A REVIEW ON RECENT DEVELOPMENTS IN SYNTHESES OF THE POST-SECODINE INDOLE ALKALOIDS. PART II: MODIFIED ALKALOID TYPES

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1. Introduction . . . 822
7. Alkaloids Lacking 7–21/3 Bond . . . 824
7.1. Simple Alkaloids (Quebrachamines/Cleavamines/Velbanamines) . . . 824
7.1.1. Through Fragmentation of Quaternary Ammonium Salts . . . 824
7.1.2. From Primary Alkaloid Types (Aspidospermanes/Iboganes) . . . 828
7.1.3. From 3,5-Disubstituted Piperidines . . . 832
7.2. Bis-Indole/Vinblastine Alkaloids . . . 836
7.2.1. Partial Syntheses . . . 836
7.2.2. Total Syntheses . . . 840
7.2.2.1. Kuehne's Approaches . . . 840
7.2.2.2. Magnus' Approach . . . 850
7.2.2.3. Fukuyama's Synthesis . . . 853
8. Alkaloids Lacking 2–7 Bond (Rhazinilam and Related Compounds) . . . 856
8.1. Partial Synthesis . . . 856
8.1.1. From Aspidospermanes . . . 856
8.1.2. From Rhazinilam . . . 859
8.2. Total Synthesis . . . 860
8.2.1. Sames' Syntheses . . . 860
8.2.2. Banwell's Syntheses . . . 863
8.2.3. Nelson's Synthesis . . . 865
8.2.4. Magnus' Synthesis . . . 867
8.2.5. Trauner's Synthesis . . . 868
8.2.6. Synthesis of Rhazinilam Analogues . . . 869
9. Aspidospermane Alkaloids with Additional Bonds . . . 874
9.1. Aspidofractinine Group . . . 874
9.1.1. Simple Alkaloids . . . 874
9.1.2. Complex Alkaloids . . . 876
9.2. Kopsane Group . . . 879
9.3. Tuboxenine/Vindolinine Group . . . 881
9.4. Kopsifoline Group . . . 882

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10. Alkaloids with a Combination of Additional and Broken Bonds 885
10.1. Kopsijasminilam Alkaloids 885
10.1.1. Magnus' Approach 885
10.1.2. Kuehne's Synthesis 888
10.2. Lapidilectine B 890
10.3. Danuphylline 892
11. References 893

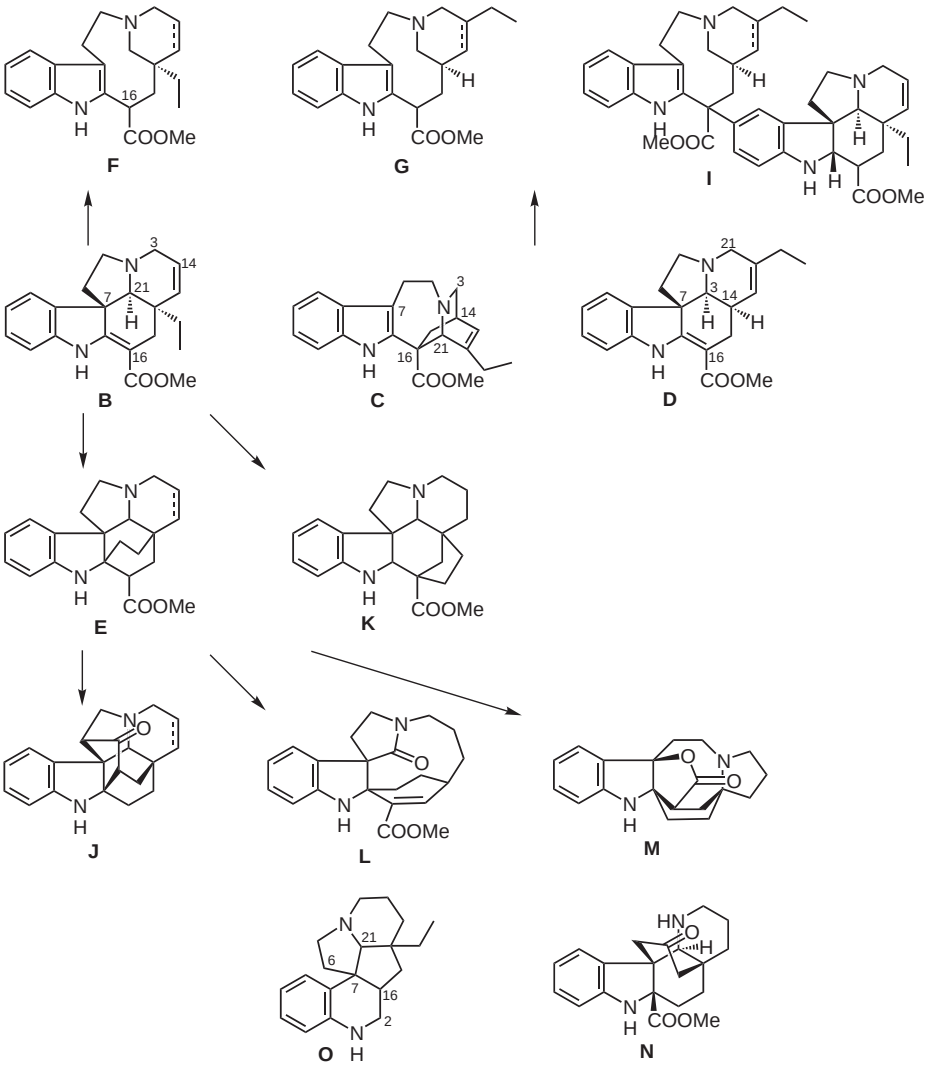
The second part of the planned review on developments in the field of total and formal total synthesis of the post-secodine indole alkaloids concentrates on modified alkaloid types, i.e. those skeletons derived from primary types by formation of additional and/or rupture of existing bonds, while connectivities next to indol(e)ine moiety remain intact. It thus reviews the synthesis of alkaloids of quebrachamine/cleavamine type including VLB-bis-indoles, rhazinilam type, aspidofractinine/kopsane and kopsifoline type, as well as kopsijasminilam alkaloids, lapidilectine B and danuphylline. It covers the literature of from 1991–1992 up to approximately end 2006. A review with 174 references.

Keywords: Indole alkaloids; Post-secodine alkaloids; Natural products; Total synthesis; Asymmetric synthesis; Quebrachamine; Cleavamine; Bis-indole alkaloids; Vinblastine; Anhydrovinblastine; Vincristine; Rhazinilam; Aspidofractinine alkaloids; Kopsane alkaloids; Kopsifoline alkaloids; Kopsijasminilam alkaloids; Lapidilectine B; Danuphylline; Complex indole alkaloids; Indole alkaloid analogues.

1. INTRODUCTION

The first part of the projected review on syntheses of the post-secodine monoterpenoid indole alkaloids dealt with the primary alkaloid types[1] and thus included synthetic approaches to aspidospermane (**B**), pseudoaspidospermane (**D**) and ibogane alkaloids (**C**) since the publication of the major reviews[2,3]. As a continuation the synthesis is discussed here of the alkaloids that emerge from the primary types by some kind of skeleton modification, i.e. formation of additional and/or rupture of existing bonds, Scheme 1. Thus, scission of a bond in aspidospermanes (**B**) gives rise to quebrachamine type (**F**); similarly, cleavamines/velbanamines (**G**) may emerge from iboganes (**C**) or pseudoaspidospermanes (**D**); more complex bis-indole alkaloids represented by the most important cleavamine-aspidospermane type (**I**) are also included. On the other hand, formation of additional rings in aspidospermanes (**B**) opens the way to aspidofractinines (**E**) and kopsanes (**J**) as well as to kopsifolanes (**K**). Included is also a section on kopsijasminilam alkaloid type (**L**) originating through fragmentation of the skeleton **E**, and synthesis of alkaloids with lapidilectane (**M**) and danuphyllane skeleton (**N**). The decision whether the skeleton fits in this chapter is based on the assumption that alkaloids with conserved

connectivities next to indol(e)/ine moiety (bonds 2–16 and 6–7) are modified ones, while those with altered connectivities fit in the projected Part III: (e.g. melonane skeleton **O** with a new 7,16-bond and 2,7-bond of skeleton **B** missing). It covers the literature published of from 1991–1992 up to approximately end 2006.



SCHEME 1
An overwiev of the modified post-secodine alkaloid types

Part III of the review will cover the synthesis of the post-secodine alkaloid groups that originate from those discussed in Part I [1] by some kind of skeletal rearrangement[4]. A chapter on some interesting alkaloid transformations will also be included.

The numbering of alkaloid skeletons used in this review is the biogenetic one proposed by LeMen and Taylor[5], see Scheme 1. As with the primary alkaloid types, natural bases discussed in this Part may again appear in both enantiomeric series due to inherently planar secodine precursors.

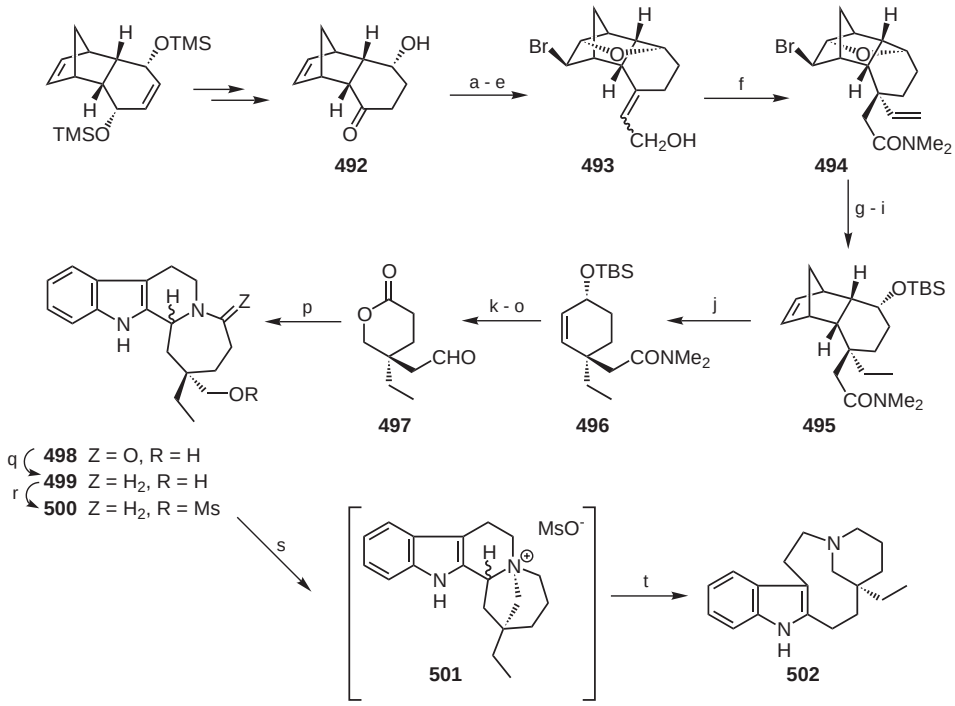
Common abbreviations are used in the description of reagents and conditions; in addition, rfl stands for reflux, and 8 °C 20 min → rt (1 h) 3 h means that the mixture was kept first 20 min at 8 °C, then warmed to rt during 1 h and, finally, kept at rt for another 3 h. In order to preserve logic and interrelations, the numbering of chapters as well as of formulae continues from Part I.

7. ALKALOIDS LACKING 7–21/3 BOND

7.1. Simple Alkaloids (Quebrachamines/Cleavamines/Velbanamines)

7.1.1. Through Fragmentation of Quaternary Ammonium Salts

Newly reported syntheses are based on previously published alternative strategies to quaternary ammonium salts. Ogasawara et al.[6] have reported on the synthesis of (+)-quebrachamine (**502**), which follows in final stages their previous work on the synthesis of (±)-**502** [7], Scheme 2. The synthesis commences with the conversion of (–)-hydroxy ketone **492** to allylic alcohol **493**, a stereoselective *ortho*-Claisen rearrangement in which produced amide **494** in a high yield (96%). This was transformed to lactone **497** with the aid of *retro*-Diels–Alder reaction (**495** → **496**). Nonstereoselective Pictet–Spengler reaction of the latter with tryptamine catalyzed by TFA, followed by immediate lactamization, afforded lactam **498** as a diastereoisomeric mixture (unspecified). Subsequent reduction to amino alcohol **499**[7] and *O*-mesylation (→ **500**) was followed by warming to initiate quaternisation. Finally, Birch reduction of **501** (Na in liquid ammonia/EtOH) provided the desired (+)-quebrachamine (**502**) in 69% yield from alcohol **499**. Quebrachamine is a widespread alkaloid; (+)-**502** was isolated inter alia from *Kopsia terengganensis*[8], while (–)-enantiomer *ent*-**502** is accessible from *Kopsia officinalis*[9].

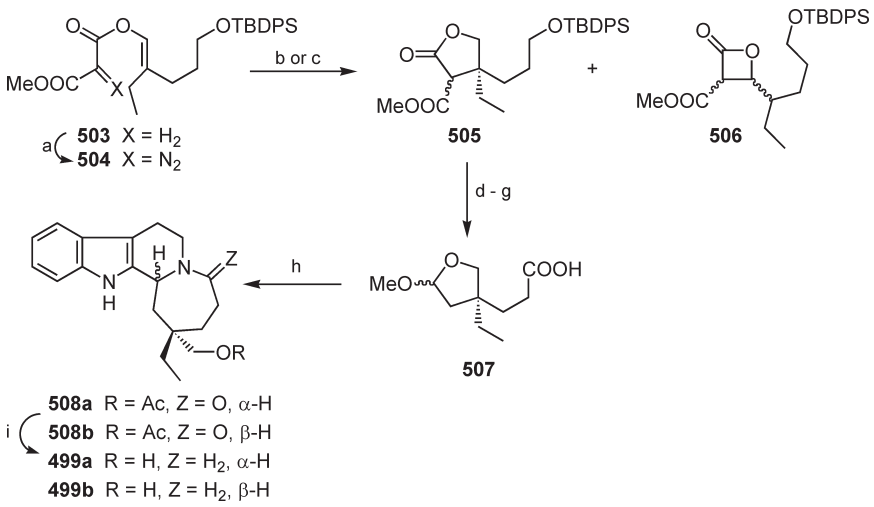


SCHEME 2

Reagents and conditions: a) NBS, CH_2Cl_2, rt (99%). b) CH_2=CHMgBr, $CeCl_3$, THF, –78 °C (87%). c) Ac_2O, DMAP (cat), py, rt (95%). d) [$PdCl_2(MeCN)_2$] (cat), THF, rt (100%). e) K_2CO_3, MeOH, rt (98%). f) $MeC(NMe_2)(OMe)_2$, Ph_2O, rfl (96%). g) H_2, 10% Pd/C, AcOEt (92%). h) Zn, AcOH/MeOH (1:10), rfl (93%). i) TBSCl, imidazole, DMF, rt (94%). j) Ph_2O, $NaHCO_3$, rfl (93%). k) $LiBHEt_3$, THF, rt (84%). l) TBAF, THF (99%). m) O_3, MeOH, –78 °C, then $NaBH_4$, then $NaIO_4$, H_2O (67%). n) Ag_2CO_3/celite, PhH, rfl (93%). o) Swern oxidation. p) Tryptamine, TFA, PhH, rfl (62%, 2 steps). q) $LiAlH_4$, dioxane, rfl (86%). r) MsCl, py, 0 °C. s) $CHCl_3$, rfl. t) Na, NH_3 (l), EtOH, –78 °C (69% from **499**)

Formal total synthesis of (±)-quebrachamine (**502**) by Wee and Yu is based on Rh(II)-initiated C–H insertion[10], Scheme 3. Conversion of malonate **503** to diazo ester **504** (88%) set the stage for the crucial lactone forming step: while the distribution of reaction products was dependent on counter-ion in Rh(II) salt, yield of γ-lactone **505** as high as 90% could be obtained with $Rh_2(OAc)_4$, together with minor amount of β-lactone **506** (8%) and water insertion products (2%). Rather straightforward transformation of **505** into acetal **507** allowed for its Pictet–Spengler condensation with tryptamine, which was mediated by acetic acid. The conversion was again nonstereoselective and provided a 1.3:1 ratio of diastereoisomers

508a and **508b** which was independent of the admixture of toluene. The epimers were separately reduced (95–96%) by $LiAlH_4$ to the known amino alcohols **499a** and **499b** [7], respectively.

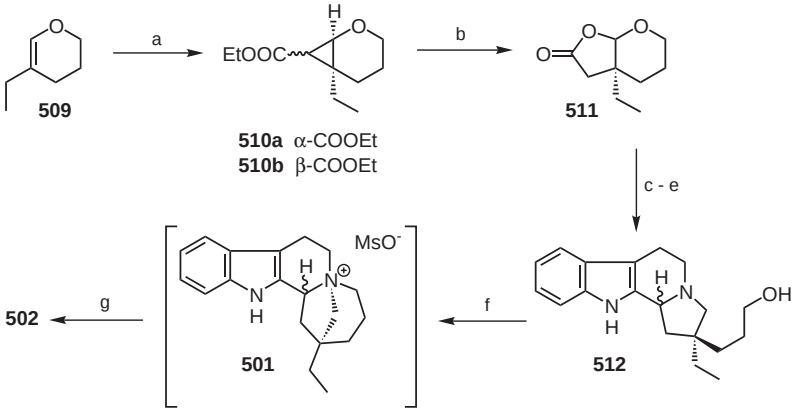


SCHEME 3

Reagents and conditions: a) MsN_3, Et_3N, MeCN, 0 °C 30 min → rt 10 h (88%). b) $Rh_2(OAc)_4$, **504** added during 5 h (finally 0.01 M), CH_2Cl_2, rfl (**505**:**506**:H_2O insertion products 90:8:2; **505** 90%). c) $[Rh_2(acam)_4]$, **504** added during 5 h (finally 0.01 M), CH_2Cl_2, rfl (**505**:**506**:H_2O insertion products 73:0:27; **505** 67%). d) NaCl (1 eq), DMSO, H_2O (2 eq), 110 °C 12 h (84%). e) TBAF (0.5 eq), THF, 0 °C → rt 40 min (93%). f) Jones oxidation, 0 °C (98%). g) DIBAL-H, Et_2O, PhMe, –78 °C 1 h, then MeOH, TsOH·H_2O (3.5 eq), –78 °C → rt (slowly) → rfl 40 min (67%). h) Tryptamine (3 eq), AcOH/PhMe (2:1), 80 °C 24 h → rfl 24 h (52–57%, **508a**:**508b** 1.3:1). i) $LiAlH_4$, THF, rt 30 min → rfl 20 h (95–96%)

Another enantioselective synthesis of (+)-quebrachamine (**502**) by Uppsala group[11] rests upon generation of optical activity through asymmetric cyclopropanation of dihydropyran **509**, Scheme 4; the synthesis follows in late stages alternative way to salt **501** designed by Kutney et al.[12] almost four decades ago. Intermolecular [2+1] addition of diazoacetate to 3-substituted dihydrofurans and -pyrans, catalyzed by Cu(I)OTf and Evans C_2-symmetric bisoxazolidine ligand, proceeded both with high diastereo- as well as enantioselectivity: With **509** and 2 mole % of catalyst there was achieved a ratio of **510a** to **510b** 91 : 9 with ee >95%. Note that unsubstituted dihydropyran (or dihydrofuran) yielded only racemic products. The major *exo*-isomer (–)-**510a** (52% isolated yield) was isomerized to bicyclic lactone (–)-**511** (77%) and after reduction to lactol (79%) was condensed

with tryptamine (as hydrochloride) in acetic acid; subsequent reduction with $NaBH_3CN$ provided tetracyclic amino alcohol **512**, again as a mixture of stereoisomers (90%). Exposure to MsCl and Et_3N induced spontaneous quaternisation (→ **501**). Finally, reduction of **501** with $LiAlH_4$ provided the expected (+)-quebrachamine (**502**) in 37% overall yield from **510a** [11].

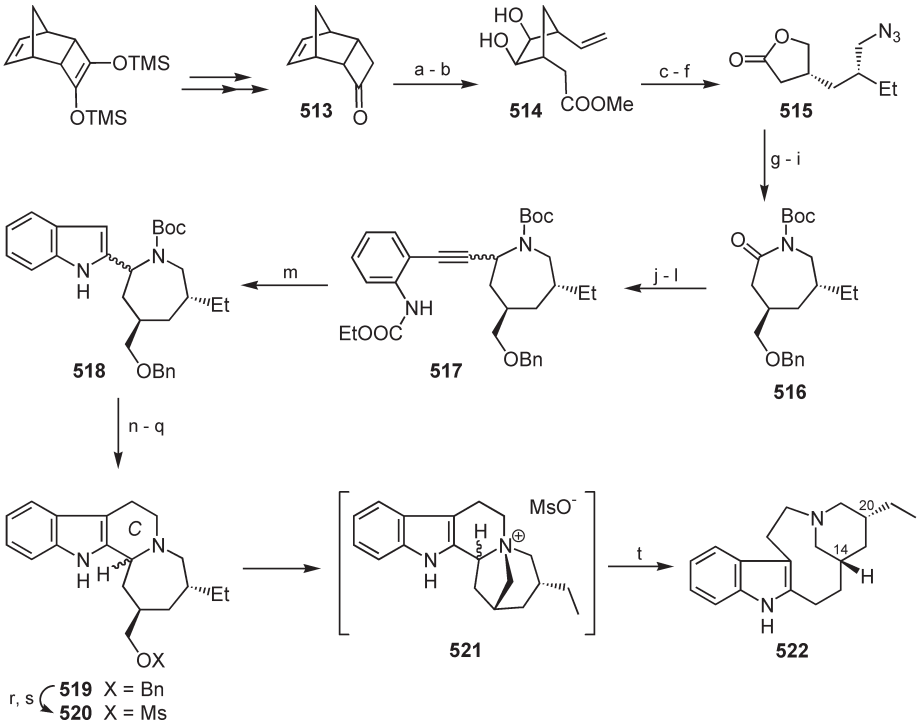


SCHEME 4

Reagents and conditions: a) $(CuOTf)_2$, Evans' catalyst (2 mole %), CH_2Cl_2, 0 °C, then $N_2CHCOOEt$ during 7 h, → rt overnight (*endo*/*exo* 9:91; **510a** 52%, ee >95%). b) 10% H_2SO_4, dioxane, rfl 15 h (77%). c) DIBAL-H, Et_2O, hexanes, –78 °C 1 h → rt (79%). d) Tryptamine·HCl (1.5 eq), 10% AcOH aq, rt 7 h, then NaOAc, rt 44 h. **e**) $NaBH_3CN$, 10% AcOH aq, rt 20 min (90%; diast. mixture). f) MsCl, Et_3N, $CHCl_3$, –10 °C → rt 40 h. g) $LiAlH_4$, *N*-methylmorpholine, rfl 13 h (67%; 37% from **510a**)

Total synthesis of (+)-(14*S*,20*R*)-15,20-dihydrocleavamine (**522**) by Kanada and Ogasawara also implements a fragmentation of the quaternary ammonium salt to generate the nine-membered ring[13], Scheme 5. The synthesis starts with transformation of (–)-cyclobutanone (**513**) to olefine-ester **514**, which includes photo [2+2] cycloreversion, and further to azido lactone **515**. Conversion of the latter into azepinone **516** set the stage for buildup of the indole moiety, which started with partial reduction of lactam carbonyl, followed by introduction of acetylene moiety (TMS–C≡CH, BuLi, Me_2AlCl; 75% after deprotection). Subsequent Sonogashira reaction (catalytic $[PdCl_2(PPh_3)_2]$ and CuI) with protected iodoaniline provided alkyne carbamate **517** in 89% yield. Closure of the pyrrole ring through 5-*endo*-Dig process was catalyzed by base and gave rise to **518** as a stereoisomeric mixture (65%); next, ring C in **518** was constructed using the gramine chemistry (→ **519**; 46%). Birch reduction of the quaternary salt **521**, obtained via mesylate **520**, completed total synthesis

of (+)-(14*S*,20*R*)-15,20-dihydrocleavamine (**522**), in 55% yield from ether **519**. (+)-(14*S*,20*R*)-**522** accompanies the major (–)-(14*S*,20*S*)-diastereoisomer in *Tabernaemontana eglandulosa*[14].



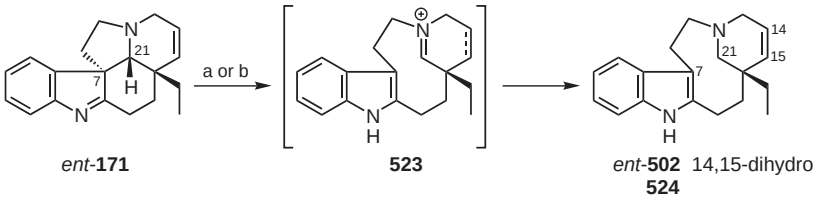
SCHEME 5

Reagents and conditions: a) OsO_4 (cat), NMO (93%). b) *hν*, MeOH (57%). c) H_2, PtO_2, AcOEt (99%). d) $NaIO_4$, then $NaBH_4$ (83%). e) MsCl, Et_3N (91%). f) NaN_3, DMF, 80 °C (92%, 2 steps). g) H_2, Pd/C, NH_3/MeOH (95%). h) BnBr, NaH, THF (84%). i) $(Boc)_2O$, *t*-BuLi, –78 °C (100%). j) $LiBHEt_3$, –78 °C, then HCl/MeOH (78%). k) *n*-BuLi, TMS–C≡CH, Me_2AlCl, CH_2Cl_2, –78 °C → 0 °C, then TBAF (75%). l) $[PdCl_2(PPh_3)_2]$ (cat), CuI (cat), Et_3N, rfl (89%). m) NaOEt, EtOH, rfl (65%). n) $Me_2N^+{=}CH_2Cl^-$. o) MeI, then KCN, DMF, 100 °C (83%, 3 steps). p) DIBAL-H, –78 °C, then 0.8 M H_2SO_4 (92%). q) BF_3, AcOH, CH_2Cl_2, 0 °C, then $NaBH_3CN$ (60%). r) Na, NH_3 (l), *t*-BuOH, THF (85%). s) MsCl, Et_3N. t) Na, NH_3 (l), *t*-BuOH, THF (64%, 2 steps)

7.1.2. From Primary Alkaloid Types (Aspidospermanes/Iboganes)

Reduction of 1,2-didehydroaspidospermanes is a well known process which, depending on the reducing agent, can provide either pentacyclic aspidospermidine (see Part I[1], Chaps 3.2.2.3–4.), or tetracyclic quebrachamine-type products; in the latter case the reaction proceeds through

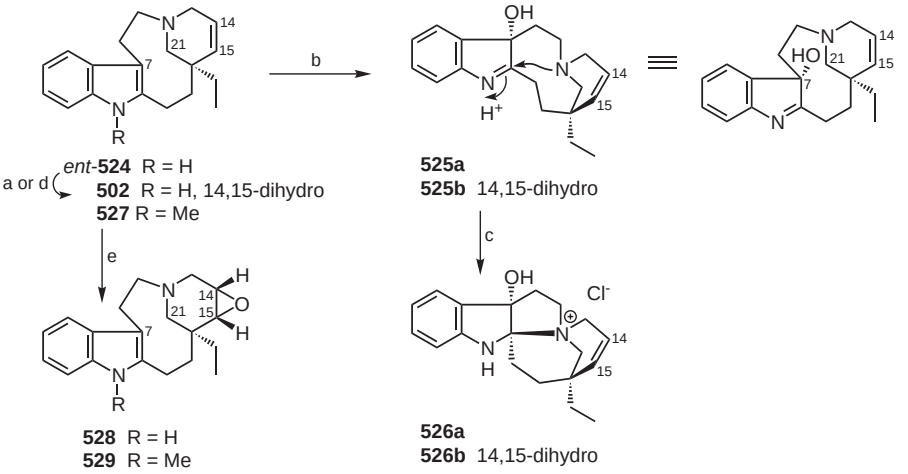
medium-size iminium intermediates **523**. Thus, the indolenine *ent*-**171**[15] was transformed either into (+)-aspidospermidine (**183**) using sodium borohydride reduction followed by catalytic hydrogenation (73% yield)[15] (see Part I[1], Chap. 3.2.2.4.), or into (–)-quebrachamine (*ent*-**502**) by hydrogenation over Pt in AcOH in 69% yield, Scheme 6. Similarly, reduction with $NaBH_3CN$, proceeding in acidic medium through the same intermediate **523**, afforded unnatural base **524** (68%).



SCHEME 6
Reagents and conditions: a) H_2, PtO_2, AcOH, rt 2 h (*ent*-**502** 69%). b) $NaBH_3CN$, AcOH, rt 1 h (**524** 68%)

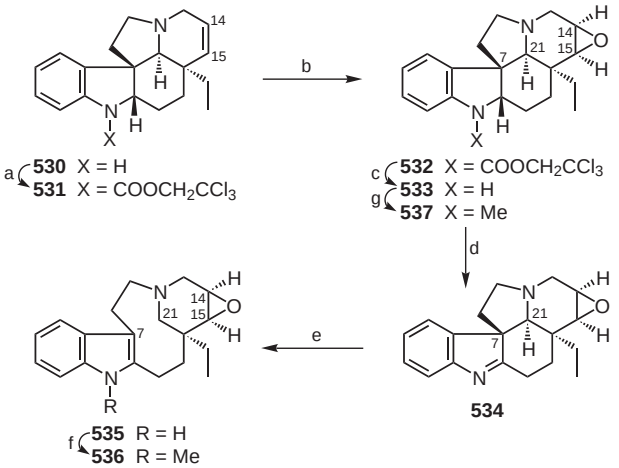
In an effort aimed at synthesis of 14,15-epoxyquebrachamines Szántay and collaborators[16] have treated (+)-14,15-didehydroquebrachamine (*ent*-**524**) obtainable from (–)-tabersonine (**60**) with dimethyldioxirane and obtained (+)-7-hydroxyindolenine **525a** (57%), which cyclized slowly on standing in solution to unnatural quaternary aminal **526a**, Scheme 7. Likewise, (+)-quebrachamine (**502**) derived from (+)-*ent*-**524** by hydrogenation (94%) provided (+)-7-hydroxyindolenine **525b** (49%), which is an enantiomer of the alkaloid (–)-rhazidigenine (*ent*-**525b**) isolated from *Amsonia sinensis*[17] and its N_b-oxide from *Aspidosperma quebracho-blanco*[18]; (–)-diastereoisomer of unknown stereochemistry was obtained from *Rhazya stricta*[19] and named strictanol. (+)-**525b** cyclized on exposure to methanolic HCl and provided (+)-rhazidine (**526b**), an enantiomer of the alkaloid previously isolated (as chloride) from *A. quebracho-blanco*[20].

