RECENT DEVELOPMENTS IN SYNTHESES OF THE POST-SECODINE INDOLE ALKALOIDS. PART III: REARRANGED ALKALOID TYPES

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The third part of a planned review on developments in the field of total and formal total synthesis of the post-secodine indole alkaloids focuses on types of rearranged alkaloids, i.e. on the skeletons with altered connectivities next to the indol(e)ine moiety, especially with a new bond to N-1. It reviews the synthesis of melodane, goniomitine, chippiine/dippinine, lirofoline and tronocarpine alkaloids, as well as alkaloids of secoschizozygane/vallesamidine, schizozygane and isoschizozygane type. It covers the literature from approximately 1991 up to May 2011. A review with 115 references.

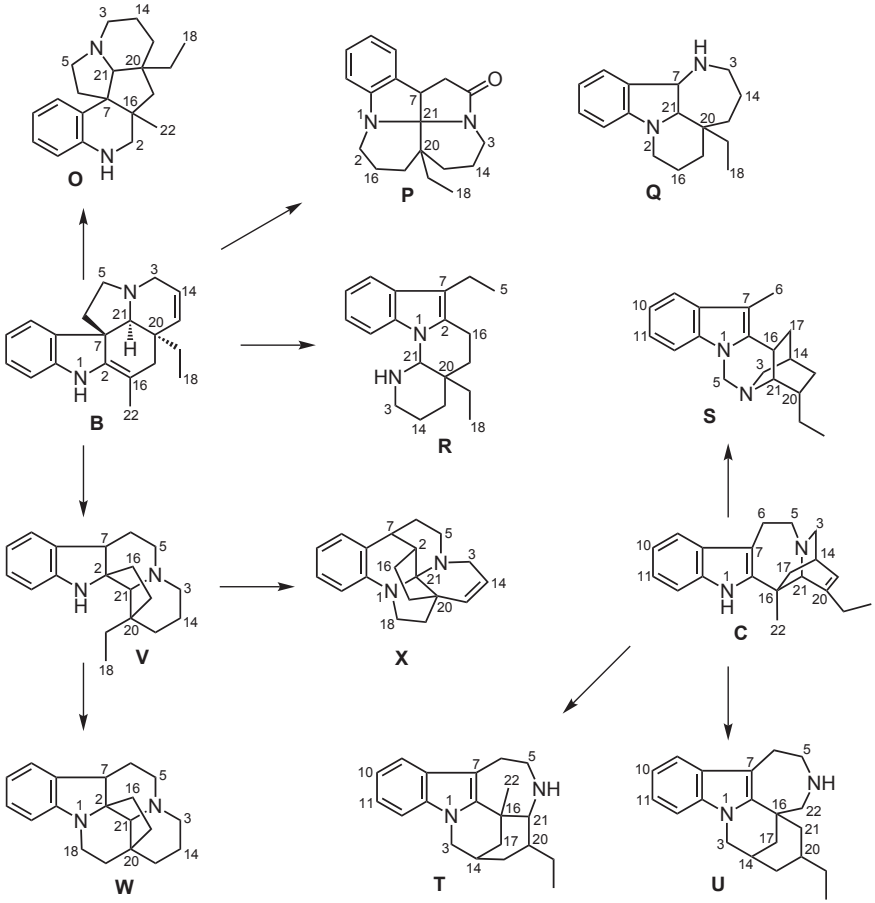
Keywords: Indole alkaloids; Post-secodine alkaloids; Total synthesis; Asymmetric synthesis; Melodane alkaloids; Meloscine; Scandine; Goniomitine; Lirofoline, Chippiine/dippinine alkaloids; Tronocarpine; Secoschizozygane alkaloids; Schizozygane alkaloids; Isoschizozygane alkaloids; Vallesamidine; Strempeliopine; Schizozygine; Isoschizogamine.

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], while the second part covered[2] synthetic approaches to alkaloids with modified aspidospermane (**B**), pseudoaspidospermane (**D**) and ibogane (**C**) skeletons. This Part of the review covers post-secodine alkaloids with rearranged skeletons that are derived from primary alkaloid types by a rearrangement, Scheme 1. It includes melodane alkaloids (**O**, with a new 2,6- and missing 6,7-bond of skeleton **B**), alkaloids of leuconoxine (**P**) and mersicarpine (**Q**) type and several alkaloid skeletons featuring a new bond attached to indole N-1 nitrogen: goniomitine (**R**) derived from aspidospermanes (**B**), as well as lirofoline (**S**), chippiine (**T**) and tronocarpine (**U**) biosynthesized probably through iboganes (**C**). Synthesis of secoschizozygane/vallesamidine (**V**) and schizozygane (**W**) alkaloids that belong to *N*-acyl-2,2,3-trialkylindolines is reviewed next followed, finally, by closely related isoschizozyganes (**X**). It covers the literature published from aproximately 1991 up to May 2011.

The remaining important alkaloid groups with eburnane and tacamane skeletons will be the subject of Part Four, together with a chapter on some selected alkaloid transformations.

The numbering of alkaloid skeletons used in this review is the biogenetic one proposed by LeMen and Taylor[3], see Scheme 1. As with primary alkaloid types, the natural bases discussed in this Part may again appear in *both enantiomeric series* due to inherently planar secodine precursors.



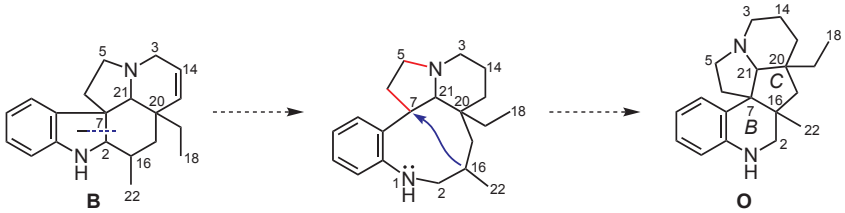
SCHEME 1
An overwiev of skeletons of the rearranged types of post-secodine alkaloids

Common abbreviations are used in the description of reagents and conditions; in addition, rfl stands for reflux, and –78 °C 20 min → rt (1 h) 3 h means that the mixture was kept first 20 min at –78 °C, then warmed to room temperature during 1 h and, finally, kept at rt for another 3 h. In or-

der to preserve logic and interrelations, the numbering of chapters, as well as of formulae continues from Parts One and Two.

10. MELODANE ALKALOIDS

Occurrence of melodane alkaloids (**O**) is limited to the genus *Melodinus*. They originate from aspidospermane precursors (**B**) by scission of 2–7 bond and a formation of 7–16 one, a process that might involve rhazinilam type intermediates, Scheme 2. The net process thus involves an expansion of ring *B* at the expense of ring *C*, which becomes 5-membered. Note that a transformation of aspidospermanes to melodanes through a flash pyrolysis of aziridines[4,5] or α-ketol rearrangement[6] was demonstrated already in 1984, see also reviews[7,8].



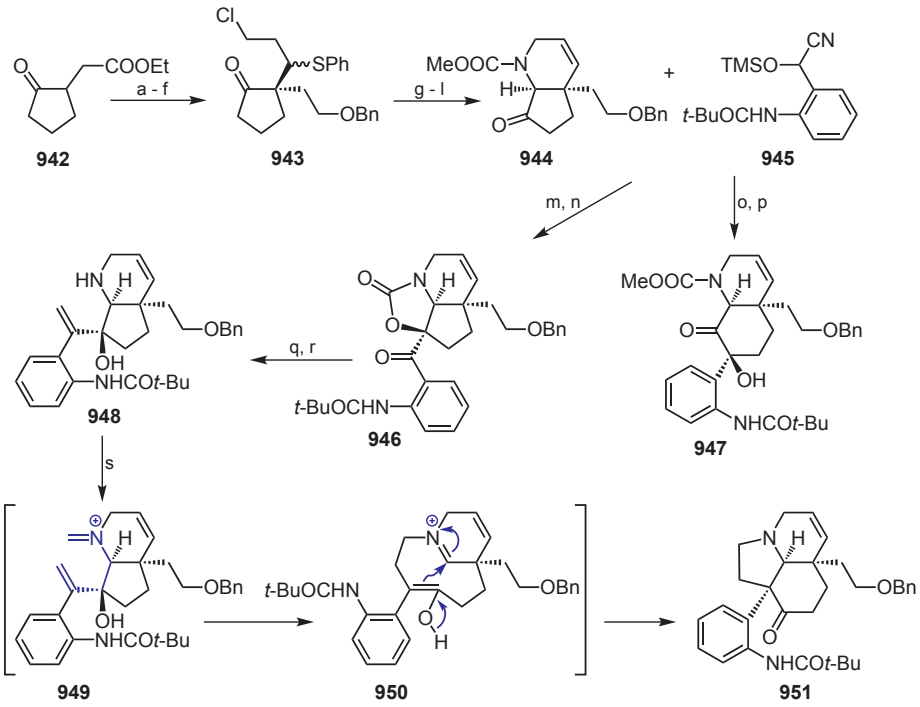
SCHEME 2
Origin of melodane alkaloids

10.1. Overman's Synthesis of (±)-Meloscine

Overman and coworkers have published a full account of their synthesis of (±)-meloscine (**956a**) and (±)-16-epimeloscine (**956b**) already in 1991 [9,10]. The synthesis features azonia-Cope rearrangement/Mannich cyclization as the crucial ring-forming sequence, review[11,12].

Bicyclic ketone **944** was made accessible[9,10] stereoselectively in 7 steps (27%) from chloro ketone **943**, itself prepared in 6 steps and 44% yield from ketoester **942**, Scheme 3A. While the lithium salt of protected cyano hydrine **945** reacted efficiently with **944**, the outcome of the reaction depended much on the reaction conditions: thus, warming the mixture to 0 °C prior to quenching with acid resulted in the formation of hydroquinolone **947** (39%) accompanied by trace amount of the desired tricycle **946**; the latter could be obtained in a yield as high as 76% provided that pH was brought to 6.5 prior to warm up. Ketone **946** was converted by Wittig reaction to olefine carbamate (93%), which was hydrolyzed to amino alcohol **948** by potassium hydroxide (84%). Exposure of amine **948** to excess

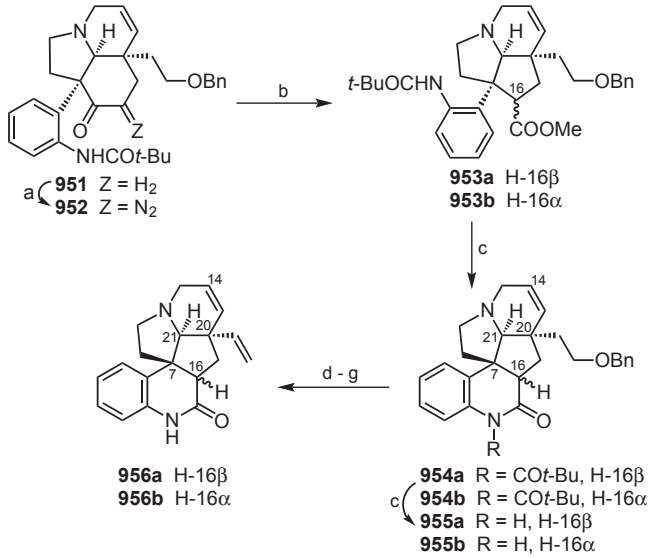
paraformaldehyde and camphorsulfonic acid (CSA; 0.5 eq) in refluxing benzene generated iminium **949** and then through stereospecific azonia-Cope rearrangement another iminium ketone-enolate **950**, which underwent internal Mannich cyclization affording hydrolilolidine **951** in 83% yield.



SCHEME 3A

Reagents and conditions: a) $(CH_2OH)_2$, PPTS (cat), PhMe, rfl 12 h (86%). b) $LiAlH_4$, Et_2O, 0 °C 1 h → 23 °C 1 h (92%). c) BnCl, $Bu_4N^+HSO_4^-$ (cat), 50% NaOH aq, 23 °C 45 min (99%). d) PPTS (10 mole %), H_2O, Me_2CO, rfl 16 h (97%, 2 steps). e) TMSCl, Et_3N, DMF, 130 °C 4 days. f) $ClCH_2CH_2CH(SPh)Cl$, $ZnBr_2$ (cat), CH_2Cl_2, 0 °C → 23 °C 1 h (57%, 2 steps). g) NaI, $NaHCO_3$, MeCOEt, 23 °C 22 h → rfl 20 h. h) NH_3 (l), $CHCl_3$, pressure flask, rt 3 days, then MeOCOCl, $KHCO_3$, $CHCl_3$, 23 °C 14 h (72%). i) BH_3, THF, 23 °C 45 min, then 30% H_2O_2, 3 M NaOH aq, 23 °C 2 h (70%). j) $(COCl)_2$, DMSO, CH_2Cl_2, –60 °C 3 h, then Et_3N, –60 °C → 23 °C. k) $NaIO_4$, MeOH aq, 23 °C 3 days. l) Et_3N, PhMe, rfl 3 days (54%). m) **945** (2 eq), *n*-BuLi (4.25 moleq), THF, –70 °C 45 min, then **944**, –70 °C 4 h, then 2.96 M HCl/MeOH (4.6 moleq), –70 °C → 0 °C. n) $LiOH \cdot H_2O$ (excess), MeOH, 0 °C → 23 °C 16 h (76%). o) Reaction as in m), –70 °C 1 h → 0 °C 1 h, then 3 M HCl/Et_2O (1:1, excess), 0 °C → 23 °C 1 h. p) $LiOH \cdot H_2O$ (excess), MeOH, 23 °C 14 h (39%). q) $Ph_3P{=}CH_2$ (excess), THF, –70 °C 1 h → 0 °C 2 days (93%). r) KOH, $EtOH/H_2O$ (4:1), 130 °C 20 h (84%). s) $(CH_2{=}O)_n$ (3 eq), CSA (0.5 eq), PhH, rfl 3 h (83%)

Diazo transfer to **951** from 2,4,6-triisopropylphenylsulfonyl azide (TIPSA) under phase-transfer condition yielded[9,10] diazoketone **952** (98%), which underwent Wolff contraction upon irradiation and gave ester carbamate **953a** (77%), accompanied by epimer **953b** (18%), Scheme 3B. Key to the successful cyclization of **953a** was slow heating, finally at 150 °C, with excess of KOH in aqueous ethanol: the cyclization is believed to proceed through carbamate **954** and affords **955a** in 87% yield, together with an epimer **955b** (8%; thermodynamic ratio); it is noteworthy that simple ester hydrolysis predominated upon rapid heating. Pentacyclic ether **955a** was transformed in 5 steps and 45% overall yield into (±)-meloscine (**956a**); an overall yield of 24-step synthesis from **942** is 3–4%. Similarly, epimeric lactam **955b** gave 47% (±)-16-epimeloscine (**956b**). Both (+)-meloscine (**956a**) and (+)-16-epimeloscine (**956b**) were isolated from *Melodinus scandens*[13,14].

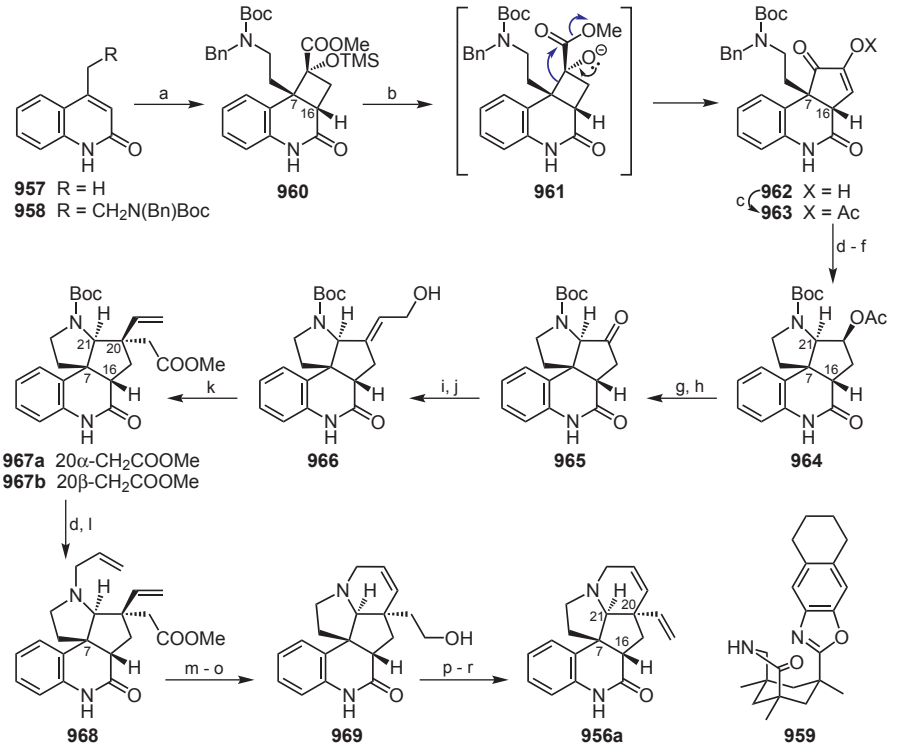


SCHEME 3B

Reagents and conditions: a) TIPSA (1.2 eq), $Bu_4N^+Br^-$ (0.3 eq), 18-crown-6 (5 mole %), 66% KOH aq, PhH, 35 °C 1 h (98%). b) hν (mercury arc lamp, Vicor filter), Et_2O/MeOH (40:2.2), 15 min (**953a** 77% + **953b** 18%). c) KOH (huge excess), EtOH/H_2O (11:2), rt 1 h → 50 °C 0.5 h → 80 °C (slowly) 4 h → 120 °C (slowly) 11 h → 150 °C 3 h, then conc to 1/2 volume, 150 °C 6 h (**955a** 87% + **955b** 8% + acid 4%). d) Na, NH_3 (l), THF, –70 °C (**a** 100%; **b** 85%). e) TsCl, py, $CHCl_3$, rt (**a** 96%; **b** 81%). f) 2-O_2NPhSeCN, $NaBH_4$, EtOH, 0 °C, then tosylate, 23 °C 14 h (**a** 58%; **b** 100%). g) *m*-CPBA, CH_2Cl_2, –70 °C 1.5 h, then Me_2S, Et_3N, –70 °C → 23 °C 4.5 h (**956a** 81%; **956b** 69%)

10.2. Bach's Synthesis of (+)-Meloscine

Following their exploratory studies on [2+2]-photocycloaddition[15,16], Selig and Bach have reported[17–19] on the total synthesis of (+)-meloscine (**956a**), which features a highly efficient and stereoselective three-step transformation of carbamate **958** into the optically active tricycle (+)-**963**, Scheme 4.



SCHEME 4

Reagents and conditions: a) hν (370 nm), CH_2=C(OTMS)COOMe (5.0 eq), **959** (2.5 eq), PhMe, –60 °C 4 h (76%). b) K_2CO_3, MeOH, 20 °C 2 h (98%). c) AcCl (1.1 eq), Et_3N (1.5 eq), THF, 0 °C 15 min (95%). d) TFA (10 v/v%), CH_2Cl_2, 20 °C 1 h. e) H_2 (1 atm), 15% $Pd(OH)_2$ (20 mole %), MeOH, 0 °C → 20 °C 18 h. f) Boc_2O (1.3 eq), Et_3N (pH 8–10), CH_2Cl_2, 20 °C 1 h (78%, 3 steps). g) K_2CO_3, MeOH, 20 °C 3.5 h (94%). h) IBX (3.0 eq), DMSO, 20 °C 18 h (94%). i) Ph_3P=CHCOOEt (1.4 eq), THF, rfl 22 h (84%). j) Dibal-H (3.75 eq), CH_2Cl_2, –45 °C 30 min (81%). k) $MeC(OMe)_3$ (3 eq), hydroquinone (0.66 eq), 135 °C 16 h (85%; **967a**:**967b** 7:3). l) CH_2=$CHCH_2Br$ (0.8 eq), K_2CO_3 (1 eq), MeCN, 20 °C 20 h (65%, 2 steps). m) Grubbs cat. II (15 mole %), PhMe, 65 °C 18 h (95%). n) Dibal-H (2.1 eq), CH_2Cl_2, –78 °C 30 min. o) $NaBH_4$ (1.2 eq), EtOH, 0 °C 20 min (70%, 2 steps). p) TsCl (10 eq), Et_3N (20 eq), CH_2Cl_2, 20 °C 18 h (72%). q) 2-O_2NPhSeCN (21 eq), $NaBH_4$ (20 eq), EtOH, 20 °C 80 h (98%). r) *m*-CPBA (1 eq), TFA (1.5 eq), CH_2Cl_2, –78 °C → 20 °C 4 h (86%)

Boc-protected amine **958** was obtained[15] in 6 steps and 48% overall yield from 4-methyl-2(1*H*)-quinolone (**957**); it underwent, upon exposure to excess methyl pyruvate silyl enol ether (5 eq) and lactam (–)-**959** (2.5 eq; a complexing agent) under irradiation in toluene at –60 °C, a highly regio-, stereo- (*exo*:*endo* > 98:2) and enantioselective [2+2]-photocycloaddition to afford (–)-cyclobutane **960** with an ee of 79% (87% yield) which could be raised to >99% by HPLC (76%). The following K_2CO_3-induced transformation of cyclobutane **960**, which might be viewed as a retro-benzilic ester rearrangement in alkoxide **961**, proceeded almost quantitatively (98%), and the resulting cyclopentadione enol (+)-**962** was acetylated (95%).

