 1.1 mmol) in CH_2Cl_2 (3 ml) at r.t. and stirred overnight. On cooling to 0^0 it was treated with a soln. of TFA (5.0 mmol, 0.4 ml) in CH_2Cl_2 (2 ml) during 10 min. After 1 h the ice bath was removed, the reaction mixture was kept overnight, and poured into an ice-cold aq. $NaHCO_3$ (5%, 50 ml). Workup involved layer separation, extraction with CH_2Cl_2, rewashing with $NaHCO_3$(aq) and brine, dried, concentrated *in vacuo* and chromatography (eluent gradient: 10-50:90-50 AcOEt/hexane) to give compound **47** (0.19 g, 65%).

Physical Property: light yellow oil.

IR: 3439 (N-H).

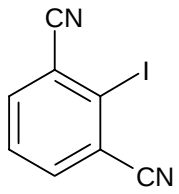
^{1}H-NMR (300 MHz): 1.15-1.26 (*m*, 1 H); 1.41-1.68 (*m*, 4 H); 1.75-1.90 (*m*, 2H); 2.31-2.65 (*m*, 4H); 2.84-3.06 (*m*, 3H); 3.28 (*s*, 1H); 3.53-3.86 (*m*, 4H); 7.06-7.17 (*m*, 2 H); 7.32 (*d*, *J* = 7.8, 1 H); 7.48 (*d*, *J* = 7.8, 1 H); 7.98 (*s*, 1 H).

^{13}C- NMR (75 MHz): 21.36 (*t*); 21.82 (*t*); 31.15 (*t*); 36.00 (*s*); 36.77 (*t*); 37.51 (*t*); 53.69 (*t*); 62.95 (*t*); 63.68 (*t*); 63.77 (*t*); 69.62 (*d*); 110.73 (*d*); 112.62 (*s*); 117.76 (*d*); 119.24 (*d*); 121.51 (*d*); 126.78 (*s*); 132.79 (*s*); 136.00 (*s*).

EI-MS: 296, 265, 196, 170.

HR-MS: 296.1888 ($C_{19}H_{24}N_2O^{+\circ}$; calc. 296.1890).

2-Iodoisophthalonitrile **52**



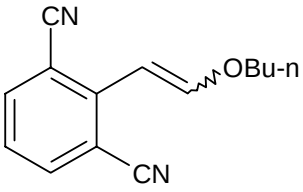
Prepared according to literature procedure[58] from metalation of isophthalonitrile with LDA at -100^0, then trapping the resulting anion with I_2.

^{1}H-NMR (300 MHz): 7.60 (*t*, *J* = 7.8, 1 H); 7.77 (*d*, *J* = 7.8, 2 H).

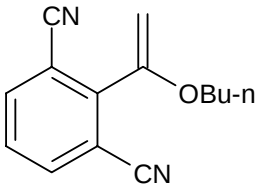
2-[(E)-2-butoxy-1-ethenyl]isophthalonitrile 53a;

2-[(Z)-2-butoxy-1-ethenyl]isophthalonitrile 53b;

2-(1-butoxyvinyl)isophthalonitrile 54



53a : *E*- config.
53b : Z- config.



54

To a soln. of **52** (0.60g, 2.36 mmol), Et_3N (0.90 g, 8.89 mmol), freshly-distilled *n*-butyl vinyl ether (9.0 g, 89.8 mmol) in toluene (9 ml) was added $Pd(OAc)_2$ (0.02 g, 0.1 mmol). The resulting mixture was heated at 110-120^0 for 2 d. Work up involved evaporation of the solvent and excess vinyl ether under reduced pressure, dilution with CH_2Cl_2 (25 ml), washing with brine, drying and chromatography to give an inseparable mixture of **53a , 53b** and **54** (mixture 0.29 g, 65%)**.** Product ratio **53a**:**53b**:**54** = 2.5:2.5:1 (according to ^{1}H NMR).

Physical Property: reddish yellow liquid.

IR: 3078, 2961, 2936, 2875, 2232, 1645, 1633, 1351, 1303, 1248.

^{1}H-NMR (300 MHz):

selected data :

53a: 6.04 (*d*, *J* = 12.6, 1 H, vinylic); 7.56 (*d*, *J* = 12.6, 1 H, vinylic).

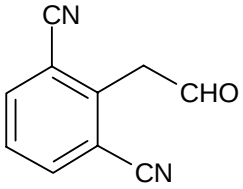
53b: 5.47 (*d*, *J* = 6.6, 1 H, vinylic); 6.52 (*d*, *J* = 6.6, 1 H, vinylic).

54: 4.52 (*d*, *J* = 3.9, 1 H, vinylic); 4.66 (*d*, *J* = 3.9, 1 H, vinylic).