On the other hand, both (+)-*ent*-**524** and (+)-**527** reacted cleanly with *tert*-butyl hydroperoxide in the presence of TFA and yielded stereoselectively unnatural α-epoxides **528** and **529** (82 and 78% yield, respectively) due to the epoxidation of the protonated starting materials from the more accessible α-face, Scheme 7; compare with ref.[1], Scheme 23. Thus, an indirect approach had to be adopted[21], Scheme 8. (–)-14,15-Didehydroaspidospermidine (**530**) derived from (–)-tabersonine (**60**) was *N*-protected and the carbamate (–)-**531** then subjected to epoxidation with *m*-CPBA in the presence of catalytic perchloric acid which produced, via a protonated



SCHEME 7

Reagents and conditions: a) *ent*-**524**, H_2, 10% Pd/C, AcOH, rt 5 h (**502** 94%). b) DMD (1.5 eq), Me_2CO, –60 °C → rt (**525a** 57%; **525b** 49%). c) **525b**, HCl/MeOH, pH → 4–5 (**526b** 84%). d) *ent*-**524**, NaH, DMF, rt 0.5 h, then MeI, rt 0.5 h (**527** 35%). e) *t*-BuOOH (1.5 eq), TFA, THF, 0 °C → rt 10 h (*ent*-**524** → **528** 82%; **527** → **529** 78%)

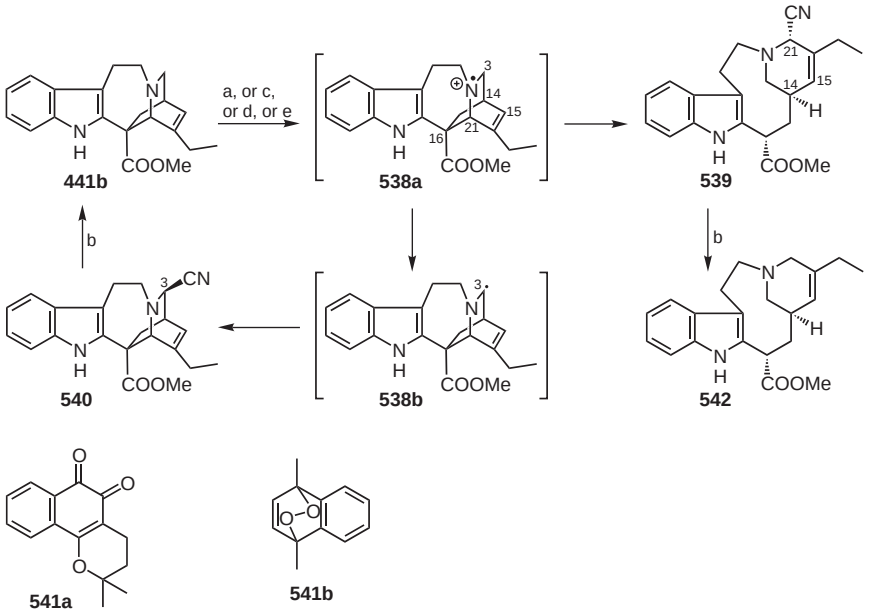


SCHEME 8

Reagents and conditions: a) $ClCOOCH_2CCl_3$, CH_2Cl_2, rt 24 h (88%). b) *m*-CPBA, $HClO_4$ aq (cat), MeOH, 0 °C → rt 18 h (79%). c) Zn, MeOH, rfl 18 h (**533** 55%). **d**) **533**, $KMnO_4$, 18-crown-6, PhH, rt 2 h (39%). e) $NaBH_4$ (in portions), rfl 1 h (80%). f) NaH, DMF, rt 0.5 h, then MeI, rt 1.5 h (35%). g) MeI, Et_3N, CH_2Cl_2, rt 10 h (**537** 69%)

conformation facilitating β-epoxidation, the desired epoxide carbamate (–)-**532** (79%). Permanganate oxidation of the derived amine (–)-**533** then gave rise to indolenine (–)-**534** (39%), whose reduction by $NaBH_4$ in refluxing ethanol afforded 80% of (+)-voaphylline (**535**), alkaloid present in *Tabernaemontana divaricata*[22] (also known as (+)-conoflorine from *Stemmadenia grandiflora*[23]); note that its enantiomer, (–)-ervayunine (*ent*-**535**), was isolated from *Ervatamia yunnanensis*[24]. Finally, N_a-methylation yielded (+)-hecubine (**536**) from *T. bovina*[25] (also known as N_a-methylvoaphylline, e.g. from *T. divaricata*[26]). Note that N_a-methylation of (–)-**533** leads to (–)-mehranine (**537**) which is contained in *T. divaricata*[26] and *T. bovina*[27] while (+)-enantiomer *ent*-**537** is accessible from *Ervatamia coronaria*[28].

Ferroud and coworkers have reported on an efficient approach to cleavamines which is based on a photochemically induced oxidative scission of ibogane precursors[29], Scheme 9. The transformation is initiated



SCHEME 9

Reagents and conditions: a) *hν* (λ > 400–430 nm), sensitizer, TMSCN, MeOH, H_2O (small amount) (DCA (1 eq) **539** 70%; FMN (0.1 eq) 91%, **539**:**540** 9:1; **541a** (0.03 eq) **539** 88%). b) $NaBH_4$, MeOH, 0 °C (**539** → **542** 80%; **540** → **441b** 100%). c) *hν* (λ > 495 nm), O_2, TPP (0.01 eq), TMSCN (2.5 eq), CH_2Cl_2, 20 °C 35 min (**540** 75%). d) *hν* (λ > 495 nm), O_2, TPP (0.04 eq), β-carotene, TMSCN (2.4 eq), CH_2Cl_2, 20 °C 5 h (**540** 87%). e) **541b** (excess), TMSCN (2.5 eq), CH_2Cl_2, rfl 4 h (**540** 75%)

by a single electron transfer producing cation radical **538a** which undergoes scission of 16–21 bond (→ **539**) and/or 3β-deprotonation (→ **538b** → **540**). Thus, irradiation of (+)-catharanthine (**441b**) with visible light in the presence of stoichiometric 9,10-dicyanoanthracene (DCA) as sensitizer and Me_3SiCN gives rise chemo- and stereoselectively (de >99%) to cleavamine-type nitrile **539** (70%), while the reaction in the presence of 0.1 equivalent of riboflavin 5′-phosphate sodium salt dihydrate (FMN) affords 91% yield of 9:1 mixture of **539** and **540**. Catalytic β-lapachone (**541a**; 3%) acting mainly in the triplet excited state is the most efficient sensitizer affording an 88% yield of **539**, which is reduced with cold $NaBH_4$ to unnatural 16-methoxycarbonylcleavamine (**542**; 80%), note that a reduction of iboganes (**C**) or pseudoaspidospermanes (**D**) similarly leads to cleavamine/velbanamine bases.

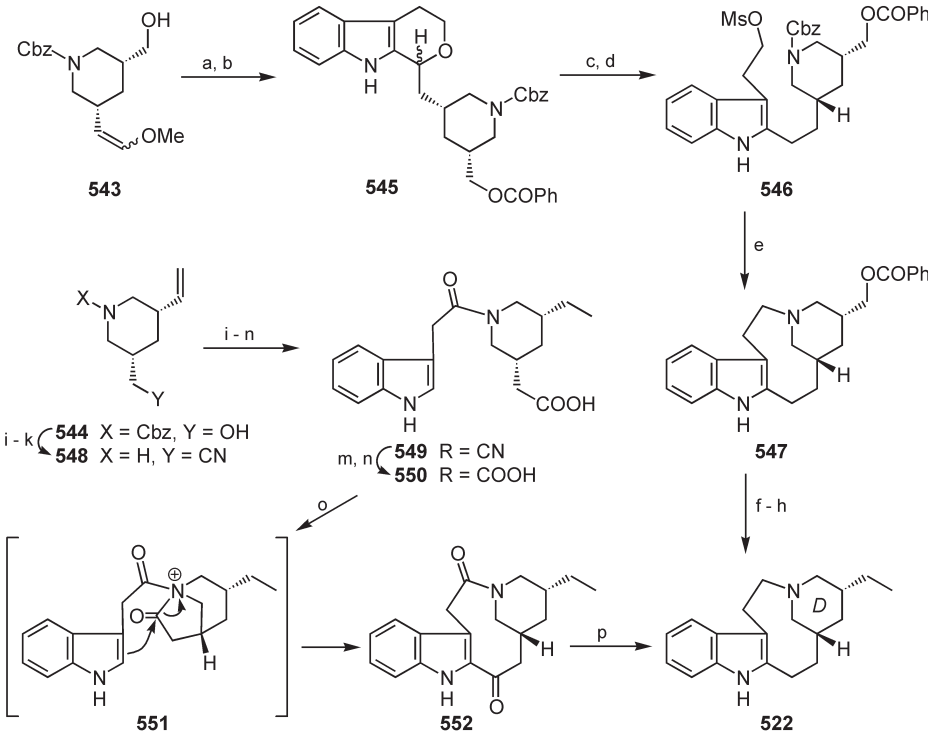
On the other hand, irradiation of (+)-**441b** in the presence of oxygen, catalytic 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine (TPP) and TMSCN represents a regio- and stereoselective route to (+)-3β-cyanocatharanthine (**540**; 75–87% yield)[30], as does an exposure of **441b** to excess 1,4-dimethylnaphthalene endoperoxide (**541b**) and TMSCN (75%), Scheme 9.

7.1.3. From 3,5-Disubstituted Piperidines

Milano group have reported[31] on two alternative approaches to (+)-(14*S*,20*R*)-15,20-dihydrocleavamine (**522**) that make use of chemoenzymatically accessible starting piperidines **543** and **544**, respectively[32,33], which were to become the ring D of the target molecule, Scheme 10. Both syntheses suffer from rather low-yielding medium-size ring formation.

Vinyl ether **543** was converted, after *O*-benzoylation, into diastereoisomeric pyranoindoles **545** (1:1) through a TFA-catalyzed oxa-Pictet–Spengler-type cyclization (74%) in the first approach[31,33]. Reductive opening of the dihydropyrane ring in **545** by Et_3SiH (44%) was followed by mesylation of the resulting alcohol (→ **546**). Hydrogenolytic removal of the *N*-protecting group set the stage for a thermal closure of the remaining ring by *N*-alkylation, which provided a 28% yield of the benzoate **547**. The latter was eventually transformed into the target (+)-(14*S*,20*R*)-dihydrocleavamine (**522**) (62% over 3 steps).

In the second synthesis[31,33], starting alcohol carbamate **544** was transformed in 3 steps into cyano piperidine **548**, which was *N*-acylated by indol-3-ylacetic acid in the presence of DPPA to give **549** (81%), Scheme 10. Straightforward conversion into acid **550** was followed by PPE-mediated internal acylation (32%), which probably proceeded through activated amide



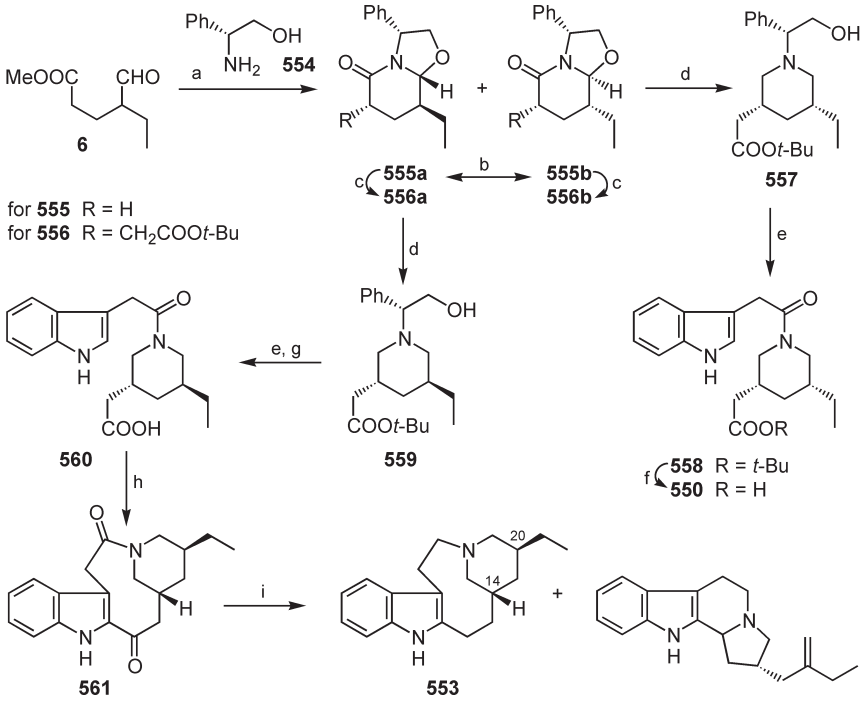
SCHEME 10

Reagents and conditions: a) PhCOCN, *i*-Pr_2NEt, CH_2Cl_2, rt (98%). b) Tryptophol, TFA (0.13 eq), 4 Å MS, CH_2Cl_2, rt 45 h (74%). c) Et_3SiH, CF_3SO_3H, CH_2Cl_2, –50 °C 6 h (44%). d) MsCl, *i*-Pr_2NEt, CH_2Cl_2, rt 3 h (98%). e) H_2, 5% Pd/C, AcOEt, rt 17 h, then PhCl, *i*-Pr_2NEt, rfl 4 h (28%). f) NaOH, MeOH aq, rt. g) TsCl, *i*-Pr_2NEt, CH_2Cl_2, rt 6 h. h) MeLi, CuI, Et_2O, –40 °C (62%, 3 steps). i) CBr_4, TPP, CH_2Cl_2, rt 3 h (88%). j) $Bu_4N^+CN^-$, CH_2Cl_2, rt 3 h (85%). k) H_2, 5% Pd/C, EtOH, 24 h (80%). l) Indole-3-acetic acid, diphenylphosphoryl azide (DPPA), Et_3N, MeCN, rt 6 h (81%). m) HCl (g)/MeOH, rt 4 h, then H_2O (93%). n) NaOH, MeOH aq, 50 °C 3 h (81%). o) PPE, $CHCl_3$, 60 °C 4 h (32%). p) $LiAlH_4$, dioxane, rfl 8 h (42%; 14% from **550**)

intermediate **551** (entropic assistence). Final double-reduction of **552** by $LiAlH_4$ (42%) completed the synthesis of the alkaloid (+)-**522**.

Synthesis of both (+)-**522** and (20*S*)-epimer (–)-**553** is based on the chemistry of chiral synthons **555**, which were obtained by condensation of the aldehyde ester **6** with (*R*)-phenylglycinol (**554**)[34,35], Scheme 11. Diastereoisomeric ratio in the bicyclic product (79%, **555a**:**555b** 89:11) could be altered by exposure to acid (methanolic HCl, **555a**:**555b** 3:7), providing thus an access to both **555a** [36] and **555b** in 70 and 60%, respectively. The following alkylation with bromoacetate (LiHMDS as a base) was highly

stereoselective. Lactam **555a** provided with high *endo*-selectivity (5:1) a mixture from which **556a** was isolated in 70% yield; likewise, lactam **555b** afforded, via an *exo*-selective process, the diastereoisomer **556b** (60%).



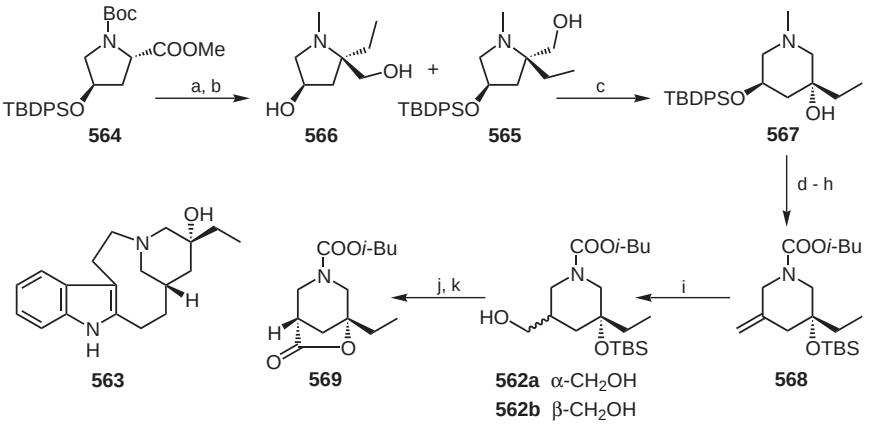
SCHEME 11

Reagents and conditions: a) Na_2SO_4 anh., Et_2O, 0 °C 1 h → 70 °C/10–15 mm Hg (79%, **555a**:**555b** 89:11). b) 3 M HCl/MeOH, 25 °C 24 h (quant, **555a**:**555b** 3:7). c) LiAMDS, –78 °C 1 h, then $BrCH_2COO$*i*-Bu, –78 °C 2 h (**555a** → 84%, *endo*:*exo* 5:1, **556a** 70%; **555b** → 75%, *exo*:*endo* 4:1, **556b** 60%). d) BH_3, THF, –78 °C → rt (**556b** → **557** 57%; **556a** → **559** 77%). e) H_2, $Pd(OH)_2$, then mixed anhydride of indole-3-acetic acid and pivalic acid (**557** → **558** 80%; **559** → 83%). f) TFA, rt 5 min (95%). g) TFA, rt 15 min (95%). h) PPA, 90 °C 30 min (64%). i) $LiAlH_4$, dioxane, rfl 18 h (**553** 34% (22% from **560**) + isomer 17%)

With the isomeric intermediates **556** at hand the Barcelona group have addressed the synthesis of diastereoisomeric dihydrocleavamines[34,35], Scheme 11. Thus, an exposure of **556b** to diborane gave 3,5-*trans*-disubstituted piperidine **557** (57%), which was transformed, by hydrogenolysis and acylation by the mixed anhydride of indole-3-acetic acid with pivalic acid, to ester **558** (80%) and, finally, upon treatment with TFA to acid **550** (95%), constituting a formal total synthesis of the alkaloid (+)-**522**. Similarly, diborane reduction of both lactam and oxazolidine moieties in **556a**

afforded piperidine **559** (77%) that was converted analogously into **560**. Subsequent strategy paralleled that used in synthesis of **522** (cf. Scheme 10) and gave rise via **561** to the diastereoisomeric (–)-(14*S*,20*S*)-dihydrocleavamine (**553**) in somewhat higher yield (22%).

Asymmetric synthesis has also been described[37,38] of a chiral piperidine **562**, which is to become an intermediate in the projected synthesis of (–)-velbanamine (**563**), Scheme 12; note that (–)-**563** was reported from *Tabernaemontana eglandulosa*[14] and its enantiomer is a degradation product of (+)-vinblastine. Proline ester **564**, obtainable from (2*S*,4*R*)-4-hydroxyproline in 3 steps and 88% yield, was quantitatively α-ethylated (LDA, HMPA, –78 °C) to give a 78:22 diastereoisomeric mixture which provided after reduction with $LiAlH_4$ (93% total) the desired alcohol **565** accompanied by a minor diol **566**. The crucial pyrrolidine-to-piperidine ring expansion in alcohol **565** was induced by exposure to TFAA followed by Et_3N and NaOH and led to 3-piperidinol **567** in 93% yield and with high diastereoselectivity (>98%). Alcohol **567** was transformed to olefine **568** in 5 steps (83% overall) and, finally, by hydroboration/oxidation sequence to alcohol **562**,



SCHEME 12

Reagents and conditions: a) LDA (2.0 eq), THF, –78 °C 1 h, then EtI (7.5 eq), HMPA (7.0 eq), –78 °C 20 min (quant, *cis*:*trans* 22:78). b) $LiAlH_4$, THF, 0 °C → rfl 2 h (93%, **565**:**566** 78:22). c) **565**, TFAA (1.2 eq), THF, 0 °C 1.2 h, then Et_3N (4.0 eq), 0 °C → rt 2 days, then 3.75 M NaOH aq (20 eq), rt 2 h (93%). d) TBSOTf (1.2 eq), 2,6-lutidine, CH_2Cl_2, rt 1 h. e) ClCOO*i*-Bu (1.0 eq), K_2CO_3 (0.6 eq), PhMe, rfl 3 h (92%, 2 steps). f) TBAF (1.0 eq), 4 Å MS, THF, rt 3.5 h. g) PCC (2.5 eq), 4 Å MS, CH_2Cl_2, rt 2.5 h (92%, 2 steps). h) $TiMe_2Cp_2$ (3.2 eq), THF, rfl 4 h (98%). i) BH_3·THF (1.1 eq), THF, 0 °C 50 min, then 3.75 M NaOH aq (4 eq), 30% H_2O_2 (8 eq), 0 °C → rt 1.5 h (94%, *cis*:*trans* 61:39). j) **557**, TBAF (5.0 eq), THF, rfl 17 h. k) TPAP (0.04 eq), NMO (3.0 eq), 4 Å MS, CH_2Cl_2/MeCN (10:1), rt 1.5 h (51%, 2 steps)

which was isolated (94%) as a mixture of epimers (**562a**:**562b** 61:39); stereochemistry of **562a** was secured by its 2-step conversion to bicyclic lactone **569**.

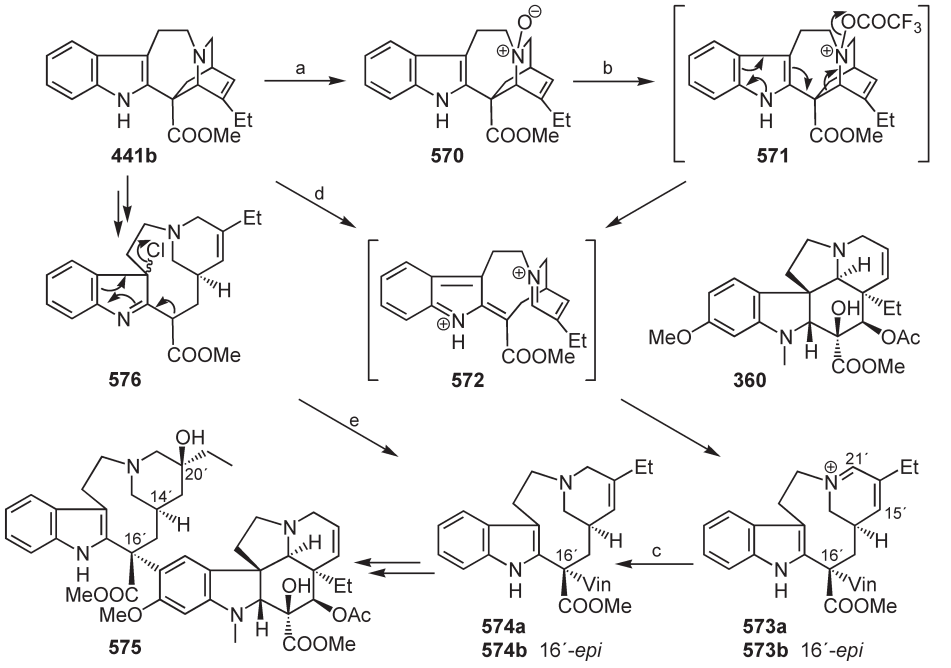
7.2. Bis-Indole/Vinblastine Alkaloids

A great plenty of bis-indole alkaloid types have been isolated from natural sources. Of them, by far the most important are those derived by combining velbanamine and highly oxygenated aspidospermane units; they possess high antitumor activity and, accordingly, they became by far the most frequent synthetic targets[39,40].

7.2.1. Partial Syntheses

Availability of building blocks, (–)-vindoline (**360**) and (+)-catharanthine (**441b**), from natural sources (especially from *Catharanthus roseus*) as well as through total synthesis made a partial synthesis of bis-indole alkaloids of the vinblastine type highly attractive, Scheme 13 [39,40]. Highly conjugated iminium **572** is generated by essentially two methods including formation of catharanthine *N*-oxide (**570**)/Potier–Polonovski reaction of **571** [41,42] (see also refs[43,44]), and/or iron(III) oxidation of **441b** [45], see also ref.[46]. Electrophilic species **572** then reacts with alkaloid (–)-**360** and affords, after reduction of ring D′-conjugated iminium **573** the desired anhydrovinblastine (**574a**) which is then transformed into vinblastine (**575**; VLB, vincaleukoblastine) by known methods. Diastereoselectivity of the addition (**572** → **573**) is of crucial importance as only **573a** leads to highly biologically active molecules. Yields of **574a** as high as 50–60% (Potier–Polonovski)[41,42] and a conversion 77% (Fe^{3+}) were reported[45] for the transformation, respectively. Anhydrovinblastine (**574a**) was obtained from *Catharanthus roseus*[47], while vinblastine (**575**) is available among others from *Catharanthus trychophyllus*[48]; note that $[\alpha]_D$ of vinblastine (**575**) is positive in $CHCl_3$ and negative in MeOH [49].

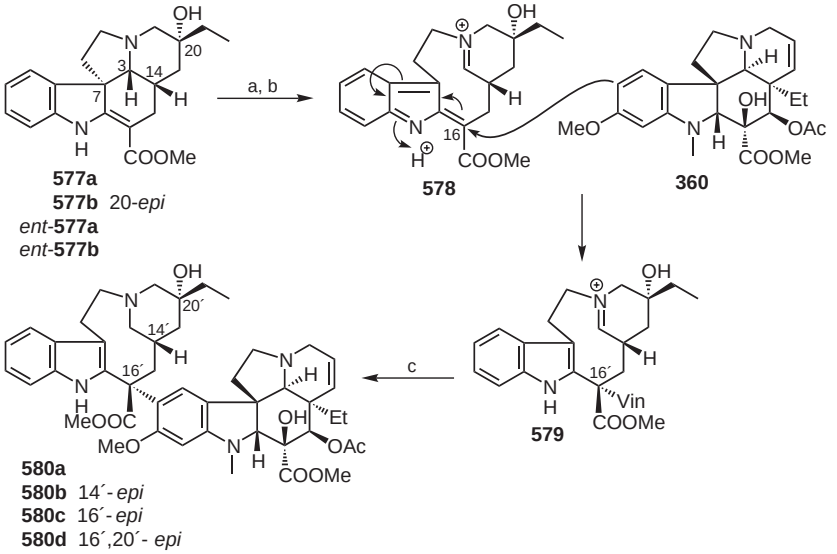
On the other hand, although fragmentation in chloroindolenine **576** generates conjugated indole species similar to **572**, it yields by coupling with (–)-**360** the undesired diastereoisomer **574b** [50], Scheme 13. As was demonstrated later, an enlargement of the central azonine ring by two carbons has had a dramatic effect on the stereochemical outcome of the coupling reaction[51]; for an excellent application see Chap. 7.2.2.3., and also Chap. 7.2.2.1.



SCHEME 13

Principal strategies of (anhydro)vinblastine synthesis from catharanthine (**441b**)
Reagents and conditions: a) *m*-CPBA. b) TFAA, **360**. c) $NaBH_4$. d) Fe^{3+} oxidation, then **360**. e) **360**, H^+

A study of mechanistic aspects of anhydrovinblastine formation through Potier–Polonovski reaction has been reported[52]. Intermediary conjugated iminiums **573** are attacked by organozinc or copper reagents from α-side providing either 21′- or 15′-anhydrovinblastine analogues[53]. Pentacyclic pseudoaspidospermanes can also be used as starting materials, as illustrated with the synthesis of four unnatural vinblastine stereoisomers **579** [54], Scheme 14. Thus, (+)-pandoline (**577a**) was treated with *tert*-butyl hypochlorite and then with vindoline (**360**) in the presence of silver tetrafluoroborate to give presumably via **578** an iminium **579**, whose reduction afforded bis-indole **580a** in 11% yield. Likewise, (+)-20-*epi*-pandoline (**577b**), (–)-pandoline (*ent*-**577a**) and (–)-20-*epi*-pandoline (*ent*-**577b**) were converted into VLB-stereoisomers **580b**, **580c** and **580d**, respectively; note the stereochemistry of vindoline addition (**578** → **579**). These and others VLB-stereoisomers were included in a circular dichroism study, a useful method for assigning the crucial C-16′-configuration of the coupled products, cf. ref.[42].



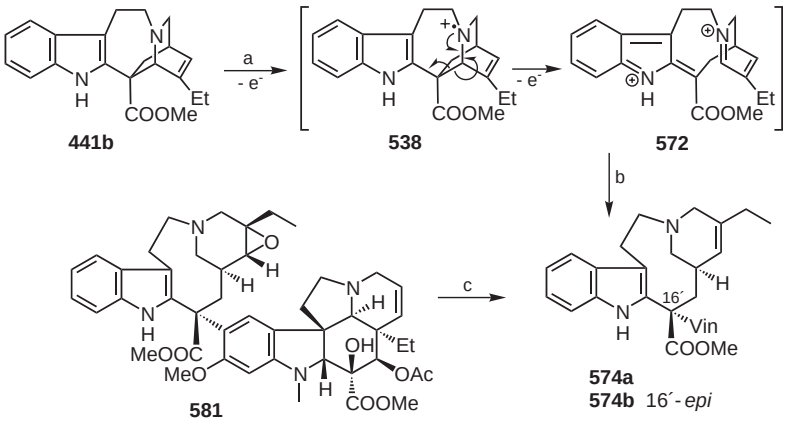
SCHEME 14

Reagents and conditions: a) **577a**, *t*-BuOCl, Et_3N, CH_2Cl_2, 0 °C 15 min. b) **360** (1 eq), $AgBF_4$, Me_2CO, 20 °C 30 min. c) KBH_4, AcOH (11.1%, 3 steps)

Based on the discovery that electron transfer reactions can initiate fragmentation of catharanthine (**441b**)[55] Tabaković and coworkers reported its anodic oxidation in the presence of vindoline (**360**) in $MeCN/Et_4N^+ClO_4^-$ at rt[56,57], followed by $NaBH_4$ reduction, Scheme 15. The process, which is believed to proceed through fragmentation of catharanthine N_b-cation-radical **538** to conjugated iminium **572**, affords with rather high stereoselectivity (**574a**:**574b** 4.3:1) the desired anhydrovinblastine (**574a**) in 52% yield. Formation of iminiums in synthesis of **574a** (50%) is reported to be induced also by irradiation with near-UV light[58,59]. Anhydrovinblastine (**574a**) is accessible (70%) also by deoxygenation of leurosine (**581**) with low-valent titanium reagent (from Cp_2TiCl_2/Zn in THF)[60,61], Scheme 15.

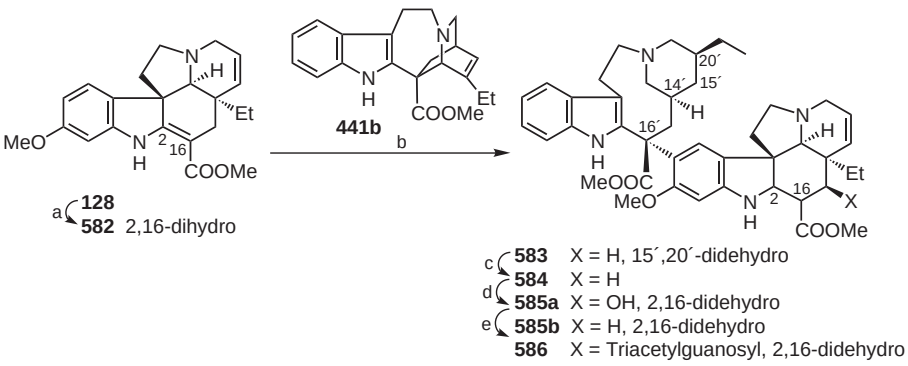
Synthesis of simple VLB-analogues commences with TFA-catalyzed condensation of vindoline (**360**) with methyl pyruvate[62]. Synthesis of anhydrovinblastine analogues modified in vindoline part was reported by the Milano group[63], Scheme 16. While application of both the Potier–Polonovsky and Fe(III)-oxidation methodology to low-nucleophilic 11-methoxytabersonine (**128**) afforded only very low yield (4%) of the coupling product, the 2,16-dihydro analogue **582** reacted with catharanthine

(**441b**) in the presence of $FeCl_3$ smoothly providing stereoselectively the bis-indole **583** in 65% yield. Saturation of the 15′,20′-double bond (→ **584**) set the stage for oxidation with benzeneseleninic anhydride (BSA), which provided stereoselectively anilinoacrylate alcohol **585a** (62%) accompanied by minor amount of **585b**. Finally, alcohol **585a** afforded on reaction with



SCHEME 15

Reagents and conditions: a) 0.6 V (vs SCE; 2.2 F/mol), vindoline (**360**) (1 eq), 2,6-lutidine (4 eq), 0.1 M $Et_4N^+ClO_4^-$. b) $NaBH_4$, MeOH, rt 30 min (**574a** 52% + **574b** 12%). c) Cp_2TiCl_2 (2.5 eq), Zn (5 eq), THF (degased), rt 45 min, then **581**, rt 15 min (**574a** 70%)



SCHEME 16

Reagents and conditions: a) $NaBH_3CN$. b) **441b**·HCl, $FeCl_3 \cdot 6H_2O$, glycine buffer/0.1 M HCl aq (2:1), rt 10 min, then (+)-**582**, rt 2 h, then $NaBH_4$ in ammonium hydroxide (65%). c) H_2, 5% Pd/C, MeOH, rt 3 h (**584** 96%). d) BSA, PhH, 35 °C 12 h (**585a** 62% + **585b** 9%). e) **585a**, tri-*O*-acetylguanosine, *i*-Pr_2NEt, TBSCl, 0 °C → rt 15 h (59%).

tri-*O*-acetylguanosine the desired **586** in 59% yield. Catharanthine skeletal isomers like **447** (see ref.[1], Chap. 4.2.1.) were also used in synthesis of anhydrovinblastine analogues[64].