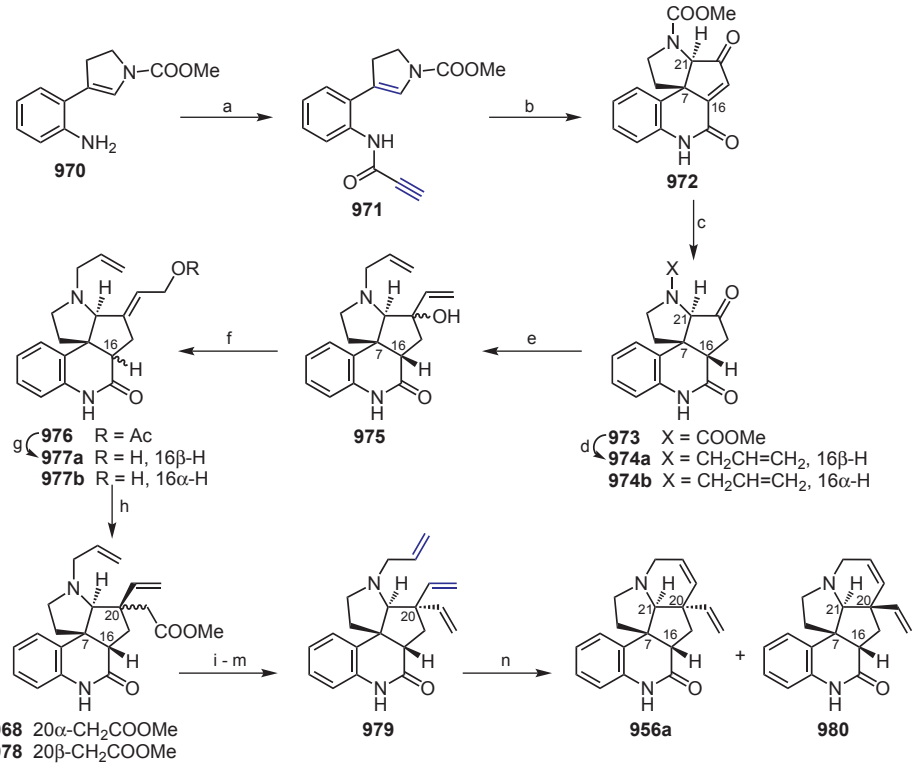
Removal[17,18] of the Boc-group in (+)-**963** with TFA and an exposure to hydrogen over Pearlman's catalyst $Pd(OH)_2$ caused hydrogenolysis, reduction of the enol acetate as well as an intramolecular reductive amination; after Boc-reprotection, the carbamate (+)-**964** was isolated as a single diastereoisomer in 78% yield, Scheme 4. The following 4-step transformation to allyl alcohol **966** (60% overall) set the stage for an *ortho*-Claisen rearrangement, which was effected by heating with excess trimethyl orthoacetate and proceeded with only moderate diastereoselectivity (85%; **967a**:**967b** 7:3). *N*-Deprotection permitted a removal of the minor isomer in a form of the spontaneously formed lactam; *N*-allylation then afforded stereohomogeneous diolefine **968** in 65% yield over 2 steps. Exposure of the latter to the Grubbs 2nd generation catalyst (15 mole %) allowed a closure of the remaining ring by a ring-closing metathesis (95%). Finally, the derived alcohol **969** was converted to (+)-meloscine (**956a**) essentially by the above discussed Overman's 3-step protocol (61%); synthesis of (+)-**956a** required 21 steps from **957** (3–4% overall).

10.3. Mukai's Synthesis of (±)-Meloscine

Mukai and collaborators have described[20] another efficient and completely stereoconvergent synthesis of racemic meloscine, which is based on a rapid construction of tetracyclic ketone **972** by an intramolecular Pauson–Khand reaction, Scheme 5; the synthesis is in some way reminiscent of the late stages of the preceding approach by Bach (*vide supra*). Aniline **970**, an early intermediate[21] in Rawal's synthesis of strychnine, was converted to propiolanilide **971** (83%) whose exposure to $[Co_2(CO)_8]$ led to the formation of dicobalt hexacarbonyl complex and then to tetracyclic enone **972** upon treatment with trimethylamine *N*-oxide (TMANO; 56% yield).

Saturation of the double bond in **972** by hydrogenation followed[20] by a removal of carbamate group in **973** by *in situ* generated trimethylsilyl

iodide and subsequent allylation gave ketone **974a** as the prevailing C-16 diastereoisomer (dr 7:2 to 3:1; 73%), Scheme 5. A reaction of the ketone **974** with vinylmagnesium chloride afforded allylalcohol **975**, the isomerization of which by sulphuric acid in refluxing acetic acic provided acetate **976** and then by basic methanolysis allylalcohol **977a** together with C-16 diastereoisomer **977b** (dr 4:1; 68% from **974**). The Claisen–Johnson rear-



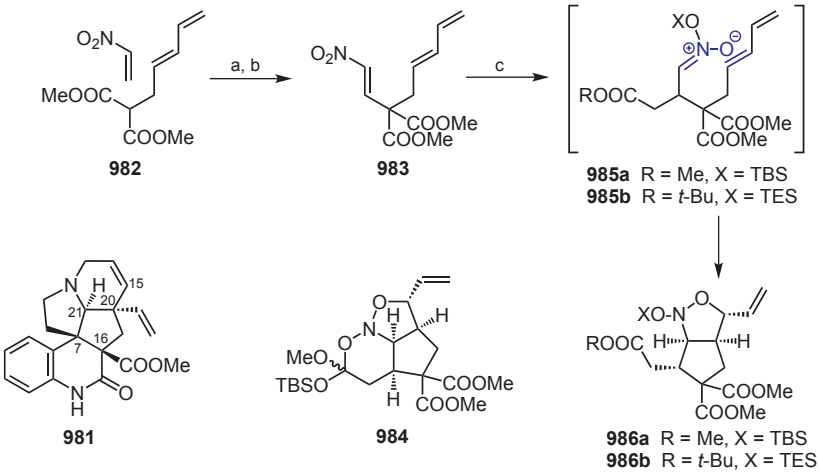
SCHEME 5

Reagents and conditions: a) HC≡C·COOH, EtN=C=NCH$_2$CH$_2$CH$_2$NMe$_2$·HCl, CH$_2$Cl$_2$, rt 1 h (83%). b) [Co$_2$(CO)$_8$] (1.2 eq), MeCN, rt 2.5 h, then TMANO·H$_2$O, rt 2 h (56%). c) H$_2$ (1 atm), 10% Pd/C, MeOH, 40 °C 21 h. d) TMSCl, NaI, MeCN, rfl 1 h, then Na$_2$S$_2$O$_3$ aq sat, NaHCO$_3$, rt 10 min, then CH$_2$=CHCH$_2$Br, K$_2$CO$_3$, rt 15 h (73% from **971**, **974a**:**974b** 7:2 to 3:1). e) CH$_2$=CHMgCl, Et$_2$O, 0 °C → rt 16 h. f) H$_2$SO$_4$ conc, AcOH, rfl 2 h. g) K$_2$CO$_3$, MeOH, rt 1 h (68% from **974**, **977a**:**977b** 4:1). h) MeC(OMe)$_3$, hydroquinone (0.7 eq), 130 °C 22 h (65%; **968**:**978** 3:1), or microwawe irradiation, 200 °C 3 h (73%; **968**:**978** 3:1). i) LiAlH$_4$, THF, 0 °C → rt 3 h (65%). j) TsCl, Et$_3$N, CH$_2$Cl$_2$, rt 27 h. k) PhSeSePh, NaBH$_4$, EtOH, 0 °C → rt 7.5 h. l) NCS, MeOH/CH$_2$Cl$_2$ (1:1), 0 °C 30 min. m) PhH, rt → 70 °C (71%, 4 steps). n) Hoveyda–Grubbs cat. II (0.05 eq), PhMe, 60 °C 10 h, then Hoveyda–Grubbs cat. II (0.05 eq), 60 °C 2 h (**956a** 99%)

rangement of allylalcohol **977** with trimethyl orthoacetate could be performed either under Bach's conditions (130 °C, 22 h; 65%) or at 200 °C upon microwawe irradiation for 3 h in 73%; note that any H-16α isomer **977b** epimerized during the reaction and the product was obtained in both cases as a 3:1 C-20 diastereoisomer mixture. The stereochemistry at C-20 was of little consequence as both **968**, itself an intermediate in Bach's synthesis, and its C-20 epimer **978** converged later to same divinyl derivative **979**. Consecutive reduction by $LiAlH_4$ (65%), *O*-tosylation, displacement with *in situ* generated sodium phenylselenide, oxidation of selenide by NCS to selenoxide and an elimination in hot benzene afforded trialkene **979** (73% overall). Final ring closing metathesis was induced by Hoveyda–Grubbs second generation catalyst at 60 °C in toluene and involved with high selectivity the β-vinyl group; the reaction provided (±)-meloscine (**956a**) in 99% yield! The overall yield of this 14-step synthesis from **970** is 7%.

10.4. Other Studies

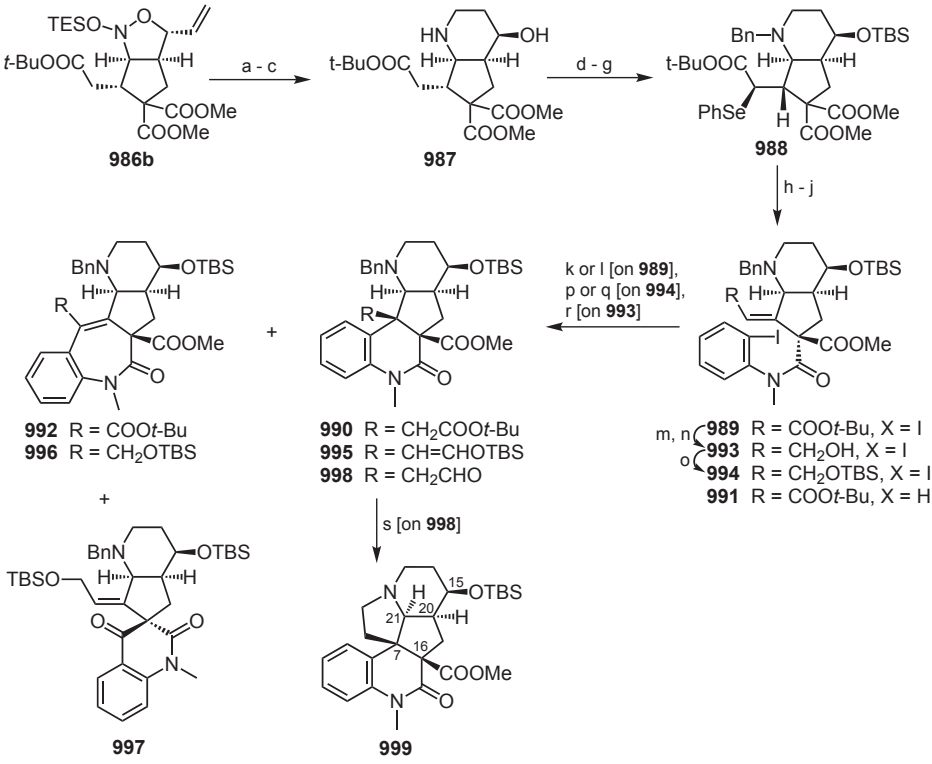
Denmark and Cottell have published[22] on a stereoselective synthesis of pentacycle **999**, an advanced model to scandine whose (+)-enantiomer (**981**) is available inter alia from *Melodinus tenuicaudatus*[23], Scheme 6. Al-



SCHEME 6A

Reagents and conditions: a) *n*-BuLi (**982** added in 20 min), THF, –78 °C → 0 °C (15 min) → –75 °C, then CH_2=$CHNO_2$/THF (25 min), –76 °C 35 min → 0 °C, then PhSeBr [$(PhSe)_2$, Br_2 (0.62 eq), THF, rt], 0 °C 1 h → rt 2.5 h (77%). b) *m*-CPBA (1.25 eq), THF, –77 °C 1 h → rt 2 h (95%). c) AcO*t*-Bu, LDA, –75 °C 20 min, then add to **983** (15 min), –75 °C 30 min, then TESCl (2 eq) –75 °C 1.5 h → rt 2.5 h (98%, dr 6:1)

though attempted reaction of nitro triene **983** with CH_2=C(OMe)OTBS failed to give any tricycle **984** through [4+2]/[3+2]-cycloaddition cascade[24], it nevertheless afforded a mixture containing bicycle **986a** through an ini-



986b **987** **988**

992 R = COO*t*-Bu
996 R = CH_2OTBS

990 R = CH_2COO*t*-Bu
995 R = CH=CHOTBS
998 R = CH_2CHO

989 R = COO*t*-Bu, X = I
993 R = CH_2OH, X = I
994 R = CH_2OTBS, X = I
991 R = COO*t*-Bu, X = H

997 **999**

SCHEME 6B

Reagents and conditions: a) (siamyl)$_2$BH, THF, –10 °C → rt 2 h, then H_2O, then $NaBO_3$ (7 eq), rt 3 h (75%). b) Ts_2O, py, 0 °C 10 min (96%). c) H_2 (360 psi), Ra-Ni, MeOH, rt 1.5 days (67%). d) BnBr (2 eq), K_2CO_3, DMF, rt 2.5 h (78%). e) TBSCl (2.5 eq), imidazole (2.5 eq), DMF, rt 12 h (84%). f) TMSCl, LDA (over 15 min), THF, –107 °C 15 min → rt (30 min). g) PhSeBr (over 15 min), THF, –106 °C 15 min → rt (30 min) (**988** 52% + epimer 15%). h) *m*-CPBA (2 eq), CH_2Cl_2, –77 °C 30 min, then *i*-Pr_2NH (2 eq), –77 °C → rt (1.5 h) (86%; dr 4:1). i) 2-Iodoaniline (3 eq), EtMgCl (2.75 eq; over 10 min), THF, –15 °C 50 min, then MeOH, –15 °C → rt (85% + 14% isomer). j) MeI (4 eq), NaH (2 eq), DMF, 0 °C 20 min → rt (1 h) (87%). k) **989**, Bu_3SnCl (0.1 eq), $NaBH_3CN$, AIBN, 70 °C (**990** 10% + **991** 42%). l) **989**, Pd(OAc)$_2$, Ph_3P, DMF, 100 °C (**990** + **991** + **992** 47%). m) TMSOTf (5 eq), Et_3N, CH_2Cl_2, 0 °C 15 min → rt 45 min. n) BH_3 (3.5 eq in 3 portions), THF, rt 13.5 h (87%). o) TBSCl, imidazole (50%). p) **994**, Pd(OAc)$_2$, Ph_3P, Et_3N, DMF (**995**:**996**:**997** 5:1:1). q) **994**, Pd(OAc)$_2$, Ph_3P, Et_3N, $Bu_4N^+Cl^-$, MeCN (**995**:**996**:**997** 4:1:0). r) **993**, Pd(OAc)$_2$ (0.1 eq), PPh_3 (0.2 eq), Et_3N (2 eq), $Bu_4N^+Cl^-{\cdot}H_2O$ (2 eq), MeCN, rfl 12 h (**998** 88%). s) H_2 (1 atm), 5% Pd/C, AcOEt, rt 12 h (88%)

tial enolate addition to nitroethylene, Scheme 6A. Capitallizing on this result, enolate of *tert*-butyl acetate (LDA) was added to **983**; subsequent silylation generated nitronate **985b**, which provided isoxazolidine **986b** by dipolar addition as a 6:1 diastereoisomeric mixture in 98% yield!

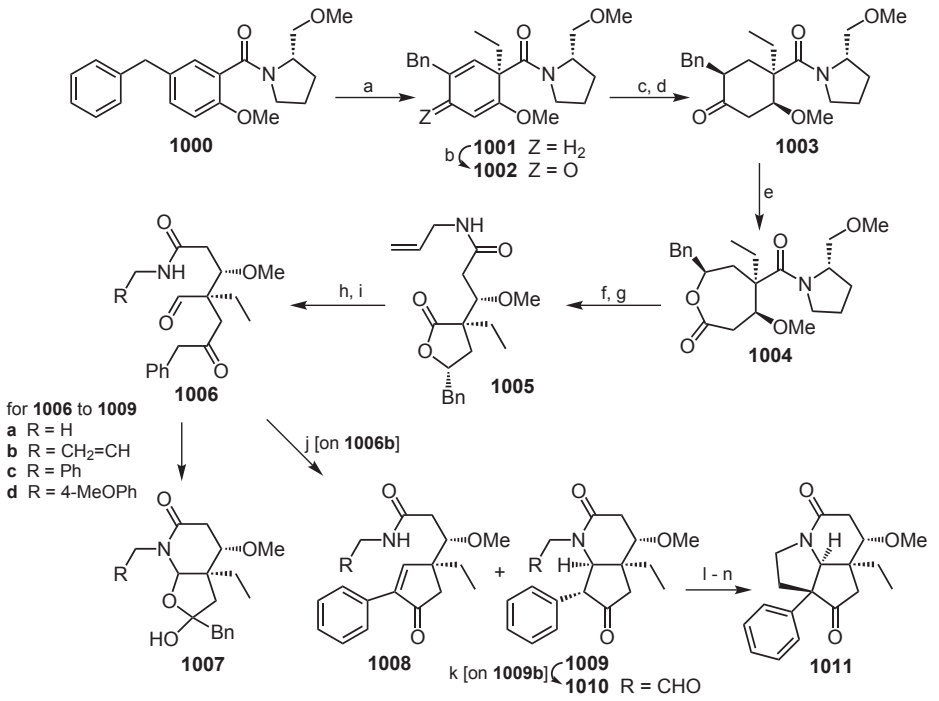
Isoxazolidine **986b** was then converted[22] in 3 steps to hydroxypiperidine **987** (48%), which did not undergo lactamization, Scheme 6B. Hence it was both *N*- (Bn, 78%) and *O*-protected (TBS, 84%) prior to conversion to acrylate *via* phenylselenenyl derivative **988** oxidation with *m*-CPBA (45%) and, finally, to anilide **989** by amidation of the more accessible methoxycarbonyl group with 2-iodoaniline/EtMgCl (85% + 14% isomer) and *N*-methylation (→ **989** 87%). Attempted radical cyclization of **989** (Bu_3SnCl + $NaBH_3CN$, AIBN) provided mainly deiodinated amide **991** along with **990** in 10% yield.

The Pd-mediated cyclization of **989** was investigated next[22], Scheme 6B. Reaction of the anilide **989** with $Pd(OAc)_2$ and PPh_3 (DMF, 100 °C) yielded again the desired 6-*exo*-trig product **990** in a low yield along with **991** and the major **992**, a product of the irreversible 7-*endo*-trig cyclization/β-hydride elimination (47%). In order to overcome the regioselectivity problem, the acrylate **989** was converted to alcohol **993** (87%) and to silylether **994** (50%). The outcome of the $Pd(OAc)_2$-mediated cyclization (PPh_3) of **994** was much dependent on base, solvent and additive; with Et_3N in DMF the ratio of **995**:**996**:**997** was 5:1:1, while with Et_3N and $Bu_4N^+Cl^-$ as additive in MeCN the ratio of **995**:**996**:**997** was 4:1:0. Finally, the allylic alcohol **993** afforded under the latter condition the aldehyde **998** in 88% yield, which was transformed into the target pentacycle **999** upon hydrogenation (88%).

Schultz and Dai have described[25] a synthesis of the tricyclic model compound **1011**, which is based on their rapid access to chiral synthons through chiral benzamide reduction/alkylation[26] (see also Part One[1], Scheme 55), Scheme 7. *O*-Methylprolinol derived benzamide **1000** was reduced by potassium in NH_3/*t*-BuOH and the resulting enolate ethylated to give dihydrobenzene **1001** (93%), which provided upon allylic oxidation (PDC/HOBT) the dienone **1002** as >20:1 mixture of diastereoisomers (82%). The latter was converted to ketone **1003** (73%), then to lactone **1004** upon Baeyer–Villiger reaction with *m*-CPBA (72%), and, finally, to butyrolactone amide **1005** upon TsOH treatment (95%) and amidation. Reduction of the lactone **1005** by $LiBH_4$ followed by Swern oxidation gave aldehyde **1006b** (82%).

The cyclization of **1006** was shown to be dependent[25] on both the reaction conditions and the *N*-substituent, Scheme 7. Thus, while exposure to

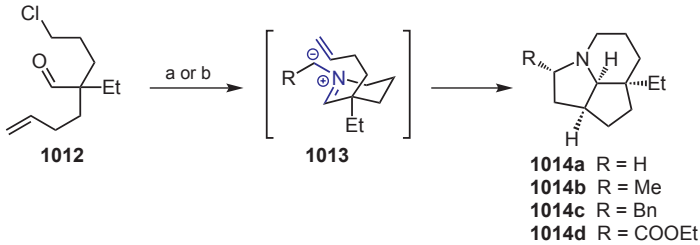
TFA (CH_2Cl_2, 25 °C) or CSA (refluxing benzene) yielded only **1007** as a diastereoisomeric mixture, treatment of **1006** with triflic acid (CH_2Cl_2, 0 °C) afforded a mixture of **1008** and **1009**, the ratio of which ranged from 10:1 (*N*-methyl) to 1:10 (*N*-benzyl) to 1:15 (*N*-*p*-MeOBn). While the ratio for *N*-allyl aldehyde **1006b** was only 1:3, the product **1009b** (72%) was smoothly converted to the target julolidine lactam **1011** by TsOH-catalyzed cyclization of aldehyde **1010** followed by Barton–McCombie radical deoxygenation.