EI-MS: 226, 211, 197, 170, 142.

HR-MS: 226.1106 ($C_{14}H_{14}N_2O^{+\cdot}$; calc. 226.1107).

2-(2-oxoethyl)isophthalonitrile 51



6 N HCl (10 ml) was added to a mixture of **53a, 53b** and **54** (0.40 g, 1.77 mmol), stirred at rt for 1 d. Workup involved dilution with CH_2Cl_2 (20 ml), washing with brine, $NaHCO_3$(aq) and brine again, dried, concentrated *in vacuo* to give compound **51** (0.21 g, 70%). Aldehyde **51** is somewhat unstable and used for the next steps without further purification.

Physical Property: yellow liquid.

IR: 2231 (CN); 1718 (C=O).

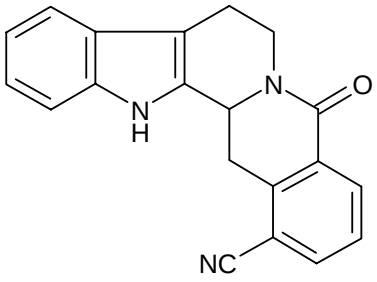
^{1}H-NMR (300 MHz): 4.32 (*s*, 2 H); 7.56 (*d*, *J* = 7.8, 1 H); 7.88 (*t*, *J* = 7.8, 2 H); 9.87 (*s*, 1 H).

^{13}C- NMR (75 MHz): 47.53 (*t*); 115.64 (*s*); 115.85 (*s*); 128.85 (*d*); 136.53 (*d*); 140.32 (*s*); 193.84 (*d*).

EI-MS: 170, 144, 142, 128, 115,114.

HR-MS: 170.0480 ($C_{10}H_6N_2O^{+\circ}$; calc. 170.0481).

5-oxo-5,7,8,13,13b,14-hexahydroisoquino[3,2,-a]β-carbolin-1-carbonitrile 55



A soln. of **51** (0.11 g, 0.65 mmol) in anh. CH_2Cl_2 (3 ml) was mixed with a soln. of tryptamine (0.12 g, 0.75 mmol) in CH_2Cl_2 (3 ml) at 0^0 and stirred for 2 h, followed by addition of a soln. of TFA (5.0 mmol, 0.4 ml) in CH_2Cl_2 (2 ml) during 10 min. After 1 h the ice bath was removed, the reaction mixture was kept overnight, and poured into an ice-cold aq. $NaHCO_3$ (5%, 20 ml). Workup involved layer separation, extraction with CH_2Cl_2, rewashing with $NaHCO_3$(aq) and brine, dried, concentrated *in vacuo* to give crude mixture that was used for the next step. The crude mixture containing the Pictet-Spengler product **C** was dissolved in MeOH (15 ml) and cautiously added with conc. H_2SO_4 (2.0 ml) during 10 min. at rt, the resulting mixture was then refluxed for 2 d. After cooling to rt, the mixture was poured into ice (50 g), basified carefully to slightly basic condition with 3 N NaOH, extraction with CH_2Cl_2, washing with brine, dried, concentrated *in vacuo* and chromatographed to give **55** (0.03 g, 15% over 2 steps).

IR: 2229 (CN); 1643 (C=O).

^{1}H-NMR (300 MHz): 2.96-3.17 (*m*, 4 H); 3.75 (*dd*, *J* = 15.6, 3.6, 1 H); 5.07 (*d*, *J* = 12.0, 1 H); 5.21 (*d*, *J* = 12.0, 1 H); 7.12-7.25 (*m*, 2 H); 7.40 (*d*, *J* = 7.5, 1 H); 7.49-7.56 (*m*, 2 H); 7.79 (*d*, *J* = 8.1, 1 H); 8.24 (*br s*, 1 H); 8.41 (*d*, *J* = 8.1, 1 H).

^{13}C- NMR (75 MHz): 20.79 (*t*); 33.41 (*t*); 39.76 (*t*); 51.42 (*d*); 109.23 (*s*); 110.84 (*s*); 111.21 (*d*); 116.92 (*s*); 118.33 (*d*); 119.63 (*d*); 122.26 (*d*); 126.28 (*s*); 127.91 (*d*); 130.21 (*s*); 131.50 (*s*); 133.14 (*d*); 135.44 (*d*); 136.66 (*s*); 140.08 (*s*); 162.91 (*s*).

EI-MS: 313, 312, 298, 255, 169.

HR-MS: 313.1221 ($C_{20}H_{15}N_3O^{+\cdot}$; calc. 313.1217).

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V. APPENDIX:

NMR SPECTRA