7.2.2. Total Syntheses

7.2.2.1. Kuehne's Approaches

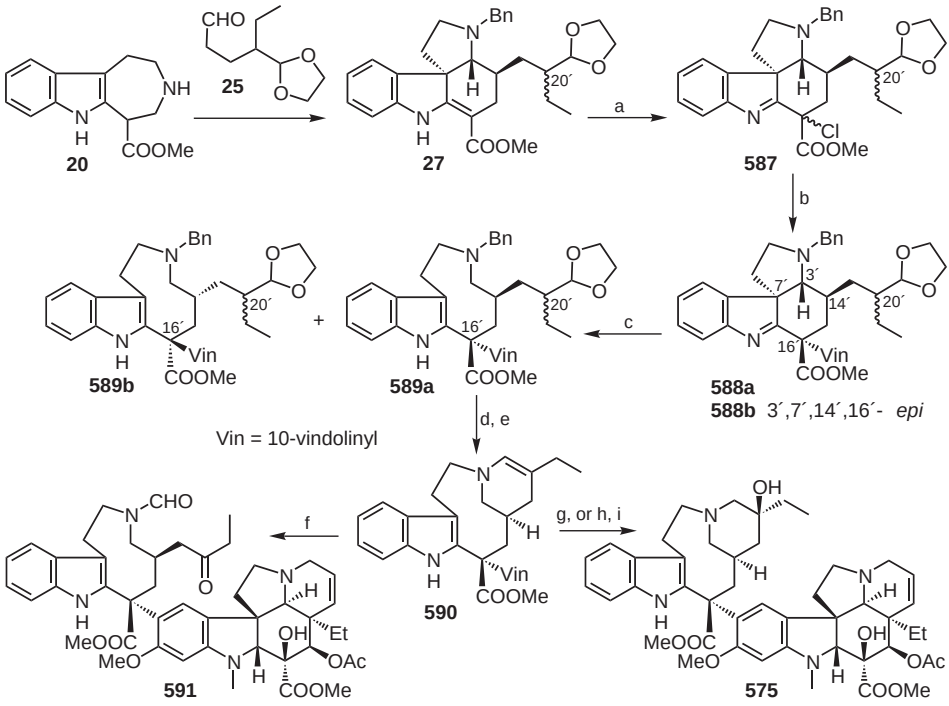
Based on their general approach to indole alkaloids, Kuehne and collaborators have developed several variants of vinblastine (**575**) and related alkaloids synthesis[39], the early stages of which have been already discussed in Part I [1], Chap. 3.1.1.

The first synthesis shown here is based on the implementation of the so called versatiline intermediate (±)-**27** [65], in which the optical activity was introduced later during the arylation step (**587** → **588**), Scheme 17. Anilinoacrylate (±)-**27** was 16′-chlorinated, and the resulting chloroindolenine (±)-**587** treated with vindoline (**360**; as hydrochloride) in the presence of excess silver tetrafluoroborate to give, with rather high stereoselectivity, the desired *parf* (priority antireflective[66]) arylated indolenines **588**; subsequent reduction by KBH_4 in acidic medium (AcOH) permitted the isolation (total yield 87%) of the desired indole **589a** in 44% yield, together with **589b** (33%), and the minor C-16′-epimers resulting from about 10% *pref* (priority reflective[66]) selectivity in the arylation step. Hydrogenolytic removal of *N*-benzyl group in **589a** and acid treatment allowed for the obtention of enamine **590** (20′,21′-anhydrovinblastine) in 93% yield from **589a**. Photochemical oxygenation converted **590** directly into natural catharinine (**591**; also vinamidine) in 70% yield. Catharinine is accessible from *Catharanthus longifolius*[67].

On the other hand, oxidation of the enamine **590** with ferric chloride and immediate reduction with $NaBH_4$ provided natural vinblastine (**575**; also VLB or vincaleukoblastine) in 31% yield[65], Scheme 17; note that previously known thallium(III) oxidation met with little success (3.6% yield).

In order to illustrate the logic of development of VLB approaches we will continue an overview of Kuehne and coworkers' adventures in optically active cleavamine-type intermediates with total syntheses published already in 1991 [68,69], Schemes 18, 19.

Following their classical scheme in early stages, indoloazepine **20** was condensed with (*S*)-aldehyde **592** to give tetracyclic amine **593**, which on quaternisation with benzyl bromide and subsequent Et_3N-induced fragmentation afforded, via secodine-like intermediate of the type **23** (see ref.[1], Chap. 3.1.1.), a 1:1 mixture of stereoisomers **594** and **595** as a result of neg-

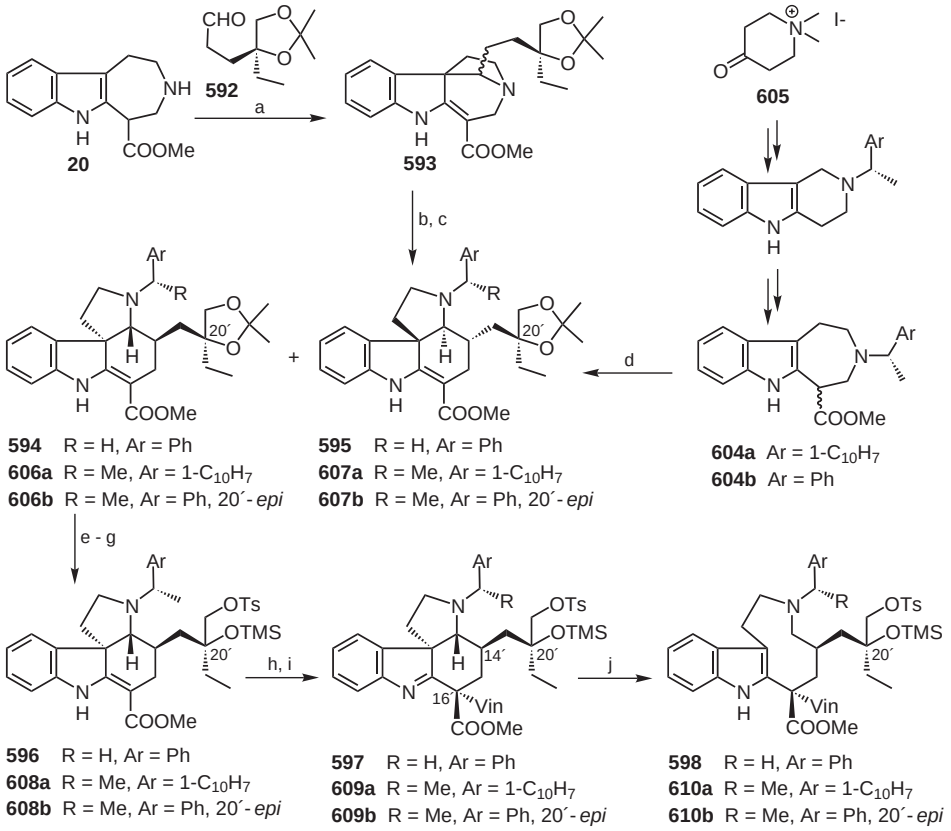


SCHEME 17

Reagents and conditions: a) *t*-BuOCl, Et_3N, CH_2Cl_2, 0 °C 30 min. b) Vindoline (**360**) hydrochloride (1 eq), $AgBF_4$ (3.87 eq), Me_2CO, rt 20 min. c) KBH_4 (15 min), AcOH (87% overall; **589a** 50.8% + **589b** 38.2% + 16′-*epi*-**589a** 5.7% + 16′-*epi*-**589b** 5.2%). d) H_2, 10% Pd/C, AcOH, 45 min (100%). e) 1 M HCl aq/H_2O (1:1), rt 30 min (93%). f) O_2, *h*ν (275 W sunlamp), CH_2Cl_2, rt 1 h (70%). g) $FeCl_3$ (2 eq), MeOH, rt → 0 °C, O_2, 0 °C 1 h, then $NaBH_4$ (31%). h) $Tl(OAc)_3$, CH_2Cl_2, 0 °C 15 min, then concentrate at 0 °C. i) $NaBH_4$, MeOH, rt (3.6%, 2 steps)

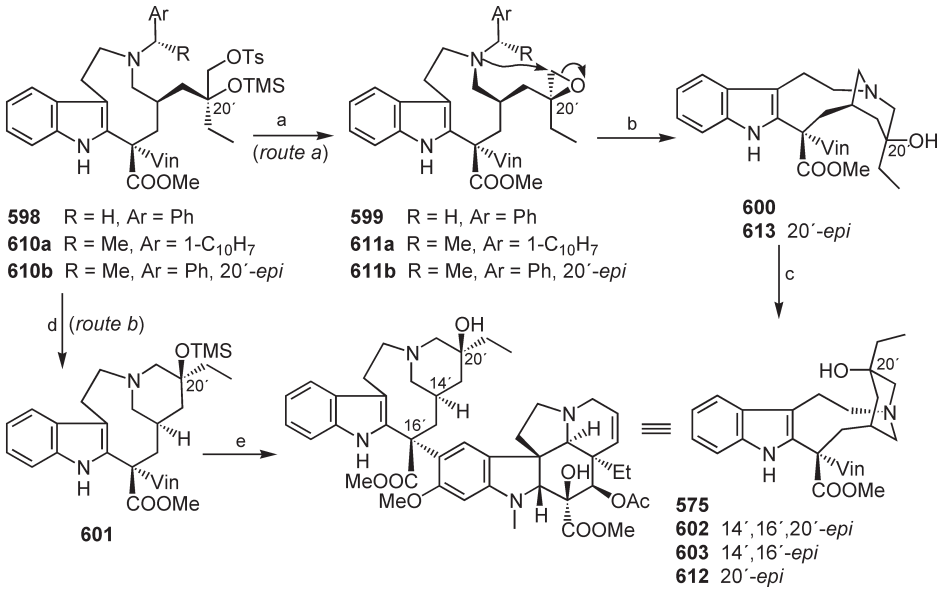
ligible effect of C-20′ chiral center on the stereochemical outcome of the [4+2] cycloaddition (94% over 3 steps), Scheme 18. Separation of **594** was achieved after an acid-catalyzed release of diol (42% of 95%); the latter was converted to *O*-silylated tosylate **596** (70%), which provided on 16-chlorination with *t*-BuOCl and following highly stereoselective coupling with vindoline (**360**) (0.95 eq) in the presence of $AgBF_4$ the C-14′,C-16′ *parf* indolenine **597**. Subsequent reduction with KBH_4 in acidic medium gave rise to the desired bis-indole **598** in 80% yield based on vindoline.

Two alternative procedures were used to convert **598** into the alkaloids[68,69], Scheme 19. Thus, the azonine tosylate **598** cyclized on desilylation (TBAF) into epoxide **599**, which underwent in refluxing metha-



SCHEME 18

Reagents and conditions: a) THF, rfl 2 h (79%). b) BnBr, THF, rfl 12 h (97%, 2 steps). c) Et_3N, MeOH (97%; **594**:**595** 1:1). d) **604a**, **592** (1.5 eq), PhMe, 70 °C → rfl 36 h (**606a**:**607a** 4:1); **604b**, *ent*-**592** (1.2 eq), PhMe, 70 °C → rfl 24 h (60%, **606b**:**607b** 3:1) e) **594** + **595**, 10% HCl aq/MeOH (1:2.5), rfl 15 min (95%, separation 42% + 26%); *a series*: **606a** + **607a**, 10% HCl aq/MeOH (1:4), rfl 30 min (50%, separation 37% + 10%); *b series*: **606b** + **607b**, 10% HCl aq/MeOH (1:4), rfl 30 min (separation 69% + 23%). f) Ts_2O, Et_3N, CH_2Cl_2, 0 °C 26 h (76%); *a series*: Ts_2O (1 h), Et_3N, CH_2Cl_2, 0 °C → rt (1 h) 24 h; *b series*: Ts_2O, Et_3N, CH_2Cl_2, 0 °C → rt 30 h. g) TfOTMS, *i*-Pr_2NEt, THF, 0 °C 15 min (**596** 92%); *a series*: TfOTMS, *i*-Pr_2NEt, THF, 0 °C 20 min (**608a** 38%, 2 steps); *b series*: TfOTMS, *i*-Pr_2NEt, THF, 0 °C 20 min (**608b** 73%, 2 steps). h) **596**, *t*-BuOCl, Et_3N, CH_2Cl_2, 0 °C 5 min; *a series*: **608a**, *t*-BuOCl, Et_3N, CH_2Cl_2, 0 °C 5 min; *b series*: **608b**, *t*-BuOCl, Et_3N, CH_2Cl_2, 0 °C 5 min. i) **360** (0.95 eq), $HBF_4 \cdot OEt_2$, Me_2CO, rt 5 min, then $AgBF_4$ (2 eq), rt 5 min; *a series*: **360** (1.0 eq), $AgBF_4$ (2 eq), Me_2CO, 0 °C 10 min; *b series*: **360** (1.0 eq), $HBF_4 \cdot OEt_2$ (2 eq), Me_2CO, rt 5 min, then $AgBF_4$ (2 eq), rt 10 min. j) **597**, KBH_4, AcOH, rt 10 min (**598** 80% based on **360**); *a series*: **609a**, KBH_4 (10 eq; slowly), AcOH, rt 15 min; *b series*: **609b**, KBH_4 (10 eq; slowly), AcOH, rt 15 min



SCHEME 19

Reagents and conditions: a) **598**, TBAF (3 eq), THF, rt 25 min (**599** 85%); *a series*: **610a**, TBAF (3 eq), THF, 0 °C → rt 15 min (**611a** 72% from **608a**); *b series*: **610b**, TBAF (2 eq), THF, 0 °C → rt 15 min (**611b** 73% from **608b**). b) **599**, MeOH, rfl 26 h, then H_2, 10% Pd/C, rt 2 h (**600** 89%); *a series*: **611a**, MeOH, rfl 40 h, then H_2, 10% Pd/C, rt 3 h; *b series*: **611b** → **613**, similar conditions. c) **600**, PhMe, rfl 8 h (**575** 95%); *a series*: PhMe, rfl 8 h (**575** 80% from **611a**); *b series*: **613** → **612**, similar conditions. d) **598**, MeOH, rfl 40 h, then H_2, 10% Pd/C, rt 2 h (**601** 90%). e) **601**, TBAF (3 eq), THF, rt 30 min (**575** 87%)

nol (no reaction in PhMe) surprisingly smooth quaternisation (*route a*). Debenzylation then provided tertiary amine **600** with compelling configuration around N_4'-nitrogen, in fact a higher-energy conformer of VLB, in 89% yield from epoxide **599**. Finally, chromatografically faster moving, natural vinblastine (**575**) was obtained by heating **600** in refluxing toluene (95%). Alternatively (*route b*), tosylate **598** quaternized upon heating in methanol (48 h) to a salt, which afforded upon hydrogenolysis on Pd/C *O*–silylated vinblastine **601** (90%). Desilylation completed an efficient alternative total synthesis of natural VLB (**575**) in 78% yield from **598**; the overall yield equals to 22%.

Vincovaline (**602**), a 14′,16′,20′-epimer of VLB, was synthesized by application of the same methodology to (*R*)-aldehyde *ent*-**592** and using 20′-*epi*-**595** as the intermediate (via *route a*)[68,69]; likewise, tetracycle **595** was

transformed into unnatural 20′-epivincovaline (**603**). (–)-Vincovaline (**602**) was isolated from *Catharanthus ovalis*[70].

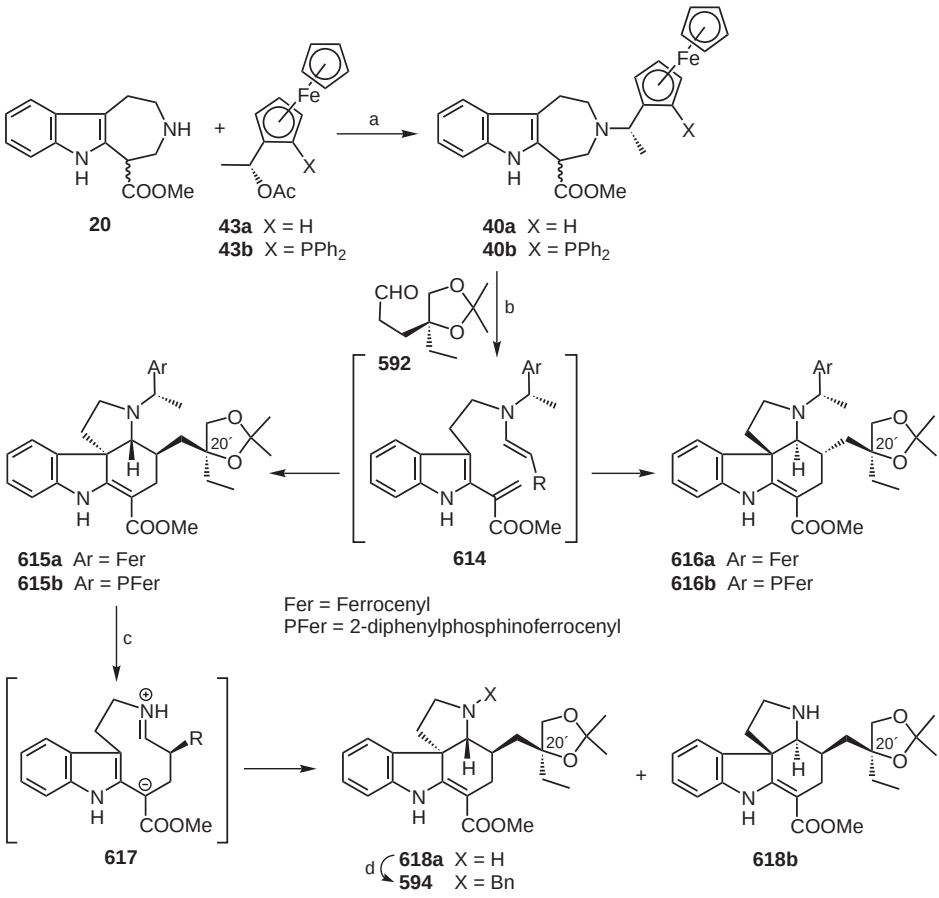
A logical extension was to alter the approach in a way such that would allow to achieve higher stereoselectivity in the crucial cycloaddition step by placing a chiral auxiliary on nitrogen in the starting indoloazepine (for discussion see ref.[1], Chap. 3.1.1.). In the first generation synthesis, chiral synthons **604a** and **604b** were prepared in 5 steps from quaternary ammonium iodide **605**, and (–)-(*S*)-1-naphthylethylamine and (–)-(*S*)-1-phenylethylamine (27 and 31% yields, respectively), in order to achieve higher π-stacking in the [4+2] cycloaddition[68], Scheme 18.

Condensation of (*S*)-aldehyde **592** with (*S*)-azepine **604a** afforded a 4:1 ratio of isomers **606a** and **607a**, from which the desired and main stereoisomeric diol could be isolated in 37% yield after deprotection[65], Scheme 18. Following essentially the above discussed route, the tosylate **608a** (38%) was chlorinated and coupled with vindoline (**360**) (→ **609a**), then reduced by KBH_4 to give azonine **610a**, which was transformed into epoxide **611a** in 72% overall yield, Scheme 19. Subsequent *N*-alkylation (40-h heating in MeOH) and hydrogenolysis of the quaternary ammonium salt afforded again the higher-energy stereoisomer **600**, which was thermally (in PhMe) transformed to natural vinblastine (**575**) in 80% yield from epoxide **611a**.

An initial step in the total synthesis of leurosidine (**612**), a C-20′ epimer of VLB, consisted in the condensation of (*S*)-azepine **604b** with (*R*)-aldehyde *ent*-**592**, which provided tetracycles **606b** and **607b** as a 3:1 mixture, Scheme 18. Subsequent hydrolysis of an acetonide allowed isolation of the major diol in 47% yield from **604b**. The diol was converted analogously to tosylate **608b** (73%). Attachment of the vindoline (**360**) in the presence of $AgBF_4$ (→ **609b**), reduction by KBH_4 (→ **610b**), and desilylation then yielded epoxide **611b** (73% from the tosylate **608b**), Scheme 19. This provided upon quaternisation (MeOH at reflux) and subsequent hydrogenolysis the expected higher-energy conformer of leurosidine **613** and, finally, the natural leurosidine (**612**) upon heating in toluene. Both (+)-leurosidine (**612**)[71] and its (+)-N_b′-oxide[72] were isolated from *Catharanthus roseus*.

Application of the second generation chiral auxiliaries is illustrated here with the synthesis of advanced intermediates **615**[73], Scheme 20. Although condensation of the aldehyde **592** with azepine **40a** (see also ref.[1], Chap. 3.1.1.), itself obtained by a displacement of (+)-(*S*)-**43a** with azepine **20** (79%), proceeded with worse diastereoselectivity compared to **604** and resulted via *E*-enamine **614** in the formation of tetracycles **615a** and **616a** in

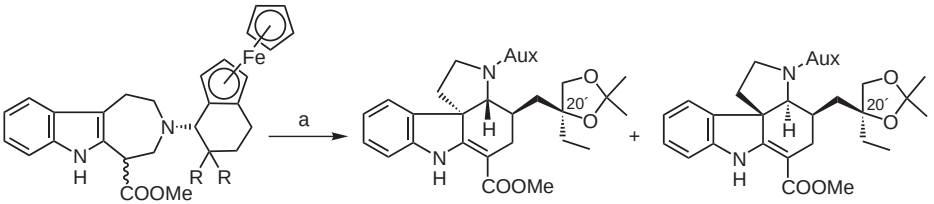
2:1 ratio (71%), a similar reaction of **40b** proved to be highly efficient. Aldehyde **592** reacted with (+)-(α*S*,*R*)-azepine **40b** highly diastereoselectively and afforded the stereoisomer **615b** as a single product in 71% yield. Solvolytic removal of the chiral auxiliary by a short heating in acetic acid produced, presumably via **617**, an equilibrium mixture of **618a** and stereoisomer **618b** (5.5:1); the secondary base (+)-**618a** was then benzylated to give the target base (+)-**594**.



SCHEME 20

Reagents and conditions: a) (+)-(*S*)-**43a** or (+)-(1*R*,*S*)-**43b** (0.66 eq), Et_3N, EtOH, rfl 2 h (**40a** 79%; **40b** 74%). b) **592** (1.2 eq), PhH, rfl 4–12 h (71%, **615a**:**616a** 2:1; **615b** 71%). c) **615**, AcOH, 70 °C 15 min (**618a** 74%, **618b** 14%). d) BnBr, K_2CO_3, Et_3N, Me_2CO, rt 6 h (72%)

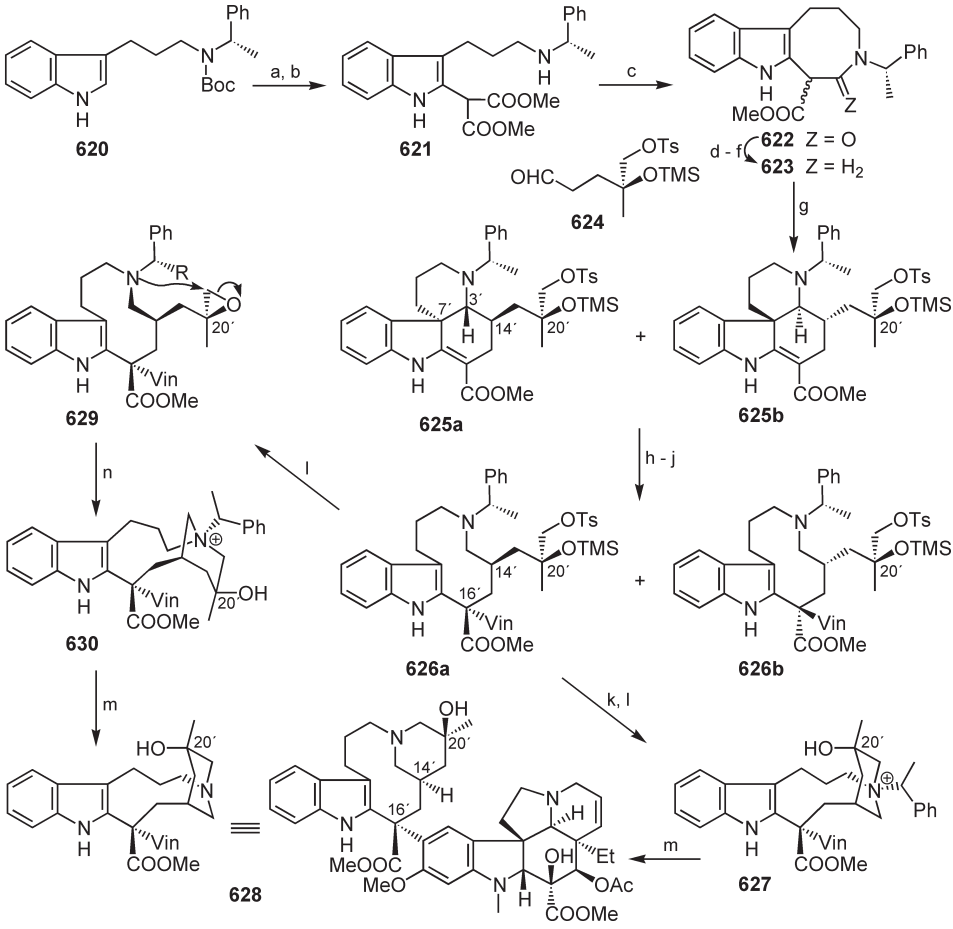
Finally, a reaction of the aldehyde **592** was tested with a racemic azepine bearing the last-generation chiral auxiliary on the nitrogen[74], Scheme 21. Thus, condensation of (*S*)-**592** with (±)-**45b** (see also ref.[1], Chap. 3.1.1.) gave rise to an inseparable 7–9:1 mixture of stereoisomers **619a** and **619b** (68%); similar reaction with the more powerful azepine **45a** was not yet described.



SCHEME 21
Reagents and conditions: a) (±)-**45b**, **592** (2 eq), PhH, rfl 4 h (68%; **619a**:**619b** 7–9:1)

A great plenty of vinblastine congeners have been prepared by Kuehne and coworkers for biological evaluation[75]. Two of the syntheses dealing with ring-homo-VLB analogues are discussed here that helped to put light also on factors influencing the energy barrier of the *N*-stereoisomers/conformers interconversion.

Synthesis of 5′-homo-VLB analogues is illustrated with the preparation of azecine **628** [76], in which a methyl group, with advantageous properties in biological testing, was substituted for C-20′ ethyl, Scheme 22. As the chiral azocine **623** could not be prepared analogously as azepines (e.g. by Pictet–Spengler condensation) it was eventually made accessible from (–)-(*S*)-carbamate **620**, which afforded 2-indolyl malonate **621** in 89% yield through Zn(II)-assisted addition of lithium malonate to the derived indolenine and a removal of the Boc-group. Thermal closure of the azocinone ring and a two-step removal of lactam carbonyl in **622** provided eventually amino ester **623**; the latter reacted in refluxing toluene with (*S*)-aldehyde **624** under formation of an isomeric mixture (89%) of tetracycles **625a** and **625b** (2:1), which were transformed into azecines **626** (62%). The major isomer **626a** cyclized thermally to quaternary salt **627**, clearly distinguishable by CD from a stereoisomeric salt **630** accessible via epoxide **629**. Both quaternary salts provided on hydrogenolysis one and the same product **628** (81% from **629**). Thus, the insertion of 5′-carbon has lowered the energy barrier too much to render the tertiary base corresponding to **630** isolable even at rt.



SCHEME 22

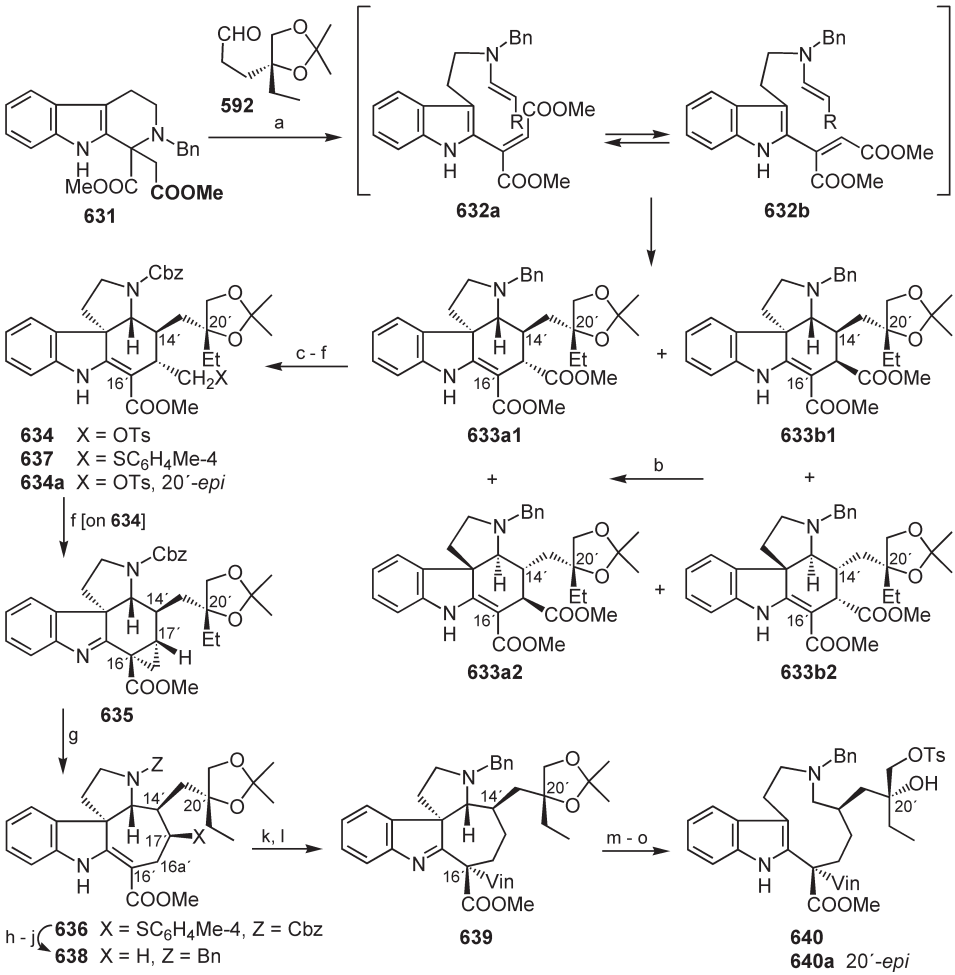
Reagents and conditions: a) *t*-BuOCl, Et_3N, THF, –60 °C 20 min, then $ZnCl_2$ (0.2 eq), 5 min, then $LiCH(COOMe)_2$, –60 °C → rt 6 h (91%). b) HCl/MeOH (sat), THF, rfl 3 h (98%). c) PhMe, rfl 12 h (85%). d) Lawesson's reagent, PhMe, 110 °C 6 h (64%). e) Ra-Ni, MeOH, warm 3.5 h (81%). f) $NaBH_3CN$ (2.5 eq), AcOH, rt 15 min (62%). g) **623**, **624** (1.16 eq), PhMe, rfl 20 h (89%; **625a**:**625b** 2:1). h) *t*-BuOCl, Et_3N, CH_2Cl_2, 0 °C 5 min. i) Vindoline (**360**) (0.95 eq), $HBF_4{\cdot}OEt_2$ (2 eq), Me_2CO, rt 5 min, then $AgBF_4$ (2.0 eq), rt 5 min. j) KBH_4 (5 eq, slowly), AcOH, rt 10 min (**626a** 39% overall; **626b** 23% overall). k) PhH (sealed), 150 °C 24 h. l) TBAF (3 eq), THF, 25 °C 4 h (**626a** → **629** 74%). m) H_2, 10% Pd/C, MeOH, 2 h (81% from **629**). n) MeOH, rfl 24 h

An access into 16a′-homo series is documented with syntheses of leurosidine and VLB analogues[77], Schemes 23 and 24. The extra carbon was provided by the COOMe group marked bold in the starting β-carboline diester **631**. Heating the diester **631** with (*R*)-aldehyde **592** provided all four possible diastereoisomers **633**, Scheme 23. The ratio **633a** to **633b** (3.4:1) was sensitive to the reaction conditions and probably did not reflect a kinetic ratio of the presumed intermediates **632**; stereoisomers **633b** could be thermally converted into **633a**. Morover, while the ratio of **633b1** to **633b2** was similar (1.4:1) to vinblastine synthesis (little effect of C-20′ chiral center, vide supra), an enhanced diastereoselectivity was noticed with the pair **633a1** and **633a2** (5:1), presumably due to an interaction of COOMe group with acetonide in the transition state **632a**. Thus, the desired stereoisomer **633a1** could be isolated in 51% yield, making thus the presence of a chiral auxiliary on nitrogen unnecessary.