SCHEME 7

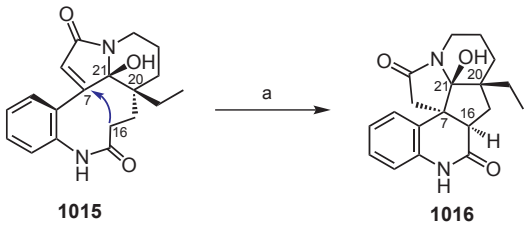
Reagents and conditions: a) K, NH_3 (l), *t*-BuOH (1 eq), THF, –78 °C, then piperylene, then EtI (93%). b) PDC (cat), celite, HOBT, PhH (82%). c) H_2 (4.1 atm), 5% Pd/C, THF. d) Li, NH_3 (l), *t*-BuOH, THF, –78 °C, then piperylene (73%, 2 steps). e) *m*-CPBA, CH_2Cl_2 (72%). f) TsOH, PhH/H_2O, rfl (95%). g) CH_2=$CHCH_2NH_2$, EDC, CH_2Cl_2, 0 °C (62%). h) $LiBH_4$, THF, MeOH. i) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, then Et_3N, –78 °C → 25 °C (**1006b** 82%). j) **1006b**, TfOH, CH_2Cl_2, 0 °C (**1009b** 72%; 3:1). k) O_3, CH_2Cl_2, then Me_2S (100%). l) TsOH, CH_2Cl_2, 25 °C (66%). m) Im_2C=S. n) Bu_3SnH, AIBN, PhH, rfl (70%, 2 steps)

Coldham and collaborators have described[27,28] a straightforward approach to CDE tricyclic models of scandine skeleton, Scheme 8. Aldehyde **1012**, obtained in 3 steps from butyronitrile (66%), was condensed with aminoacids $RCH(NH_2)COOH$ in refluxing xylene to afford *via* [3+2]-cycloaddition of intermediary azomethine ylide **1013** tricycles **1014** in good yield and with complete stereocontrol. Likewise, **1012** upon reaction with ethyl glycinate provided the tricycle **1014d** as a single stereoisomer (72%).



SCHEME 8
Reagents and conditions: a) $RCH(NH_2)COOH$ (excess), PhMe, rfl 18 h (**1014a** 82%; **1014b** 78%; **1014c** 60%). b) H_2NCH_2COOEt, *i*-Pr_2NEt, PhMe, rfl 2 h (**1014d** 72%)

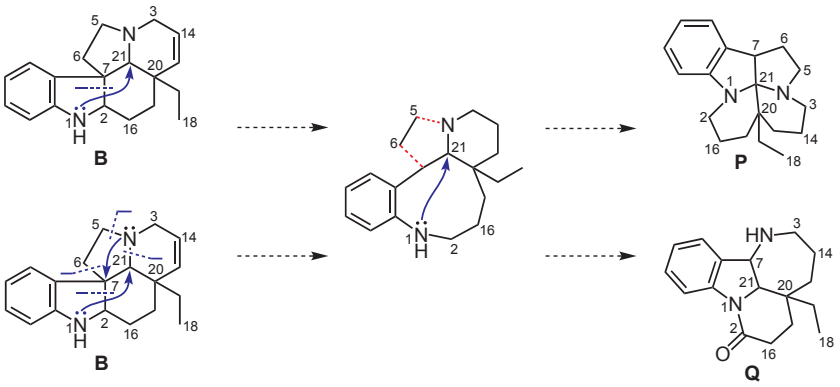
Noteworthy, although rather old, is the report[29,30] on a rapid access to meloscine skeleton from rhazinilam type alkaloid, Scheme 9. Thus a treatment of (–)-leuconolam (**1015**), an alkaloid related to rhazinilam, with potassium hydroxide at rt provided (–)-**1016** in 80% yield; for further information see also ref.[8]



SCHEME 9
Reagents and conditions: a) KOH, MeOH, rt 6 h (80%)

11. ALKALOIDS POSSIBLY DERIVED THROUGH RHAZINILAM

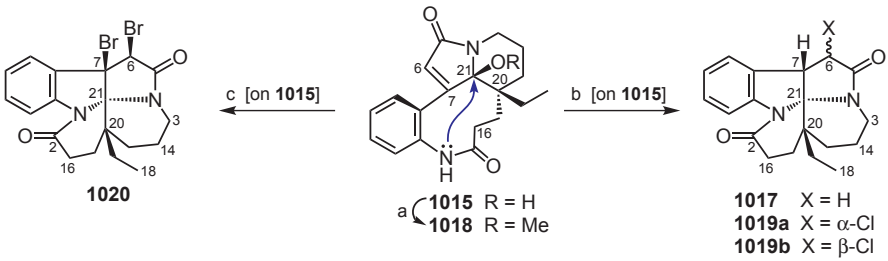
Two alkaloid skeletons are presented here – leuconoxine (**P**) and mersicarpine (**Q**) which might be biogenetically related to aspidospermanes (**B**) through rhazinilam type specii (see ref.[2], Chap. 8.), Scheme 10.



SCHEME 10
Alkaloid types related to aspidospermanes (**B**) possibly through rhazinilam type specii

11.1. Leuconoxine Group

Although no total synthesis was reported to date, the formation of leuconoxine carbon skeleton from (–)-1,2-didehydroaspidospermidine (*ent*-**267**) was demonstrated[31] as early as two decades before the isolation of the first alkaloid, (–)-leuconoxine (**1017**)[32], from *Leuconotis eugenifolius*; see also ref.[2] (Scheme 34) for related model study. Later on, a facile cyclization of (–)-leuconolam (**1015**) to 6-chloroleuconoxine (**1019**) was published[29,30] by Goh and Ali, Scheme 11. Thus, while treatment of **1015** with diluted hydrochloric acid in methanol provided ether **1018** (87%), more concentrated acid caused transformation to (–)-6-chloroleuconoxine (**1019a**) and epimeric (+)-**1019b** in 35 and 45%, respectively. Likewise, upon treatment with bromine in chloroform, hemiaminal **1015** underwent smooth conver-



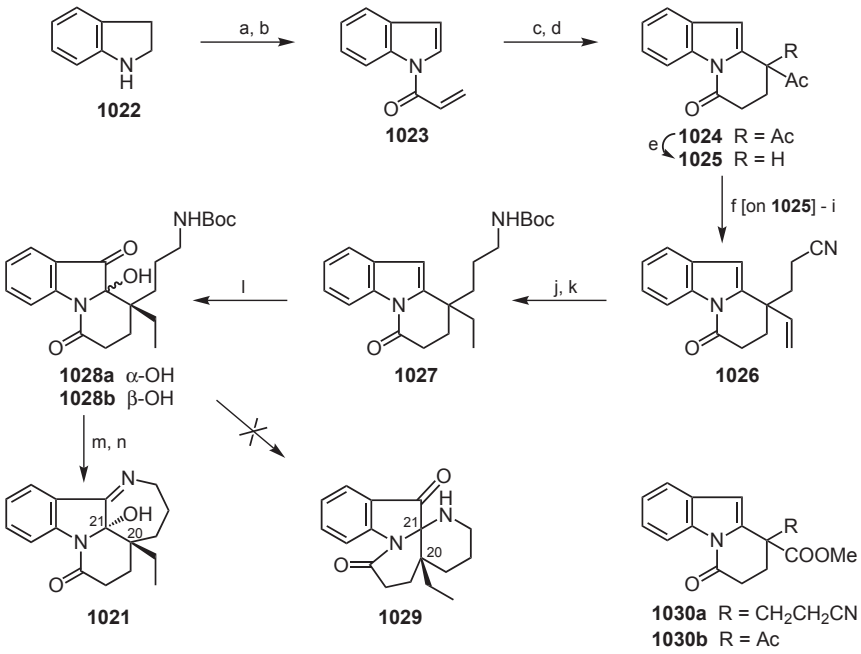
SCHEME 11
Reagents and conditions: a) HCl, MeOH (87.5%). b) HCl aq conc/MeOH, rt overnight (**1019a** 35% + **1019b** 45%). c) Br_2, $CHCl_3$, rt overnight

sion to (–)-dibromoleuconoxine (**1020**) in 95% yield; for further information see also ref.[8]

11.2. Mersicarpine

11.2.1. Kerr's Synthesis

The first total synthesis of racemic mersicarpine (**1021**) by Kerr and coworkers[33] is based on radical Mn(III)-mediated construction of tricyclic lactam **1024**, Scheme 12. Initially, tricycles **1030** were constructed from indoline (**1022**) but their elaboration into the target molecule proved impossible, in case of **1030b** due to its propensity to undergo retro-Claisen



SCHEME 12

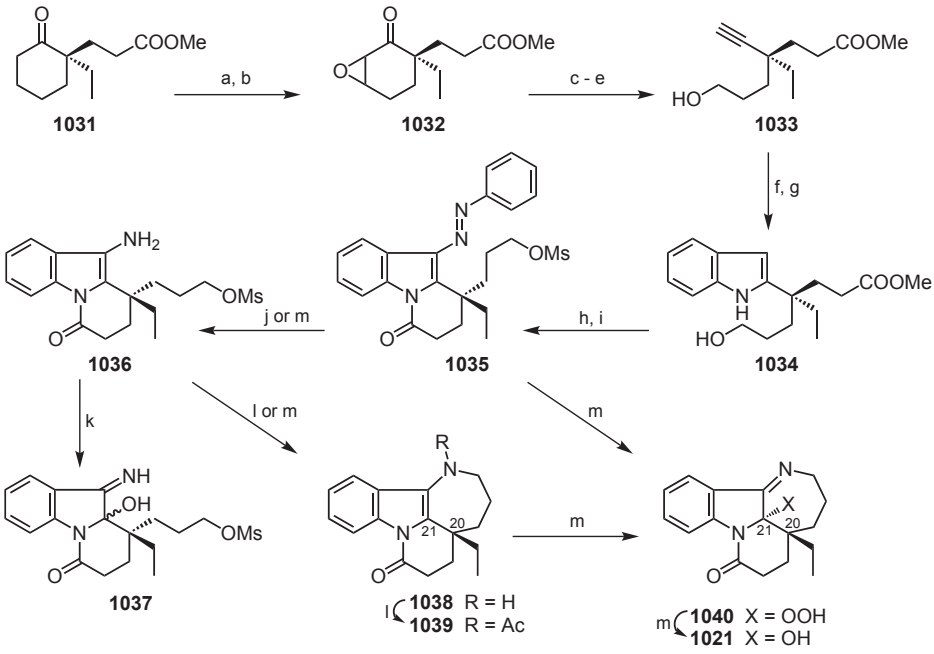
Reagents and conditions: a) CH_2=CHCOCl, K_2CO_3, THF (97%). b) DDQ, PhMe, rfl (81%). c) $AcCH_2Ac$, K_2CO_3, THF, rfl (98%). d) $Mn(OAc)_3$, AcOH, rfl (60%). e) $NaHCO_3$, MeOH (95%). f) CH_2=CHCN, KO*t*-Bu, THF (74%). g) $NaBH_4$, THF (quant). h) CS_2, NaH, THF, then MeI (73%). i) DME, 170 °C (microwave), (74%, 2 cycles). j) H_2, PtO_2, $CHCl_3$, EtOH. k) Boc_2O, Et_3N, CH_2Cl_2 (82%, 2 steps). l) Oxone, Me_2CO, TBAS, EDTA, MeCN aq (93%). m) TfOTBS, 2,6-lutidine, CH_2Cl_2. n) TBAF, THF (82%, 2 steps)

condensation. This was utilized in an altered strategy which commenced with the two-step conversion of indoline (**1022**) to acrylamide **1023** (79%). K_2CO_3-mediated Michael addition of acetylacetone to **1023** (98%) was followed by $Mn(OAc)_3$-induced radical cyclization in refluxing acetic acid. The resulting diacetyl derivative **1024** (60%) underwent a clean deacetylation with $NaHCO_3$ in methanol (95%) and then the ketone **1025** was submitted to Michael addition to acrylonitrile (KO*t*-Bu as catalyst; 74%). Transformation of the acetyl to vinyl in the product proved to be exceptionally difficult and finally succeeded by Chugaev elimination of methyl xanthate. Hydrogenation of nitrile **1026** over Adams catalyst led after Boc-protection to carbamateindole **1027** (82%) which upon smooth oxidation with *in situ* generated dimethyldioxirane yielded ketone **1028** (93%). Given the epimerizability of the hemiaminal moiety it was of little consequence that **1028** had been obtained as a 1:1 mixture of diastereoisomers. Removal of the protecting group followed by 7-membered ring imine formation proceeded uneventfully and gave the target (±)-mersicarpine (**1021**) in 82% yield; interestingly, no product of alternative cyclization leading to leuconoxine-type tetracycle **1029** was obtained. (–)-Mersicarpine (**1021**) was isolated[34] from *Kopsia fruticosa* and *K. arborea*.

11.2.2. Fukuyama's Synthesis

Soon after, Fukuyama and collaborators have disclosed[35] their approach to synthesis of natural (–)-mersicarpine (**1021**), Scheme 13. The synthesis commenced with the known[36] preparation of (–)-(*R*)-ketoester **1031** from 2-ethylcyclohexanone by the asymmetric Michael protocol; the ee 87% was raised to 99% by recrystallization of the corresponding semicarbazone. **1031** was converted to epoxyketone **1032** (a mixture of 2 diastereoisomers; 63% over 2 steps), which resisted all attempts at Eschenmoser-type fragmentation (tosyl and nosyl hydrazide) as did an application of aminoaziridines. Finally, the derived (*Z*)-semicarbazone (89%) underwent fragmentation by Warkentin's procedure consisting of lead tetraacetate oxidation to 1,3,4-oxadiazoline and subsequent Eschenmoser–Tanabe fragmentation yielding (–)-alkynal (60%) which gave (+)-alkynol **1033** upon $NaBH_4$ reduction (87%). Sonogashira coupling of **1031** with 2-iodoaniline gave a product (78%) that cyclized to (+)-(*R*)-indole **1034** upon gold(III) catalysis (78%). Reaction of (+)-**1034** with benzenediazonium chloride proceeded almost quantitatively (97%) and the product was converted to azinelactam (+)-**1035** by exposure to sodium hydride followed by mesylation (77%).

Hydrogenolysis of (+)-**1035** over 10% Pd/C permitted[35] the isolation of 3-aminoindole **1036** in 66% yield but could lead, due to the tendency of intermediates upon workup and purification to autoxidation, up to the target molecule **1021** in irreproducible yields, Scheme 13. It is also of interest to note that compound **1037**, a product together with **1021** of $NaHCO_3$ action on **1036** under non-degassed condition, failed to cyclize to **1021**; compare with the closure of the azepine ring in **1028** → **1021** (*vide supra*). Detailed study of the process revealed that the azepine ring needs to be closed (→ **1038**, isolable as acetamide **1039**) prior to the oxidation and led to the development of a highly efficient one-pot procedure including consecutive treatment of (+)-**1035** with hydrogen over Pd/C (→ **1036**), refluxing of the



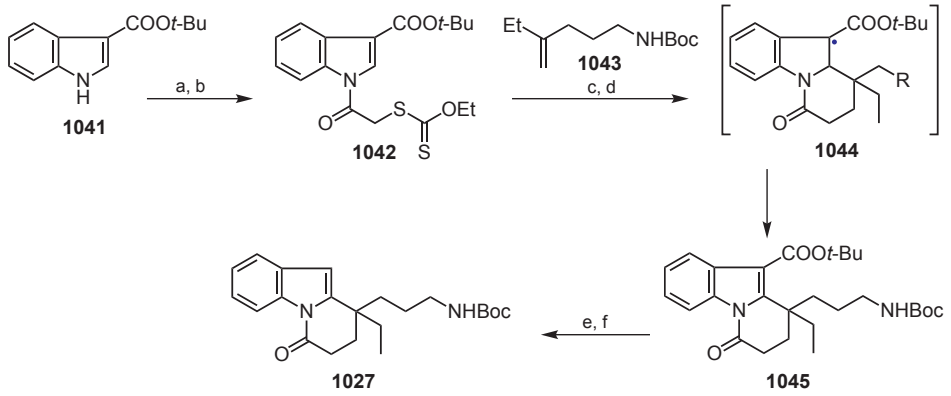
SCHEME 13

Reagents and conditions: a) IBX, DMSO, 85 °C (72%). b) H_2O_2, NaOH, MeOH aq, 0 °C (88%). c) $H_2NCONHNH_2$·HCl, NaOAc, EtOH aq, rt (89%). d) $Pb(OAc)_4$, CH_2Cl_2, –10 °C (60%). e) $NaBH_4$, MeOH, 0 °C (87%). f) 2-$IC_6H_4NH_2$, [$Pd(PPh_3)_4$], CuI, Et_3N, DMF, 80 °C (78%). g) $NaAuCl_4$·$2H_2O$, EtOH, rt (78%). h) $PhN_2^+Cl^-$, NaOAc, *i*-PrOH/H_2O/dioxane, 0 °C (97%). i) NaH, 4 Å MS, PhMe, rt, then MsCl, Et_3N, 0 °C (77%). j) H_2 (1 atm), 10% Pd/C, *i*-PrOH, CH_2Cl_2, rt (66%). k) O_2, AcOEt rt (10%). l) $NaHCO_3$, *i*-PrOH, degassing by freeze-thaw cycles, rfl, then Ac_2O, py (56%). m) H_2 (1 atm), 10% Pd/C, *i*-PrOH, CH_2Cl_2, rt, then $NaHCO_3$, degassing by freeze-thaw cycles, rfl, then air, rt, then Me_2S, rt (**1035** → **1021** 96%)

degassed solution with sodium bicarbonate (→ **1038**), stirring under oxygen/air and, finally, reduction with dimethylsulfide (**1040** → **1021**); overall yield as high as 96% of (–)-mersicarpine (**1021**) is reported for the whole procedure!

11.2.3. Other Studies

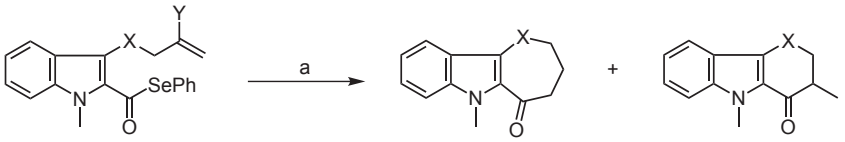
Formal synthesis of (±)-mersicarpine was achieved by Zard and Biechy[37] with their efficient synthesis of tricycle **1027**, Scheme 14. Xanthate **1042** was obtained from the indole **1041** by *N*-chloroacetylation followed by the substitution with potassium ethyl xanthate (55%) and subjected to a radical-mediated reaction with ene-carbamate **1043**. Addition of 1.4 equivalents of dilauroyl peroxide (DLP) to refluxing mixture of **1042** and **1043** (3 eq) induced the radical process leading to a radical **1044** which disproportionated to **1045** and the corresponding indoline; immediate exposure to manganese dioxide afforded lactam ester **1045** (78%). A treatment of the ester-carbamate **1045** with trifluoroacetic acid and subsequent re-protection of the resulting amine (84% overall) completed the synthesis of the target molecule **1027**.



SCHEME 14
Reagents and conditions: a) $ClCH_2COCl$, NaOH, $Bu_4N^+HSO_4^-$, CH_2Cl_2. b) KSC(S)OEt, Me_2CO (55%, 2 steps). c) **1043** (3 eq), DLP (1.4 eq), $ClCH_2CH_2Cl$. d) MnO_2 (78%, 2 steps). e) TFA, PhMe. f) Boc_2O, Et_3N (84%, 2 steps)

Bennasar and coworkers disclosed[38] the results of a model study to azepinoindole moiety **1047**, Scheme 15. A comparison of the radical cyclization of selenoesters **1046a** and **1046b** with tributylstannane (Et_3B as initiator, similar results with AIBN or at lower concentrations) has revealed

that the presence in starting material of the carbamate nitrogen had positive effect on the azepinoindole formation (11% (+ 62% **1048a**) and 29% (+ 45% **1048b**), respectively). As expected, the cyclization could be controlled by vinylic bromine: radical cyclization of selenoester **1046c** provided azepinoindole **1047c** as the major product (62% + 19% **1048c**).



1046a X = CH_2, Y = H
1046b X = NCOOMe, Y = H
1046c X = NCOOMe, Y = Br

1047a X = CH_2
1047b X = NCOOMe
1047c X = NCOOMe

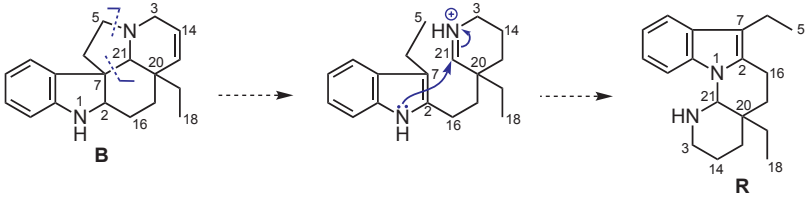
1048a X = CH_2
1048b X = NCOOMe
1048c X = NCOOMe

SCHEME 15
Reagents and conditions: a) Bu_3SnH (2 eq), Et_3B (2 eq), PhH (0.07 M in hydride), dry air, rt 2–7 h (**1046a** → **1047**a 11% + **1048a** 62%; **1046b** → **1047b** 29% + **1048b** 45%; **1046c** → **1047c** 62% + **1048c** 19%)

12. ALKALOIDS WITH A NEW BOND ATTACHED TO INDOLE NITROGEN N-1

12.1. Goniomitine

With only one alkaloid of this structural type existing, the skeleton is derived by rearrangement of aspidospermane skeleton (**B**) through rupture of the 7,21-bond (thus skeleton **F** could be an intermediate) and the N-4–C-5 bond and subsequent trapping of iminium by indole N-1 nitrogen, Scheme 16; see also refs[7,8].