Ester **633a1** was converted to tosylate **634** and further to indolenine cyclopropane **635** on exposure to DBU (91%)[77], Scheme 23. Heating with thiophenol induced fragmentation and high yield (98%) was obtained of β-anilinoacrylate carbamate **636** together with minor amount (16:1) of **637**. Subsequent 3-step conversion to tertiary base **638** set the stage for coupling with vindoline (**360**), which even in this homo-series proceeded with excellent *parf*-selectivity[66] and which, through the reduction of an unstable indolenine **639** eventually afforded the crucial azecine tosylate **640**.

Diol monotosylate **640** provided in refluxing methanol quaternary ammonium salt **641**, hydrogenolyzed at 0 °C to base **642** with "unnatural" conformation of ring D′ as identified by CD spectrum[77], Scheme 24. This same base **642** was obtained alternatively through conversion of **640** by DBU into epoxide **643** (94%), quaternisation (→ **641**), and hydrogenolysis at 0 °C, indicating thus that the former quarternisation had proceeded also through the epoxide intermediate (compare with the outcome in quaternisation of protected diol tosylates like **626a**). Stabilized by hydrogen bonding of axial hydroxyl with tertiary nitrogen, the base **642** resisted all attempts at conversion to **644** even by prolonged refluxing in toluene. However, incremental addition of trifluoroacetic acid to CD_3OD solution caused isomerisation with the best ratio of 1:1 of 16′-homoleurosidine (**644**) to **642**.

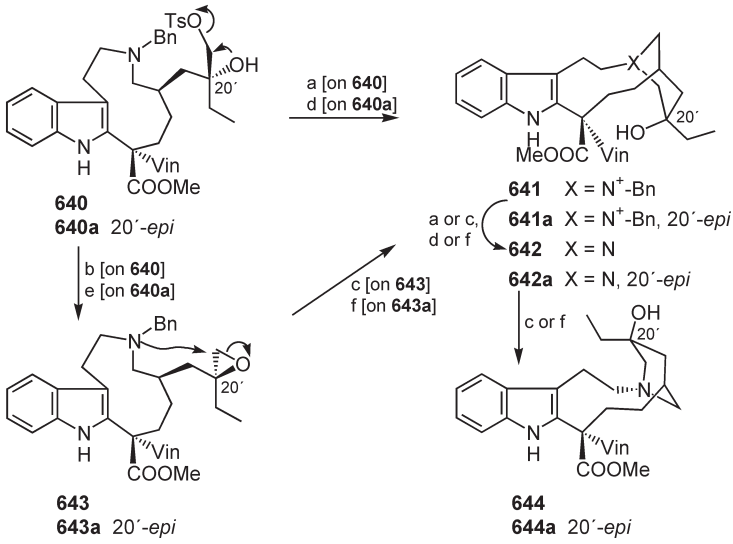
On the other hand, 5-step inversion of the C-20′-configuration in **633a1** included H_2SO_4/SiO_2 induced epoxide opening (94% de) and the resulting 20′-*epi*-tosylate **634a** was transformed into 20′-*epi*-azecine **640a** essentially by the above procedure[77], not specified in Scheme 23. Reactivity of 20′-*epi*-azecine **640a** was similar to **640** and provided exclusively a quater-



SCHEME 23

Reagents and conditions: a) **592**, neat, SiO_2, 130 °C 3 h, then $NaBH_4$, MeOH, CH_2Cl_2, 0 °C 10 min (**633a1** + **633a2** 62.6% (5:1), **633b1** + **633b2** 18.5% (1.4:1); **633a1** 50.9%). b) **633b**, 150 °C 24 h (→ **633a**). c) DIBAL-H, THF, hexanes, 0 °C 45 min → rt 3 h (84.9%). d) $HCOO^-N^+H_4$, 10% Pd/C, MeOH, AcOEt, rfl 2 h (88.5%). e) CbzCl, $NaHCO_3$, 95% Me_2CO aq, 0 °C 10 min (94.5%). f) Ts_2O, Et_3N, DMAP (cat), CH_2Cl_2, rt 3 h (→ **634**), then DBU, rt 12 h (**635** 91.2%). g) 4-MeC_6H_4SH, neat, 110 °C 1.5 h (97.9%, **636**:**637** 16:1). h) Bu_3SnH (3 eq), AIBN (1 eq), PhMe, rfl 28 h (75.1%). i) H_2, 10% Pd/C, Et_3N, AcOEt, rt 1 h (72.5% + indolenine 14.1%). j) BnBr, Et_3N, K_2CO_3, Me_2CO, rt 10 h (**638** 70.2%). k) *t*-BuOCl, Et_3N, CH_2Cl_2, 0 °C 10 min. l) Vindoline (**360**), $HBF_4 \cdot OEt_2$ (2 eq), Me_2CO, rt 5 min, then $AgBF_4$ (2 eq), 0 °C 10 min → rt 20 min. m) KBH_4 (excess, during 30 min), AcOH, 0 °C. n) 10% HCl aq/MeOH (8:15), rfl 15 min (26% from **638**). o) Ts_2O, Et_3N, CH_2Cl_2, 0 °C 12 h (**640** 55.4% + 27.4% ditosylate)

nary salt identified by CD as **641a**[77], Scheme 24. Hydrogenolysis at 0 °C gave rise to the product base, which existed in solution as an equilibrium mixture of **642a** and **644a**. The ratio was shown to be both solvent (1:2.3 in $CDCl_3$ at 25 °C) and temperature dependent (1:8.8 in CD_3OD at –30 °C); addition of TFA caused a complete conversion to the salt of 16′-homovinblastine (**644a**).

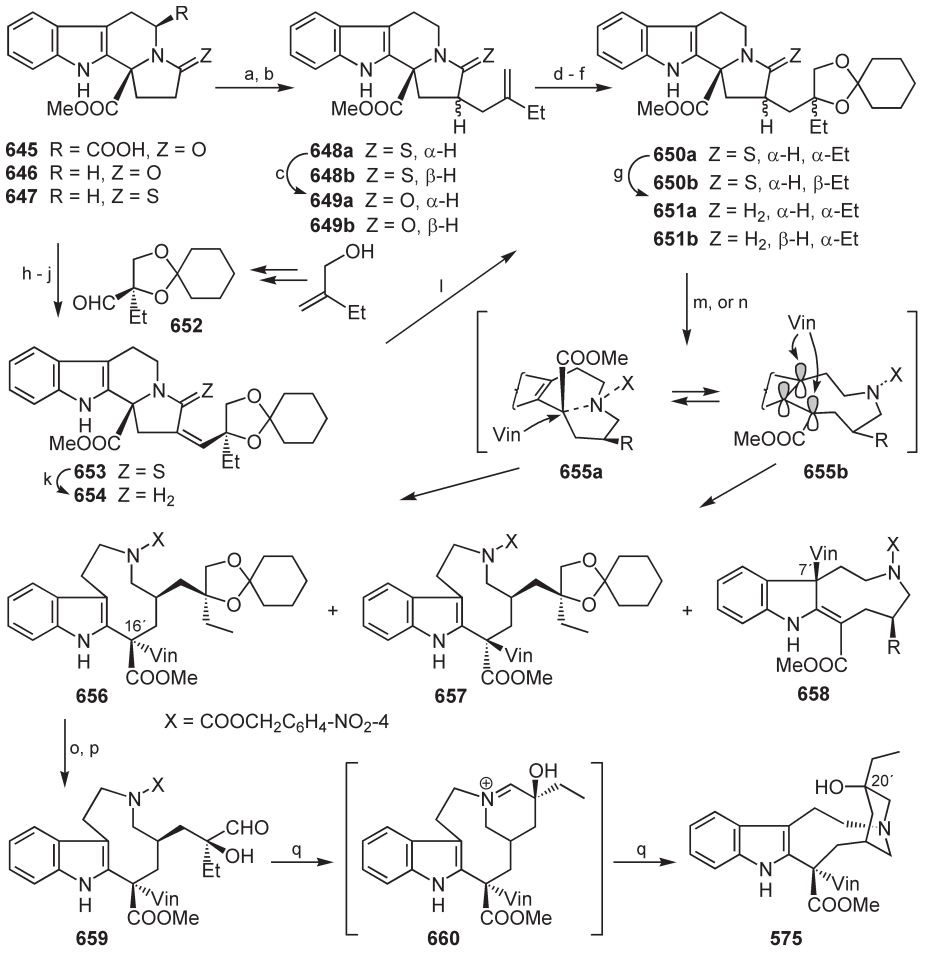


SCHEME 24

Reagents and conditions: a) **640**, MeOH, rfl 23 h (→ **641** + vindoline-deacetylated salt), then H_2, 10% Pd/C, MeOH, 0 °C 10 min (**642** 68.2% + 24% vindoline-deacetylated product). b) **640**, DBU, THF, rt overnight (**643** 92%). c) **643**, MeOH, rfl 15 h, then H_2, 10% Pd/C, MeOH, 0 °C 20 min (**642** 78% + trace amount vindoline-deacetylated product). d) **640a**, MeOH, rfl 23 h (→ **641a**), then H_2, 10% Pd/C, MeOH, 0 °C 20 min (83.3%, **642a**:**644a** 1:2.3 in $CDCl_3$, 1:3 in CD_3OD, 1:4.7 in CD_3OD at –10 °C, 1:8.8 in CD_3OD at –30 °C). e) **640a**, DBU, THF, rt 16 h (**643a** 93.6%). f) **643a**, MeOH, rfl 13 h, then H_2, 10% Pd/C, MeOH, 0 °C 20 min (83.7%, **642a**:**644a** ratio as above)

7.2.2.2. Magnus' Approach

Magnus and collaborators have described a total synthesis of vinblastine (**575**), which is based on a non-oxidative formation of the bis-indole intermediate **656**[49], Scheme 25. The synthesis suffers from unfavourable stereoselectivity in early stages. As the allylation of (+)-lactam **646**, easily accessible from acid **645**[78], to **649** was inefficient, it was converted to (+)-thiolactam **647**, which afforded via thio-Claisen methodology allylated



SCHEME 25

Reagents and conditions: a) (+)-**645**, CH_2=C(Et)CH_2Br, $MeNO_2$, rt 78 h. b) DBU, THF, 0–5 °C → 25 °C 4.5 h (75%, (+)-**648a**:(+)-**648b** 1:2.2). c) **648**, *m*-CPBA (0.5 h), CH_2Cl_2, 4 °C → 25 °C 1 h (87%, (+)-**649a** 27%). d) **649a**, OsO_4 (2.5 wt.%), NMO, Me_2CO aq, 25 °C 15 h. e) 1-Methoxycyclohexene, Amberlyst H 15, THF, 25 °C 16 h (80%, 1:1.32). f) Lawesson's reagent (0.6 eq), PhMe, 80 °C 4 h → 25 °C 12 h ((+)-**650a** 35% + (+)-**650b** 42%). g) (+)-**650a**, Ra-Ni, THF, 25 °C 16 h ((–)-**651a** 94%). h) **647**, (+)-(*R*)-**652**, $Sn(OTf)_2$, *N*-ethylpiperidine, THF, rt 10 h (75%). i) Ts_2O, Et_3N, CH_2Cl_2, rt 5 h (91%). j) DBU, CH_2Cl_2, rt 15 min (88%). k) Ra-Ni (deact), Me_2CO, untill complete. l) H_2, 10% Pd/C, MeOH, rt overnight ((–)-**651a** 44% + (+)-**651b** 43%). m) (–)-**651a**, 4-$O_2NC_6H_4CH_2OCOCl$ (2.6 eq), vindoline (**360**; 4 eq), CH_2Cl_2, 25 °C 72 h (**656**:**657**:**658** 0:52:40%). n) (–)-**651a**, 2,6-di-*t*-Bu-4-Mepy (3 eq), 4-$O_2NC_6H_4CH_2OCOCl$ (2.6 eq), vindoline (**360**; 4 eq), $MeNO_2$, –20 °C 64 h (**656**:**657**:**658** 59:31:0%). o) (–)-**656**, 2 M HCl aq/THF (1:1), 25 °C 10 h (83%). **p**) SO_3, py, Et_3N, DMSO, 25 °C 3 h (77%). **q**) H_2, 10% Pd/C, MeOH, 25 °C 2 h (89%)

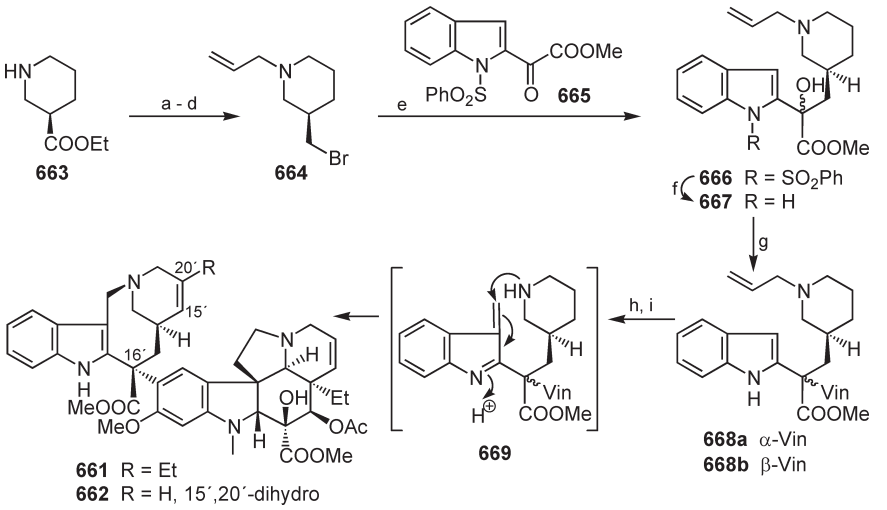
thiolactams (75%) with unwanted stereoisomer (+)-**648b** strongly predominating (2.2:1). Conversion of **648** into **649** permitted separation of the desired lactam (+)-**649a** (27%), which underwent consecutively nonstereoselective dihydroxylation (1:1.32) with OsO_4/NMO, acetalisation (80%) and conversion to thiolactams **650**, of which the desired minor epimer (+)-**650a** (35%) was treated with Ra-Ni and gave the crucial amino ester (–)-**651a** in 94% yield.

Alternatively, thiolactam (+)-**647** underwent aldol reaction under Mukayiama's conditions ($Sn(OTf)_2$) with (+)-(*R*)-aldehyde **652** [49,79], itself derived from 2-ethylallylalcohol by Sharpless asymmetric epoxidation, Scheme 25. Stereochemically homogeneous (+)-aldol (75%) was dehydrated to olefine thiolactam (+)-**653** (80%), whose direct reduction with Ra-Ni to **651** proceeded with high, but undesired diastereoselectivity (**651b**:**651a** ca. 8:1). Consequently, **653** was treated with deactivated Ra-Ni (→ **654**) prior to final hydrogenation, which provided 1:1 mixture of bases, of which (–)-**651a** was obtained in 43% yield.

The crucial coupling reaction with (–)-vindoline (**360**; 4 eq) was initiated by chloroformate (2.6 eq); believed to proceed through intermediacy of **655a** and/or **655b** the process was surprisingly not found to be sensitive to solvent polarity and temperature[49], see also refs[80,81]. Thus, coupling in CH_2Cl_2 at 25 °C provided through **655b** a mixture of bis-indoles (–)-**657** (52%) and (–)-**658** (40%), while in $MeNO_2$ at 25 °C it afforded a mixture of (–)-**656**:(–)-**657** (11:89) and traces of **658**, and at –20 °C the desired product (–)-**656** was the main product (59%) accompanied by **657** (33%), Scheme 25. Intermediate (–)-**656** was transformed into vinblastine (**575**) in a straightforward way by its conversion to hydroxyaldehyde (–)-**659** (64%), and then by hydrogenation through the intermediary iminium **660** into the alkaloid **575** (89%); overall yield from **651a** equalled to 34%.

Among many vinblastine-alkaloid analogues[82] navelbine (**661**, also vinorelbine) is an important anticancer agent which is accessible through Polonovski–Potier-type fragmentation of vinblastine (**575**)[83]; for recent synthesis see ref.[84]. Magnus and Thurston have reported on synthesis of the pharmacologically active (+)-(16′*S*)-base **662** [85], Scheme 26. (–)-(*R*)-Ester **663** was converted in 4 steps into bromide **664** which, as a Grignard reagent, reacted with keto ester **665** to give hydroxy ester **666** as a 1:1 mixture of diastereoisomers (68%). These could be, but were not separated because the crucial coupling of the indole-deprotected alcohol **667** (88%) with vindoline (**360**) in refluxing 1% HCl in methanol provided again a 1:1 mixture of epimers in 49% yield. The separated tertiary amine **668a** was deprotected with α-chloroethyl chloroformate and the derived secondary

amine was subjected to Mannich condition (formaldehyde in acidic medium). The 8-membered ring in 3-methyleneindolenine **669** was closed rather efficiently providing azocine (+)-**662** in 81% yield.

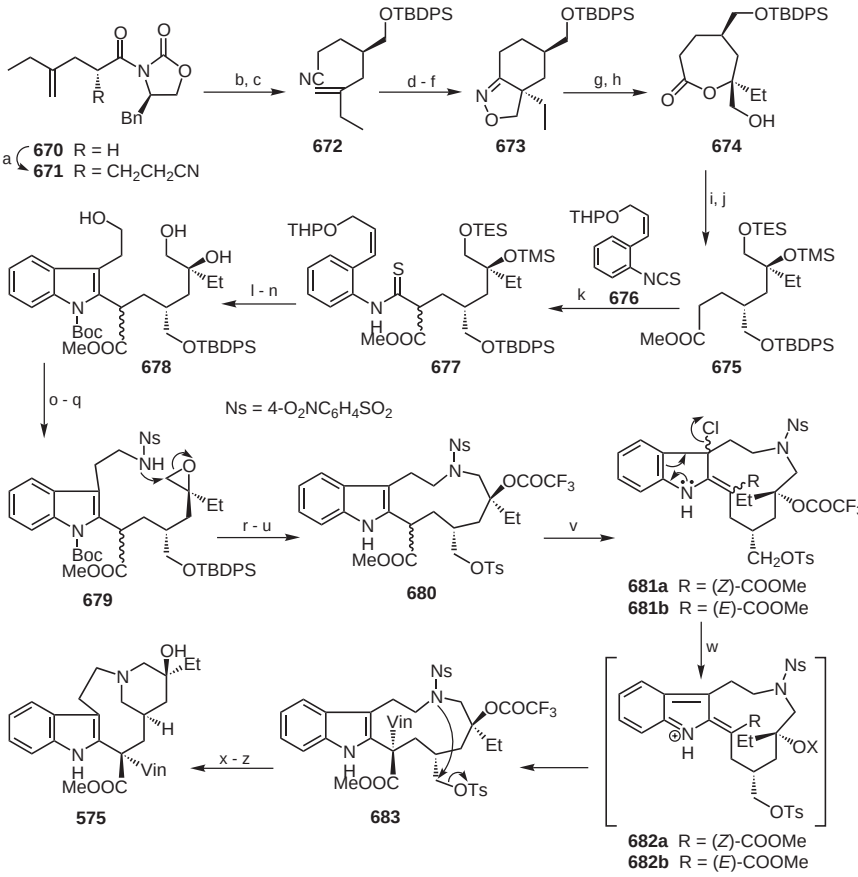


SCHEME 26

Reagents and conditions: a) $LiAlH_4$, THF, rfl 1 h (89%). b) CH_2=$CHCH_2Br$ (2 eq), Et_3N (10 eq), EtOH, rfl 12 h (66%). c) MsCl, Et_3N, CH_2Cl_2 (99%). d) LiBr (2 eq), Me_2CO, rfl 18 h (80%). e) Mg, THF, rfl 3 h → rt, then **665** (0.8 eq), 0 °C 30 min (68%, 1:1). f) Sodium naphthalenide in THF, DME, –50 °C (88%). g) Vindoline (**360**; 1.1 eq), 1% HCl/MeOH, rfl 2 h (49%, **668a**:**668b** 1:1). h) **668a**, ClCOOCHClMe (2 eq), proton sponge (1.1 eq), $ClCH_2CH_2Cl$, 25 °C 3 h (82%). i) 37% $(CH_2O)_n$, AcOH, dioxane, 35 °C 24 h (81%)

7.2.2.3. Fukuyama's Synthesis

Fukuyama and coworkers have published[86] de novo synthesis of (+)-vinblastine (**575**), which includes also total synthesis of (–)-vindoline (**360**) (see ref.[1], Chap. 3.3.2.), Scheme 27, see refs[87–89] and also ref.[90]. Chirality was induced early by applying Evans' protocol in converting imide **670** into nitrile imide **671** (82%). Transformation of the latter into nitrile **672** set the stage for a conventional 3-step generation of nitriloxide, which underwent highly enantioselective [3+2] addition and provided isoxazoline **673** (59% for 3 steps). Its conversion into ester **675** included regioselective Baeyer–Villiger reaction, which was best effected with *m*-CPBA in acetic acid (→ **674**), and subsequent methanolysis.

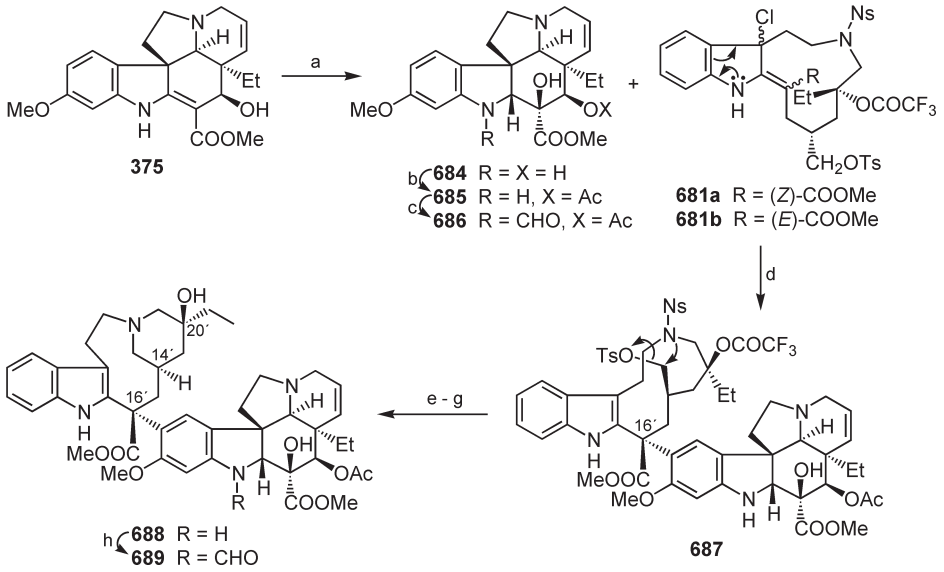


SCHEME 27

Reagents and conditions: a) CH_2=CHCN, *i*-PrOTiCl_3, *i*-Pr_2NEt, CH_2Cl_2, 0 °C 9 h (70%). b) $NaBH_4$, THF/H_2O, 0 °C 20 min → rt 12 h (92%). c) TBDPSCl, imidazole, DMF, rt (92%). d) DIBAL-H, CH_2Cl_2, –78 °C 20 min. e) $HONH_2$·HCl, NaOAc, EtOH, rt 1 h. f) NaOCl aq, CH_2Cl_2, rt 3.5 h (59%, 3 steps). g) Zn, AcOH, rt 4 h (66%). h) *m*-CPBA (excess), AcOH, rt 41 h. i) K_2CO_3, MeOH, rt 45 min (80%, 2 steps). j) TESCl (1.2 eq), imidazole (3 eq), DMF, rt 1 h, then TMSCl (1.2 eq), rt 45 min (92%). k) LDA, THF, –78 °C 70 min, then **676**, –78 °C 45 min → 0 °C 15 min (76%). l) Bu_3SnH (2 eq), Et_3B (0.2 eq, THF, rt 1 h (67%). m) Boc_2O, DMAP (0.1 eq), Et_3N, CH_2Cl_2, rt (87%). n) AcOH/H_2O (95:5), 80 °C 1 h (71%). o) TsCl (1.05 eq), Bu_2SnO (1 eq), Et_3N, CH_2Cl_2, rt 15 h (84%). p) $NaHCO_3$, DMF, 80 °C 3 h (90%). q) $NsNH_2$ (2 eq), DEAD (1.5 eq), Ph_3P (1.5 eq), PhMe, rt 40 min (88%). r) K_2CO_3 (2 eq), DMF, 90 °C 22 h (82%). s) TFA/CH_2Cl_2 (1:1), rt 2 h (85%). t) TsCl (1.1 eq), $Me_2N(CH_2)_3NMe_2$ (1.5 eq), MeCN/PhMe (1:1), rt 1 h (88%). u) TFAA (2 eq), py (5 eq), CH_2Cl_2, rt 20 min (90%). v) *t*-BuOCl (1.1 eq), CH_2Cl_2, 0 °C 10 min. w) (–)-Vindoline (**360**; 0.88 eq based on **680**), TFA (excess), CH_2Cl_2, 0 °C 10 min → rt 50 min (97% based on **360**; 85% based on **680**). x) Et_3N (1 eq), CH_2Cl_2, rt 40 min (quant). y) $HSCH_2CH_2OH$, DBU, Me_2CO, rt (76%). z) $NaHCO_3$, *i*-PrOH aq, rt 24 h (66%)

Construction of the indole moiety was addressed next which commenced with an addition of metallated ester **675** to isothiocyanate **676** (76%)[86], Scheme 27. The malonate thioanilide **677** underwent radical cyclization with Bu_3SnH (67%). Removal of protecting groups afforded indole acetate triol **678**, in which a chemoselective tosylation in the presence Bu_2SnO of the diol primary hydroxyl initiated a 3-step preparation of oxirane 4-nitrobenzenesulfonamide **679**. The following closure of 11-membered ring was achieved by regioselective opening of the oxirane ring in **679** and the product (81.5%) was transformed into **680**.

The following conversion to **683** belongs to the true highlights of this total synthesis[86], Scheme 27 (see also ref.[90]). Electrophilic chlorination by *t*-BuOCl of diastereoisomeric indole acetate **680** produced chloroacrylate **681**, which might have been present as the (*E*)-isomer **681b**; in such a case the following TFA induced coupling with (–)-vindoline (**360**) could have proceeded through a highly conjugated iminium **682b**, thus accounting for



SCHEME 28

Reagents and conditions: a) *m*-CPBA, $MeOH/CH_2Cl_2$ (1:9), $NaHCO_3$ aq satd, 0 °C 10 min, then $NaBH_3CN$, 10% HCl/MeOH → pH 3, 0 °C 5 min, then $NaBH_3CN$, 0 °C 3 min → rt 30 min, then Na_2CO_3 → pH 10, then $NaHSO_3$, rt 3 h (59% from **375**). b) NaOAc, Ac_2O, 0 °C 12 h (88%). c) HCOOH, Ac_2O (quant). d) **681** (excess), **685**, TFA, CH_2Cl_2, 0 °C → rt 20 min (75%). e) Et_3N, CH_2Cl_2, rt 40 min (98.5%). f) $HSCH_2CH_2OH$ (in 6 portions), DBU, Me_2CO, rt 2.5 h (61%). g) $NaHCO_3$, *i*-PrOH aq, rt 20 h (57%). h) Ac_2O/HCOOH (11:5), 50 °C 1 h → rt, then **688**, rt 1.5 h (87%)

the extraordinary high diastereoselectivity: This transformation of **680** produced sulfonamide tosylate **683** as a single stereoisomer and in 97% (!) yield based on **360** (or 85% from **680**). Finally, selective *O*- and *N*-deprotection of **683** and a closure of the D′-piperidine ring completed the first truly total synthesis of (+)-VLB (**575**).

The authors completed also total synthesis of (+)-vincristine (**689**)[91], the strategy of which is outlined in Scheme 28. (–)-16-Hydroxy-11-methoxytabersonine (**375**) was converted to N_a-demethylvindoline (**685**) by sequential treatment with *m*-CPBA (→ **376**) (see ref.[1], Chap. 3.3.2.), reduction with $NaBH_3CN/NaHSO_3$ (→ **684**; 59%) and selective *O*-acetylation with NaOAc, Ac_2O (88%). Albeit the derived N_a-formyl derivative **686** failed to couple with chloro acrylate **681** due to lowered C-10 nucleophilicity, analogous treatment of the base **685** with **681** initiated by TFA proceeded smoothly and stereoselectively to give bis-indole **687** as a sole product in 75% yield. The following conversion to **688** (34%) paralleled that in the VLB synthesis above, and the total synthesis was completed by *N*-formylation (87%), which produced (+)-vincristine (**689**); (+)-**689** is isolable among others from *Vinca rosea*[92].

8. ALKALOIDS LACKING 2–7 BOND (RHAZINILAM AND RELATED COMPOUNDS)

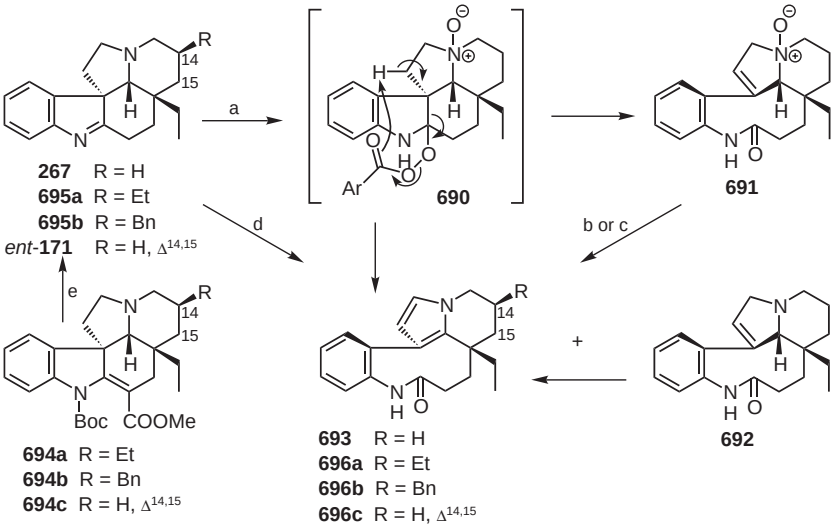
Although rhazinilam might be, at least in some isolations, an artefact rather than the natural alkaloid, it received considerable attention of synthetic chemists at least in part due to its profound paclitaxel-like activity[93].

8.1. Partial Synthesis

8.1.1. From Aspidospermanes

French chemists have described an improved transformation of (+)-1,2-didehydroaspidospermidine (**267**) into (–)-rhazinilam (**693**)[94–96], which is based on previous results of the Smith's group[97], Scheme 29. Upon exposure to *m*-CPBA (+)-**267** affords diastereoselectively *N*-oxide **691** (65%) possibly through fragmentation in peroxy intermediate **690** [95]. *N*-Oxide **691** is then converted by treatment with ferrous sulfate to a mixture of rhazinilam (**693**) and its dihydro analogue **692** (45 and 9%, respectively), which is slowly autoxidated to **693**. In a more efficient way, *N*-oxide **691** is subjected to Polonovski condition (Ac_2O, Et_3N) to give (–)-rhazinilam (**693**) in 81% yield; "one-pot" procedure affords (–)-**693** in 50% yield from (+)-**267** [94,96]. Similarly, an application of the "one-pot" procedure to indolenines **695** de-

rived from β-anilino acrylates **694** provided rhazinilam analogues **696** with the same efficiency (50%). (–)-Rhazinilam (**693**) was isolated inter alia from *Vallesia glabra*[98]; 5,21-dihydrorhazinilam (**692**), an unstable natural precursor of rhazinilam[99], was obtained from both *Leuconotis griffithii* and *L. eugenifolia*[100,101].

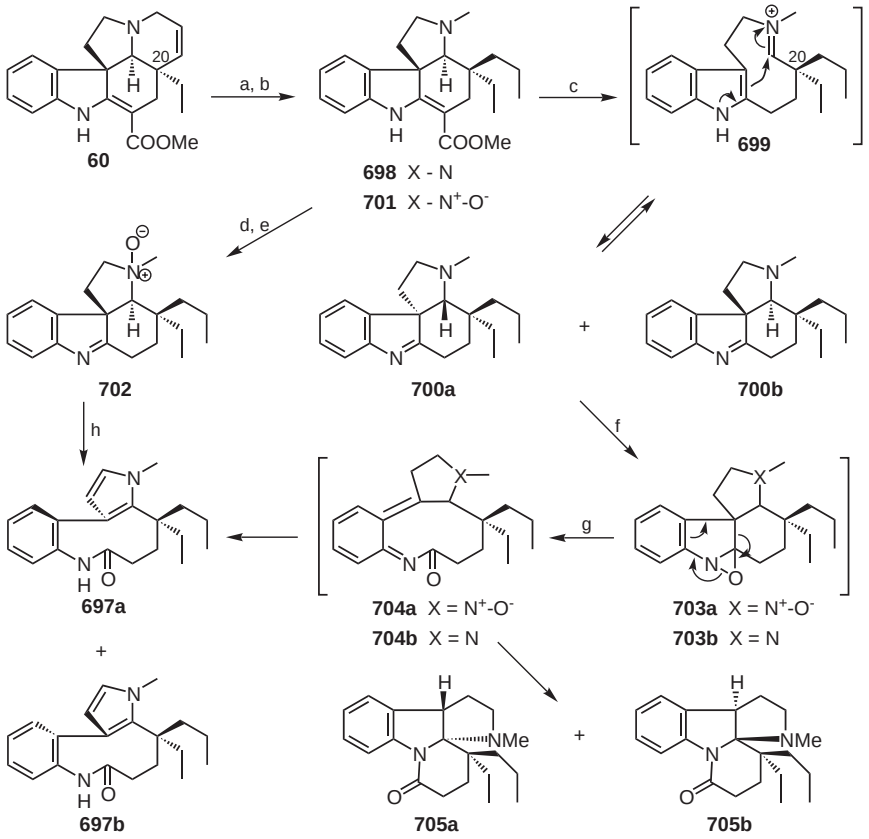


SCHEME 29

Reagents and conditions: a) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, –20 °C 4–8 h (**691** 65%). b) $FeSO_4$, H_2O, rt (**693** 45% + **692** 5%). c) Ac_2O, CH_2Cl_2, 0 °C → rt 30 min (**693** 81%). d) condition a, then Et_3N, Ac_2O, CH_2Cl_2, –20 °C → rt 30 min (**693** 50%; **696a**–**696c** 50%). e) **694**, 12 M HCl aq, 110 °C 5 min (**695** 100%; *ent*-**171** 95%)

Lévy and collaborators have reported on synthesis of D-secorhazinilam analogues **697**[96], Scheme 30. Emde degradation of (–)-tabersonine (**60**) gave rise to D-nor base **698**; subsequent treatment with hot hydrochloric acid provided indolenine **700** as an equimolecular mixture of diastereoisomers (86%). That the outcome of the reaction is a result of equilibrium via **699** with negligible impact of C-20 center was proved by similar conversion of N_b-oxide **701**, which yielded stereochemically homogeneous indolenine **702**. Exposure of **700** to *m*-CPBA was suggested to proceed through oxaziridine N_b-oxide **703a** (compare to **690**), which fragmented upon thermolysis to quinonoid intermediate **704a** and afforded finally a 1:1 mixture of norrhazinilams **697** (31%), accompanied by a 26% yield of tetra-

cyclic aminals **705a** and **705b** (1:1); formation of the latters is explained in terms of incomplete N_b-oxidation and intermediacy of **703b** and **704b**. Note that individual atropoisomers **697** suffer epimerisation at 80 °C (DMSO-d_6) to the one and the same 1:1 mixture of **697a** and **697b**, which is formed also from indolenine **702** (16%), Scheme 30.

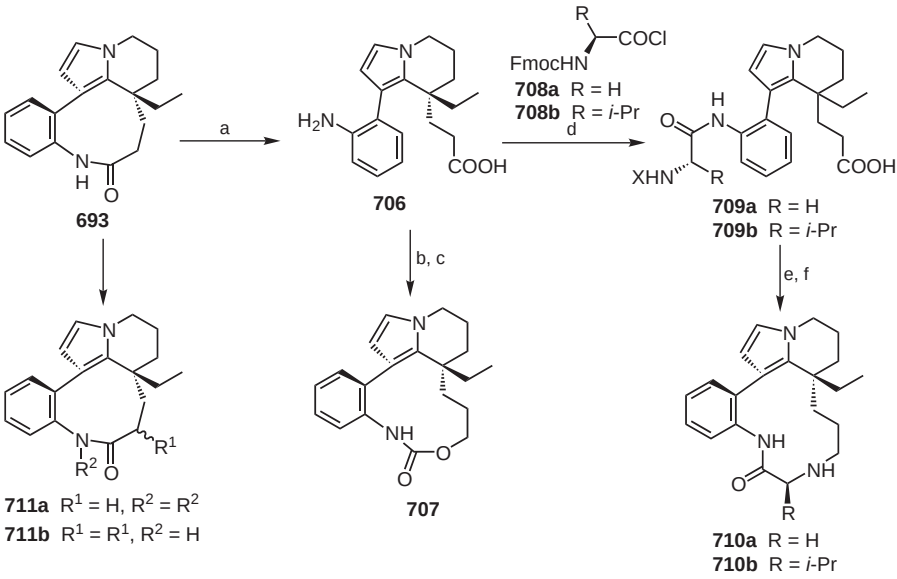


SCHEME 30

Reagents and conditions: a) MeI, $CHCl_3$ (sealed tube), 40 °C 36 h (100%). b) H_2, PtO_2, Na_2CO_3, EtOH, rt 16 h (78%). c) **698**, 2 M HCl aq, rfl 20 min (86%; **700a**:**700b** 1:1). d) **701**, *m*-CPBA, CH_2Cl_2, 0 °C 1 h (96%). e) 2 M HCl aq, rfl 20 min (70%). f) **700**, *m*-CPBA (more than 3 eq), CH_2Cl_2, 0 °C 1 h. g) PhMe, rfl 1 h (31%, **697a**:**697b** 1:1 + 26%, **705a**:**705b** 1:1). h) *m*-CPBA oxidation, then thermolysis (16%, **697a**:**697b** 1:1)

8.1.2. From Rhazinilam

Gif group have reported on partial synthesis from rhazinilam of a series of rhazinilam analogues as outlined in Scheme 31[102]. (–)-Rhazinilam (**693**) afforded on alkaline hydrolysis with KOH upon microwave heating the corresponding (–)-acid **706** (85%), which was reduced with $LiAlH_4$ (69%) and converted to 11-membered-ring analogue (–)-**707** with NaHMDS/triphosgene (21%). On the other hand, the acid **706** reacted with acid chlorides **708** to give anilides **709**, which were deprotected and cyclized by HOBT and *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU) method in a low yield to analogues **710** with 12-membered central ring; both compounds appeared as a mixture of 2 conformers/diastereoisomers (**710a** 1:1; **710b** 85:15). Both **707** and **710** showed lower activity towards tubulin, as did a series of analogues prepared by substitution of rhazinilam (**693**) on nitrogen (→ **711a**) or in α-position (→ **711b**).



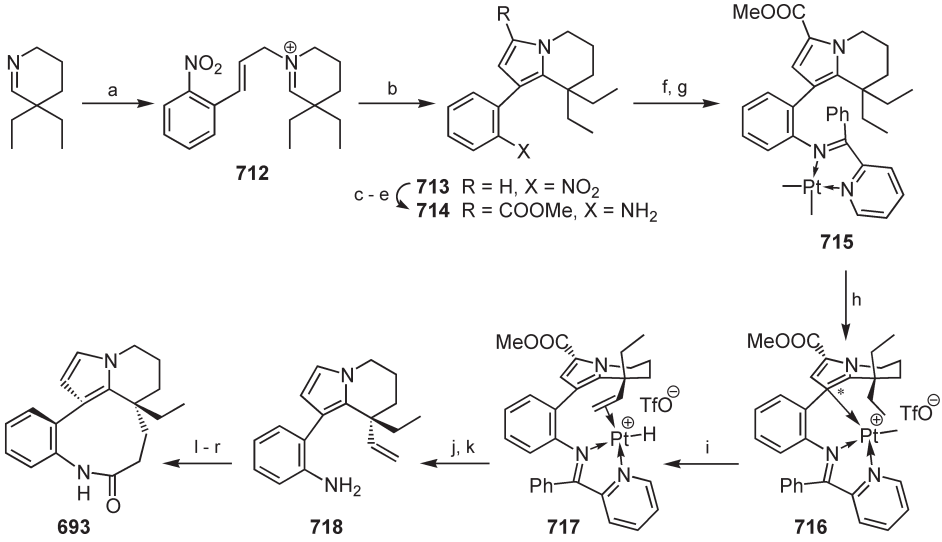
SCHEME 31

Reagents and conditions: a) KOH (42 eq), EtOH/H_2O (1:1), sealed tube, microwave irradiation, 120 °C 30 min (85%). b) $LiAlH_4$, THF, 0 °C → rfl 22 h (69%). c) NaHMDS (1 eq), THF, 20 °C, then $(Cl_3CO)_2C{=}O$ (1 eq), 0 °C 10 min (21%). d) **708** (1 eq), 10% $NaHCO_3$ aq, CH_2Cl_2, 20 °C 1.5 h (**709a** 96%; **709b** 66%). e) piperidine (excess), THF, 20 °C 2.5 h (**a** 88%; **b** 92%). f) TBTU (3 eq), HOBT (3 eq), *i*-Pr_2NEt (4 eq), DMF, 20 °C 1 d (**710a** 30%; **710b** 10%)

8.2. Total Synthesis

8.2.1. Sames' Syntheses

Sames and coworkers have published on a new synthesis of rhazinilam (**693**), which is based on a diastereoselective activation of C–H bond in unactivated diastereotopic alkyl groups[103], a problem not yet satisfactorily solved in organic synthesis. In this particular case, the activating complex was built up on an aniline nitrogen, which was later incorporated in the target molecule. In the synthesis of racemic rhazinilam (±)-**693** [104], Scheme 32,

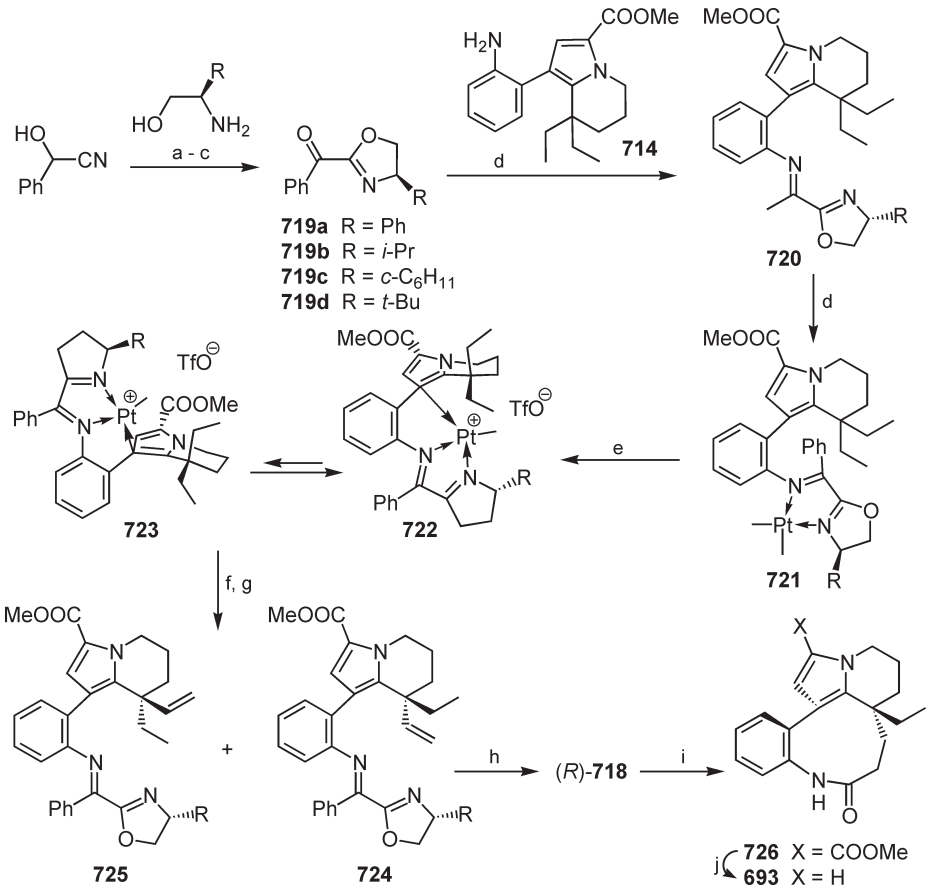


SCHEME 32

Reagents and conditions: a) 2-Nitrocinnamyl bromide, DMF, 80 °C 15 min (90%). b) Ag_2CO_3 (2 eq), PhMe or xylenes, rfl 45 min (65–70%/1–5 mmol; 51%/22 mmol). c) Cl_3CCOCl. d) NaOMe, MeOH. e) H_2 (1 atm), Pd/C (88%, 3 steps). f) 2-(PhCO)py (1.5 eq), TsOH (cat), PhMe, rfl 30 h (83%). g) $[PtMe_2(\mu\text{-}SMe_2)]_2$ (0.5 moleq), PhMe, rt 18 h (88%). h) TfOH, CH_2Cl_2, –40 °C 15 min. i) F_3CCH_2OH, 70 °C 72 h (90% by NMR). j) 0.5 M KCN aq, CH_2Cl_2, rt 30 h. k) $HONH_2 \cdot HCl$, NaOAc, MeOH, rt 30 min (60% from **715**). l) Boc_2O, DMAP (76%). m) OsO_4, $NaIO_4$. n) $Ph_3P{=}CHCOO\textit{t}\text{-Bu}$. o) H_2, 10% Pd/C (76%, 3 steps). p) TFA, CH_2Cl_2, –78 °C (75%). q) PyBOP, HOBT, $\textit{i}\text{-}Pr_2NEt$. r) NaOH, MeOH aq, then HCl aq (80%, 2 steps)

iminium salt **712** was cyclized/aromatized by exposure to silver carbonate, and the pyrrole **713** thus formed (51–70%) was, after stabilization by introduction of methoxycarbonyl group, converted into aniline **714** (88%). Its condensation with phenyl 2-pyridyl ketone provided imine, which by interaction with platinum complex $[PtMe_2(\mu\text{-}SMe_2)]_2$ afforded complex **715** (73%). The latter was further transformed by exposure to trifluoromethanesulfonic acid causing loss of methane into salt **716**, featuring dative bond between platinum and pyrrole carbon C*, which has thus rather sp^3 hybridization. Subsequent thermolysis caused, under concomitant loss of another methane molecule, an activation of one, favorably spatially oriented, ethyl group accompanied by hydride β-elimination and provided hydride complex **717** (90%). Aniline **718** liberated from **717** (60% from **715**) was finally transformed in conventional way (7 steps) into target (±)-**693**.

In an enantioselective synthesis of (–)-rhazinilam (**693**)[105], the authors have used chiral inductors **719**, easily accessible from mandelonitrile, to differentiate the diastereotopic ethyl groups in **721**, Scheme 33. Condensation of phenyl oxazolyl ketones **719** with aniline **714** furnished Schiff bases **720** converted by exposure to $[PtMe_2(\mu\text{-}SMe_2)]_2$ into platinum complexes **721** (45–48%), the treatment of which with triflic acid provided a diastereoisomeric mixture of **722** and **723** (1:1 to 3:2). The stereochemical outcome of the following C–H activation by heating with 2,2,2-trifluoroethanol was strongly temperature-dependent: The most promising ligand **719c** afforded platinum hydride complexes (analogous to **717**), as well as **724c**:**725c** ratio as high as 7.5:1 at 60 °C (30% conversion), and 4.4:1 at 70 °C (66% conversion) corresponding to 76 and 64% ee, respectively. Unfortunately, the most powerful *tert*-butyl ligand **719d** (**724d**:**725d** >20:1 at 60 °C) was shown to be preparatively useless due to too low conversion (<10%). Note that the ratio **722** to **723** is much different from that of the platinum hydride complexes and the decomplexed imines **724**:**725** (15–42% from **720**), which could be separated by HPLC. Finally, the derived (–)-(*R*)-aniline **718** was transformed into (–)-**693** by a highly simplified 2-step procedure, commencing with a direct olefine carbonylation/macrolactamization (10 atm CO, 10% Pd/C, 1,4-bis(diphenylphosphino)butane (dppb), HCOOH, DME, 150 °C 4 days) in 58%, followed by removal of the methoxycarbonyl group from **726** (90%); overall yield of (–)-**693** from **724** equals to 52%.



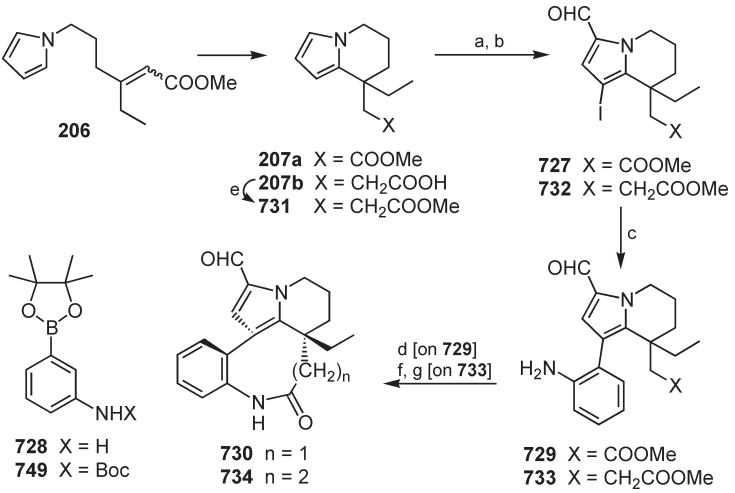
SCHEME 33

Reagents and conditions: a) HCl, MeOH, $CHCl_3$, 0 °C → rt 16 h. b) Et_3N, CH_2Cl_2, rt 16 h (40%) c) DMP, CH_2Cl_2, rt 1 h (71–80%). d) TsOH (cat), PhMe, rfl 30 h (**720a** 73%; **720b** 68%; **720c** 65%). d) $[PtMe_2(\mu\text{-}SMe_2)]_2$ (0.5 moleq), PhMe, rt 24 h (**721a** 48% (3.5:1 ratio by ^{1}H NMR); **721b** 46%; **721c** 45%). e) TfOH (1 eq), CH_2Cl_2, –40 °C 15 min (**722a**:**723a** 3:2 by ^{1}H NMR; **722b**:**723b** 1:1; **722c**:**723c** 3:2). f) F_3CCH_2OH, heat 72 h (**a** 60 °C/6:1 by ^{1}H NMR (conversion 20%), 65 °C/3.8:1 (60%), 70 °C/3:1 (63%); **b** 60 °C/5.5:1 (16%), 65 °C/4:1 (60%), 70 °C/3:1 (65%); **c** 60 °C/7.5:1 (30%), 65 °C/5.5:1 (58%), 70 °C/4.4:1 (66%)). g) KCN aq, CH_2Cl_2, rt 30 h, then HPLC separation (**724** + **725** 15–42% from **720**). h) $HONH_2 \cdot HCl$ (1.8 eq), NaOAc (2.4 eq), MeOH, rt 30 min (quant). i) CO (10 atm), 10% Pd/C (0.05 eq), HCOOH (2 eq), dppb (0.2 eq), DME, 150 °C 4 d (58%). j) 50% NaOH aq, MeOH, 50 °C 30 min → rt, pH → 2, 50 °C 4 h (90%)

8.2.2. Banwell's Syntheses

Banwell and coworkers reported on total synthesis of rhazinal (**734**) and the corresponding B-nor base **730** [106,107] from indolizines **207b** and **207a** (see ref.[1], Chap. 3.2.1.), respectively, Scheme 34. Regioselective Vilsmeier–Haack formylation of indolizine **207a** to attenuate pyrrole basicity/reactivity (95%) and following iodination (I_2, $AgOCOCF_3$) furnished iodoaldehyde **727** (75%) which, under condition of Suzuki–Miyuara cross-coupling ($[Pd(PPh_3)_4]$ (4%), Na_2CO_3 aq) reacted with 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**728**, 1.5 eq) to give crucial amino ester **729** (76%). Lactamization in the latter was efected by excess *t*-BuOK and yielded unnatural base **730** (78% brsm)[106].

Synthesis of (±)-rhazinal (**734**) commenced with esterification (DCCI, DMAP) of acid **207b** [107], Scheme 34. The ester **731** was converted essentially by the above procedure to iodo aldehyde **732** (78%), and then to aniline **733** (64%). In this case, a stepwise procedure was used consisting of alkaline

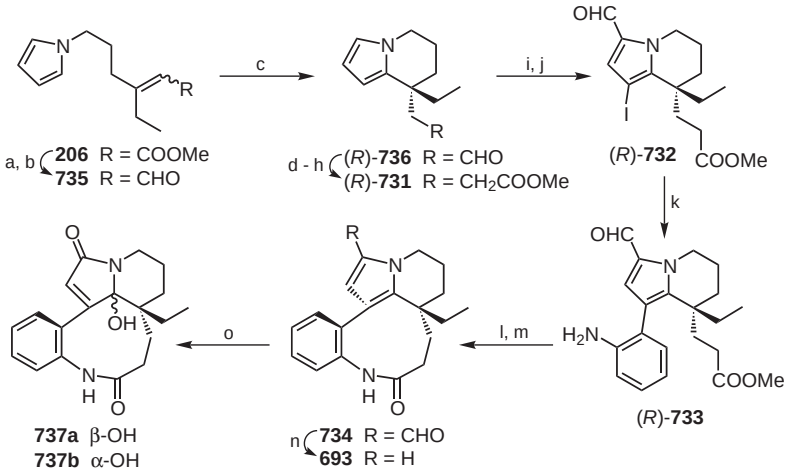


SCHEME 34

Reagents and conditions: a) $POCl_3$ (1.07 eq), DMF (excess), Et_2O, 0 °C 30 min → 18 °C 3 h (**207a** → 95%; **731** → 78%). b) I_2 (1.1 eq), $AgOCOCF_3$ (1.1 eq), $CHCl_3$, 0 °C → 18 °C 4 h (**727** 75%; **732** quant). c) **728** (1.5 eq), $[Pd(PPh_3)_4]$ (4%), 2 M Na_2CO_3 aq (excess), PhMe, MeOH, 80 °C 2 h (**729** 76%; **733** 64%). d) *t*-BuOK (3 eq), *t*-BuOH, 18 °C 3 h (**730** 78% brsm). e) DCCI, DMAP (cat), CH_2Cl_2/MeOH (3:1), 18 °C 3 h (**731** 72%). f) KOH (excess), EtOH, 18 °C 3 h. g) EDCI, DMAP, CH_2Cl_2, 18 °C 3 h (**734** 68%)

hydrolysis of **733** followed by EDCI/DMAP-induced lactam formation, which afforded a 68% yield of racemic rhazinal (**734**); (–)-rhazinal (**734**) was isolated from *Kopsia teoi*[108]. (–)-**734** was made also accessible by formylation of (–)-rhazinilam (**693**)[95].

Asymmetric synthesis of rhazinilam-type bases was also developed in the Laboratory[109], which rests upon intramolecular Michael addition of pyrrole to acrylaldehyde, Scheme 35. Acrylate **206** was converted in two steps to acrylaldehyde **735** with about the same isomer ratio (*E*/*Z* ca. 1:1), which was directly, without separation of isomers, subjected to reaction with MacMillan's first generation catalyst (20 mole %), as it was expected that the generated iminiums would rapidly interconvert. The expected (*R*)-indolizine **736** was obtained after 3 days reaction at –20 °C in 81% yield



SCHEME 35

Reagents and conditions: a) DIBAL-H (2.2 meq), THF, –78 °C → 18 °C 4 h (91%). b) $BaMnO_4$ (8 eq), CH_2Cl_2, 18 °C 2 days (76%; *E*/*Z* ca. 1:1). c) (5*S*)-2,2,3-trimethyl-5-benzyl-4-imidazolidinone (20 mole %), THF/H_2O (20:1), –20 °C, 3 days (81%). d) $NaBH_4$ (1.5 eq), THF/EtOH (20:1), 18 °C 2 h (84%; 70–75% ee). e) MsCl (2 eq), Et_3N (2 eq), CH_2Cl_2, 0 °C 30 min (95%). f) NaCN (20 eq), DMPU, 18 °C 24 h (91%). g) KOH (excess), MeOH/H_2O (3:4), rfl 16 h. h) DCC (2.2 eq), DMAP (10 mole %), MeOH/CH_2Cl_2 (1:3), 18 °C, 3 h (63%, 2 steps). i) $POCl_3$ (1.1 eq), DMF (12 eq), Et_2O, 0 °C → 18 °C 3.5 h (78%). j) I_2 (1.1 eq), $AgOCOCF_3$ (1.1 eq), $CHCl_3$, 0 °C → 18 °C 4.5 h (quant). k) **728** (1.0 eq), [$Pd(PPh_3)_4$] (cat), 2 M Na_2CO_3 aq (excess), PhMe/MeOH (4:1), 90 °C 1.5 h (64%). l) KOH (excess), EtOH, 18 °C 3 h. m) EDCI (1.4 meq), DMAP (1.1 meq), CH_2Cl_2, 18 °C 3 h (68%, 2 steps; ca. 74% ee). n) [$RhCl(PPh_3)_3$] (1.1 meq), dioxane, 100 °C 2 h (89%; 70–75% ee). o) PCC (2.6 meq), 4 Å MS, CH_2Cl_2, 18 °C 16 h (**737a** 28% + **737b** 46%)

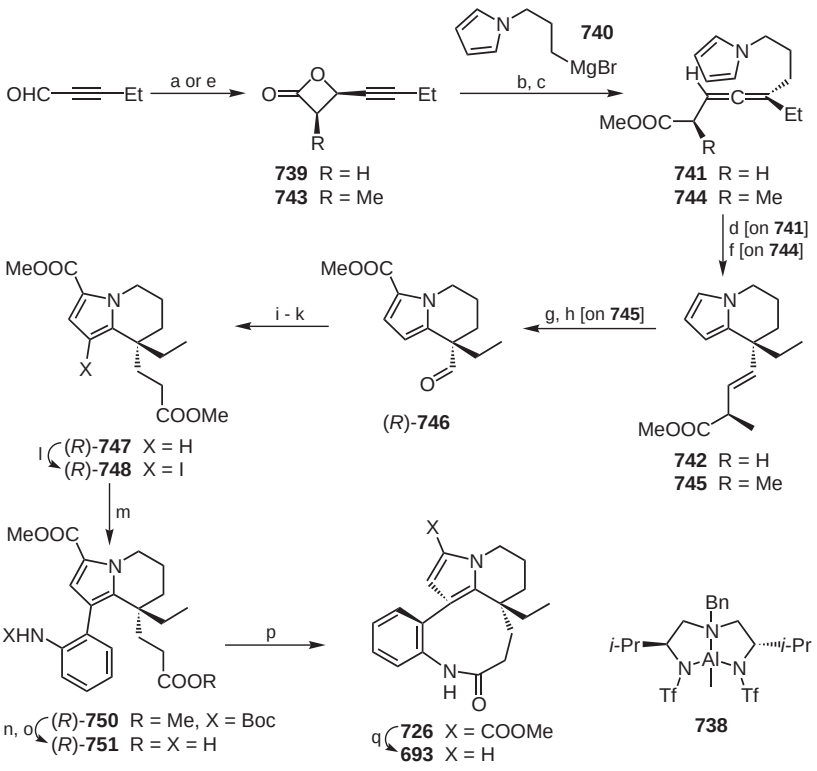
and with ca. 74% ee as determined in the next step. Aldehyde (*R*)-**736** was converted in 5 steps to ester (*R*)-**731**, and then transformed via (*R*)-**732** and (*R*)-**733** to (–)-rhazinal (**734**) with ca. 74% ee.

(–)-Rhazinilam (**693**) could not be synthesized by the same strategy as the iodination of **731** failed to give the desired iodide[109]. It was, therefore, prepared by deformylation of (*R*)-**734** with Wilkinson rhodium catalyst (89%), Scheme 35. Related hydroxylactams were made available by direct oxidation of (–)-rhazinilam with excess PCC. (–)-Leuconolam (**737a**) and (+)-epileuconolam (**737b**) were obtained in 28 and 46% yields, respectively; alkaloid (–)-**737a** and probable isolation artefact (+)-**737b** were isolated from both *Leuconotis griffithii* and *L. eugenifolia*[100,101].

8.2.3. Nelson's Synthesis

While related to Banwell's synthesis in late stages, the approach by Nelson and collaborators uses a completely different strategy for assembling optically active indolizine propionates, which is based on Au(I)-catalyzed annulation/chirality transfer of enantioenriched allenes[110], Scheme 36. Optical activity was induced already in the first step consisting in cyclocondensation of 2-pentynal with acetyl bromide catalyzed by the in situ generated aluminum complex **738** to give β-lactone **739** (79%) with 97% ee. Copper (I)-catalyzed SN2′ addition of Grignard reagent **740** to **739** and esterification then provided allene **741** (88%, ee). It was assumed that the Lewis basic methoxycarbonyl group could direct Pd(II)-complexation by both enhancing the electrophilicity of the double bond and effectively stereodirecting an attack of pyrrole *anti* to metal by keeping the latter *syn* oriented. Indeed, exposure of **741** to 20% [$PdCl_2(MeCN)_2$] afforded 92% yield of indolizine **742**, however, with only 37% ee.