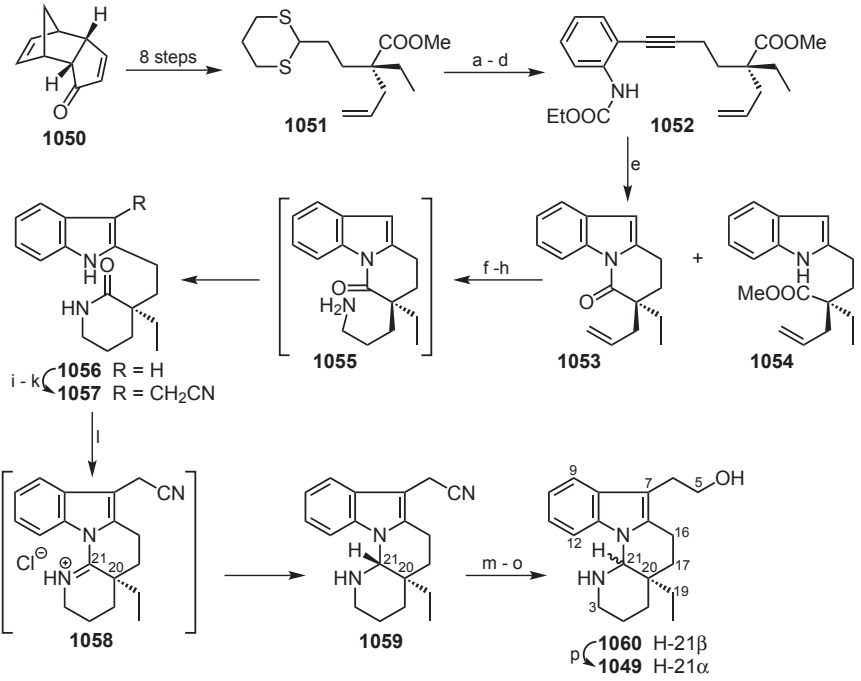


SCHEME 16
Origin of the goniomitine skeleton from aspidospermanes

12.1.1. First Total Synthesis

Soon after the isolation[39] of (–)-goniomitine from *Gonioma malagasy* the total synthesis was reported by Takano and collaborators[40], which also served to determine its absolute configuration as depicted in **1049**, Scheme 17.

The synthesis starts with the eight-step transformation of optically active enone **1050** to ester thioacetal **1051**. The latter compound was further transformed to terminal alkyne whose cross-coupling with ethyl 2-iodophenylcarbamate ($[PdCl_2(PPh_3)_2]$ (2%), CuI (5%)) provided alkyne carbamate **1052** in 81% yield. A treatment of **1052** with an excess sodium ethoxide induced the cyclization to lactam **1053** (70%) accompanied by ester **1054** (11%). The former underwent, on sequential hydroboration with dicyclohexylborane/H_2O_2, Mitsunobu reaction with phthalimide and hydrazinolysis the intermediary amine **1055**, which immediately cyclized



SCHEME 17

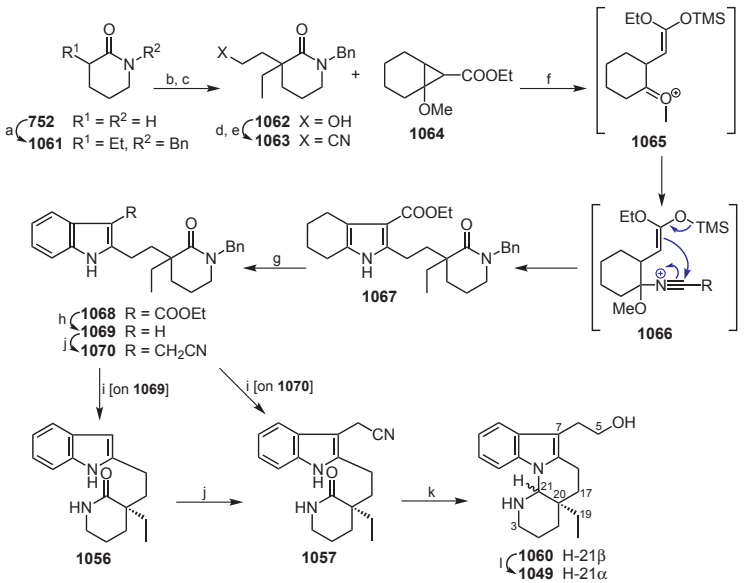
Reagents and conditions: a) MeI (ca. 1 eq), $CaCO_3$ (5 eq), 10% MeCN aq, rfl 1 h. b) CBr_4 (2 eq), Ph_3P (4 eq), Et_3N (3 eq), CH_2Cl_2, 0 °C 5 min. c) LDA (3 eq), THF, –78 °C 10 min (82% overall). d) 2-I-$C_6H_4NHCOOEt$ (1.1 eq), $[PdCl_2(PPh_3)_2]$ (2%), CuI (5%), Et_3N, rfl 30 min (81%). e) NaOEt (10 eq), Et_3N (5%), EtOH, rfl 3 h (**1053** 70% + **1054** 11%). f) $(c\text{-}C_6H_{11})_2BH$ (1.5 eq), THF, 0 °C 30 min, then 10% NaOH aq (1 eq), 30% H_2O_2 (3 eq), 0 °C 30 min. g) phthalimide (1.3 eq), Ph_3P (1.3 eq), $(i\text{-}PrO_2CN)_2$ (1.3 eq), THF, 0 °C 10 min. h) $NH_2NH_2 \cdot H_2O$ (4 eq), EtOH, rfl 2 h (65% overall). i) $H_2C{=}N^+Me_2Cl^-$ (1.5 eq), CH_2Cl_2, rt 30 min. j) MeI, MeOH, rt 10 min. k) NaCN (1.3 eq), DMF, 100 °C 10 min (78% overall). l) $POCl_3$ (6 eq), PhMe, rfl 2 h, then $NaBH_4$, MeOH, 0 °C (84%). m) Dibal-H (1.5 eq), CH_2Cl_2, –75 °C 10 min. n) diluted H_2SO_4 aq. o) $NaBH_4$ (49% overall). p) 30% HCl/MeOH (1:10), rfl 30 min (82%)

to lactam **1056** in 65% overall yield from **1053**; likewise, ester **1054** was converted to **1056** in 44% yield.

Subsequent installation[40] of cyanomethyl group using Mannich chemistry (**1056** → **1057**, 78% overall) preceded cyclization, which was induced by refluxing phosphoryl chloride and the intermediary iminium **1058** provided *trans*-aminal **1059** as a single stereoisomer in 84% yield, Scheme 17. A three-step manipulation of cyanomethyl group gave 49% yield of 21-*epi*-goniomitine (**1060**), whose acid treatment yielded (82%), finally, the thermodynamically more stable natural (–)-goniomitine (**1049**) defining thus its absolute configuration as (20*R*,21*S*).

12.1.2. Pagenkopf's Synthesis

Morales and Pagenkopf have published[41] on the synthesis of racemic goniomitine (±)-(**1049**) that parallels in late stages the Takano efforts, Scheme 18. Their approach, which features the chemistry of activated



SCHEME 18

Reagents and conditions: a) *n*-BuLi (2 eq), EtI, THF, then BnBr (83%). b) LDA, $THPOCH_2CH_2Br$, THF, –78 °C → rt (92%). c) TsOH (cat), MeOH (90%). d) MsCl, Et_3N, CH_2Cl_2. e) NaCN, MeCN, μw, 130 °C (70%, 2 steps). f) **1063**, **1064** (2.9 eq), TfOTMS (1.05 eq), $EtNO_2$, –30 °C (74%). g) Pd/C, mesitylene, rfl (98%). h) NaOH, EtOH aq (1:1), μw, 150 °C (75%). i) **1069** or **1070**, Na, NH_3 (l), THF (97%). j) Takano's protocol (**1056** → **1057** traces; **1069** → **1070** 70%). k) Takano's procedure (37% overall). l) TsOH (cat), MeOH, Et_3N (79%)

cyclopropanes[42,43] and also a new indole synthesis[44], starts from δ-valerolactam (**752**) which was one-pot *C*,*N*-dialkylated to lactam **1061** (83%). As the direct introduction of the propionitrile moiety provided at best 38% yield of **1063** (acrylonitrile, $ZnCl_2$, TfOTMS, Et_3N) the latter was preferably prepared *via* a 4-step procedure commencing with THPO-ethylation of **1061** (92%) and intermediacy of hydroxyethyllactam **1062**.

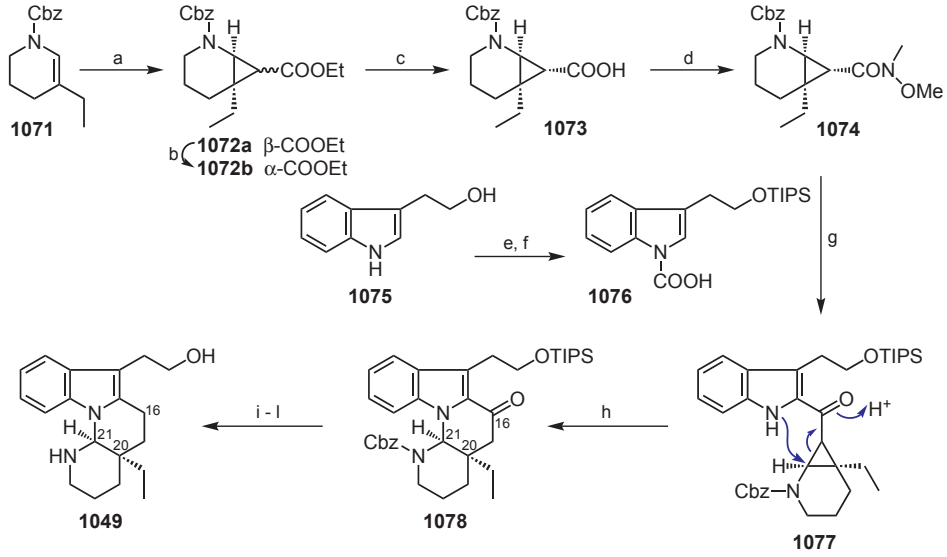
Nitrilelactam **1063** reacted[41] with excess bicyclic ester **1064** in the presence of stoichiometric trimethylsilyl triflate and afforded, likely *via* **1065** and subsequent cyclization of **1066**, tetrahydroindole **1067** in 74% yield, which was efficiently dehydrogenated to indole **1068** on palladium on carbon in refluxing mesitylene (98%), Scheme 18. Microwave-assisted alkaline hydrolysis/decarboxylation of ester **1068** provided indole **1069** (75%), which upon *N*-debenzylation (sodium in liquid ammonia; 97%) gave the indole **1056** constituting a formal total synthesis of (±)-**1049**. Surprisingly, repetition of Takano's protocol on **1056** led to trace amount of **1057** only but, luckily, afforded acetonitrile **1070** in 70% yield from indole **1069**. *N*-Debenzylation of **1070** gave smoothly the known indole **1057** (97%) which, by following Takano's procedure, was transformed without problems into (±)-21-*epi*-goniomitine (**1060**) and, finally, to (±)-goniomitine (**1049**) by acidic epimerization.

12.1.3. Waser's Synthesis

Recently, Waser and co-workers have described[45a] yet another synthesis of racemic goniomitine (**1049**), which is based on the crucial fragmentation/cyclization of cyclopropyl ketone **1077**, Scheme 19. The strategy capitalizes on the fact that the process has to lead inevitably to goniomitine skeleton as the C-3 position in **1077** is blocked by a substituent against homo-Nazarov type reaction (which would otherwise give an aspidospermane tetracyclic precursor); see also review[45b].

Thus, the CuOTf catalyzed cyclopropanation of enamide **1071** (secured in 3 steps from δ-valerolactam (**752**)) with ethyl diazoacetate provided a 1:1 mixture of diastereoisomers **1072** (76%) which could be isomerized with boron trifluoride to the *exo*-isomer and then hydrolyzed (NaOH) to acid **1073** in 91% yield. The unstable acid was converted to Weinreb's amide **1074** using MeNHOMe·HCl together with 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-*N*-methylmorpholinium chloride (DMTMM) as a coupling reagent and *N*-methylmorpholine as a base (93%). Ketone **1077** was obtained by reaction of **1074** with the dilithio-salt (*t*-BuLi/TMEDA) of **1076** in which the indole nitrogen was temporarily protected as the carbamic acid; yield 36%

(48% brsm). The crucial fragmentation/*N*-acyliminium cyclization was induced by toluenesulfonic acid (0.2 eq in CH_2Cl_2 at rt, 10 min) and proceeded with full stereocontrol to the desired tetracycle **1078** (93%). Subsequent removal of the C-16 carbonyl and both the protecting groups proceeded uneventfully and afforded racemic goniomitine (**1049**) in 77% overall yield.



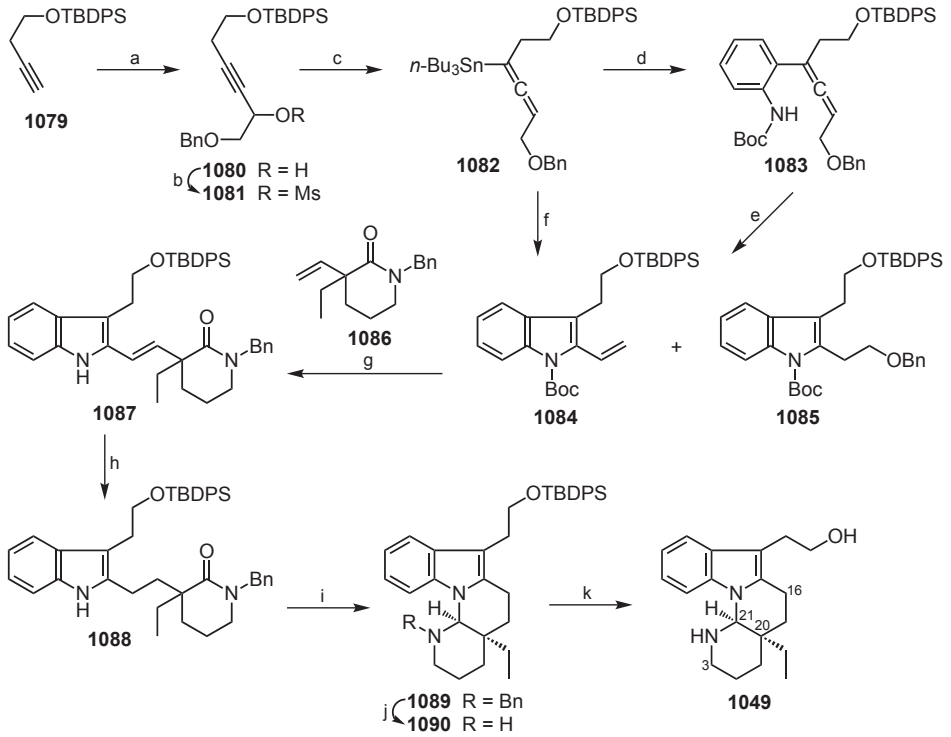
SCHEME 19

Reagents and conditions: a) $N_2CHCOOEt$ (4 eq, added over 18 h), [$(CuOTf)_2$·PhMe] (0.02 eq), CH_2Cl_2 (76%, dr 1:1). b) BF_3·OEt_2 (0.15 eq), CH_2Cl_2, –20 °C → 0 °C. c) NaOH, EtOH/THF/H_2O (3:1:1), 60 °C 2 h (91%, 2 steps). d) DMTMM (1.5 eq), THF, rt 1 h, then MeNHOMe·HCl (1 eq), NMM (2 eq), rt 36 h (93%). e) TIPSCl, imidazole, DMF, rt 1 h (quant). f) *n*-BuLi, Et_2O, 0 °C → rfl 2 h → 0 °C, then CO_2 (g), 0 °C 30 min. g) **1076** (1.5 eq), *t*-BuLi (3 eq), TMEDA (2 eq), THF, –78 °C 3 h, then added to **1074** (20 min), 0 °C 20 min (36%, 48% brsm). h) TsOH (0.2 eq), CH_2Cl_2, rt 10 min (93%). i) $NaBH_4$, MeOH, 0 °C → rt 3 h. j) Ac_2O, py, rt overnight. k) H_2, Pd/C, EtOH. l) TBAF (4.4 eq), THF, rt 30 min (77% overall)

12.1.4. Mukai's Syntheses

Mukai and coworkers have described[46] a synthesis of both racemic and optically active goniomitine, which features the authors' 2-vinylindole synthesis[47] and alkene cross-metathesis as the important steps, Schemes 20 and 21. Synthesis of 2-vinylindole synthon **1084** commenced with the preparation from benzyloxyacetaldehyde of alkynol **1080** (84%) which was converted into mesylate **1081** and then reacted with tributylstannane in the presence of LDA and copper(I) bromide (Marshall's conditions) to give

stannylallene **1082** (80%, 2 steps), Scheme 20. Stille coupling with *tert*-butyl 2-iodophenylcarbamate (3 mole % [$Pd_2(dba)_3$], CuI, tri-α-furylphosphine (TFP)) afforded arylallene **1083** (75%) which cyclized upon treatment with potassium carbonate to indoles **1084** and **1085** in yields 56 and 17%, respectively, based on allene **1082**. However, when the Stille coupling of **1082** was executed as above and in the presence of tetrabutylammonium chloride (TBAC), the desired vinylindole **1084** was obtained directly in 80% yield.

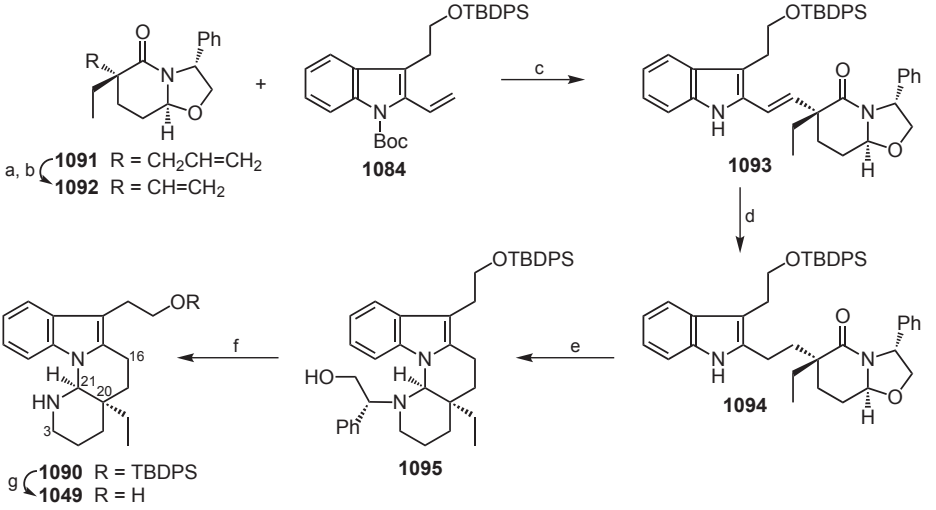


SCHEME 20

Reagents and conditions: a) $BnOCH_2CHO$, *n*-BuLi, THF, –78 °C → rt 22 h (84%). b) MsCl, Et_3N, CH_2Cl_2, 0 °C → rt 20 min (97%). c) LDA, *n*-Bu_3SnH, CuBr·SMe_2, THF, –78 °C 1 h (80%, 2 steps). d) 2-I-PhNHBoc (1 eq), TFP (0.3 eq), [$Pd_2(dba)_3$] (3 mole %), CuI (0.11 eq), DMF, rt 15 h (75%). e) K_2CO_3, EtOH, rt 5 h (**1084** 56% + **1085** 17%, 2 steps). f) 2-I-PhNHBoc (1.28 eq), TBAC (3.29 eq), TFP (0.26 eq), $Pd_2(dba)_3$ (3 mole %), CuI (0.12 eq), DMF, rt 2 h (80%). g) Hoveyda–Grubbs cat. II (0.3 eq), neat, 140 °C 3 h (42%). h) H_2 (1 atm), 5% Pd/C, AcOEt, rt 23 h (97%). i) Dibal-H, THF, –78 °C → rt (87%). j) H_2 (1 atm), 20% $Pd(OH)_2$, AcOH/EtOH (5:2), rt 2 h. k) TBAF, THF, rt 14 h (48%, 2 steps)

In the synthesis of racemic goniomitine[46], the other partner for cross-metathesis – the vinyllactam **1086** – was made accessible from hydroxyethyllactam **1062** [41], Scheme 20. The cross-metathesis of the vinyl piperidone **1086** with the 2-vinylindole **1084** (1.06 eq) was effected with 30 mole % Hoveyda–Grubbs 2nd generation catalyst at 140 °C for 3 h without solvent; the product of simultaneous splitting off the Boc-group, alkene **1087**, was isolated in 42% yield together with some unreacted **1086**. Saturation of the double bond in **1087** led to lactam **1088** (97%), the reduction of which with diisobutylaluminum hydride provided directly tetracycle **1089** (87%). Subsequent removal of the *N*-benzyl group by hydrogenolysis and *O*-desilylation (TBAF) completed the total synthesis of racemic goniomitine (**1049**).