β-Lactone **743**, which allowed more convenient assessment of stereochemistry, was prepared next[110] by condensation of 2-pentynal with propionyl chloride in the presence of 10% of *O*-trimethylsilylquinine (72%, 99% ee, ≥98% de). Reaction with Grignard reagent **740** as described above provided allene **744** as a single diastereoisomer (89%). Of the catalytic systems tested in the following step the in situ generated catalyst AuOTf·PPh_3 worked best and gave a 92% yield of indolizine **745** with dr 97:3. Introduction of methoxycarbonyl group into (–)-**745** (99%) commenced a transformation via **746** to indolizinecarboxylate **747** (71% overall), which was iodinated (89%). Suzuki–Miyaura cross-coupling of iodide **748** with *tert*-butyl-*N*-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carba-



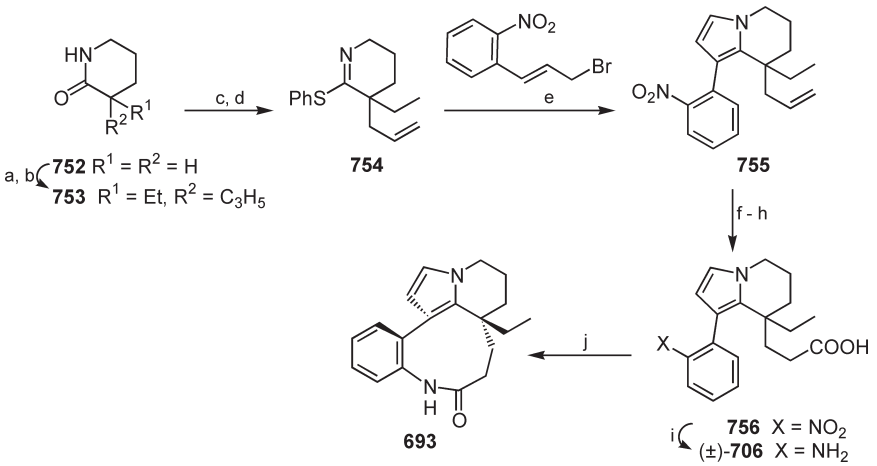
SCHEME 36

Reagents and conditions: a) AcBr (1.85 eq during 3 h), **738** (5 mole %), *i*-Pr_2NEt, CH_2Cl_2, –78 °C 12 h (**739** 79%, 97% ee). b) **740**, CuCN (10 mole %), LiBr (0.22 eq), THF, –78 °C 15 min (88 or 89%). c) $TMSCHN_2$, PhH/MeOH (2.5–3:1), rt 30 min (**741** 98%; **744** 94%). d) $[PdCl_2(MeCN)_2]$ (20 mole %), CH_2Cl_2, rt 1 h (**742** 92%, 37% ee). e) EtCOCl (2 eq during 3 h), *O*-trimethylsilylquinine (10 mole %), $MgCl_2$ (1 eq), *i*-Pr_2NEt, Et_2O/CH_2Cl_2 (2.5:10.5), –78 °C 12 h (**743** 72%, >99% ee, >99% de). f) **744**, $Ph_3P.AuOTf$ (5 mole %), CH_2Cl_2, rt 16 h (**745** 92%, 94% de). g) **745**, Cl_3CCOCl, CH_2Cl_2, rt 1 h, evap; then NaOMe (excess), MeOH, rt 30 min (99%). h) OsO_4 (10 mole %), NMO, Me_2CO/H_2O (17:4), 0 °C → rt 2 days (92%). i) $NaIO_4$, THF/H_2O (3:1), 0 °C → rt 16 h (76%, 94% ee). j) Ph_3P=CHCOOMe, PhMe (6 eq), 80 °C 2 days (95%). k) H_2, 10% Pd/C, MeOH, rt 16 h (quant). l) I_2 (1.2 eq), $AgOCOCF_3$ (1.2 eq), $CHCl_3$, 0 °C → rt 16 h (89%). m) **749** (2 eq), $[Pd_2(dba)_3]$ (2.5 mole %), SPhos (10 mole %), K_3PO_4 (excess), THF/H_2O (4:1), rt 1 h → 40 °C 1.5 days (86%). n) $Ba(OH)_2 \cdot 8H_2O$, MeOH, rt 2 h. o) TFA (excess), CH_2Cl_2, rt 1 h. p) CH_2Cl_2 solution added over 12 h to HATU (excess), *i*-Pr_2NEt, DMF/CH_2Cl_2 (5:2), rt 4 h (74%, 3 steps). q) 50% NaOH aq, MeOH, 50 °C 30 min, then pH → 2 (1 M HCl aq), 50 °C 4 h (96%)

mate (**749**; Scheme 34) was catalyzed by $[Pd_2(dba)_3]$ (2.5%) and Buchwald's SPhos ligand (10%) and provided arylindolizine **750** (86%), which was chemoselectively deprotected ($Ba(OH)_2$, then TFA) to give amino acid **751** (93%). Formation of the lactam ring in **751** was mediated by excess *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU) and the resulting lactam **726** (74% over 3 steps) was finally converted to (–)-rhazinilam (**693**) with 94% ee.

8.2.4. Magnus' Synthesis

Magnus and Rainey have developed a synthesis of racemic rhazinilam (**693**), which is based on an efficient build up of the indolizine **755** [111], Scheme 37. Sequential alkylation of **752** provided lactam **753** in 55% yield, which was converted to imino thioether **754** (81%). The following reaction with 2-nitrocinnamyl bromide and treatment with DBU at 0 °C furnished directly indolizine **755** in 71%, without necessity to change the oxidation state of original carbonyl carbon. Sequential conversion of allyl group in



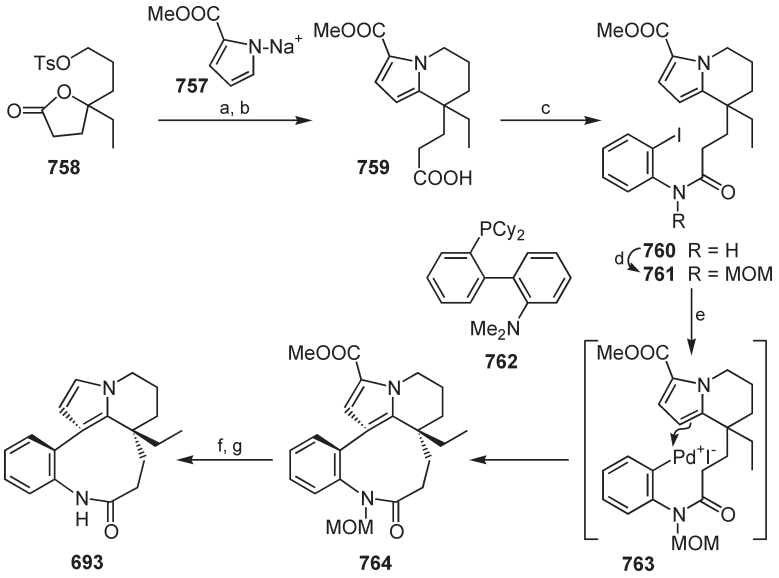
SCHEME 37

Reagents and conditions: a) *n*-BuLi (2 eq), THF, –78 °C → 0 °C 1 h, then EtI (1.5 eq), 0 °C 45 min (90%). b) *n*-BuLi (1 eq), THF, –78 °C → 0 °C 1.25 h, then TMSCl (1.1 eq), 0 °C 1.75 h, then LDA (1.5 eq), 0 °C 45 min → –78 °C, then CH_2=$CHCH_2Br$ (excess), –78 °C → 0 °C 1.25 h (61%). c) PCl_5 (1 eq), PhMe, rfl 3 h. **d**) PhSH (3 eq), Et_3N (3 eq), THF, rt 2.5 h (81%). e) PhMe, 100 °C 15 min, then DBU, THF, 0 °C → rt (71%). f) BH_3·SMe_2 (3 eq), THF, 0 °C 1 h, then 3 M NaOH aq, then 30% H_2O_2, 0 °C → rt (78%). g) SO_3·py (3 eq), Et_3N, DMSO, THF, rt 45 min (66%). h) $AgNO_3$, KOH aq, EtOH, rt 30 min (94%). i) H_2 (20 psi), Ra-Ni, MeOH, rt 1.5 h (98%). j) 2-Chloro-1-methylpyridinium iodide, Et_3N, PhMe, THF, rt 2 h (51%)

755 into propanoic acid **756** (48% over 3 steps) and reduction of the nitro group set the stage for eventual closure of the lactam ring in aniline acid (±)-**706** using Mukaiyama condition (51%); (±)-rhazinilam (**693**) was obtained in an overall 9% yield.

8.2.5. Trauner's Synthesis

While all approaches discussed so far featured the closure of central azonine ring through lactam formation, Trauner and collaborators used a different strategy which is based on the aryl coupling[112], Scheme 38. Alkylation of sodium salt **757** with tosylate **758**[97] provided amine-lactone (94%) which, upon exposure to aluminum chloride, underwent a Friedel–Crafts alkylation (55%). Acid **759** was transformed to amide **760** (75%) by treatment with 2-iodoaniline under Mukaiyama's condition. As the crucial coupling did not work with amide **760**, the latter was *N*-protected (→ **761**) prior to exposure to $Pd(OAc)_2$ and DavePhos ligand (**762**) (10 mole % each).



SCHEME 38

Reagents and conditions: a) **757**, **758** (94%). b) $AlCl_3$ (55%). c) 2-Iodoaniline, 2-chloro-1-methylpyridinium iodide, Et_3N (75%). d) MOMCl, NaH (85%). e) $Pd(OAc)_2$ (10 mole %), **746** (10 mole %), K_2CO_3 (47%). f) BCl_3 (large excess), low temp. (60%). g) NaOH aq, then HCl aq, heat (85%)

Biaryl formation in **761**, proceeding probably through an attack by pyrrole on Pd^+-species **763** (formally a Heck-like process), completed the build-up of the rhazinilam skeleton (→ **764**; 47%). Finally, removal of protecting groups from **764** yielded the desired (±)-rhazinilam (**693**) in 51% yield.

8.2.6. Synthesis of Rhazinilam Analogues

Most of the work devoted to syntheses of rhazinilam analogues was due to French chemists[93,113] who have shown the crucial importance of aryl rings angle in biaryl systems for maintaining the antitubulin-like activity, cf. also ref.[114]. With molecules **765** and **766** (n = 0–2) the preferable substitution pattern is that with R = Et, see Fig. 1.

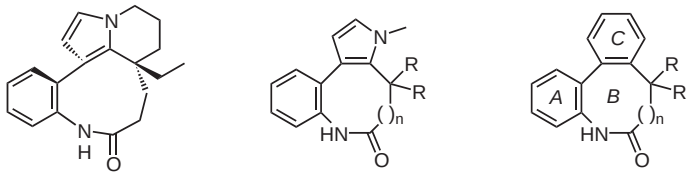
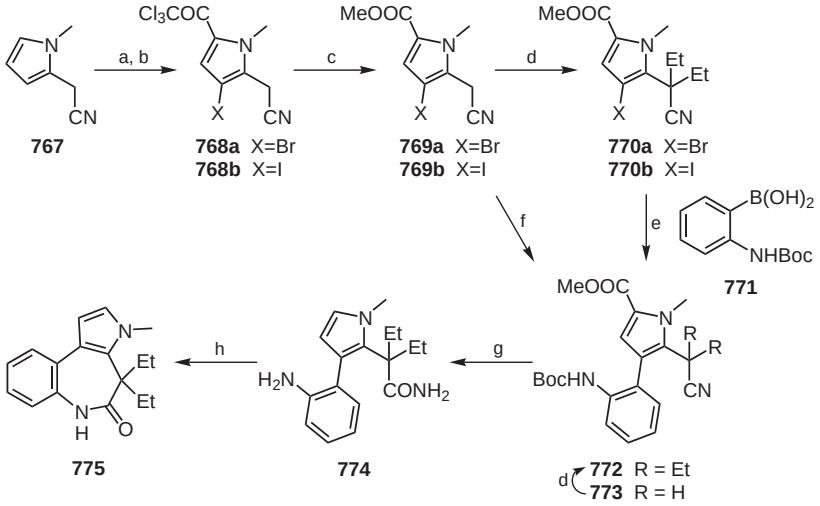


FIG. 1
Rhazinilam analogues

Synthesis of **775** commenced with a high-yielding protection of C-5 in pyrrole **767** by trichloroacetyl group (98%) and equally efficient introduction of halogen at C-3[115], Scheme 39. Conversion of protecting group in **768** to methoxycarbonyl was induced by cold sodium methoxide (→ **769**, 95%). Subsequent diethylation (EtI/*n*-BuLi) set the stage for Suzuki cross-coupling of the thus formed aryl halides **770** (54%) with boronic acid **771**, which was catalyzed by [$PdBnCl(PPh_3)_2$] (3 mole %) and worked equally well with the two halides **770** (→ **772**, 47–48%). Note that with less sterically branched halides **769** the Suzuki coupling of **771** was substrate sensitive affording much higher yield of **773** from iodide **769b** (80 and 35%, respectively); following diethylation of **773** (44%) completed somewhat more efficient approach to **772**. Quantitative transformation of **772** to caprolactam **775** was achieved through consecutive treatment with sodium hydroxide, hydrochloric acid (→ **774**) and refluxing concd sulfuric acid. Not surprisingly, 7-membered lactam **775** was inactive on disassembly of microtubules. On the other hand, it acted, like colchicinoids, as an inhibitor of tubulin assembly; for synthesis of other pyrroles **765** see refs[116,117].



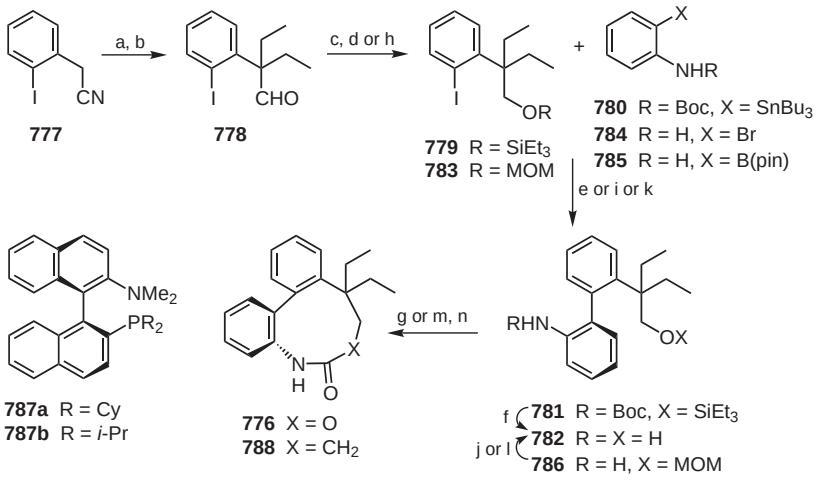
SCHEME 39

Reagents and conditions: a) Cl_3CCOCl, Et_2O, 0 °C (98%). b) NBS or NIS, Me_2CO, rt (**768a** 98%, **768b** 99%). c) NaOMe, MeOH, 0 °C (98%). d) LDA, EtI, –78 °C → 0 °C (**769** → **770** 54%; **773** → **772** 44%). e) **771** (1.1 eq), [$PdBnCl(PPh_3)_2$] (3 mole %), K_3PO_4 (1.5 eq), DME aq, rfl 3 h (**770a** → **772** 48%, **770b** → **772** 47%). f) **771** (1.1 eq), [$PdBnCl(PPh_3)_2$] (3 mole %), Na_2CO_3 (1.5 eq), DME aq, rfl 3 h (**769a** → **773** 35%, **769b** → **773** 80%). g) 50% NaOH aq, MeOH, rfl 3 h, then 10% HCl aq, rt 15 min (100%). h) concd H_2SO_4, rfl 10 min (100%)

The most promising compound of general formula **766** was shown to be, based on an in vitro antimitotic screening, the biphenyl carbamate **776** [118]; first generation synthesis of this rhazinilam analogue is based on Stille coupling, Scheme 40. Aryl iodide **779**, conveniently prepared via **778** from arylacetonitrile **777** in 4 steps, was subjected to Stille coupling with stannane **780** ([$PdBnCl(PPh_3)_2$], 4 mole %) and provided biphenyl **781** in 49% yield. Complete removal of protecting groups by TFA (→ **782**) set the stage for a closure of the nine-membered carbamate ring which was effected by exposure to triphosgene, and the target biphenyl **776** was obtained in 88% yield over two steps. In an alternative approach[119], iodide **783** reacted with borane **785** generated in situ by borylation from aryl bromide **784** under condition of Suzuki coupling to afford protected biaryl **786** (78%), Scheme 39. Exposure of **786** to hydrochloric acid provided the anilino-alcohol **782** (86%) and, finally, **776**.

It was demonstrated[120] in an asymmetric variant of the Suzuki coupling of iodide **783** with borane **785** that the most promissing chiral ligands were binaphthyls **787**, Scheme 40. (–)-(*aR*)-Biaryl **782** was isolated in 56 and 49%

yield and with ee 40 and 41% from the reaction with ligand **787a** and **787b** and subsequent deprotection, respectively. Biaryl (–)-(*aR*)-**782** (ee 40%) was transformed into carbamate (–)-(*aR*)-**776** (98% yield) of the same ee which could be brought to 92% by recrystallization.



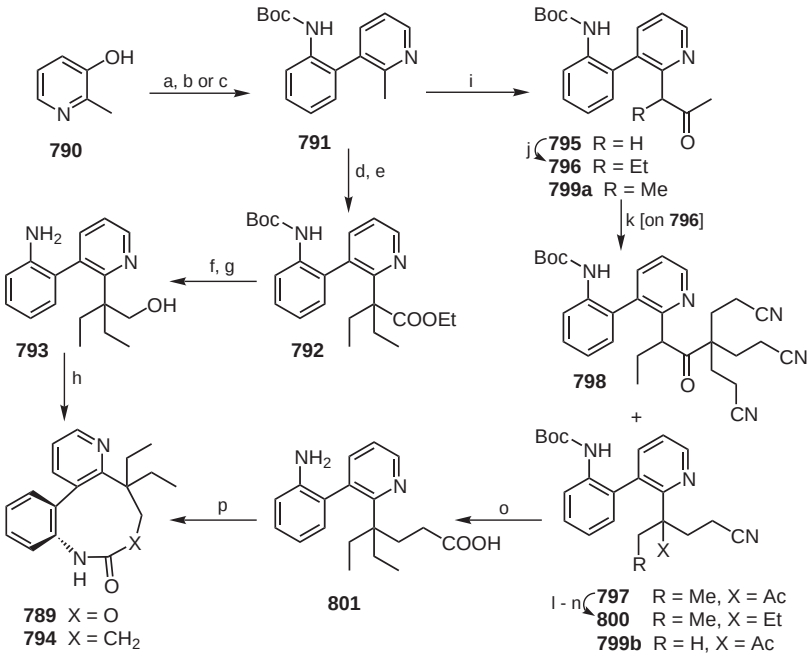
SCHEME 40

Reagents and conditions: a) EtI, LDA, THF, –78 °C → rt 2.20 h (93%). b) DIBAL-H, PhMe/hexanes, –70 °C 30 min → rt 1 h (50%). c) $NaBH_4$, MeOH, rt 40 min (86%). d) Et_3SiCl (excess), py, rt 30 min (**779** 100%). e) **779**, [$PdBnCl(PPh_3)_2$] (4 mole %), PhMe, rt 10 min, then **780** (1.15 eq), 110 °C 10 h (**781** 49%). f) **781**, TFA, CH_2Cl_2, 0 °C 15 min (**782** 95%). g) $(Cl_3CO)_2C{=}O$, py, CH_2Cl_2, –74 °C 30 min (**776** 93%). h) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 0 °C → rt 16 h (**783** 90%). i) **784**, $Pd(OAc)_2$ (5 mole %), PCy_2(*o*-biph) (0.2 eq), pinacolborane (3 eq), Et_3N (4 eq), dioxane, 25 °C → 80 °C 1 h, then H_2O (degased), **783** (0.67 eq), $Ba(OH)_2{\cdot}8H_2O$ (3 eq), 100 °C 1 h (**786** 78% based on **783**). j) **786**, 36% HCl aq/MeOH (1:4), rt → rfl 1 h (**782** 86%). k) **783**, **785** (1.5 eq), $Ba(OH)_2{\cdot}8H_2O$ (2 eq), **787a** (6.7%), [$Pd_2(dba)_3$]$CHCl_3$ (0.27 eq), H_2O (degased)/dioxane (1:5), 80 °C 1 h. l) **786**, 36% HCl aq/MeOH (1:2), 0 °C → 35 °C 1 h ((–)-**782** 56% based on **783**, ee 40%). m) $(Cl_3CO)_2C{=}O$ (1 eq), py (10 eq), CH_2Cl_2, –78 °C 30 min ((–)-**776** 98%, ee 40%). n) Crystallization from CH_2Cl_2/heptane (ee 92%)

Suzuki-patterned synthesis of lactam **788** [121] and related rhazinilam analogue[122] can also be found in the literature.

Synthesis of pyridine analogues of both **776** and **788** was reported by the Gif group[123], which makes use of the picoline methyl group acidity, Scheme 41. Synthesis of nine-membered carbamate **789** commences with an efficient one-pot conversion of 3-hydroxypicoline (**790**) to biaryl **791** (95%) using Suzuki cross-coupling of the derived triflate with 2-pivaloylamino-

phenylboronic acid. Base-induced extension of the methyl group in **791** to acetate (91%) and stepwise ethylation gave rise to acetate **792** (60%). The following reduction with $LiAlH_4$ provided the corresponding alcohol in moderate yield (28 or 78% brsm) which afforded anilino-alcohol **793** (72%) upon treatment with dilute sulfuric acid at 160 °C and, finally, upon exposure to triphosgene, the desired rhazinilam analogue **789** (70%).

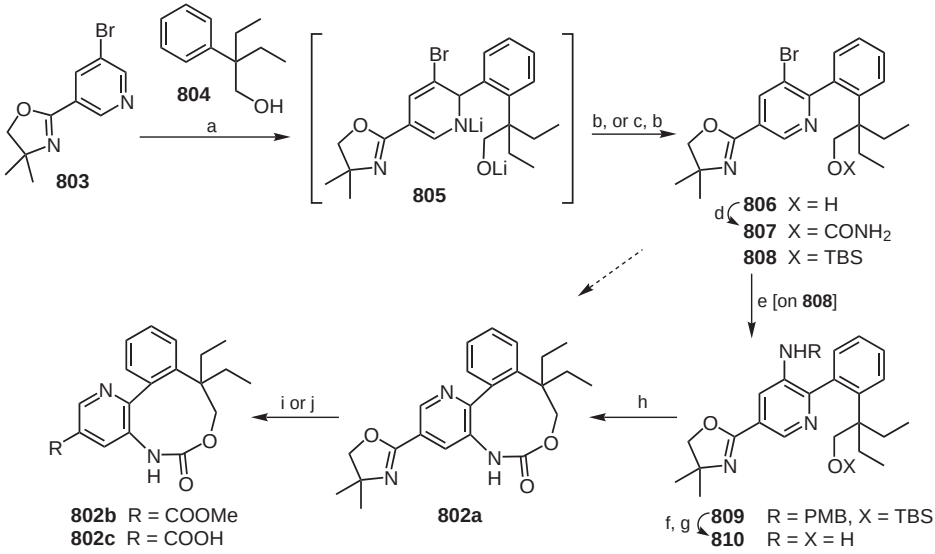


SCHEME 41

Reagents and conditions: a) Tf_2O, py 20 °C 75 min (73%). b) 2-(Pivaloylamino)phenylboronic acid (1.3 eq), $[Pd(PPh_3)_4]$, 2 M K_2CO_3 aq, PhMe, EtOH, rfl 6 h (95%). c) a + b, one pot (95%, 2 steps). d) *n*-BuLi/*t*-BuONa/*i*-Pr_2NH (3.5 eq), THF, –70 °C 1 h, then $(EtO)_2CO$ (3.5 eq), –70 °C 40 min (91%). e) LDA (3.1 eq), THF, –70 °C 10 min, then EtI (3.1 eq), –70 °C → 20 °C 3 h, then repeat whole procedure (60%). f) $LiAlH_4$, THF, 0 °C → 40 °C 4 h (28%, 77.8% brsm). g) 30% H_2SO_4, 160 °C 2 h (72%). h) $(Cl_3CO)_2C{=}O$ (1 eq), DMAP, CH_2Cl_2, –70 °C 15 min → 20 °C 4 h (**789** 70%). i) *n*-BuLi (1.1 eq), THF, –20 °C 1 h → –70 °C, $MeCONMe_2$, –70 °C 30 min (84%). j) *n*-BuLi, THF, –70 °C 10 min → 20 °C (40 min), then EtI, rfl 16 h (76%). k) $CH_2{=}CHCN$, $BnMe_3N^+OH^-$, *t*-BuOH, 25 °C 7 days (**797** 26% + **798** 10%). l) 797, $NaBH_4$, EtOH, 20 °C 16 h (88%). m) H_2SO_4 (1 eq), HMPA, 220–225 °C 1.5 h (42%). n) H_2 (1 atm), Pd/C, MeOH, 20 °C 1 h (93%). o) 30% H_2SO_4 aq, 160 °C 2 h (92%). p) HOBT, EDCI, Et_3N, $CHCl_3$, 50 °C 1.5 days (**794** 95%)

Preparation of **794** began[123] with the conversion of **791** to acetone **795** (84%), which was monoethylated by *n*-BuLi/EtI method (→ **796**, 76%), Scheme 41. The following base-catalyzed Michael addition of acrylonitrile was surprisingly inefficient and afforded a low yield of the desired nitrile **797** (26%) accompanied by a product of γ,γ,γ-tris(cyanoethylation) **798** (10%); note that similar cyanoethylation of **799a** provided **799b** in 82% yield. Subsequent three-step transformation of acetyl in **798** to ethyl group yielded nitrile **800**, which was hydrolyzed and deprotected by hot sulfuric acid (→ **801**, 92%) and then subjected to lactamization by HOBT/EDCI method (→ **794**, 95%). All nine-membered ring compounds were tested for their ability to inhibit the cold-disassembly of microtubules; the carbamate **776** showed highest activity with the order **776** > **789** > **788** ≈ **794**.

Marsais and coworkers have reported[124] on synthesis of rhazinilam isomeric pyridine analogues **802**; build up of the biaryl moiety in this case is based on addition of aryllithium to pyridine followed by oxidation, Scheme 42.



SCHEME 42

Reagents and conditions: a) **803** (2 eq), *s*-BuLi (6 eq), hexane, rfl 6 h → rt, then **804** (1 eq), THF, rt 1 h. b) Chloranil (1.5 eq), PhMe, rfl 2 h (**806** 26%). c) TBSCl, hexane/THF, rt 16 h. d) $Cl_3CCONCO$ (1.3 eq), CH_2Cl_2, 0 °C → rt 30 min (**807** 70%). e) **808**, $PMBNH_2$ (1.2 eq), $[Pd_2(dba)_3]$ (1.5%), BINAP (3.6%), *t*-BuONa (1.4 eq), PhMe, rfl 16 h (83%). f) TFA, 25 °C 16 h (80%). g) K_2CO_3, MeOH aq, 25 °C 1 h (97%). h) $COCl_2$ (1.02 eq), Et_3N, THF, 0 °C → 25 °C 1 h (84%). i) concd H_2SO_4/EtOH (1:9), rfl 5 h (**802b** 20%). **j**) 0.9 M H_2SO_4, rfl 5 h (**802c** 15%)

Thus, phenethyl alcohol **803** was ortho-lithiated upon exposure to excessive *s*-BuLi and then added regioselectively to pyridine **804**. The resulting dihydropyridine **805** was treated with chloranil to give biaryl alcohol **806** in overall 26% yield. As the derived carbamate **807** failed to give any cyclized **802a** under various condition, silylether bromide **808** was prepared either from **803** (21%) or from **806** (67%) and subjected to Buchwald–Hartwig amination with *p*-methoxybenzylamine ($[Pd_2(dba)_3]$, BINAP, *t*-BuONa). The resulting **809** (83%) provided upon deprotection with TFA (80%) and a treatment with potassium carbonate (97%) the anilino-alcohol **810**, which efficiently cyclized to nine-membered carbamate **802a** (84%) with phosgene. None of **802a** and the derived **802b**, **802c** showed any antitubulin activity.

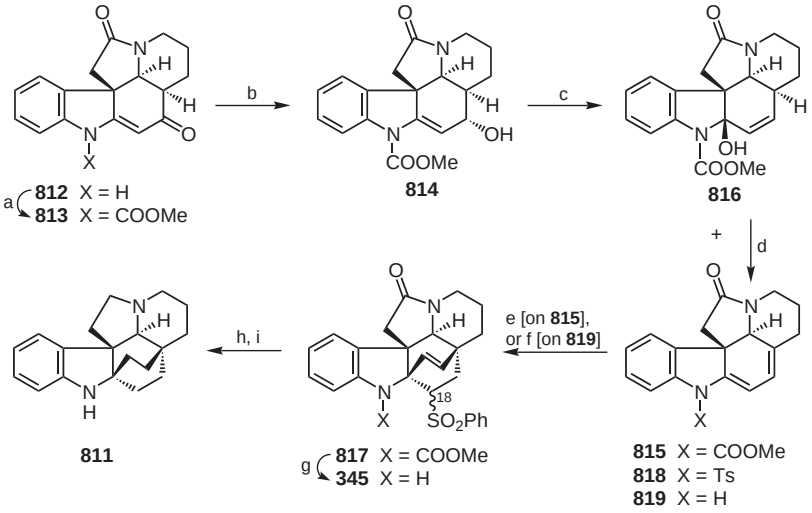
9. ASPIDOSPERMANE ALKALOIDS WITH ADDITIONAL BONDS

9.1. Aspidofractinine Group

9.1.1. Simple Alkaloids

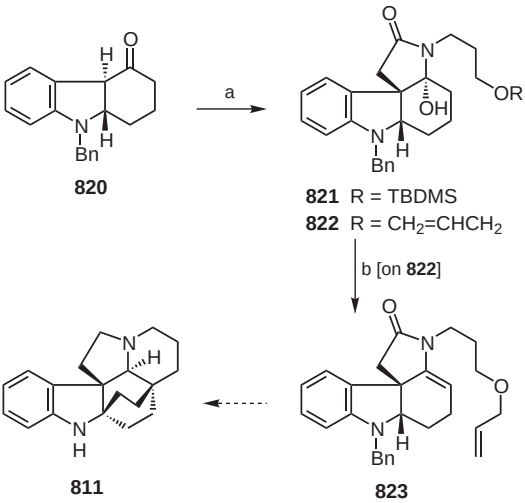
Wenkert and Liu have extended their rapid approach to aspidospermane skeleton[125] to synthesis of racemic aspidofractinine (**811**)[126], which is the simplest member of the group, Scheme 43. Luche reduction of the unsaturated ketone carbamate **803** provided stereoselectively allylic alcohol **814** (75%), whose exposure to boron trifluoride etherate afforded diene carbamate **815** (88%) accompanied by a small amount of an isomeric alcohol **816**. In the crucial step, 1,3-diene **805** was heated with phenylvinyl sulfone and afforded hexacyclic sulfone **807** in a reasonable yield (75%) and as a single stereoisomer of undetermined C-18 configuration. It is worthy to note that the corresponding sulfonamide **808** was completely unreactive under similar condition, whereas diene **809** (existing mostly as the indolenine tautomer) yielded hexacycle **345** (87%!), accessible also from **807**. Reduction of sulfone **345** (Ra-Ni, then $LiAlH_4$) finally provided (±)-aspidofractinine (**801**); note that (–)-enantiomer is a natural alkaloid from *Aspidosperma refractum*[127]. For conversion of **345** to aspidospermidine see ref.[1], Chap. 3.2.4.1.

An efficient construction of tetracyclic enamide **823** was reported by French group[128], which constitutes a formal total synthesis of (±)-aspidofractinine (**811**)[129], Scheme 44. Thus, an alkylation of *trans*-ketone **820** with *N*-substituted iodoacetamides (KH) produced stereoselectively *cis*-lactams



SCHEME 43

Reagents and conditions: a) *n*-BuLi, THF, –78 °C 40 min, then ClCOOMe, –78 °C 15 min → rt (96%). b) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, rt 24 h (75%). c) $BF_3 \cdot OEt_2$ (neat), rt 5 min → 45 °C 15 min → 60 °C 10 min (**815** 88% + **816** 3%) d) PhH, rfl 4 h (quant). e) $PhSO_2CH{=}CH_2$, PhH (sealed tube), 125 °C 96 h (**817** 75%). f) $PhSO_2CH{=}CH_2$, PhH (sealed tube), 90 °C 24 h (**345** 87%). g) EtSLi, HMPA, THF, 0 °C 1 h → rt 60 h (93%). h) Ra-Ni (W-2), *i*-PrOH, rfl 2 h (88%). i) $LiAlH_4$, THF, rfl 1 h (76%)



SCHEME 44

Reagents and conditions: a) KH, THF, rt 5 min, then $ICH_2CONHCH_2CH_2CH_2OR$, rt 10 min (**821** 80%; **822** 95%). b) **822**, (±)-CSA, 4 Å MS, CH_2Cl_2, rfl 12 h (nearly quant)

821 (80%) and **822** (95%), respectively. Subsequent CSA-catalyzed dehydration transformed the last mentioned compound into enamide **823** almost quantitatively.

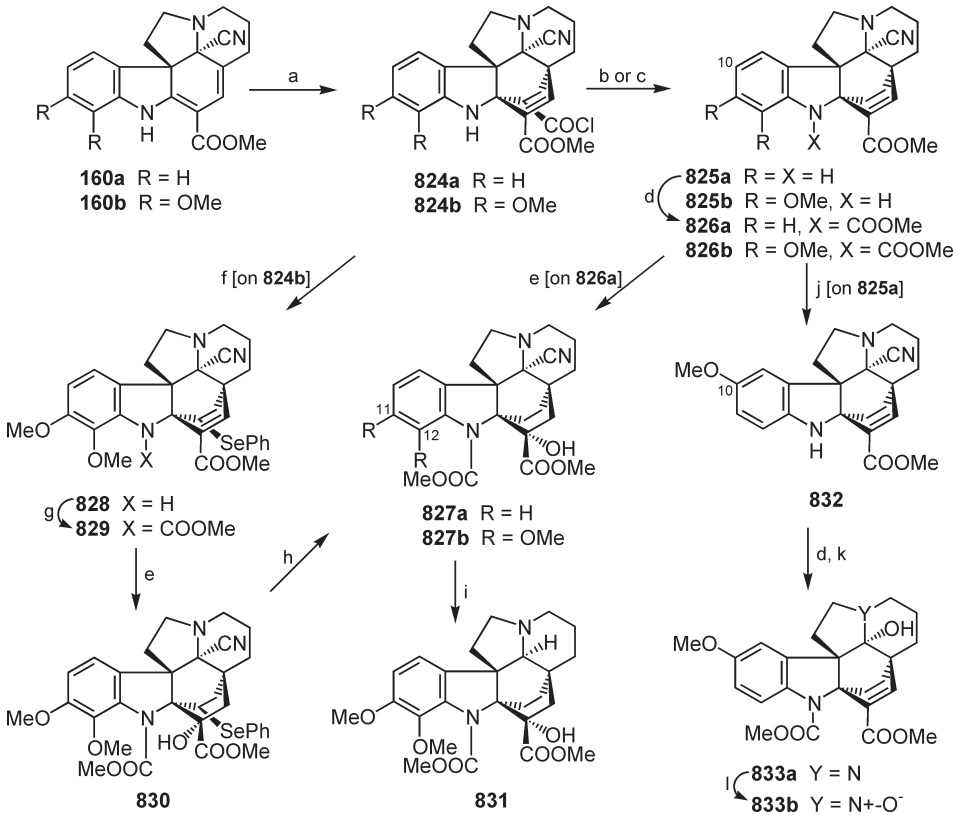
9.1.2. Complex Alkaloids

A new strategy for synthesis of hexacyclic alkaloids was reported by Magnus and collaborators[130–132] using pentacyclic dienes **160** as advanced intermediates (see ref.[1], Chap. 3.1.4.), Scheme 45. A [4+2] cycloaddition of **160a** with acryloyl chloride provided regio- and stereoselectively acid chloride **824a** which was converted into hexacyclic acrylate **825a** by a two-step procedure, consisting of ester formation with 1-hydroxy-2-thiopyridone (69% over 2 steps), followed by photochemical reductive decarboxylation (39% from **160a**). The following reaction of aniline **825a** with triphosgene/pyridine, followed by a treatment with methanol, as described by Danishefsky, provided carbamate **826a** (90%). Finally, an application of the Isayama procedure, consisting of treatment with catalytic tris(dipivaloylmethanato)-manganese(III)/phenylsilane/O_2 in *i*-PrOH, to acrylate **826a** afforded 11,12-didemethoxylahadinine B (**827a**) in 86% yield[131].

A slightly different strategy had to be adopted in preparation of lahadinine B ((±)-**827b**) due to the failure of analogously prepared indoline **825b** to undergo *N*-carbamoylation, Scheme 45. Thus, the acid chloride **824b** was converted into phenyl selenide **828** (45% from **160b**), which eventually provided the carbamate **829** (86%) by exposure to KHMDS/18-crown-6/CO_2 and then to Me_2SO_4, a method that failed when applied to **825b**. Reduction/hydroxylation as above transformed acrylate **829** into lactate **830** in high yield (83%). Removal of the selenium by a tin hydride reduction completed the synthesis of lahadinine B ((±)-**827b**), whose (–)-enantiomer was isolated from *Kopsia pauciflora*[133]. Finally, a reduction of the aminonitrile moiety by triethylsilane in acidic medium converted **827b** into (±)-11-methoxykopsilongine (**831**)[130,132]; (–)-**831**, known also as *N*-methoxycarbonyl-11,12-dimethoxykopsinaline, was isolated from *Kopsia griffithii*[134].

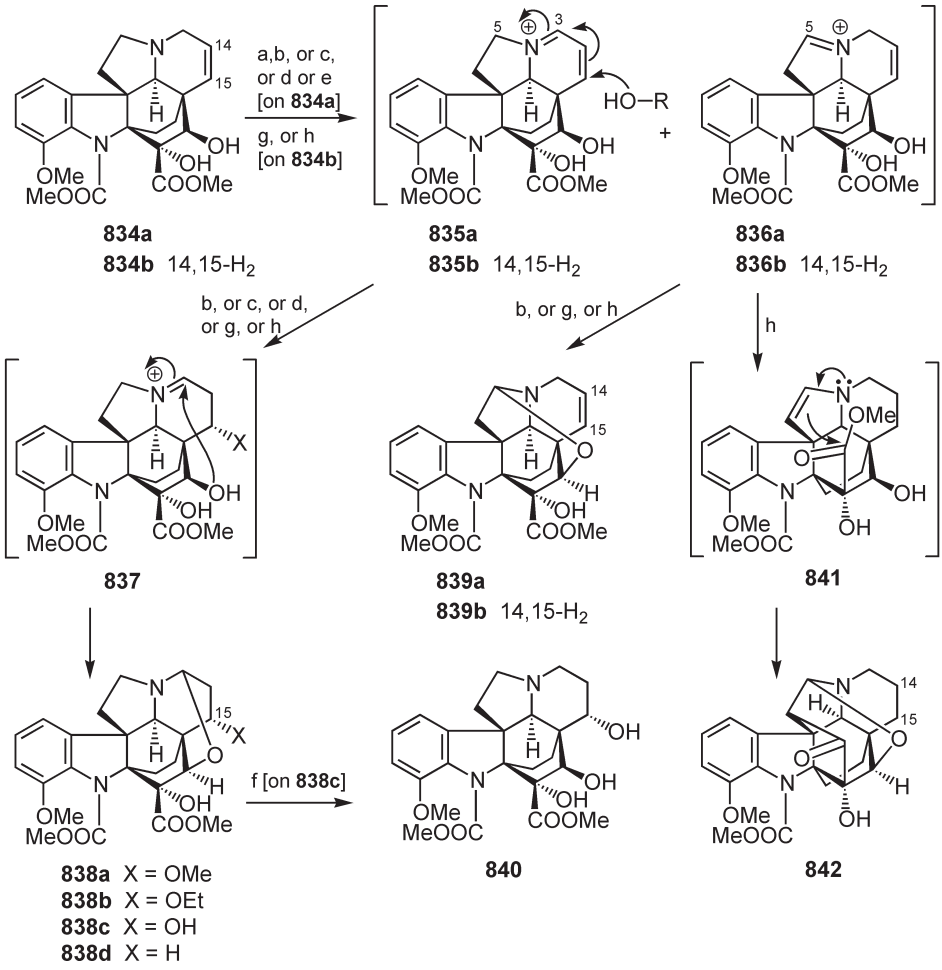
On the other hand, an installation of the methoxy group at C-10 of **825a** using oxidation by $PhI(OAc)_2$ in methanol followed by an immediate reduction of the quinoid intermediate with zinc was an initial step (86%) in the conversion of **825a** into kopsidasine (**833a**)[131], Scheme 45. The resulting aminonitrile **832** was *N*-carbamoylated using again the triphosgene procedure; an exposure to silver tetrafluoroborate followed by a treatment with

aqueous $NaHCO_3$ caused a conversion to hemiaminal and completed thus the synthesis of (±)-kopsidasine (**833a**). The latter was converted to kopsidasine *N*-oxide ((±)-**833b**) by treatment with *m*-CPBA [131]; both (–)-**833a** and (–)-**833b** are available from *Kopsia dachyrachis*[135].



SCHEME 45

Reagents and conditions: a) **160a**, CH_2=CHCOCl, PhMe, 75 °C 5 days; **160b**, CH_2=CHCOCl (neat), rt 1 day. b) **824a**, 1-hydroxy-2-thiopyridone, Et_3N, CH_2Cl_2, rt 2 h (69%, 2 steps), then *hν*, *t*-BuSH, 10 °C 1.5 h (**825a** 39%, 3 steps). c) **824b**, 1-hydroxy-2-thiopyridone sodium salt, CH_2Cl_2, 0 °C 5 min → rt 2 h, then *hν*, *t*-BuSH, 20 °C 1.75 h (**825b** 37%, 3 steps). d) $(COCl_2)_3$, py, CH_2Cl_2, 0 °C 10 min → 23 °C 45 min, then MeOH, 0 °C → 23 °C 1 h (**825a** → **826a** 90%, **832** → 54%). e) [Mn(dpm)$_3$], $PhSiH_3$, O_2, *i*-PrOH, $ClCH_2CH_2Cl$, 0 °C 10 min → 23 °C 6 h or 7 days (**826a** → **827a** 86%; **829** → **830** 83%). f) 1-Hydroxy-2-thiopyridone sodium salt, CH_2Cl_2, 0 °C 5 min → rt 1.75 h, then *hν*, $(PhSe)_2$, 20 °C 30 min (41%, 3 steps). g) KHMDS, 18-crown-6, THF, –78 °C 10 min, then CO_2 (g), –78 °C 10 min, then Me_2SO_4, –78 °C 15 min → rt 30 min (86%). h) Ph_3SnH, PhMe, rfl 24 h (83%). i) TFA, CH_2Cl_2, 0 °C 5 min, then Et_3SiH, 0 °C 15 min → rt 4 days (93%). j) $PhI(OAc)_2$, MeOH, 0 °C 45 min, then Zn, rt 30 min. k) $AgBF_4$, THF, rt 1 h, then $NaHCO_3$ aq, rt 10 min (78%). l) *m*-CPBA, CH_2Cl_2, rt 4 h (47%)



SCHEME 46

Reagents and conditions: a) **834a**, *m*-CPBA, CH_2Cl_2. b) TFAA, CH_2Cl_2, 0 °C → rt 3 h, evapd, then ROH, rt overnight (**838a** 17% + **839a** 27%; **838b** 18% + **839a** 40%). c) **834a**, anodic oxidation (Pt gauze), $Et_4N^+ClO_4^-$, 2,6-lutidine, CH_2Cl_2, MeCN, evapd, then ROH, rt 25 h (**838a** 72%; **838b** 70%). **d**) **834a**, anodic oxidation (Pt gauze), $Et_4N^+ClO_4^-$, 2,6-lutidine, CH_2Cl_2, MeCN, evapd, then MeCN aq, rt 4 days (**838c** 15–20%). e) **834a**, anodic oxidation (carbon anode), 0.1 M $LiClO_4$, 2,6-lutidine, CH_2Cl_2, ROH (**838a** 36%; **838b** 55%). f) $NaBH_4$, MeOH, rt 30 min (90%). g) **834b**, anodic oxidation (Pt gauze), $Et_4N^+ClO_4^-$, 2,6-lutidine, CH_2Cl_2, MeCN, evapd, then ROH, rt (**838d** 20% + **839b** 55%). h) **834b**, anodic oxidation (carbon anode), 0.1 M $LiClO_4$, 2,6-lutidine, CH_2Cl_2, MeOH (**838d** 27% + **839b** 22% + **842** 25%)

Transformation of (+)-kopsingine (**834a**) into kopsidines was reported by two groups, Scheme 46. Husson and collaborators[136] have used the Polonovski–Potier reaction to generate, albeit nonregioselectively, the conjugated iminium **835a**, which underwent an addition of *O*-nucleophile (ROH) to give an enamine. Internal addition of an alcohol in related iminium **837** then gave (+)-kopsidine A (**838a**) and (+)-kopsidine B (**838b**) as the minor products (17 and 18%, respectively); an aminal **839a** resulting from the direct intramolecular closure in an isomeric 5-iminium **836a** was the major product in both cases (27 and 40%, respectively). (+)-Kopsidine A (**838a**) and (+)-kopsidine B (**838b**) are available from *Kopsia teoi*[137,138].

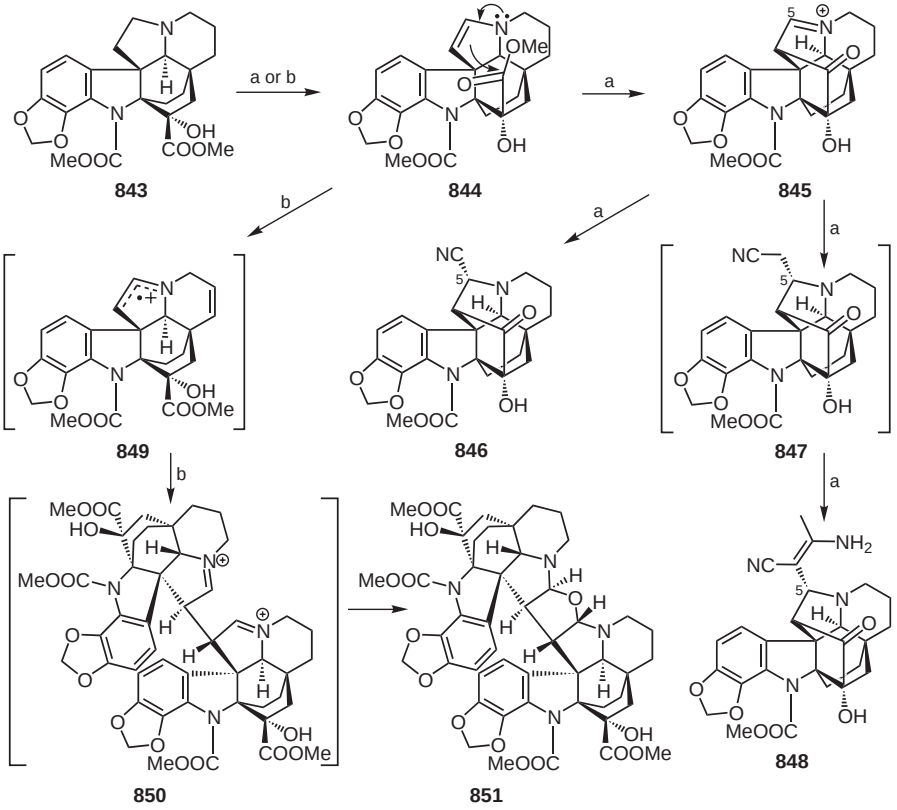
In a more efficient procedure, Kam et al.[139,140] have generated the iminium **835a** regioselectively by an electrochemical oxidation of **834a** in the presence of lutidine as a proton scavenger, Scheme 46. The following addition of methanol or ethanol resulted in formation of (+)-kopsidine A (**838a**) and (+)-kopsidine B (**838b**) in high yields (72 and 70%, respectively). Exposure of the iminium **835a** to an aqueous acetonitrile afforded (+)-**838c**, albeit in rather low yield (15–20%); (+)-kopsidine C (**838c**) is accompanied in *K. teoi* by (–)-kopsidine D (15-*epi*-**838c**)[138]. When the electrooxidation was run under modified condition (0.1 M $LiClO_4$), and in the presence of alcohol ROH, it produced directly the alkaloids **838a** (36%) and **838b** (55%), respectively. Base **838c** afforded by borohydride reduction another alkaloid, (+)-kopsinganol (**840**), in 90% yield; (+)-**840** was isolated from *Kopsia teoi*[141].

In absence of a directional effect of the 14,15-double bond, an electrochemical oxidation of **834b** produced both iminium intermediates **835b** and **836b**, which afforded[139,140,142] through an internal *O*-addition heptacyclic aminals **838d** (20%) as well as **839b** (55%), Scheme 46. However, an application of the modified electrooxidation procedure to **834b** resulted in a mixture of three products: in addition to **838d** (27%) and **839b** (22%), a kopsane-type octacyclic ketone **842** was formed (25%), see also Chap. 9.2. It originates presumably by an intramolecular enamine acylation in ester enamine **841** and subsequent closure of the remaining ring by an intramolecular *O*-addition to the resulting 5-iminium; note that **842** is a 14,15-dihydro analogue of the alkaloid (+)-kopsinitarine A, itself isolated from *Kopsia teoi*[143,144].

9.2. Kopsane Group

An electrooxidation of kopsamine (**843**), a methylenedioxy analogue of the alkaloid **831**, has also been reported by Kam and coworkers[140,145], Scheme 47. Thus, electrochemical oxidation of **843** on platinum anode in acetonitrile

(0.1 M $Et_4N^+ClO_4^-$) afforded kopsane-type cyanoamine **846** (23%) and acrylonitrile **848** (22%). They are likely to originate via internal acylation in enamine **844** generating 5-iminium **845** which is trapped by cyanide (→ **846**) and/or acetonitrile anion (→ **847**); an α-anion of **847** then provides **848** by reaction with another acetonitrile molecule. However, an electrooxidation of **843** in absence of acetonitrile (0.1 M $LiClO_4$ in MeOH)

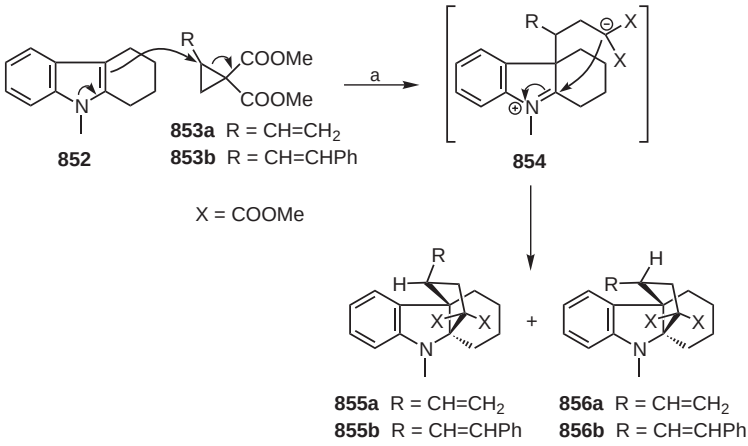


SCHEME 47

Reagents and conditions: a) Anodic oxidation (Pt gauze; 1.05 V), 2,6-lutidine (2 eq), 0.1 M $Et_4N^+ClO_4^-$/MeCN (**846** 23%; **848** 22%). b) anodic oxidation (carbon anode, 0.95 V), 2,6-lutidine (2 eq), 0.1 M $LiClO_4$/MeOH (**851** 30%)

took a different course yielding C_2-symmetric dimeric product **851** (30%); the latter is presumably derived from enamine **844** by further oxidation to cation-radical **849** which dimerises to bis-iminium **850** and, finally, affords **851** upon quenching.

Kerr and collaborators have reported on a synthesis of model tetracycles to heptacyclic kopsane alkaloids[146], Scheme 48. Substituted cyclopropane dicarboxylates **853** were shown to be opened regioselectively in the presence of Lewis acids by tetrahydrocarbazole **852** and afforded via indoleninium **854** tetracyclic products **855** and **856**. In most cases studied the reaction conducted with catalytic $Yb(OTf)_3$ at 13 kbar for 7 days provided equimolar mixture of stereoisomers (e.g. with **853a**). However, most significant cyclopropane **853b** provided 49% yield of a product with the desired epimer **855b** luckily strongly predominating (3:1); for preliminary study see refs[147,148].



SCHEME 48

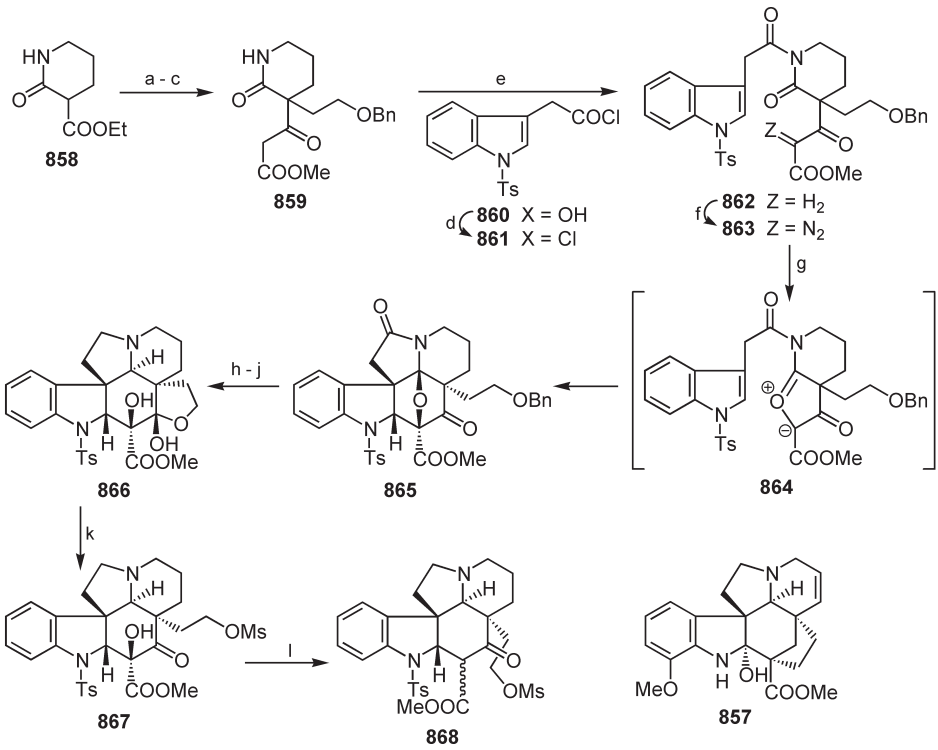
Reagents and conditions: a) **853** (1.1 eq), $Yb(OTf)_3$ (5 mole %), MeCN, 13 kbar, rt 7 days (**853a** → **855a**:**856a** 1:1, 21%; **853b** → **855b**:**856b** 3:1, 49%)

9.3. Tuboxenine/Vindolinine Group

No new total synthesis of tuboxenine/vindolinine alkaloids has appeared except for a model study based on radical cyclizations[149,150], which was already discussed in Part I [1], Scheme 52.

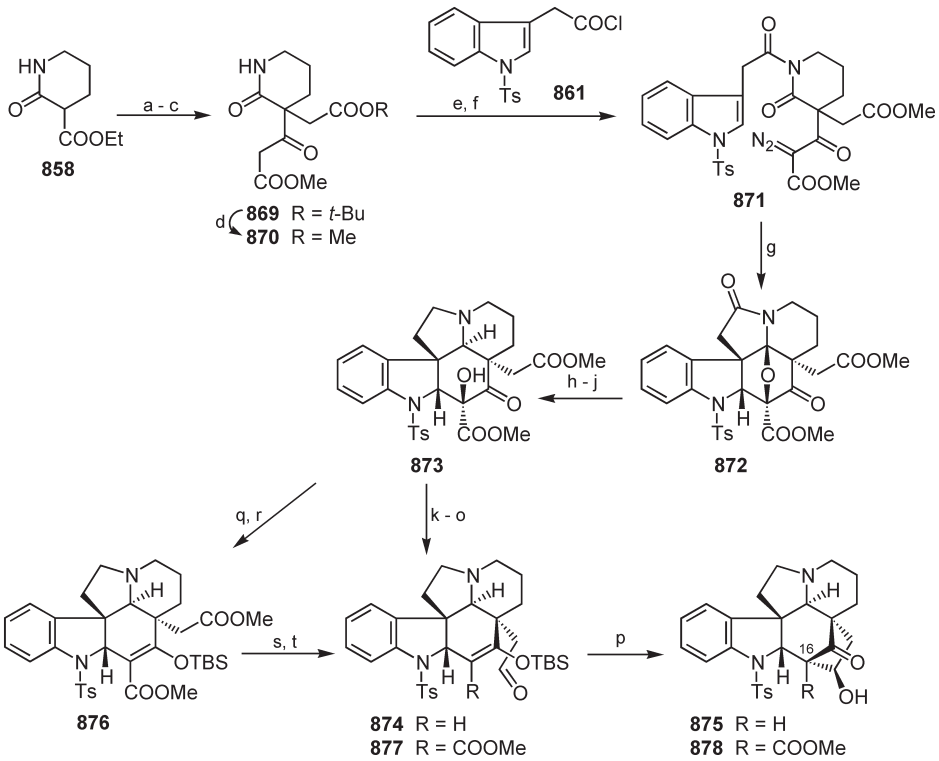
9.4. Kopsifoline Group

Soon after the isolation of kopsifolines A–F (e.g. the major alkaloid kopsifoline A (**857**)) , featuring a new variant of modified aspidospermane skeleton from a Malayan *Kopsia* species[151,152], Padwa and collaborators have reported[153] on their synthetic endeavours in the field that feature dipolar addition of the in situ generated dipoles[154,155] and silyl enol ethers as nucleophiles in the closure of the F-ring as the key steps.



SCHEME 49

Reagents and conditions: a) *n*-BuLi (1 moleq), $BnOCH_2CH_2I$ (1 eq), THF, –78 °C → rfl 3 days (70%). b) KOH (2 moleq), THF/H_2O (1:1), rt overnight (91%). c) CDI (1.18 eq), CH_2Cl_2, rt overnight, evap, THF, add to ($MeOOCCH_2COOK$ (2 eq), $MgCl_2$ (2 eq), DMAP (0.1 eq), THF/MeCN (2:1), rt 2 h), Et_3N (2 eq), rt overnight (82%). d) $(COCl)_2$ (3.3 eq), CH_2Cl_2, rt 5 h. e) **861** (1.2 eq), 4 Å MS, CH_2Cl_2, rt 12 h (84%). f) Et_3N (1.2 eq), MeCN, rt 30 min, then MsN_3 (1.05 eq), rt 5 h (88%). g) $Rh_2(OAc)_4$ (cat), PhH, rfl 1 h (90%). h) P_2S_5 (0.41 moleq), $(TMS)_2O$ (0.69 moleq), PhH, rfl 3 h (90%). **i**) Ra-Ni (excess), H_2 (1 atm), THF, rt 14 h (95%). j) H_2 (1 atm), PtO_2 (cat), concd HCl aq (1 drop), MeOH/THF (5:1), rt 12 h (51%). k) MsCl (5 eq), Et_3N (excess), CH_2Cl_2, 0 °C 1.5 h (85%). **l**) SmI_2, HMPA (60%)



SCHEME 50

Reagents and conditions: a) *n*-BuLi (1.1 moleq), *t*-BuOOCCH$_2$Br (1:1 eq), Bu$_4$N$^+$I$^-$ (0.21 eq), THF, –78 °C → rt 15 days (90%). b) LiOH (3 moleq), THF/H$_2$O (1:1), rt 12 h (91%). c) CDI (1.2 eq), CH$_2$Cl$_2$, rt 12 h, evap, THF, add to (MeOOCCH$_2$COOK (2 eq), MgCl$_2$ (2 eq), DMAP (0.1 eq), THF/MeCN (2:1), rt 2 h), Et$_3$N (2 eq), rt 12 (60%). d) HC(OMe)$_3$ (excess), TsOH·H$_2$O (1 eq), MeOH, 100 °C 4 h (99%). e) **861** (1.05 eq), 4 Å MS, CH$_2$Cl$_2$, rt 12 h (91%). f) Et$_3$N (1.07 eq), MeCN, 0 °C 20 min, then MsN$_3$ (2 eq), rt 1.5 h (89%). g) Rh$_2$(OAc)$_4$ (cat), PhH, rfl 1 h (98%). h) P$_2$S$_5$ (0.39 moleq), (TMS)$_2$O (1.64 eq), PhH, rfl 6 h (90%). i) Ra-Ni (excess), H$_2$ (1 atm), THF, rt 14 h (87%). j) H$_2$ (1 atm), PtO$_2$ (cat), concd HCl aq (1 drop), MeOH/THF (5:1), rt 12 h (95%). k) Cs$_2$CO$_3$ (5.45 moleq), MeCN, rfl 1 h (75%). l) SmI$_2$, HMPA, THF, 0 °C (72%). m) TBDMSOTf (2.5 eq), Et$_3$N, CH$_2$Cl$_2$, rt 1 h. n) LiAlH$_4$, THF, 0 °C 4 h. o) TPAP (0.35 eq), NMO (1.75 eq), 4 Å MS, MeCN, 0 °C → rt 4 h (68% 3 steps). p) CsF (excess), MeCN, 100 °C 1 h (**874** → **875** 78%; **877** → **878** 34% 2 steps). q) SmI$_2$, HMPA, THF, 0 °C (93%). r) TBDMSOTf (3.6 eq), Et$_3$N, CH$_2$Cl$_2$, rt overnight (96%). s) LiAlH$_4$, THF, –78 °C → 0 °C 5 h (91%). t) TPAP (0.3 eq), NMO (1.49 eq), 4 Å MS, MeCN, 0 °C → rt 12 h (→ **877**)

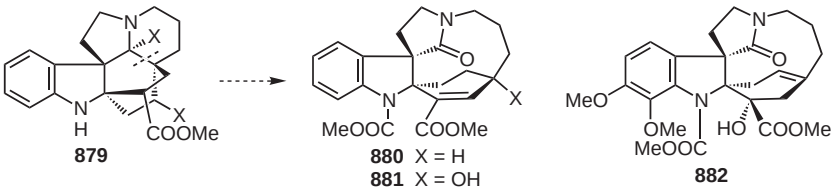
In the first approach, Scheme 49, it was expected that the final ring could be closed by an internal alkylation. Thus, the lithium salt of the commercially available piperidone **858** was alkylated with benzyloxyethyl iodide (70%) and hydrolyzed to carboxylic acid (91%), which was activated with 1,1′-carbonyldiimidazol (CDI) and converted to β-keto ester **859** (82%) by reaction with magnesium methyl malonate. *N*-Acylation of **859** with acid chloride **861** (4 Å MS) provided β-keto ester **862** (84%) affording diazo compound **863** (88%) on diazo-transfer with MsN_3 (Et_3N). A treatment of **863** with catalytic $Rh_2(OAc)_4$ generated the dipole **864**, which cycloadded over the indole double bond in *endo*-fashion and gave rise to hexacyclic lactam **865** in a high yield (90%). Removal of lactam carbonyl via thiolactam/Ra-Ni treatment and subsequent hydrogenation/hydrogenolysis provided hemiacetal **866** in 44% yield over 3 steps. Exposure to mesyl chloride (Et_3N) afforded mesylate **867** (85%), the lactic moiety of which was reduced by titration with samarium(II) iodide (60%). Unfortunately, all attempts at cyclization of the resulting mesylate β-keto ester **868** have failed.

Synthesis of advanced model compounds **875** and **878** in the second approach rests upon the aldol reaction, Scheme 50. β-Keto ester **869** [156], accessible by the above discussed protocol (49% over 3 steps), was transesterified (99%) and then converted to diazo compound **871** (81%). $Rh_2(OAc)_4$ induced dipolar *endo*-cycloaddition was even more efficient in this case and afforded hexacyclic lactam **872** in almost quantitative yield (98%). Three-step conversion of lactam **872** to diester **873** (74%) preceded transformation of the latter to aldehyde **874**, which consisted of cesium carbonate removal of lactate methoxycarbonyl group (75%), SmI_2 reduction of resulting carbonate (72%), ketone carbonyl silylation (TBDMSOTf, Et_3N), reduction ($LiAlH_4$) and final oxidation with tetrapropyl perruthenate (TPAP)/NMO (68% over 3 steps). Cesium fluoride induced aldol cyclization in **874** proceeded smoothly and yielded the desired hexacycle **875** in 78%. Alternatively, and more closely to alkaloids (all of them bear methoxycarbonyl group at C-16), SmI_2 reduction of **873** (93%) and silylation (TBDMSOTf, 96%) gave rise to silyl enol ether **876**, the oxidation state of C-18 carbon in which was adjusted to aldehyde **877** (2-step method as above) prior to final CsF-induced cyclization, leading to hexacyclic aldol **878** in 31% yield over the last 3 steps.