Synthesis of (–)-goniomitine (**1049**) started[46] with the two-step preparation of vinyllactam (–)-**1092** from known[48] allyllactam **1091** (66%), Scheme 21. Application of the above "neat" cross-metathesis procedure with 30 mole % Hoveyda–Grubbs 2nd generation catalyst to **1084** and lactam **1092** (3.5 eq) had failed, however, the reaction was conveniently



SCHEME 21

Reagents and conditions: a) O_3, MeOH, –78 °C 15 min, then $NaBH_4$, –78 °C → rt 2 h (87%). b) 2-O_2N·PhSeCN, *n*-Bu_3P, THF, rt 3 h, then 30% H_2O_2 aq, 0 °C → rt 9 h (76%). c) Hoveyda–Grubbs cat. II (0.32 eq), xylene, 140 °C 3 h (65%). d) H_2 (1 atm), 5% Pd/C, AcOEt, rt 27 h (92%). e) NaH (17.8 eq), Et_2O, 0 °C 30 min, then Dibal-H (1.07 eq), 0 °C → rt 10 min, repeat three-times (62%). f) H_2 (1 atm), 20% $Pd(OH)_2$, *n*-PrOH/1,4-dioxane (1:1), rt 11 h. g) TBAF, THF, rt 14 h (61%, 2 steps)

carried out in xylene at 140 °C for 3 h, and the *N*-deprotected indole (–)-**1093** was obtained (65%) together with some unreacted lactam **1092**. Hydrogenation of **1093** over 5% Pd/C saturated selectively the double bond (92%); the following reduction of (–)-**1094** with Dibal-H failed, but succeeded in the presence of a base which is believed to enhance the reactivity through the formation of ate-complexes: Reduction with excess of diisobutylallane (added in portions) in the presence of a large excess of sodium hydride furnished the desired tetracycle (–)-**1095** (62%), which upon debenzylation and desilylation gave eventually (–)-goniomitine (**1049**).

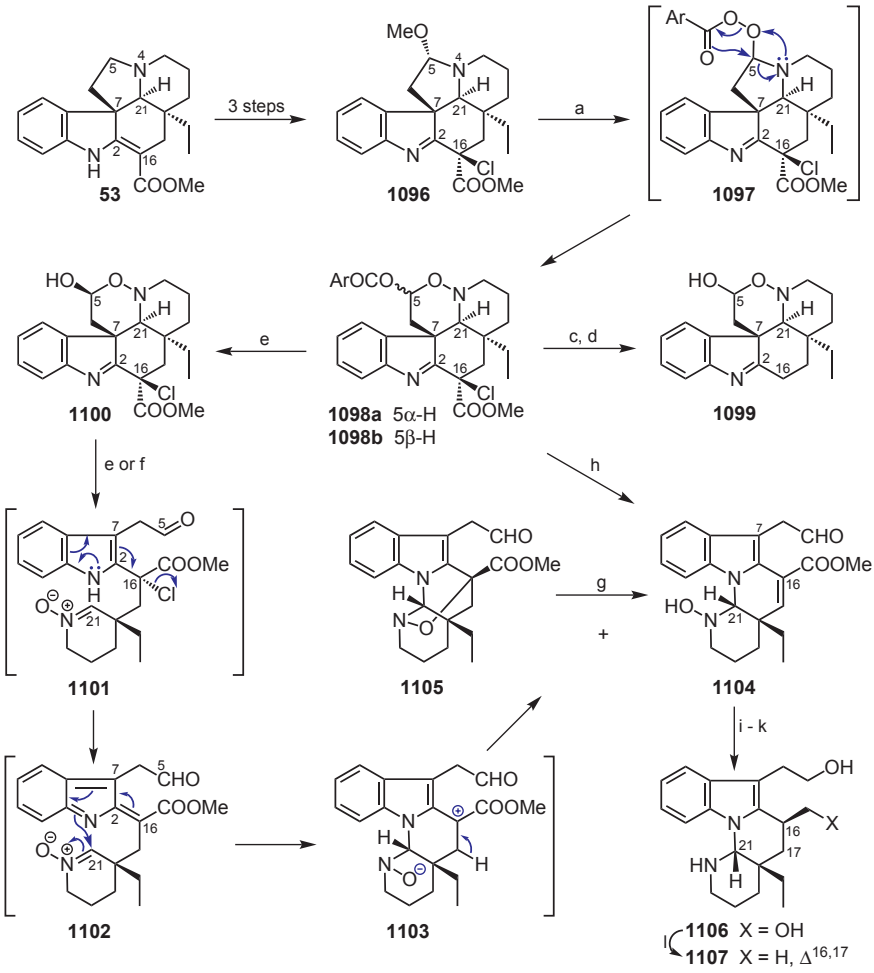
Using the same strategy, but starting from (+)-*ent*-**1092**, the authors have synthesized[46] unnatural goniomitine enantiomer (+)-*ent*-**1049**.

12.1.5. Lewin's Studies

Lewin et al. have reported[49] on the presumably biomimetic transformation of the aspidospermane precursor to tetracyclic aminal **1104** possessing the skeleton of goniomitine, which is based on an efficient method for the cleavage of the N-4–C-5 bond in the aspidospermane skeleton, Scheme 22. The synthesis commenced with the exposure of 5-methoxyaspidospermane **1096**, easily accessible from vincadifformine (**53**), to *meta*-chloroperbenzoic acid. The reaction proceeded probably through ring expansion in **1097** and afforded acetal **1098** (82%) as an epimeric mixture with **1098a** predominating (3:1). Removal of the methoxycarbonyl group was addressed next by a treatment of chloroindolenine **1098** with sodium iodide (quant) followed by a classical heating with hydrochloric acid. As the yield in the last step (→ **1099**) was discouraging (18%), an alternative route was examined.

Thus, the acetal ester **1098** was hydrolyzed[49] to hemiacetal **1100** (71%) prior to the crucial exposure to trifluoroacetic acid (TFA/CH_2Cl_2 1:99, rt 20 min), which could have proceeded through a ring-opening (→ **1101**) and loss of hydrogen chloride (an activation of the indole; → **1102**), Scheme 22. Subsequent cyclization in the highly conjugated quinonoid imine **1102** by a stereoselective addition to the nitrone could have generated carbocation **1103** which accounts for the formation of both tetracycle **1104** (loss of a proton; 42%) and pentacycle **1105** (oxide addition; 11%). As the TFA treatment of **1105** gave mainly **1104**, the reaction time of **1100** with TFA was prolonged to 15 h at rt to give the tetracycle **1104** (52%) almost free of **1105**. Furthermore, the epimeric acetal ester mixture **1098** could be transformed to **1104** directly by prolonging the reaction time to 2 days (48%).

The attempted transformation of **1104** to the (+)-enantiomer of goniomitine was not fruitfull[50], resulting among others in the formation of 16β-hydroxymethylgoniomitine (**1106**), the acid treatment of which provided only olefine **1107** (75%), Scheme 22.

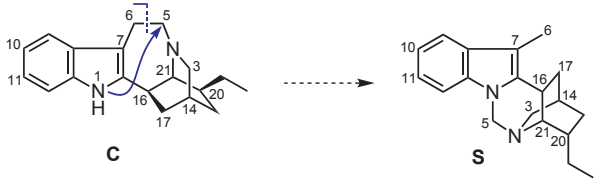


SCHEME 22

Reagents and conditions: a) *m*-CPBA, CH_2Cl_2, rt 3 h (82%, 3:1). b) NaOH, MeOH, rt 5 min (71%). c) NaI, AcOH, rt 1.5 h (quant). d) conc HCl aq, 110 °C 10 min (18%). e) TFA/CH_2Cl_2 (1:100), rt 20 min (**1104** 42% + **1105** 11%). f) TFA/CH_2Cl_2 (1:100), rt 15 h (**1104** 52%). g) **1105**, TFA, rt 4 h (**1104** 40%). h) TFA/ CH_2Cl_2 (1:100), rt 45 h (**1104** 48%). i) $LiAlH_4$, THF, rfl 3 h (57%). j) H_2 (1 atm), 10% Pd/C, MeOH, rt 5 h (35%). k) 1.9 M $TiCl_3$ in 2 M HCl (3 moleq), MeOH, rt 20 h (66%). l) 30% HCl/MeOH (1:10), 120 °C 1.5 h (75%)

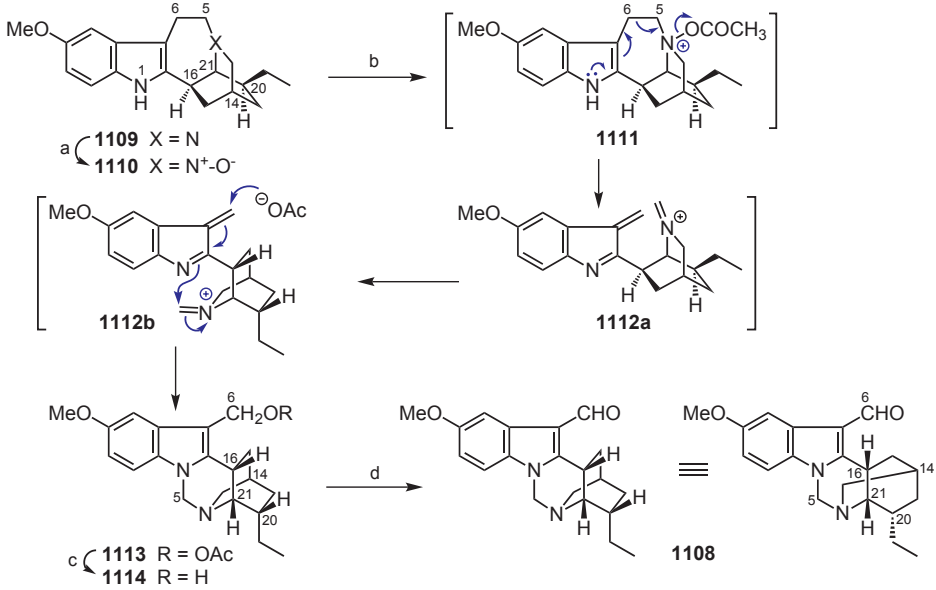
12.2. Lirofoline

There are just two alkaloids of this structural type known to date; the skeleton is derived from ibogane (**C**) by oxidative fragmentation of the C-5–C-6 bond followed by an addition of the indole N-1 nitrogen on an intermediary iminium, Scheme 23.



SCHEME 23
Origin of the lirofoline skeleton from iboganes

A report[51] by Kam and coworkers on the isolation of a new indole alkaloid (–)-lirofoline A (**1108**) from *Tabernaemontana corymbosa* was accompanied by its, presumably biomimetic, preparation from the ibogane alkaloid ibogaine (**1109**), Scheme 24. Ibogaine *N*-oxide (**1110**) was subjected to the

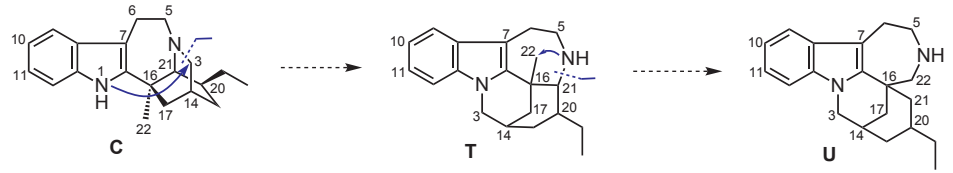


SCHEME 24
Reagents and conditions: a) *m*-CPBA (1 eq), CH_2Cl_2, –30 °C. b) Ac_2O, CH_2Cl_2, –10 °C. c) NaOH (70%, 2 steps). d) TPAP (5 mole %), NMO (20 eq), 4 Å MS (30%)

Polonovskii reaction with acetic anhydride at –10 °C which induced a facile skeletal rearrangement. Fragmentation in **1111** induced a rupture of the C-5–C-6 bond and the thus generated 3-methyleneindoleninium **1112a** underwent ring closure *via* its rotamer **1112b** to yield acetateindole **1113**, which was hydrolyzed by alkali to **1114** (70% overall). Oxidation of the alcohol **1114** with catalytic tetrapropyl perruthenate (TPAP) in the presence of *N*-methylmorpholine *N*-oxide (NMO) completed the synthesis of the alkaloid (and also proved its absolute configuration). Note that already several decades ago the ring system of this alkaloid was obtained repeatedly as side product in transformations of ibogaine (**1109**)[52] and catharanthine (**441b**)[53].

12.3. Rearranged Alkaloid Types with N-1–C-3 Bond from Iboganes

There are two structurally closely related alkaloid types whose formation from iboganes (**C**) starts presumably with oxidative cleavage of the C-3–N-4 bond and then cyclization of a released aldehyde onto the indole N-1 nitrogen, Scheme 25. The chippiine/dippinine class of alkaloids (**T**) thus built might be transformed into the skeleton of tronocarpine (**U**, single alkaloid) upon cleaving the N-4–C-21 bond and following formation of N-4–C-22 bond (lactamization).

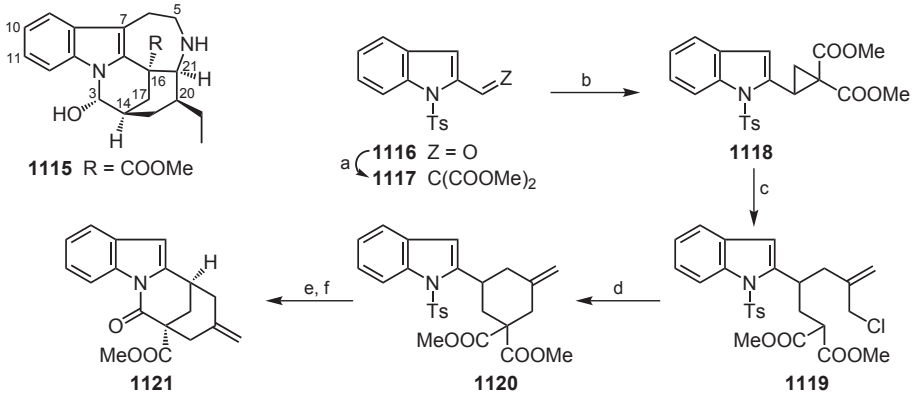


SCHEME 25
Origin of rearranged alkaloid types with N-1–C-3 bond from iboganes

12.3.1. Chippiine/Dippinine Group

Kerr and Sapeta have described[54] a straightforward approach to tetracyclic lactam ester **1121** which might serve as a model to chippiine/dippinine group of alkaloids represented by 10,11-demethoxychippiine (**1115**), Scheme 26; note that (–)-**1115** is isolable from *Tabernaemontana markgrafiana*[55] and *T. divaricata*[56]. Thus, an application of the Corey–Chaikovsky cyclopropanation to methylenemalonate **1117** afforded cyclopropane **1118** (73% over 2 steps) which was subjected to titanium-tetrachloride-mediated ring-opening with 2-(trimethylsilylmethyl)allylchloride. The malonate

1119 (95%) then underwent internal alkylation to **1120** (97%). Now that the tosyl group had played its role, it was removed with Mg in refluxing MeOH, which caused also partial (1:3) cyclization to the target lactam **1121**; exposure of raw mixture to K_2CO_3/DMF completed lactamization to **1121** (47% over 2 steps).



SCHEME 26

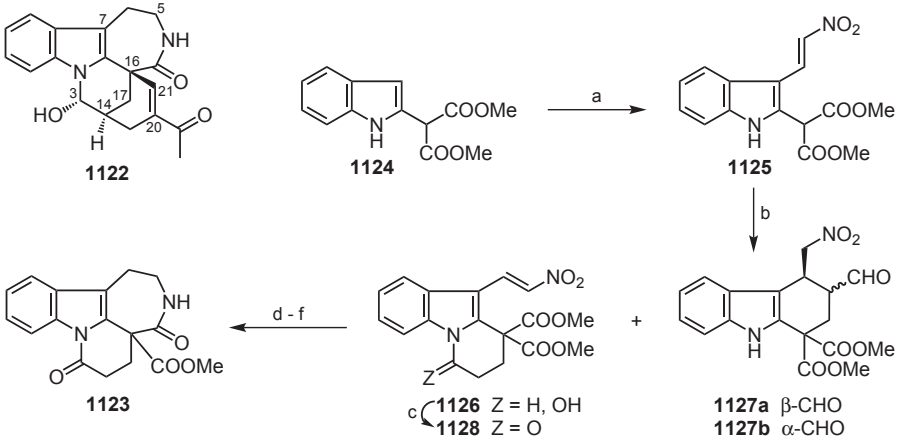
Reagents and conditions: a) $CH_2(COOMe)_2$, $TiCl_4$, py, THF/CH_2Cl_2, 0 °C → rt (87%). b) $Me_3S^+O\ I^-$, NaH, DMSO (84%). c) $TMSCH_2C(=CH_2)CH_2Cl$, CH_2Cl_2, –78 °C → rt (95%). d) NaH, DMF, 0 °C (97%). e) Mg, MeOH, rfl. f) K_2CO_3, DMF, CH_2Cl_2, 50 °C (47%, 2 steps)

The chemistry described above may serve also as a model to the skeleton of tronocarpine (*vide infra*).

12.3.2. Tronocarpine

(+)-Tronocarpine (**1122**) is an alkaloid present in *Tabernaemontana corymbosa* and represents yet another variant of rearranged ibogane skeleton[57]. It was five years before its isolation when Mahboobi and co-workers had synthesized[58] tetracyclic dilactam **1123** which has later on become a popular model target to tronocarpine, Scheme 27. The synthesis commenced with the introduction of a nitrovinyl moiety at C-3 of the starting indole **1124** (48%). The malonate **1125** afforded by reaction with acrolein (triton B as base) pyridoindole **1126** (44%) together with stereoisomeric carbazole carboxaldehyde **1127** (35%). Oxidation of carbinoamine **1126** (CrO_3, py) gave rise to lactam **1128** (84%) and then upon sodium borohydride reduction (silica gel, $CHCl_3$/*i*-PrOH) to saturated nitro compound (85%). The primary amine generated by subsequent hydrogenation over Pd/C slowly

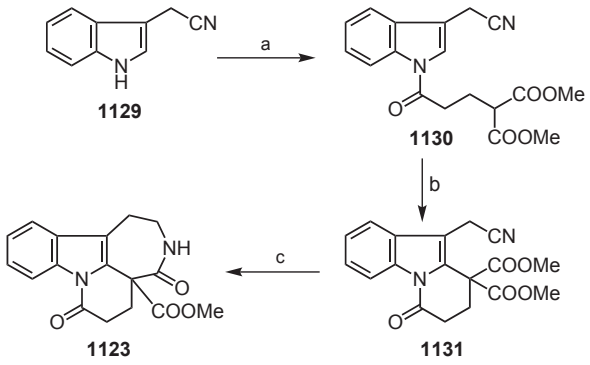
cyclized to dilactam **1123**, a process that was completed by a brief treatment with acid (32% over 2 steps).



SCHEME 27

Reagents and conditions: a) $Me_2NCH{=}CHNO_2$, TFA (excess), CH_2Cl_2, 0 °C 8 h → rt 5 h (58%). b) $CH_2{=}CHCHO$, Triton B (cat), THF, 0 °C → rt 3 h (**1126** 44% + **1127** 35%; **1127a**:**1127b** 53.6:46.4). c) CrO_3, py, 0 °C 30 min → rt 4 h (84%). d) $NaBH_4$, silica gel, $CHCl_3$/*i*-PrOH (8:1), 0 °C → rt 3 h (85%). e) H_2, 5% Pd/C, MeOH, rt. f) HCl aq (→ pH 2) rt (32%, 2 steps)

Kerr and Magolan were the first to report[59] on the synthesis of dilactam **1123** as a model compound to the alkaloid, Scheme 28. Malonate **1130** afforded upon a treatment with manganese(III) acetate in refluxing methanol, presumably through cyclization of the derived malonyl radical onto

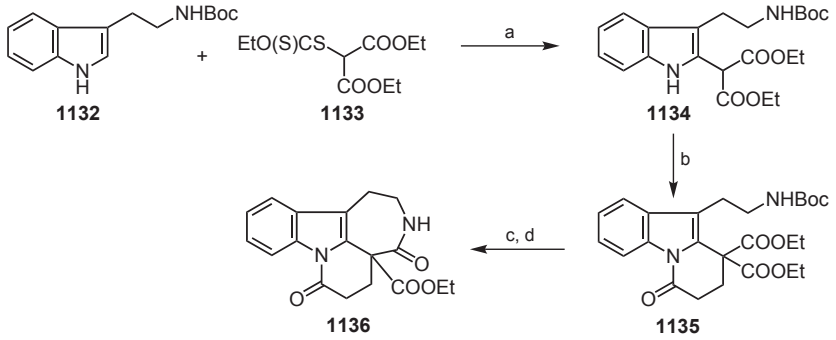


SCHEME 28

Reagents and conditions: a) $(MeOOC)_2CHCH_2CH_2COCl$, NaH, DMF, rt. b) $Mn(OAc)_3$ (3 eq), MeOH, rfl 18 h (72%). c) H_2 (4 atm), Ra-Ni, EtOH, THF, 2 days (87%)

C-2 of indole, the lactam **1131** (72%). Prolonged hydrogenation over Raney-Ni transformed **1131** into the target molecule **1123** in 87% yield.

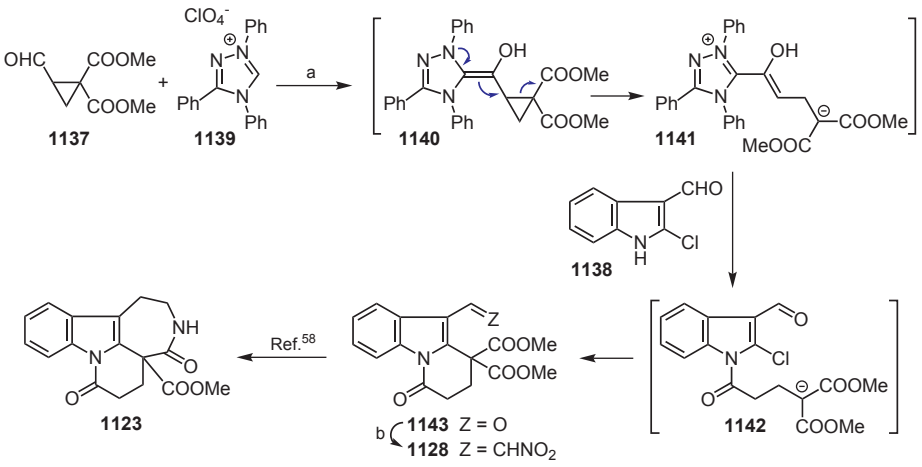
Miranda and collaborators have published the synthesis[60] of the same tetracyclic dilactam (safe for the ester group) which is based on a radical aromatic substitution at C-2 of the protected tryptamine **1132**, Scheme 29. Thus, a reaction of **1132** with xanthate **1133** was initiated by a slow portionwise addition of dilauroyl peroxide (1.8 eq) which also served as the oxidant. The indole malonate **1134** (62%) underwent annulation upon reaction with ethyl acrylate and sodium hydride as a base (→ **1135**; 62%). Consecutive treatment of the latter with TFA and then with excess of K_2CO_3 in MeOH completed the synthesis of the target dilactam **1136** (82% over 2 steps).