10. ALKALOIDS WITH A COMBINATION OF ADDITIONAL AND BROKEN BONDS

10.1. Kopsijasminilam Alkaloids

Two research groups have independently reported on syntheses of kopsijasminilam type of indole alkaloids, which are based on conceptually different approach to presumably biomimetic fragmentation[157–159] in hexacyclic bases **879** (see the dashed line) leading to the target alkaloids of kopsijasminilam (→ **880**, **881**) and pauciflorine type (→ **882**), Scheme 51.

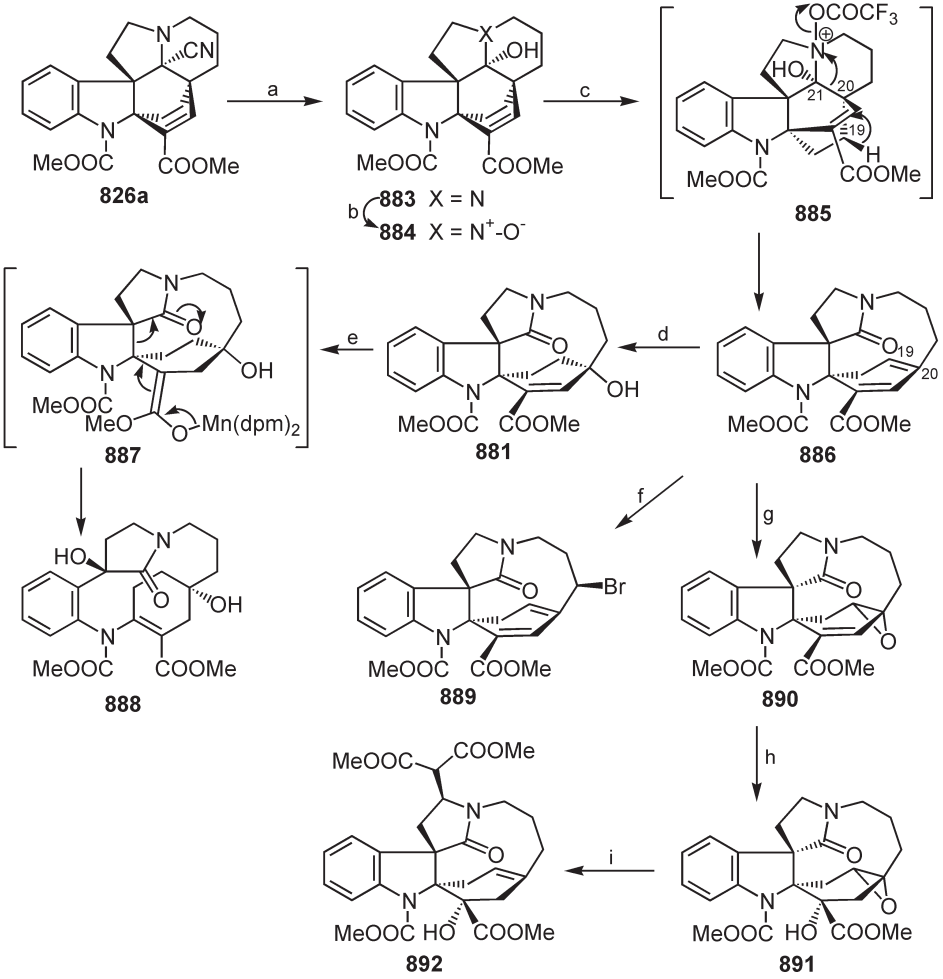


SCHEME 51
Presumably biogenetic-like approach to kopsijasminilam alkaloids

10.1.1. Magnus' Approach

Synthetic endeavours by Magnus and collaborators commenced with conversion of the aminonitrile **826a** to carbinolamine **883** [132,160], Scheme 52. A treatment of the derived *N*-oxide **884** with TFAA installed, via Grob-like fragmentation in **885**, the desired pentacyclic skeleton of the target alkaloids (→ **886**, 90%). In an attempt to install the lactic ester moiety, the diene ester **886** was treated with phenylsilane (2.5 eq) and catalytic tris(dipivaloylmethanato)manganese(III) [$Mn(dpm)_3$] in an oxygen atmosphere to arrive at hydroxyacrylate (±)-**881** instead (48%); note that (–)-**881** is a natural base kopsijasminilam, which is available from *Kopsia jasminiflora*[161].

Further exposure of kopsijasminilam (**881**) to the same reagents caused[132,160], a fragmentation of the indoline moiety rather than α-hydroxylation in manganese enolate **887** affording tetracycle **888** (26%), Scheme 52. An attempted protection of 19,20-double bond in **886** by bromination ($py{\cdot}HBr_3$) provided allylic bromide **889** (41%), however, an epoxidation with *m*-CPBA afforded a 92% yield of the epoxide **890** which, upon reduction/hydroxylation as above, yielded the desired lactate epoxide **891** (45%). Unfortunately, an application of the Ganem procedure (N_2=C(COOMe)$_2$,

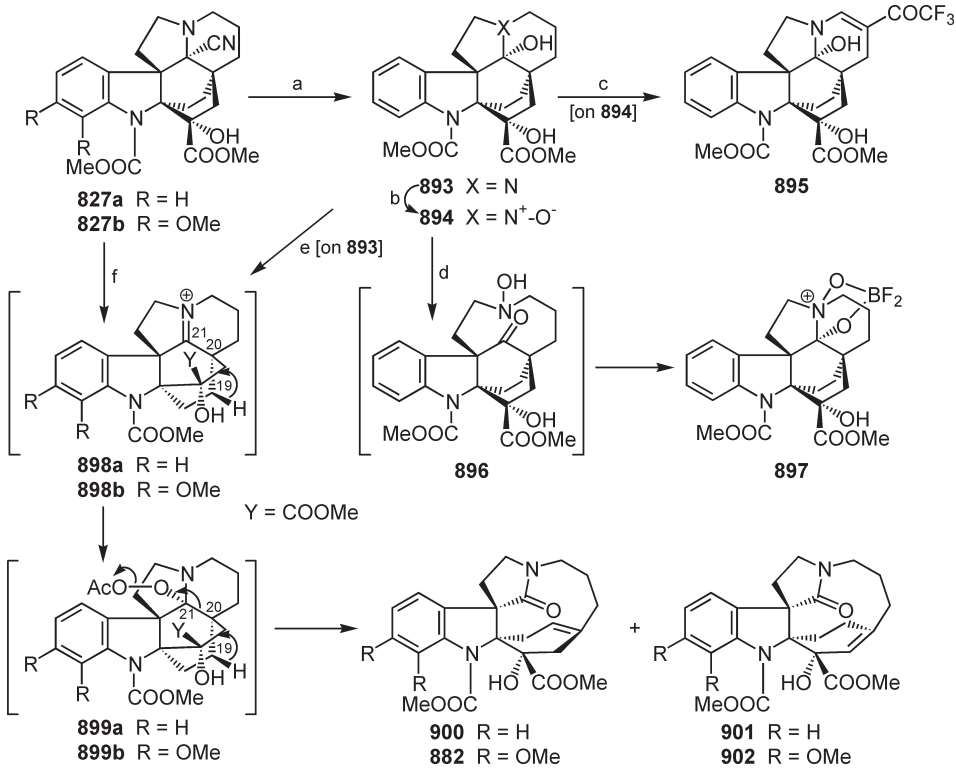


SCHEME 52

Reagents and conditions: a) $AgBF_4$ (5 eq), THF, rt 1 h, then $NaHCO_3$ sat aq, rt 10 min (**883** 97%). b) *m*-CPBA, CH_2Cl_2, rt 1.5 h (89%). c) **884**, TFAA, CH_2Cl_2, –30 °C → 0 °C (30 min) → rt 1 h (90%). d) O_2, [Mn(dpm)$_3$] (cat), $PhSiH_3$ (2.5 eq), *i*-PrOH/$(CH_2Cl)_2$ (3:2), –30 °C 1 h → 0 °C 1 h, then $PhSiH_3$ (2.5 eq), [Mn(dpm)$_3$] (cat), 0 °C → rt 1 h (48%). e) O_2, [Mn(dpm)$_3$] (cat), $PhSiH_3$ (5 eq), *i*-PrOH/$(CH_2Cl)_2$ (3:2), 0 °C → rt 18 h (26%). f) py·HBr_3 (1 eq), $CHCl_3$, –60 °C 1 h → rt 3 h (41%). g) *m*-CPBA (1.5 eq), CH_2Cl_2, 0 °C 1 h (92%). h) O_2, [Mn(dpm)$_3$] (cat), $PhSiH_3$ (2.5 eq), *i*-PrOH/$(CH_2Cl)_2$ (3:1), 0 °C 10 min → rt 18 h (48%). i) N_2=C(COOMe)$_2$, $Rh_2(OAc)_4$, PhH, rfl (46%)

$Rh_2(OAc)_4$) to epoxide **891** caused not only deoxygenation but also carbene insertion and provided malonate **892** (46%).

Slightly different strategy uses intermediates of the type **827** with 16α-hydroxyl already installed[132,160], Scheme 53. A treatment with silver tetrafluoroborate of the aminonitrile **827a** followed by $NaHCO_3$ quench afforded carbinolamine **893** (81%), which was converted with *m*-CPBA into the *N*-oxide **894** (51%). Exposure to TFAA did not induce fragmentation in **894** and yielded trifluoroacetylated enamine **895** instead (75%), while reac-



SCHEME 53

Reagents and conditions: a) $AgBF_4$ (5 eq), THF, rt 1 h, then $NaHCO_3$ sat aq, rt 10 min (**893** 81%). b) *m*-CPBA, CH_2Cl_2, 0 °C 20 min (51%). c) TFAA (1.2 eq), py (+ eq), CH_2Cl_2, –10 °C 1 h (75%). d) $BF_3{\cdot}OEt_2$ (1.5 eq), CH_2Cl_2, 0 °C 20 min (87%). e) crude **893**, column chromatography using AcOEt containing traces AcOOH (**891** + **893** + **894** + **900**). f) $AgBF_4$ (5 eq), THF, rt 15 min, then add AcOOH (5 eq), AcOEt, rt 30 min (**827a** → **900**:**901** 4:1 (65%) + small amount **893** and **891**; **827b** → 66%, **882**:**902** 4:1)

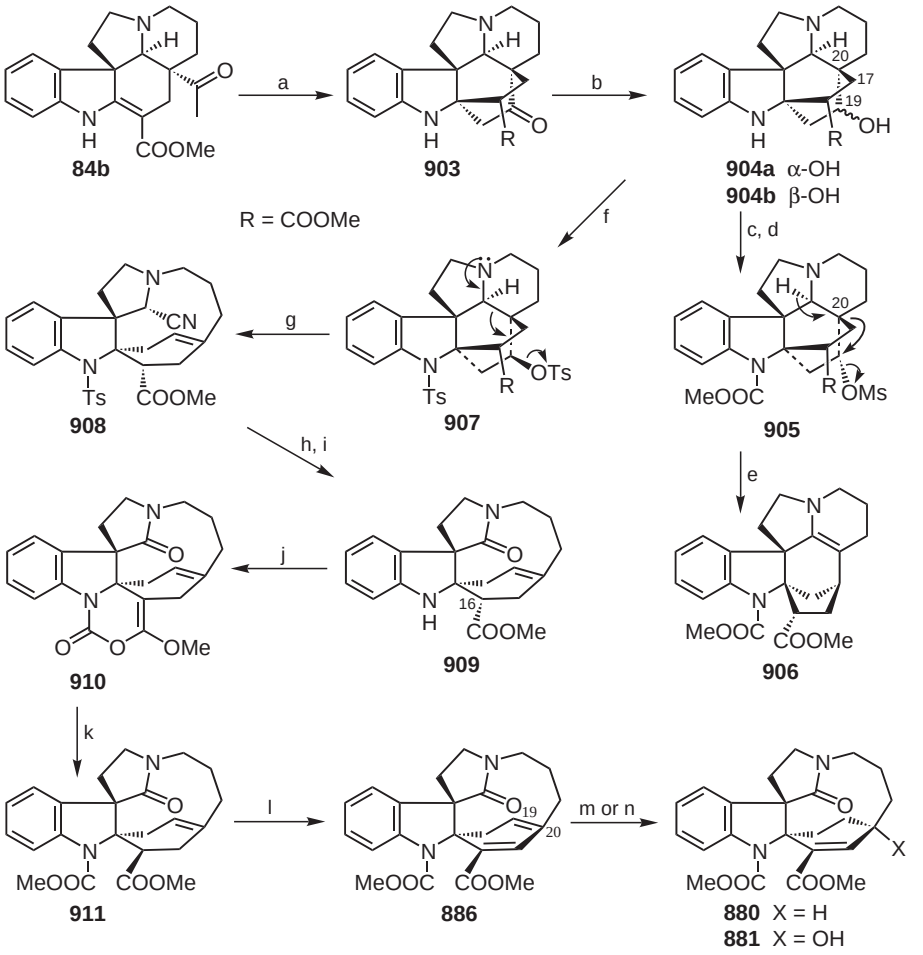
tion with $BF_3 \cdot OEt_2$ led to cyclic difluoroborate **897** (87%), presumably via hydroxylamine ketone **896**. However, the carbinolamine **893** underwent repeatedly the desired fragmentation (**899a** → **900**, 66%) upon column chromatography, which was ascribed to the presence of finite peracid in AcOEt cosolvent (**898a** → **899a**); 11,12-didemethoxypauciflorine B (**900**) and oxirane **891** were identified as products together with **893** and **894**. Notably, exposure to $AgBF_4$ and a quench with peracetic acid in AcOEt transformed **827a** to a 4:1 mixture of **900** and isomer **901** (65%), accompanied by small amounts of epoxide **891** and carbinolamine **893**.

Transformation of cyanoamine **827b** to (±)-pauciflorine B (**882**) was straightforward[132,160], Scheme 53. Using the procedure as above aminonitrile **827b** afforded, via **898b** and **899b**, a 4:1 isomeric mixture of **882** and **902** (66%), from which pure (±)-**882** was obtained; (–)-pauciflorine B (**882**) is a minor alkaloid from *Kopsia pauciflora*[162].

10.1.2. Kuehne's Synthesis

Kuehne and collaborators have described synthesis of kopsijasminilam alkaloids, which is based on an alternative strategy of ten-membered ring formation (**907** → **908**)[158,163], Scheme 54. The synthesis started with the known[164] acid-catalyzed conversion of racemic minovincine (**84b**), (see ref.[1], Chap. 3.1.2.), to hexacyclic ketone **903** the reduction of which could be stereocontrolled by the choice of reagent, from **904a**:**904b** 15:1 (Super-Hydride, –78 °C) to 1:4 (DIBAL-H, –78 °C). The mesylate **905** derived from α-alcohol **904a** underwent a base-catalyzed rearrangement on treatment with Et_3N affording undesired enamine **906** (83%) due to the antiperiplanar bond migration (C-17 from C-20 to C-19).

On the other hand, β-tosylate **907** accessible from **904b** fragmented upon exposure to hot KCN as expected and an intermediary iminium was trapped by the cyanide anion, Scheme 54. The cyanoamine **908** (89%) was converted to pyrrolidinone **909**, which underwent C-16 epimerization upon sequential treatment with triphosgene, then MeOH at 0 °C (→ **910** 91%), followed by a stereoselective oxazine ring-opening with hot NaOMe (92%). Ester **911** was efficiently converted to the diene **886** with LiHMDS and 3-phenyl-2-phenylsulfonyloxaziridine at –78 °C (86%). Finally, the diene **886** was transformed either to deoxykopsijasminilam (**880**) by catalytic hydrogenation of the more accessible 19,20-double bond (92%) or to the kopsijasminilam (**881**) upon reaction under oxygen with $[Mn(dpm)_2]$ (20 mole %) and $PhSiH_3$ (85%). (–)-Deoxykopsijasminilam (**880**) is also a natural alkaloid from *K. jasminiflora*[161].



SCHEME 54

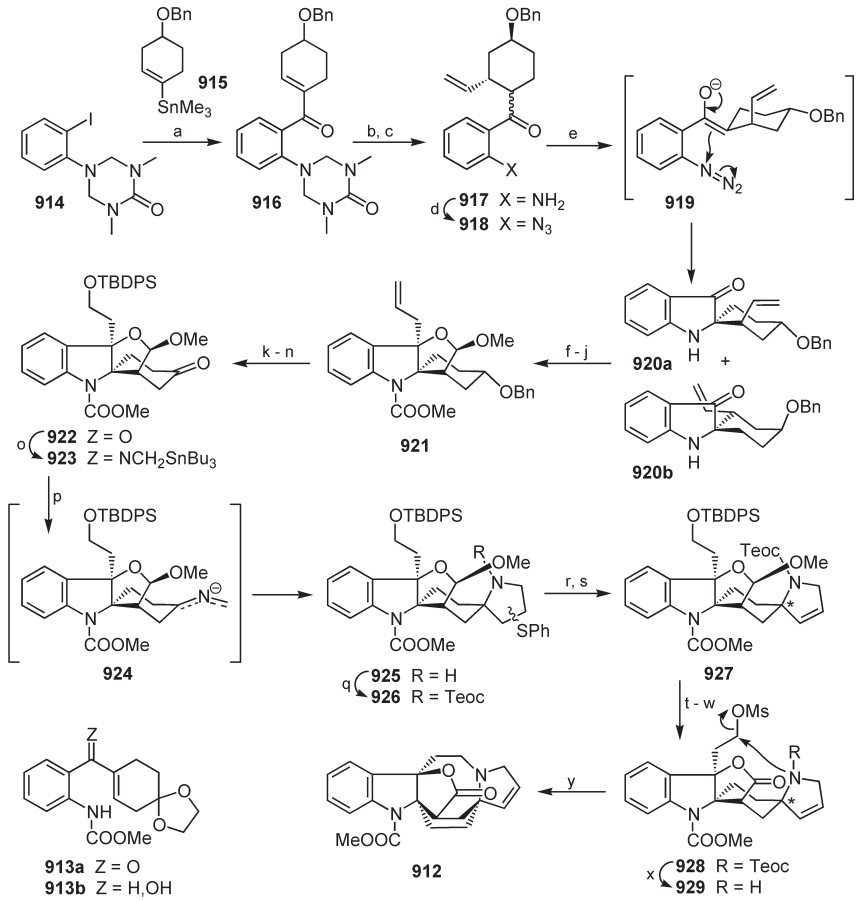
Reagents and conditions: a) 5 M HCl (g)/MeOH, rfl 24 h (44%; 85% brsm). b) $NaBH_4$, MeOH, 0 °C → rt (86%; **904a**:**904b** 1.3:1), or $NaBH_4/CeCl_3$ (**904a**:**904b** 2:1), or Super-Hydride, –78 °C (**904a**:**904b** 15:1), or DIBAL-H, THF, –78 °C 3 h (72%; **904a**:**904b** 1:4). c) MsCl, Et_3N, DMAP (cat), CH_2Cl_2, 0 °C → rt overnight (91%). d) ClCOOMe, Na_2CO_3, CH_2Cl_2, rt overnight (86%). e) Et_3N, EtOH/H_2O (4:1), 60 °C 6 h (83%). f) Ts_2O, py, 0 °C → rt overnight (89%). g) KCN (3 eq), EtOH/H_2O (3.4:1), rfl 2 h (89%). h) O_2, *t*-BuOK (3 eq), 18-crown-6 (1 eq), THF, rt 3 h (90%). i) Na naphthalenide, DME, –78 °C 5 min (95%), or LDA, THF, –78 °C 30 min (42% brsm), or Na/Hg, Na_2HPO_4, MeOH, rfl 12 h (86%). j) Triphosgene (3 eq), py, CH_2Cl_2, 0 °C → rt 40 min, then py, MeOH, 0 °C 30 min (91%). k) NaOMe, MeOH, rfl 2 h (92%). l) KHMDS (2 eq), THF, –78 °C 1 h, then 3-phenyl-2-phenylsulfonyloxaziridine, –78 °C 1 h (86%). m) H_2, 10% Pd/C, EtOH, rt 1 h (**880** 92%). n) O_2, [Mn(dpm)$_2$] (20 mole %), $PhSiH_3$ (2.5 eq), –10 °C 1 h (**881** 85%)

10.2. Lapidilectine B

Pearson and coworkers have described the first total synthesis of the lapidilectane alkaloid lapidilectine B (**912**)[165,166], which features Smalley cyclization of an azido ketone enolate (**918** → **919** → **920**) and a [3+2] cycloaddition of azaallyllithium (**923** → **924** → **925**)[167,168] as the key steps, Scheme 55. As the palladium-catalyzed aminocarbonylative cyclization of enone carbamates **913** failed to provide indoxyl-type products, the synthesis strategy was altered in that an electrophilic nitrogen (the azide in **918**) was substituted for the aniline nitrogen (as in **913**). Thus, Stille carbonylative coupling of aryl iodide **914** with vinylstannane **915** provided enone **916** (98%), which was converted in 2 steps into a 3:1 mixture of aniline epimers **917** (57%) and then to azido ketone **918** via the diazonium salt. A treatment with potassium hydroxide in cold *i*-PrOH induced the Smalley cyclization as illustrated in the enolate **919** to give a mixture of isomeric indoxyls **920** (68% over 2 steps) in which the desired indoxyl predominated (2.2:1). The major stereoisomer **920a** was transformed to tetracycle **921** and then to ketone **922**. Exposure of the latter to aminomethyl tributylstannane in the presence of Me_3Al generated imine (or azaallylstannane) **923** which, without isolation, was treated with *n*-BuLi to generate azaallyllithium **924** cycloadding with phenyl vinyl sulfide at –78 °C under formation of a regio- and stereoisomeric and/or rotameric mixture of pyrrolidines **925** (75%). The addition proceeded with rather high diastereofacial selectivity as judged from the 4:1 and 7:1 ratio at spirocarbon (*) in pyrrolines **927** and **928**, respectively (vide infra).

Teoc-protected amine sulfide **926** was converted via sulfoxide elimination to pyrroline **927** in 75% yield, Scheme 55. Demethylation of lactol ether with boron trichloride and oxidation with PCC gave a lactone (45%), which was converted to mesylate **928** (81%). Finally, deprotected amine **929** underwent a closure of eight-membered ring in the presence of base affording (±)-lapidilectine B (**912**) in 45% yield from **928**; (+)-lapidilectine B is available from *Kopsia lapidilecta*[169,170].

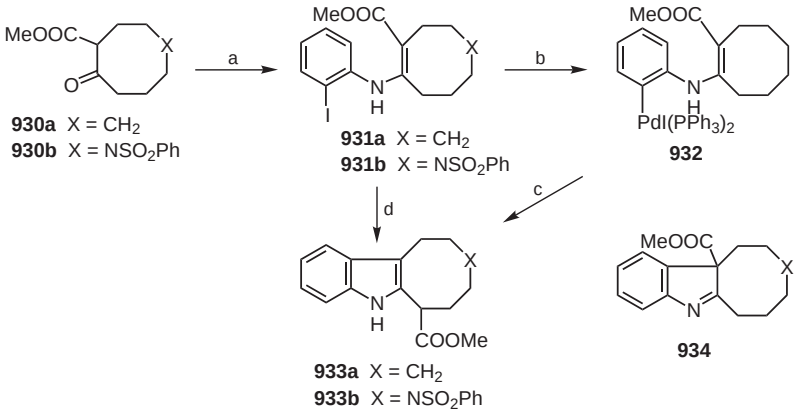
Japanese authors have described an unsuccessful model synthesis of tricyclic esters **934** [171], Scheme 56. Condensation of keto esters **930** with 2-iodoaniline provided enamines **931**. Heck cyclization under optimum condition (10 mole % $[Pd(PPH_3)_4]$, 1 moleq Ag_3PO_4, hot DMSO) of **931a** did not provide any indolenine **934**, but rather indole **933a** in quantitative yield, although an exposure of **931a** to stoicheiometric $[Pd(PPH_3)_4]$ afforded crystalline palladium species **932** in 86% yield (X-ray); note that **932** afforded upon exposure to 1 moleq Ag_3PO_4 in DMA one and the same in-



SCHEME 55

Reagents and conditions: a) CO (6.0 at), $[Pd_2(dba)_3]$ (cat), Ph_3As, LiCl, 4 Å MS, NMP, 70 °C 12 h (98%). b) (2-Thienyl)Cu(CN)Li (3 eq), CH_2=$CHMgBr$ (3 eq), $BF_3{\cdot}OEt_2$, THF, –78 °C 10 h (84%). c) concd HCl (10 eq), MeOH, rt 30 min (68%). d) concd HCl (3 eq), $NaNO_2$ (2 eq), EtOH, 0 °C 30 min, then NaN_3 (4 eq), H_2O. e) KOH (5 eq), *i*-PrOH, 15 °C 1 h (**920a**:**920b** 2.2:1, 68%, 2 steps). f) **920a**, *t*-BuLi, THF, –78 °C → –50 °C 1 h, then MeOCOCl (2 eq), 0 °C 1 h (89%). g) OsO_4 (cat), NMO, Me_2CO, rt 8 h (87%). h) CH_2=$CHCH_2MgBr$ (3 eq), THF, –40 °C → rt 3 h. i) $NaIO_4$, THF aq, pH 7, rt 3 h (75%, 2 steps). j) CSA (5 eq), MeOH, rt 2 h (82%). k) O_3, py, CH_2Cl_2, MeOH, –78 °C 5 min, then $NaBH_4$ (80–87%). l) TBDPSCl, imidazole, CH_2Cl_2, 0 °C → rt 3 h (88%). m) $Pd(OH)_2$, cyclohexene, EtOH, rfl 4 h (82–92%). n) *n*-$Pr_4N^+RuO_4^-$, NMO, 4 Å MS, CH_2Cl_2, rt 1 h (95%). o) $Bu_3SnCH_2NH_2$, Me_3Al, PhMe, 0 °C 30 min. p) $PhSCH$=CH_2 (3 eq), *n*-BuLi, THF, –78 °C 15 min (72%). q) TeocCl, *i*-Pr_2NEt, CH_2Cl_2, rt 1 h (91%). r) *m*-CPBA (1 eq), $NaHCO_3$, CH_2Cl_2, –30 °C → rt 2 h (88%). s) Py, Cl_2C=CCl_2, 140 °C 4 h (85%). t) BCl_3, CH_2Cl_2, –10 °C 1 h. u) PCC, celite, CH_2Cl_2, rt 2 h (45%, 2 steps). v) HF·py, THF, rt 2 h (88%). w) MsCl, *i*-Pr_2NEt, CH_2Cl_2, –10 °C → rt 30 min (92%). x) TFA, MeCN, rt 30 min. y) *i*-Pr_2NEt, MeCN, 60 °C 10 h, then DBU (2 eq), rt 30 min (45%, 2 steps)

dole **933a** (25%). Similarly, enamine **931b** was transformed under Heck conditions as above to azecinoindole **933b** (69%) in a process which is believed to proceed via enamine double bond isomerization in **931b**/5-*endo*-cyclization.

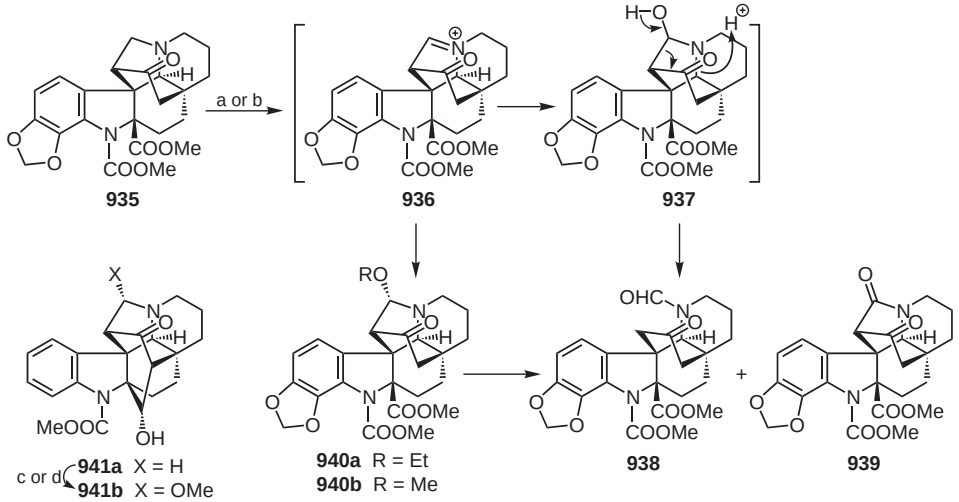


SCHEME 56

Reagents and conditions: a) 2-Iodoaniline, TsOH (1.0–2.0 eq), PhH, rfl 39 h–4 days (**931a** 60%; **931b** 58%). b) **931a**, $[Pd(PPh_3)_4]$ (1 moleq), Et_3N (2.3 eq), MeCN, 80 °C 32 h (86%). c) **932**, Ag_3PO_4 (1 moleq), DMA, 100 °C 35 h (**933a** 25%). d) $[Pd(PPh_3)_4]$ (10 mole %), Ag_3PO_4 (1 moleq), DMSO, 100 °C 15–18 h (**933a** quant; **933b** 69%)

10.3. Danuphylline

Soon after isolation of (–)-danuphylline from *Kopsia dasyrachis*[172,173] Kam and collaborators have announced a synthesis of the alkaloid by electrochemical oxidation[174], Scheme 57. Oxidation of hexacyclic (+)-methyl 11,12-methylenedioxychanofruticosinate (**935**), itself a major alkaloid in the leaves, at Pt anode in 30% CH_2Cl_2/MeCN provided, after chromatography on silica gel with CH_2Cl_2 a mixture of danuphylline (**938**) in 45% yield and lactam **939** (5%); chromatography with $CHCl_3$/0.5% EtOH as stabilizer yielded α-ethoxy derivative **940a** (61%), accompanied by minor amounts of **938** (4%) and **939** (5%); the ratio **938** to **940a** was dependent on a contact time with silica gel. The process consists in the formation via immonium **936** of carbinolamine **937** and subsequent retroaldol fragmentation affording danuphylline (**938**). Similar fragmentation occurs also in both **940a** and α-methoxyamine **940b**, which is formed in high yield by oxidation of **935** at carbon anode in methanol, but which affords a mixture of **938** (21%) and **940b** (72%) upon chromatography with CH_2Cl_2/1% MeOH.



SCHEME 57

Reagents and conditions: a) Anodic oxidation (Pt gauze anode; 1.2 V, 2 F/mol), 0.1 M $Et_4N^+ClO_4^-$, 2,6-lutidine (2 eq), 30% CH_2Cl_2/MeCN, chromatography silica gel/CH_2Cl_2 (**938** 45% + **939** 5%) or chromatography silica gel/$CHCl_3$–0.5% EtOH (**938** 4% + **939** 5% + **940a** 61%). b) Anodic oxidation (vitreous C anode; 1.1 V, 2 F/mol), 0.1 M $LiClO_4$, 2,6-lutidine (2 eq), MeOH (crude only **940b**), if chromatography silica gel/CH_2Cl_2–1% MeOH (**938** 21% + **940b** 72%). c) Anodic oxidation (vitreous C anode; 1.05 V, 2 F/mol), 0.1 M $LiClO_4$, 2,6-lutidine, MeOH, chromatography silica gel/CH_2Cl_2–1% MeOH (**941b** 45%). d) Anodic oxidation (Pt gauze anode; 1.2 V, 2 F/mol), 0.1 M $Et_4N^+ClO_4^-$, 2,6-lutidine (2 eq), 30% CH_2Cl_2/MeCN (stable immonium salt), chromatography silica gel/CH_2Cl_2–2% MeOH (**941b** 71%)

It is of interest to note that heptacyclic 5α-hemiaminal **941b** analogously accessible from fruticosamine (**941a**) is stable under these conditions and does not undergo such a fragmentation[174].

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