SCHEME 29

Reagents and conditions: a) **1133** (2.5 eq), DLP (1.8 eq, slow, portionwise addition), $ClCH_2CH_2Cl$, 85 °C 9 h (62%). b) CH_2=CHCOOEt (4.5 eq), NaH (2.5 eq), THF, rt 16 h (62%). c) TFA (excess), CH_2Cl_2, rt 2 h. d) K_2CO_3 (9 eq), MeOH, rt 4 h (82%, 2 steps)

Another straightforward synthesis of dilactam **1123** by Wang and collaborators[61] takes advantage of a *N*-heterocyclic carbene[62] catalyzed annulation of δ-valerolactam ring onto 2-chloroindole **1138** with aldehyde ester **1137**, Scheme 30. The process commences by the generation of a carbene upon action of DBU (2 eq) on triazolium salt **1139**, which reacts with cyclopropane carboxaldehyde **1137** (3 eq) to form – presumably – *via* opening of the cyclopropane ring in **1140** an intermediate **1141**. Subsequent *N*-acylation of indole **1138** provides malonate **1142**; the intramolecular substitution completes the cascade process furnishing lactam aldehyde **1143** in 50% yield at 68% conversion. Condensation of the aldehyde **1143** provided the known nitroalkene **1128** (63%) which was transformed to **1123** as described above[58].

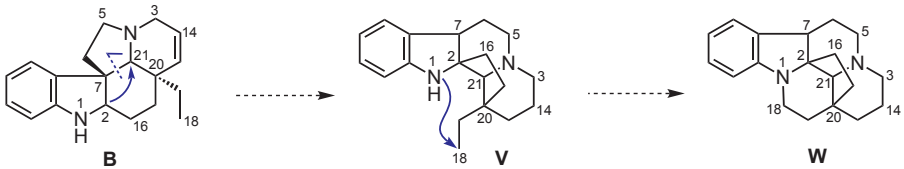


SCHEME 30

Reagents and conditions: a) **1137** (3 eq), **1138** (1 eq), **1139** (0.4 eq), DBU (2 eq), $MgSO_4$ (anhydrous), PhMe, 60–70 °C 40 h (68% conversion, 50% yield). b) NH_4OAc (2.5 eq), $MeNO_2$, 100 °C 12 h (63%)

13. 2,2,3-TRIALKYLINDOLINE ALKALOIDS

Scission of 7,21-bond in aspidospermanes (**B**) and subsequent formation of 2,21-bond leads to skeleton of vallesamidine/secoschizozygane alkaloids (**V**, few members), Scheme 31. The formation of the N-1–C-18 bond (lactamization) then completes the construction of the schizozygane skeleton (**W**).



SCHEME 31

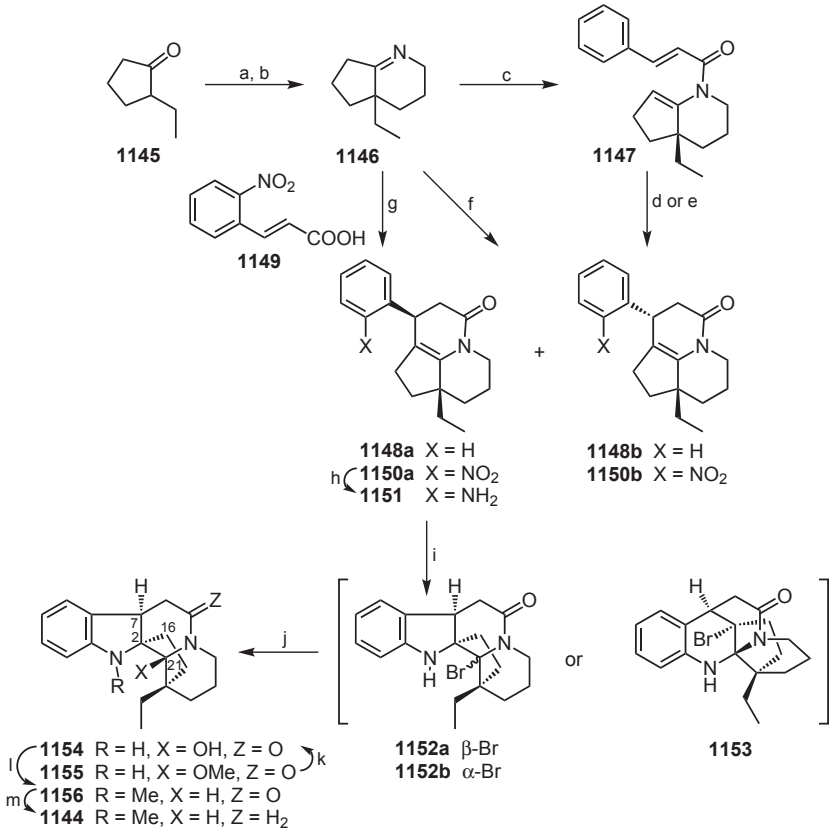
Origin of the secoschizozygane and schizozygane skeleton from aspidospermanes

13.1. Secoschizozygane/Vallesamidine Group

13.1.1. Heathcock's Synthesis

Although published already in 1989–1990, the synthesis of (±)-vallesamidine (**1114**) by Heathcock and coworkers[63,64] is presented here,

Scheme 32, because two other groups (*vide infra*) have achieved formal syntheses by preparation of Heathcock's intermediates. Bicyclic imine **1146** was obtained from ketone **1145** by Michael addition of acrylonitrile (57% brsm) followed by a highly efficient reduction on Raney-Ni (95%), and then



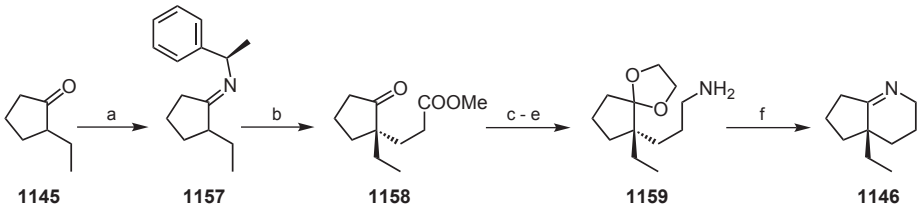
SCHEME 32

Reagents and conditions: a) CH_2=CH·CN (0.5 eq), NaOEt (0.9 eq), THF, rt 2.5 h (57% brsm). b) H_2 (3.9 atm), Ra-Ni powder, KOH, MeOH, rt 20 h (95%). c) cinnamoyl chloride, Et_3N, CH_2Cl_2, 25 °C 15 min (88%). d) cinnamic acid (1.25 eq), decalin, 145 °C 3 days (**1147**:**1148a**:**1148b** 94:4:2). e) hν (254 nm), PhH, rt 10 h (42%, **1148a**:**1148b** 6:94). f) cinnamic acid (1.25 eq), decalin, 145 °C 5 h (65%, **1148a**:**1148b** 6:1). g) **1149** (1.25 eq), **1149**·NH_3 (1.25 eq), dioxane, rfl 90 h (**1150a**:**1150b** > 20:1, **1150a** 42% brsm + **1146** 19.5% + 2-nitrotoluene 7.2% + indole 3%). h) H_2 (3.9 atm), PtO_2, MeOH, rt 1.5 h (99%). i) NBS, CH_2Cl_2, 25 °C 15 min. j) $AgNO_3$ (1.2 eq), MeOH aq (1:3), 25 °C 45 min (**1154** 77% + **1155** 20%). k) **1155**, 60% AcOH aq (**1154** quant). l) $NaBH_3CN$ (15.5 eq), AcOH aq (2:1), 25 °C 30 min → 50 °C 2 h, then $(CH_2=O)_n$, $NaBH_3CN$ (5.15 eq), 25 °C overnight (90%). m) $LiAlH_4$ (6 moleq), THF, rfl 2.5 h (92%)

transformed to enamide **1147** by reaction with cinnamoyl chloride. However, the original strategy had to be somewhat altered after an acid-catalyzed cyclization of **1147** was shown to be highly ineffective, and a photochemical approach provided, in accordance with the presumed conrotatory mechanism, predominantly the unwanted diastereoisomer (**1148a**:**1148b** 1:2 in hexane and 6:94 in benzene). Exposure of the imine **1146** to a hot cinnamic acid provided a mixture with **1148a** predominating (6:1) in 65% yield. Analogous reaction of **1146** with acid **1149**, which under optimum conditions (presence of ammonium nitrocinnamate, refluxing dioxane) proceeded with even higher diastereoselectivity (**1150a**:**1150b** > 20:1), permitted an isolation of the desired tricycle **1150a** in acceptable yield (42% brsm).

Compound **1150a** was reduced[63,64] to aniline **1151** (quant), which cyclized upon treatment with bromosuccinimide to pentacyclic bromides **1152** or **1153**, Scheme 32. Subsequent exposure to silver nitrate provided hemiaminal **1154** and its *O*-ether **1155** in an almost quantitative yield (77 and 20%, respectively). The following reduction/reductive methylation using $NaBH_3CN$ as the reducing agent gave lactam **1156** (90%) which, upon final heating with $LiAlH_4$ to reflux, afforded racemic (±)-vallesamidine (**1144**) in 92% yield. (–)-Vallesamidine (**1144**) was isolated from *Vallesia dichotoma*[65] and *Strempeliopsis strempelioides*[66].

The formal synthesis of vallesamidine has been achived[67] by a Brazilian group with the synthesis of (+)-(*S*)-**1146** by using the d'Angelo asymmetric protocol[68], Scheme 33. Condensation of ketone **1145** with (+)-(*R*)-1-phenylethylamine was catalyzed by TsOH and provided imine **1157**, which on diastereoselective addition to methyl acrylate and acid hydrolysis yielded ketoester (+)-**1158** (70%) with 90% ee. Consecutive ketalization with ethylene glycol (75%), ammonolysis (90%) and a quantitative reduction with



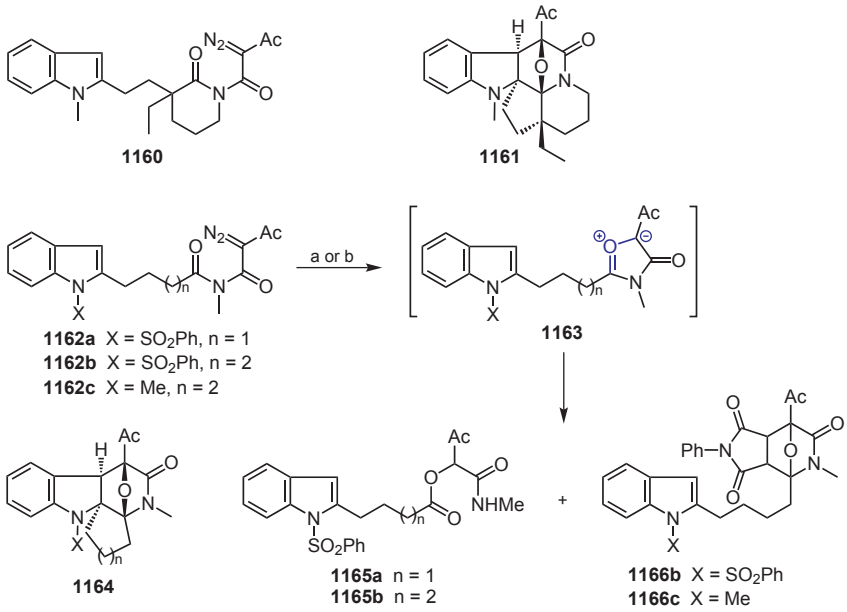
SCHEME 33

Reagents and conditions: a) (+)-(*R*)-$PhCH(Me)NH_2$, TsOH (cat), PhMe, rfl. b) CH_2=CH·COOMe, rt, then 10% AcOH aq, rt (70%, ee 90%). c) $HOCH_2CH_2OH$, TsOH (cat), PhMe, rfl (75%). d) NH_4OH aq, rt (90%). e) $LiAlH_4$, THF, rfl (quant). f) 10% HCl aq, rt (96%)

$LiAlH_4$ afforded ketal amine (–)-**1159** which, upon a treatment with hydrochloric acid, provided the desired bicycle (+)-(*S*)-**1146** in 96% yield and with the same ee.

13.1.2. Padwa's Approach

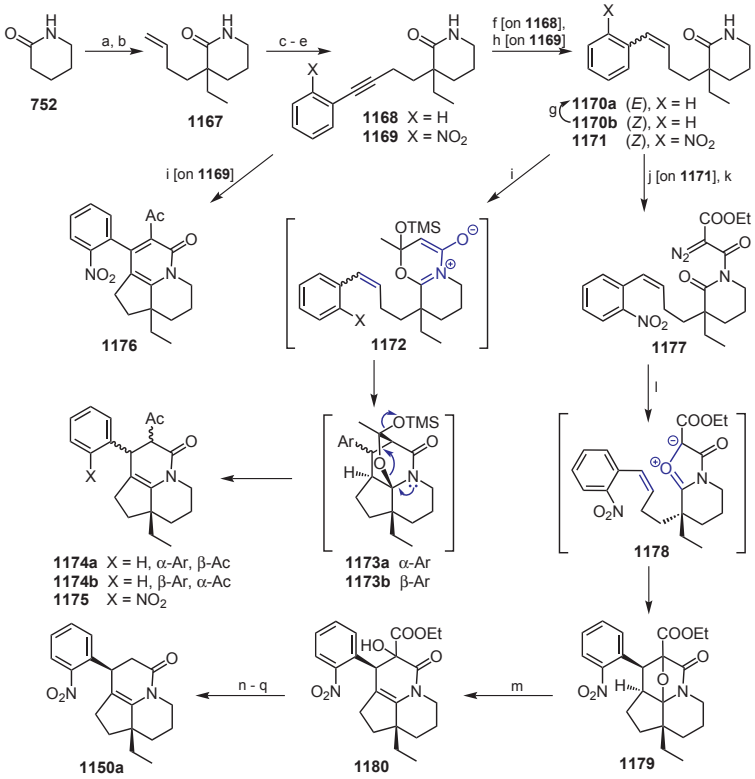
Padwa's explorations on intramolecular [4+2] and [3+2] cycloaddition approaches to various natural products[69–79] have also included studies on the synthesis of vallesamidine. The idea was[80] to generate isomünchnone dipole from diazoimide **1160** and, if the indole 2,3-double bond would serve as a dipolarophile in the cycloaddition, to build the vallesamidine skeleton (→ **1161**), Scheme 34. The approach had to be abandoned as none of the diazoimides **1162** provided upon exposure to rhodium(II) catalyst any tetracycle **1164**. Generation of the dipole **1163** was verified by the isolation of its hydrolysis products **1165** and, unequivocally, by the formation of cycloadducts **1166** in high yields upon reaction with *N*-phenylmaleimide.



SCHEME 34

Reagents and conditions: a) **1162a**, $Rh(OCOCF_2CF_2CF_3)_2$ (cat), PhH, rfl 30 min (**1165a** 50%). b) **1162b**, $Rh(OCOCF_2CF_2CF_3)_2$ (cat), PhH, rt 4 h (**1165b** 78%). c) as in b with *N*-phenylmaleimide (**1166**b 62%). d) **1162**c, $Rh(OAc)_2$ (cat), *N*-phenylmaleimide, PhH, rfl 1.5 h (**1166**c 77%)

Later on, Padwa and coworkers have reported on the preparation[81] *via* key stereoselective dipolar addition of racemic tricycle **1150a**, which constitutes also a formal synthesis of (±)-vallesamidine (**1144**), Scheme 35. The



SCHEME 35

Reagents and conditions: a) CH_2=$CHCH_2CH_2Br$ (1.2 eq), *n*-BuLi (2.1 eq), THF, –78 °C → rt overnight. b) EtI (1.2 eq), *n*-BuLi (2.1 eq), THF, –78 °C → rt overnight (63%, 2 steps). c) Br_2, CCl_4, 0 °C 30 min. d) KHMDS (5 eq), PhMe/THF (1:1), 0 °C 30 min (73%, 2 steps). e) Ar-X (3 eq), $[PdCl_2(PPh_3)_2]$ (cat), Ph_3P (cat), CuI (cat), Et_3N, 25 °C 2 h (**1168** from PhI 95%; **1169** from 2-Br-$C_6H_4NO_2$ 73%). f) **1168**, H_2, [$NaBH_4$ + $Ni(OAc)_2.4H_2O$; 0.18 eq], $H_2NCH_2CH_2NH_2$ (0.37 eq), EtOH abs, rt (**1170b** 96%). g) PhSH (0.51 eq), AIBN (1.3 eq), 80 °C 8 h (92%). h) **1169**, 1,1,3,3-tetramethyldisiloxane (1 eq), $[Pd_2(dba)_3{\cdot}CHCl_3]$ (2.6%), $(2\text{-MePh})_3P$ (cat), AcOH (1 eq), PhH, rt 40 min (**1171** 88%). i) Diketene (1.2 eq), TfOTMS (0.13 eq), PhH, rfl 1 day (**1170a** → **1174a** 63%; **1170b** → **1174b** 61% + enol 31%; **1171** → **1175** 0%; **1169** → **1176** 77%). j) **1171**, EtO_2CCH_2COCl, PhH, rfl. k) 4-$AcNHC_6H_4SO_2N_3$, Et_3N, MeCN, rt (86%, 2 steps). l) $Rh(OCOC_3F_7)_2$ (cat), PhH, rfl 1 h (85%). m) TfOTMS (5 eq), CH_2Cl_2, 0 °C → rt 1 h (95%). n) NaH (1.2 eq), THF, rt 1 h, then PhOCSCl (1.2 eq), rt 30 min (83%). o) Bu_3SnH (4.9 eq), AIBN (1 eq), PhMe, 75 °C 12 h (88%). p) KOH aq/THF, 65 °C 4 h. q) xylene, rfl 3 h (90%)

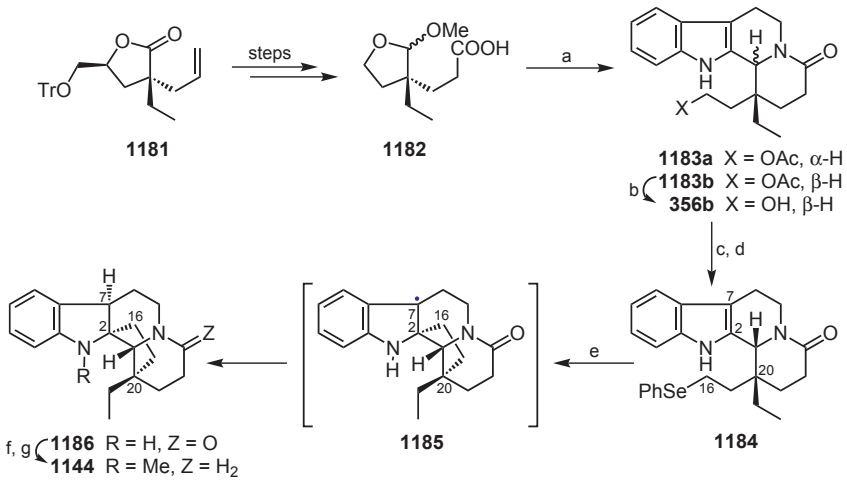
intermediary piperidone alkenes (**1170** and **1171**), as well as alkynes **1168** and **1169** could not be prepared by direct alkylation of δ-valerolactam (**752**) with the corresponding alkenyl or alkynyl halide and thus a stepwise construction of the molecules had to be adopted. 3,3-Disubstituted piperidone **1167** was obtained[81,82] from **752** in 2 steps (63%), then transformed into a terminal alkyne by bromination/LDA treatment (73%) and subjected to the Sonogashira coupling with iodobenzene or 2-bromonitrobenzene upon catalysis with $[PdCl_2(PPh_3)_2]$ and CuI to give the disubstituted alkynes **1168** (95%) and **1169** (73%), respectively. The alkyne **1168** was hydrogenated to (*Z*)-alkene **1170b** on nickel boride (96%), while the presence of nitro group in **1169** made it necessary to use the Trost–Braslau method (1,1,3,3-tetramethyldisiloxane, $[Pd_2(dba)_3]$ (cat), $(2\text{-MePh})_3P$ (cat), AcOH) (→ **1171**; 88%). Finally, **1170b** underwent isomerization to (*E*)-alkene **1170a** upon heating with thiophenol and excessive AIBN (92%), cf. Chap. 14.3. and Scheme 46 for slightly different conditions from **752**.

In model experiments[81,82], lactams **1170** were reacted with diketene and trimethylsilyl triflate as catalyst to prepare the 1,3-oxazinium betaine (→ **1172**), which underwent [4+2] cycloaddition followed by nitrogen mediated fragmentation of **1173**, Scheme 35. The stereochemistry of the product could be controlled by the geometry of dienophile, affording 63% yield of **1174a** from (*E*)-styrene **1170a** *via* **1173a** and 61% yield of **1174b** plus 31% of the corresponding acetyl enol tautomer from (*Z*)-isomer **1170b** (through **1173b** then epimerization), respectively. Unfortunately, (*Z*)-nitrostyrene **1171** failed to give any cycloadduct **1175** due to possibly a complexation of TfOTMS to the nitro group, resulting in net *N*-acetoacetylation of **1171** only (88%; *Z*:*E* 1:1); note that **1169**, an alkyne analogue of **1171**, reacted smoothly affording 77% yield of the corresponding pyridone **1176** (1:1 atropisomeric mixture).

Therefore, the strategy was altered[81] and the starting *Z*-alkenyllactam **1171** was first converted through acylation with malonyl ester chloride and a diazo transfer with 4-acetamidobenzenesulfonyl azide to diazo amide **1177** in 86% yield, which was exposed to catalytic rhodium(II) perfluorobutyrate in boiling benzene, Scheme 35. A highly stereoselective transformation of **1177** to tetracyclic lactam **1179** was induced, which proceeded through a dipolar addition in an intermediary isomünchnone **1178** (85%). Ring-opening of cycloadduct **1179** by trimethylsilyl triflate afforded lactate **1180** (95%) which preceded a removal of both the hydroxy (Barton–McCombie deoxygenation; 73%) and the ethoxycarbonyl groups furnishing the target tricycle **1150a**.

13.1.3. Okada's Radical Approach

The total synthesis of (–)-vallesamidine by Okada and collaborators[83,84] is based on a highly efficient radical construction of 2,2,3-trisubstituted indoline from 2,3-disubstituted indole (**1184** → **1186**), Scheme 36. Optically active acetal acid **1182**, secured in ten steps from the chiral lactone **1181**, afforded upon a nonstereoselective Pictet–Spengler condensation with tryptamine in refluxing AcOH a 1:1 mixture of acetates **1183**, from which the *cis*-isomer (+)-**1183b** was obtained (43%) and hydrolyzed to lactam alcohol (+)-**356b** (72%). Transformation of the alcohol **356b** to selenide (+)-**1184** involved the formation of a mesylate and proceeded in an overall yield of 63%. Crucial radical cyclization of **1184** was initiated by tributyltin hydride/AIBN and provided the desired pentacyclic lactam (+)-**1186** in a yield as high as 91%. A two-step transformation of the lactam **1186** to (–)-vallesamidine (**1144**) completed the first total synthesis of the optically active alkaloid (72%). The success of the cyclization stems presumably from rather sufficient stability of the radical **1185** as compared to an ionic cyclization of alcohols **356**, which inherently ends up in rearrange-

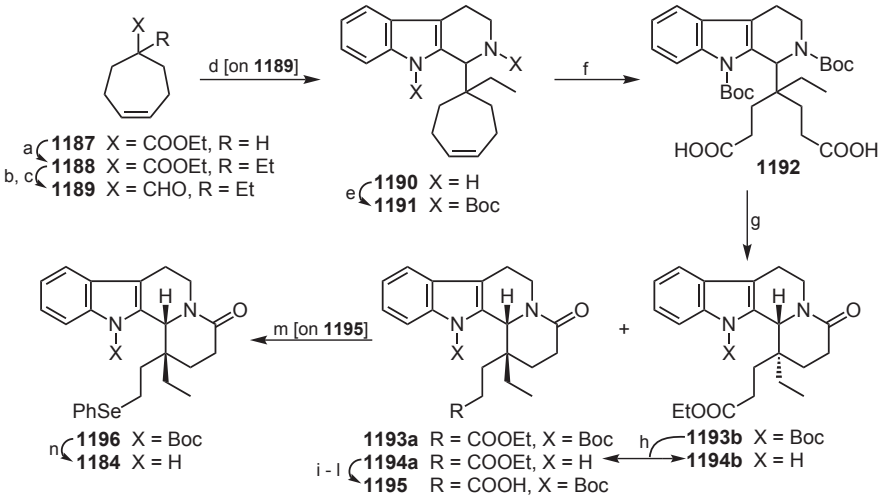


SCHEME 36

Reagents and conditions: a) tryptamine, AcOH, rfl 6 days (**1183a** 44% + **1183b** 43%). b) **1183b**, 20% NaOH aq, MeOH, rt 1 h (72%). c) **356b**, MsCl, DMAP (3.4 eq), py, 0 °C 2 h (92%). d) $(PhSe)_2$ (2.35 eq), $NaBH_4$ (4.46 eq), EtOH, 0 °C 30 min → rt, $NaBH_4$ frequently added during 3 h (68% + 4% eburnane skeleton). e) Bu_3SnH (4 eq), AIBN (2.4 eq), 100 °C 0.5 h (91%). f) $(CH_2{=}O)_n$ (20 eq), $NaBH_3CN$ (3 eq), MeCN, rt 10 min (87%). g) $LiAlH_4$, THF, 70 °C 0.5 h (82%)

ment of quinonoid iminiums to aspidospermane skeletons, see refs[85,86], and also ref.[87] (cf. also Part One[1], Scheme 55).

The synthesis of selenane **1184** by Ho and Chen constituted[88] another formal synthesis of (±)-vallesamidine, Scheme 37. Ester **1187** was converted in a straightforward way to aldehyde **1189** (68% overall), which was condensed with tryptamine and then treated with trifluoroacetic acid. The tetrahydro-β-carboline **1190** thus formed (61%) was then Boc-protected (60%). Scission of the double bond in **1191** by $KMnO_4$ under PT conditions gave diacid **1192** which underwent esterification/lactam formation in refluxing ethanolic TsOH and afforded diastereoisomeric lactam esters *cis*-**1193a** (16%) and *trans*-**1193b** (21%). The latter epimerized upon treatment with refluxing TFA to a mixture of acids *cis*-**1194a** (31%) and *trans*-**1194b** (42%).



SCHEME 37

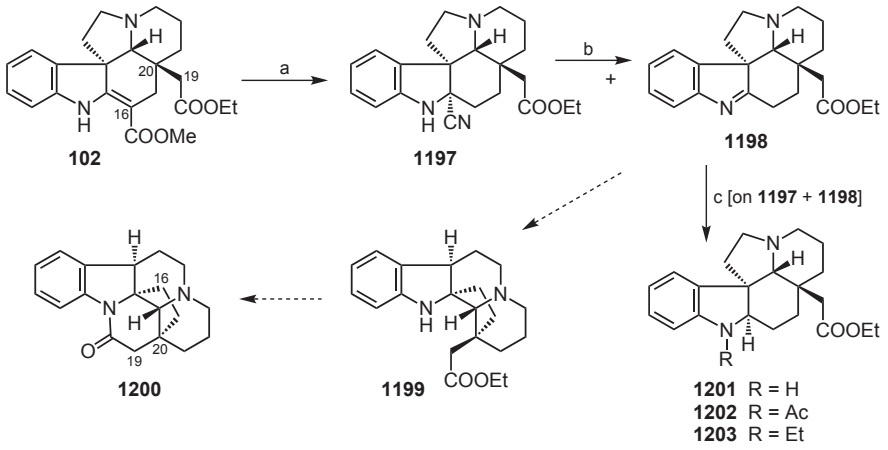
Reagents and conditions: a) LDA, THF, –78 °C 30 min, then EtBr, –78 °C 1 h → rt overnight (95%). b) $LiAlH_4$, THF, 0 °C 30 min → rt overnight (92%). c) PCC, Na_2CO_3, 4 Å MS, CH_2Cl_2, rt 1 h (78%). d) **1189**, tryptamine (1.1 eq), CH_2Cl_2, rt overnight, then TFA (5 eq), 0 °C 1 h → rt overnight (61%). e) Boc_2O, DMAP, CH_2Cl_2, 50 °C overnight (60%). f) $KMnO_4$ (during 30 min), $Bu_4N^+Br^-$ (cat), THF/water (1:6), 0 °C → rt overnight. g) TsOH (cat), EtOH/$CHCl_3$, rfl 18 h (**1193a** 16% + **1193b** 21%). h) **1193b**, TFA (excess), CH_2Cl_2, rfl overnight (**1194a** 31% + **1194b** 42%). i) **1194a**, 50% KOH aq/EtOH, rt overnight (67%). j) BnOH, TMSCl, THF, rfl 18 h. k) Boc_2O, DMAP, CH_2Cl_2, 50 °C overnight (82%). l) H_2, 5% Pd/C, $NaHCO_3$, MeOH, rt 2 h (82%). m) **1195** + diastereoisomer, ClCOOEt, NMM, THF, 0 °C 30 min, then Et_3N, 1-hydroxy-2-thiopyridone, PhSeSePh, CH_2Cl_2, 30 min, then hν (λ 300 nm), 0 °C 1 h (**1196** 24% + diastereoisomer 41%). n) 50% KOH aq/MeOH, rt 2 days (92%)

The *cis*-acid **1194a** underwent[88] a four-step transformation *via* benzyl ester to protected acid **1195**, Scheme 37. An acid mixture (**1195** + diastereoisomer) was subjected to Barton's decarboxylation procedure in the presence of diphenyl diselenane which permitted the isolation of protected selenane **1196** (24%) together with a diastereoisomer (41%). Alternatively, this same procedure but without any interceptor/scavenger was attempted on **1195** but failed to give any secoschizozygane skeleton, which was attributed to Boc-protection of the indole nitrogen. Finally, **1196** was Boc-deprotected by alkaline hydrolysis to give the target selenane **1184** (92%).

13.2. Schizozygane Group

13.2.1. Saxton's Approach

Saxton and Belattar have reported[89] on an unsuccessfull attempt at straightforward synthesis of (±)-strempeliopine (**1200**) from the known[90] vincadifformine analogue **102**, Scheme 38, by using reductive rearrangement of an indolenine **1198** to form pentacyclic amino ester **1199**, a process analogous to that adopted previously by Hájíček and Trojánek in their total synthesis of both racemic[91] and (–)-strempeliopine[92], see also ref.[8]; (–)-**1200** was isolated[66] from *Strempeliopsis strempelioides*. Anilino acrylate **102** (see also Part



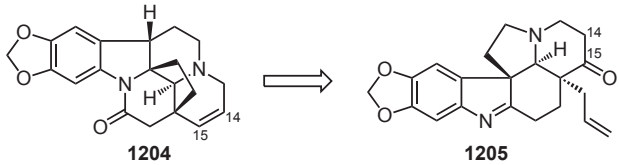
SCHEME 38

Reagents and conditions: a) NaCN (large excess), HMPA, 75 °C 4.5 days (**1197** 47% + **1198** 21%). b) $AgBF_4$ (1.25 eq), THF, rt 4 h (34%). c) **1197** + **1198** (2.2:1), $AgBF_4$, THF, rt 4 h, then evaporate, then Zn, $CuSO_4 \cdot 5H_2O$ (cat), AcOH, 105 °C 6 h (**1201** (11%) + **1202** (18%) + **1203** (16%)

One[1], Scheme 16), bearing an ester functionality at C-19, yielded upon solvolysis with NaCN in hot HMPA a mixture of indolenine **1198**[90] (21%) and cyanoamine **1197** (47%), convertible into the former by a treatment with $AgBF_4$. Unfortunately, an attempt at the reductive rearrangement with zinc and catalytic Cu^{2+} in hot acetic acid led exclusively to products of a direct reduction of the indolenine **1198** – aspidospermane base **1201** (11%), as well as its *N*-acetyl **1202** (18%) and *N*-ethyl derivative **1203** (16%).

13.2.2. Hájíček's Approach

The authors have anticipated that schizozygine (**1204**) could be synthesized by adopting their previous strategy from the strempeliopine case, notably the reductive rearrangement of aspidospermane **1205** bearing 15-carbonyl group as a precursor of the 14,15-double bond as the key step, Scheme 39; note that (+)-**1204** is the principal alkaloid of *Schizozygia caffaeoides*[93], for absolute configuration see ref.[94]

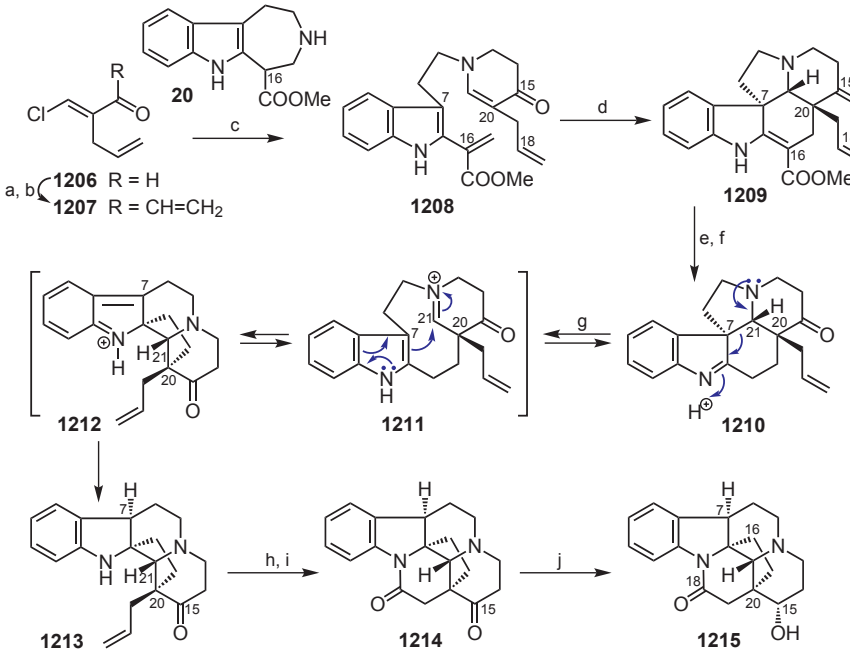


SCHEME 39
Strategy proposal for schizozygine synthesis

In order to prove the compatibity of anticipated conditions with the presence of a ketone carbonyl, Hájíček and Pilarčík have synthesized[95] racemic 15α-hydroxystrempeliopine (**1215**), Scheme 40. Thus, following Kuehne's general strategy[96] the unsaturated ketone **1207**, prepared from aldehyde **1206** in two steps (38%), reacted smoothly with azepine **20** in methanol at r.t. to give, after 20 min a 76% yield of acrylate **1208**, which underwent a stereospecific [4+2] cycloaddition upon heating to reflux in toluene and afforded vincadifformine analogue **1209** (22%).

Alkaline hydrolysis of anilinoacrylate **1209** and subsequent decarboxylation in boiling benzene furnished[95] indolenine **1210** (63%), Scheme 40. Exposure of **1210** to zinc and catalytic copper(II) sulfate in hot acetic acid as described previously[91,92,97] induced reductive rearrangement *via* indole iminium **1211** and quinonoid iminium **1212** to the crucial pentacycle **1213** in 48% yield. Na-Formylation and ozonolytic scission of the terminal double bond gave (±)-15-oxostrempeliopine (**1214**; 27% overall). Finally, a re-

duction of the ketone was shown to be highly stereoselective even with sodium borohydride (90%) and afforded 15α-alcohol **1215**, which could not be dehydrated corroborating thus its relative configuration.

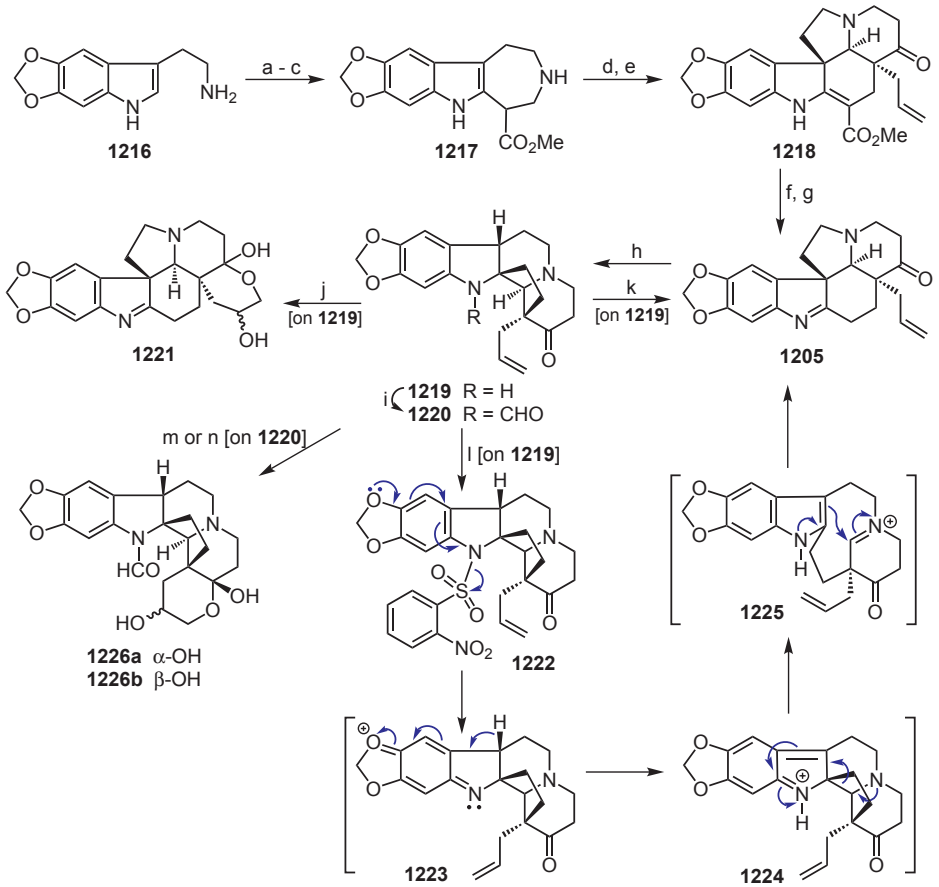


SCHEME 40

Reagents and conditions: a) CH_2=CHMgBr, THF, 0 °C (46%). b) Dess–Martin periodinane, CH_2Cl_2, 0 °C → rt (83%). c) **1207**, MeOH, rt 20 min, rapid isolation under cooling (76%). d) PhMe, rfl 20 h (22%). e) KOH, EtOH, rfl 4 h. f) PhH, rfl 3 h (63%, 2 steps). g) Zn, $CuSO_4 \cdot 5H_2O$ (cat), AcOH, 105 °C 5 h (48% + 19% 18-methylene-15-oxoquebrachamine). h) HCOOH, Ac_2O, rt overnight. i) O_3, 1 M H_2SO_4, MeOH, 0 °C 50 min, then 30% H_2O_2, 0 °C → rt 18 h (27%, 2 steps). j) $NaBH_4$, EtOH, 0 °C → rt (90%)

With these promising results at hand, Hájíček and Pilarčík have started[98] the work at the total synthesis of (±)-schizozygine (**1204**), Scheme 41. 5,6-Methylenedioxytryptamine (**1216**) condensed with methyl chloropyruvate to give tetrahydro-β-carboline (81%), which was transformed almost quantitatively to azepine **1217** using essentially Kuehne's protocol[99] (heating in pyridine followed by a reduction with $NaBH_3CN$). A reaction of **1217** with the unsaturated ketone **1207** yielded an acrylate (69%), whose internal [4+2] cycloaddition in refluxing toluene was much more efficient (as compared to **1208**) and provided anilino acrylate **1218** in a yield as high

as 86%. A two-step conversion to indolenine **1205** proceeded uneventfully (83%) as did the reductive rearrangement, which provided the crucial secoschizozygane **1219** in promising yield (66%) accompanied by 12% of 18-methylene-10,11-methylenedioxy-15-oxoquebrachamine (not shown).



SCHEME 41

Reagents and conditions: a) $ClCH_2CO{\cdot}COOMe$, MeOH, charcoal, rfl 20 h (81%). b) Py, rfl 40 min (99%). c) $NaBH_3CN$, AcOH, then conc HCl aq (88%). d) MeOH, hydroquinone (10 mole %), 20 °C 20 min (69%). e) PhMe, rfl 24 h (86%). f) KOH, MeOH, rfl 3 h (87%). g) PhH, rfl 3 h (95%). h) Zn, $CuSO_4{\cdot}5H_20$ (cat), AcOH, 105 °C 4 h (66% + 12% 18-methylene-10,11-methylenedioxy-15-oxoquebrachamine). i) HCOOH, Ac_2O, rt 2 h (96%). j) **1219**, OsO_4 (0.02 eq), $NaIO_4$ (2 eq), dioxane/H_2O (3:1), 0 °C → 20 °C 3 h (**1221** 13%). k) **1219**, AD-mix-α, *t*-BuOH/H_2O (1:1), 0 °C 15 h (**1205** 80%). l) **1219**, 2-NsCl (2.5 eq), *i*-Pr_2NEt (3 eq), CH_2Cl_2, rt 4 h (**1205** 96%). m) **1220**, OsO_4 (0.01 eq), oxone (4 eq), DMF, rt 3 h (**1226** 10%). n) **1220**, OsO_4 (1 eq), DMAP (2 eq), *t*-BuOH/H_2O (1:1), 20 °C 18 h (**1226** 93%)

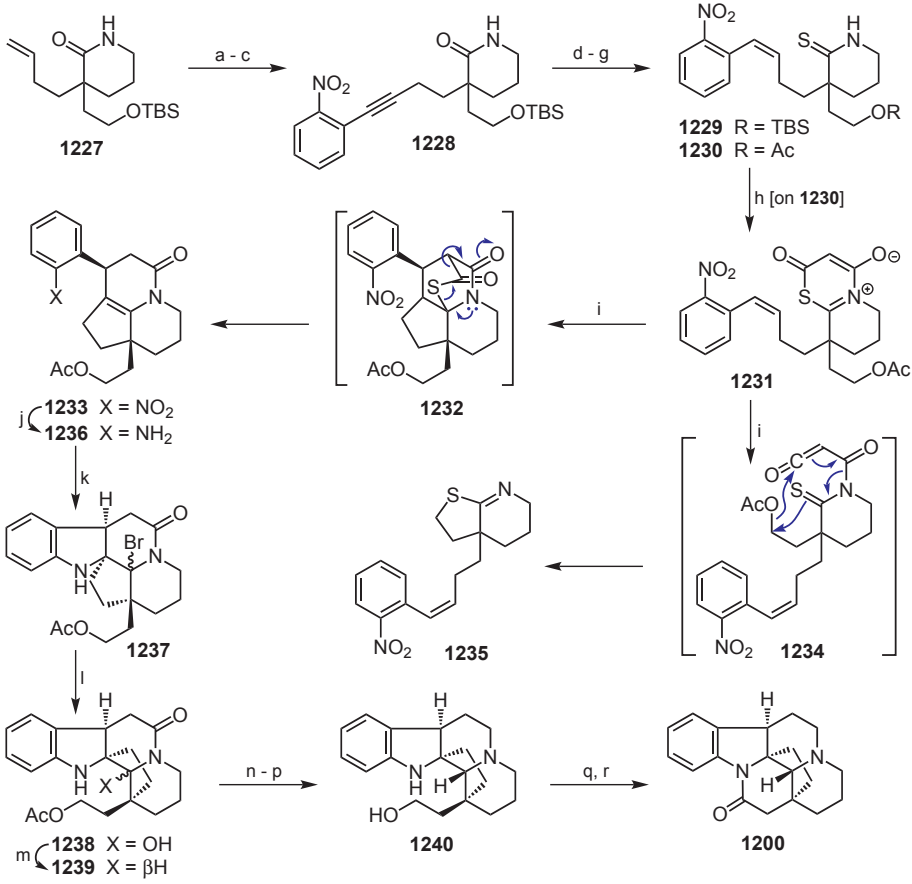
All attempts to cleave by ozonolysis double bond in indoline **1219** as well as in formamide **1220** met with no success, as did almost all other methods resulting in the formation of tarry products[98], Scheme 41. Quite surprisingly, exposure of **1219** to Lemieux–Johnson oxidation permitted the isolation of the rearranged aspidospermane **1221** (13%), as did a treatment with AD-mix-α, which left the terminal double bond intact and induced a clean transformation back to the indolenine **1205** in 80% yield. Anticipating that nosylation of the indoline could stabilize the molecule towards oxidation reagents (→ sulfonamide **1222**), **1219** was treated with an excess of 2-nitrobenzenesulfonylchloride and *i*-Pr_2NEt. However, the indolenine **1205** was isolated in an almost quantitative yield which might have originated through a scission with participation of oxygen in the primary product (**1222** → **1223**) and subsequent intermediacy of **1224** and **1225**; note that these same specii in reversed order are the presumed intermediates in the reductive rearrangement of **1205** (cf. **1211** → **1212** in Scheme 40). On the other hand, reaction of formamide **1220** with catalytic osmium tetroxide and oxone gave a low yield of diastereoisomeric hemiacetal **1226** (13%), a compound which could be efficiently prepared by dihydroxylation with stoichiometric OsO_4 (93%).

13.2.3. Padwa's Synthesis

Padwa and collaborators have reported on the synthesis[100] of (±)-strempeliopine (**1200**), which relies upon [4+2] cycloaddition of a cross-conjugated betaine[101,102] as the crucial skeleton-building step (for general reviews see Chap. 13.1.2.), Scheme 42. As the lactams **1228** or **1229** could not be secured by direct alkylation with an alkynyl or alkenyl halide, a multistep procedure had to be adopted: 3,3-Disubstituted piperidone **1227**, obtained in 2 steps from δ-valerolactam (**752**; 62% overall), was converted into terminal alkyne by bromination/LDA treatment (66%) and then subjected to Sonogashira coupling with 2-iodonitrobenzene upon catalysis with [$PdCl_2(PPh_3)_2$] and CuI to give a disubstituted alkyne **1228** (79%). The alkyne was reduced with 1,1,3,3-tetramethyldisiloxane by the Trost–Braslau method ([$Pd_2(dba)_3$] (cat), (2-MePh)$_3$P (cat), AcOH) to alkenes (88%) with 9:1 stereoselectivity in favor of the desired *cis*-isomer which could not be converted directly to thiolactam **1229** with Lawesson's reagent (<15%), but was transformed uneventfully to **1230** after a change of the protecting group to acetyl (61% overall).

Thiolactam **1230** reacted[100] with carbon suboxide to afford the isolable bright yellow dipole **1231** (80%) which led upon thermolysis in toluene at

200 °C *via* **1232** to the desired tricycle **1233** albeit only in 31% yield, Scheme 42; the yield could not be improved as a part of the dipole **1231**



SCHEME 42

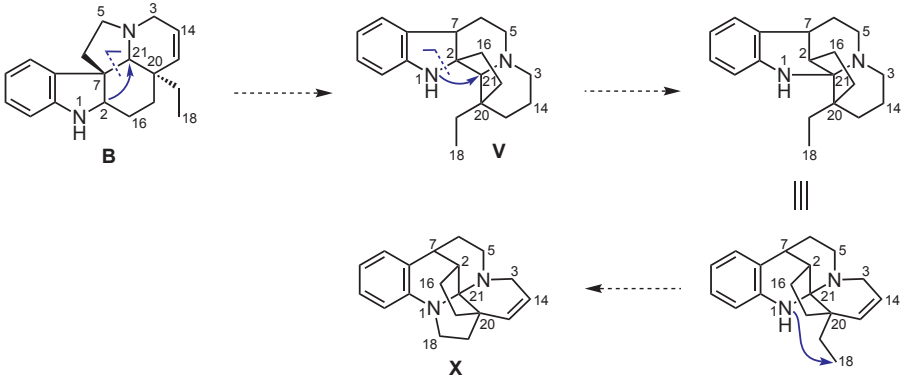
Reagents and conditions: a) Br_2, CCl_4, rt 1 h. b) LDA (excess), THF, –78 °C → rt (2 h) 15 h (66%, 2 steps). c) 2-I-$C_6H_4NO_2$ (1.19 eq), [$PdCl_2(PPh_3)_2$] (2.5%), CuI (5.0%), *i*-Pr_2NH (excess), THF, rt 15 h (79%). d) 1,1,3,3-tetramethyldisiloxane (1 eq), [$Pd_2(dba)_3$·$CHCl_3$] (2.4%), (2-MePh)$_3$P (10%), AcOH (1 eq), PhH, rt 2 h (88%; *Z*:*E* 9:1). e) TBAF (1.45 eq), THF, 0 °C 30 min → rt 3 h (87%). f) Ac_2O, DMAP, Et_3N, CH_2Cl_2, 0 °C 1 h (98%). g) Lawesson's reagent (0.61 moleq), PhMe, rfl 2 h (**1230** 71%). h) O=C=C=C=O, CH_2Cl_2, Et_2O, –78 °C → rt 45 min (80%). i) PhMe (sealed tube), 200 °C 1 h (**1233** 31% + **1235**). j) H_2 (4 atm), 10% Pd/C, EtOH, THF, rt 15 h. k) NBS, CH_2Cl_2, rt 20 min. l) $AgNO_3$, MeOH aq, rt 1 h (21%, 3 steps). m) $NaBH_3CN$, AcOH aq, rt 30 min → 50 °C 2 h (69%). n) Lawesson's reagent (0.57 moleq), PhMe, rfl 2 h (93%). o) H_2, Ra-Ni, THF, rt 1.5 h (64%). p) K_2CO_3, MeOH, 0 °C 2 h → rt 1 h (99%). q) Dess–Martin periodinane (2 eq), CH_2Cl_2, rt 45 min. r) PDC, CH_2Cl_2, rt 1 h (29%)

was consumed through an alternative pathway shown in **1234** leading to a similar yield of bicyclic imine **1235**. Construction of the vallesamidine skeleton, patterned after the Heathcock's vallesamidine strategy (cf. Chap. 13.1.1.), commenced with reduction of the nitro group in **1233** followed by a treatment of the labile aniline enamine **1236** with *N*-bromosuccinimide. The resulting pentacyclic bromide **1237** was converted to hydroxy amide **1238** (unknown stereochemistry) with silver nitrate (21% from **1233**) and then to stereohomogeneous indoline **1239** by reduction with $NaBH_3CN$ (69%).

The lactam oxygen in **1239** was best removed[100] by a two-step procedure (thionation with Lawesson's reagent/Ra-Ni desulfurization; 60%) and the resulting ester was quantitatively hydrolyzed to pentacyclic alcohol **1240** with K_2CO_3, Scheme 42. The synthesis of racemic strempeliopine (**1200**) was completed by an exposure of the alcohol **1240** first to Dess–Martin periodinane and then to PDC (29%).

14. ISOSCHIZOZYGANE GROUP

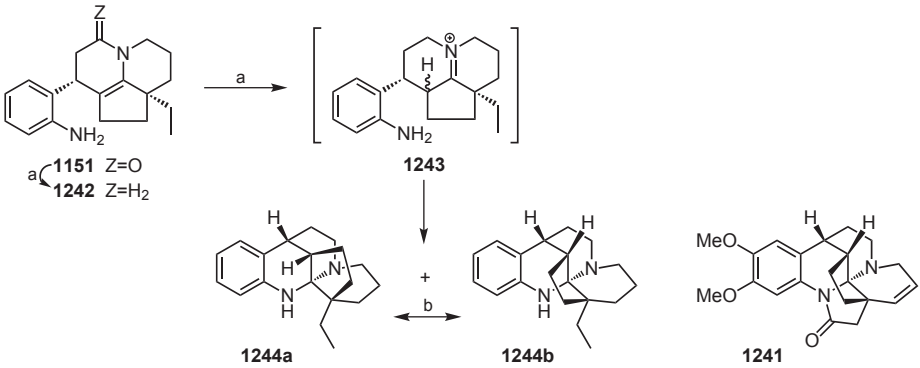
The vallesamidine/secoschizozygane skeleton (**V**) can serve as common precursor for both the schizozygane (**W**; Chap. 13.) and the isoschizozygane (**X**) alkaloids, Scheme 43. Subsequent expansion of the indoline skeleton in **V** to tetrahydroquinoline (scission of the N-1–C-2 bond and formation of the N-1–C-21 one as a part of the aminal moiety) and lactamization (formation of N-1–C-18 bond) completes the construction of the hexacyclic isoschizozygane framework **X**.



SCHEME 43
Origin of the isoschizozygane skeleton from aspidospermanes

14.1. Heathcock's Synthesis

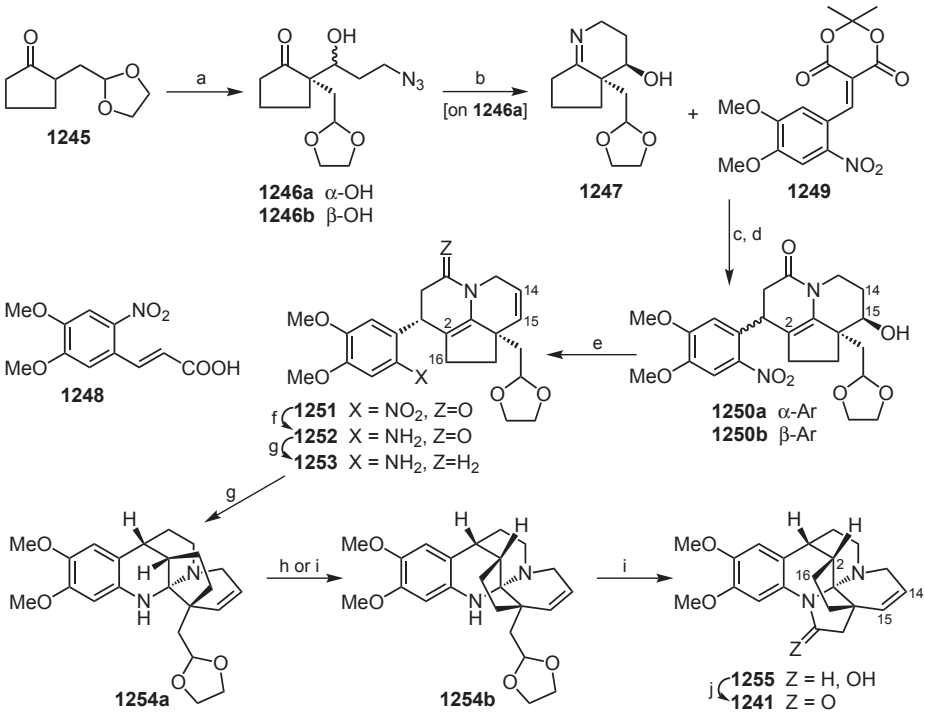
The total synthesis of racemic isoschizogamine (**1241**) was published by Heathcock and Hubbs[103]. In a model study, the authors tested the feasibility of the crucial aminal moiety formation as outlined in Scheme 44. Enamine **1242**, accessible from the enamide **1151** by reduction with $LiAlH_4$, underwent already during work-up a smooth addition of aniline nitrogen to intermediary immonium **1243** to form a mixture of aminals, in which the unwanted stereoisomer **1244a** prevailed (7:5); any of the stereoisomers equilibrated in acetic acid to a mixture with the "naturally"-configured amine **1244b** dominating (85:15).



SCHEME 44
Reagents and conditions: a) $LiAlH_4$ (1 moleq), THF, rfl 20 h (**1244a** 47% + **1244b** 34%). b) **1244a** or **1244b**, AcOH, rt 2 h (**1244a**:**1244b** 15:85)

Encouraged by these results the authors have developed[103] the total synthesis of (±)-isoschizogamine (**1241**), which is reminiscent of their strategy exploited in the vallesamidine case (cf. Chap. 13.1.1.), Scheme 45; note that the hydroxy group in bicyclic imine **1247** served as a precursor of the 14,15-double bond. In order to achieve high diastereoselectivity in the formation of aldol **1246**, the thermodynamic potassium enolate of cyclopentanone **1245** was generated by a slow addition of KHMDS and then transformed optimally to the corresponding boronate (Bu_2BOTf), whose aldol reaction with azidopropanal provided aldol **1246a** in an acceptable yield (49%) and with the ratio **1246a**:**1246b** higher than 95:5. The aldol **1246a** rearranged upon hydrogenation over 10% Pd/C to bicyclic imine **1247** in 71% yield.

Surprisingly, imine **1247** failed[103] to add to dimethoxy analogue **1248** of the cinnamic acid **1149** (cf. Scheme 32), as did to the corresponding acid chloride, azide, anhydride and ester, Scheme 45. However, the imine **1247** underwent Michael addition to Meldrum's derivative **1249**; subsequent cyclization in refluxing toluene yielded the target enamide **1250a** (67%) as the strongly prevailing diastereoisomer (88:12). The consecutive dehydration with $[Ph(F_3C)_2CO]SPh_2$ (74%) and a reduction of the nitro group in compound **1251** with $NaBH_4$ and $Cu(acac)_2$ afforded an unstable aniline



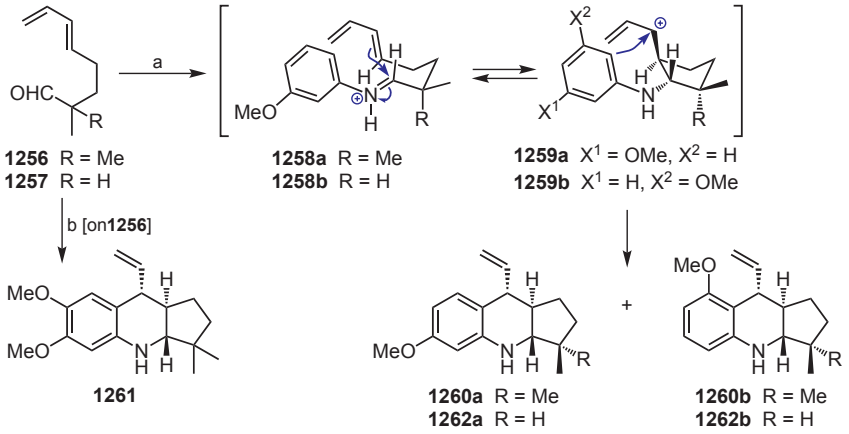
SCHEME 45

Reagents and conditions: a) KHMDS (1.1 eq, during 2 h), THF, rt, then Lewis acid, then 3-azidopropanal (1.25 eq), –78 °C 1 h: LiBr (5 eq, 0 °C 20 min: 67%, **1246a** 40% + **1246b** 27%); Bu_2BOTf (1.05 eq, –78 °C 30 min: **1246a** 49%, **1246a**:**1246b** > 95:5); *i*-Bu_2AlH (1.05 eq, –78 °C 30 min: **1246a** 55% + **1246b** 16%). b) **1246a**, H_2, 10% Pd/C, EtOH, rt 1 h (71%). c) **1247**, CH_2Cl_2, –40 °C, then **1249** (1.1 eq), –40 °C 20 h → rt (3 h). d) PhMe, rfl 10 min (**1250a** 65% + **1250b** 9%). e) **1250a**, $[Ph(F_3C)_2CO]SPh_2$ (1.1 eq), CH_2Cl_2, rt 1 h (74%). f) $NaBH_4$ (9.8 moleq), $Cu(acac)_2$ (0.3 eq), EtOH, rt 20 min, then **1251**, THF, rt 4.5 h. g) $LiAlH_4$, THF, rfl 14 h. h) AcOH aq (1:1), rt 1 h (**1254a**:**1254b** 3:7). i) AcOH aq (1:1), rfl 3 h. j) PDC, CH_2Cl_2, rt 3.5 h (27% from **1251**)

enamide **1252**, which was immediately reduced by $LiAlH_4$. The resulting enamine **1253** cyclized in this case stereoselectively to unwanted aminal **1254a**. The latter could be upon exposure to aqueous acetic acid either epimerized (rt, 1 h) to a stereoisomeric mixture **1254b**:**1254a** (7:3), or was converted under more forcing conditions (rfl, 3 h) directly into hemiaminal **1255**, the oxidation of which with PDC then completed (27% from **1251**) an 8-step synthesis of (±)-**1241** in an overall 7% yield from ketone **1245**. (–)-Isoschizogamine (**1241**) was obtained[104,105] from *Schizozygia caffaeoides*; for absolute configuration see ref.[106].

14.2. Magomedov's Approach

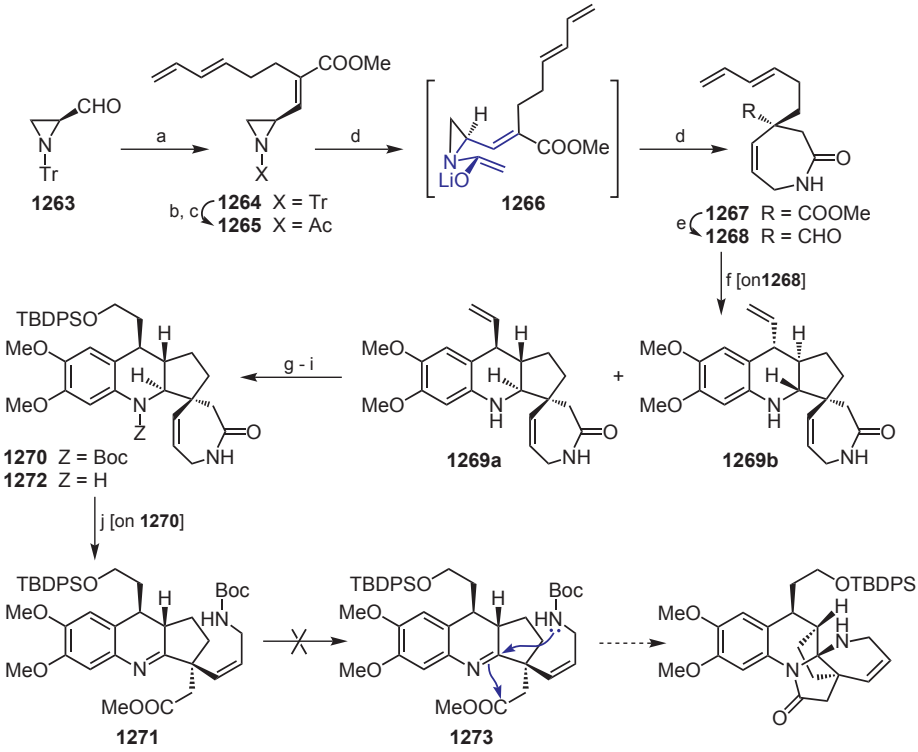
Magomedov reported[107] on a model synthesis of cyclopenta[b]quinoline subunits to isoschizozygane alkaloids, which is based on a formal hetero [4+2] cycloaddition of arylimines, Scheme 46. The reaction was shown to be acid catalyzed with the best yields and regioisomer ratios achieved with catalytic TsOH in refluxing aromatic hydrocarbon. Thus, the condensation of aldehyde **1256** with *meta*-anisidine in refluxing benzene (5 mole % TsOH) gave predominantly tricycle **1260a** (75%) accompanied by regioisomer **1260b** (10%). The cyclization proceeds in a conformation with lesser steric interaction **1258a** and the following electrophilic aromatic closure preferably in allylic cation **1259a**; three chiral centers are formed



SCHEME 46

Reagents and conditions: a) *m*-Anisidine (1 eq), TsOH (5 mole %), PhH, rfl 1 h (**1256** → **1260a** 75% + **1260b** 10%; **1257** → **1262a** 76% + **1262b** 11%). b) **1256**, 3,4-dimethoxyaniline (1 eq), TsOH (5 mole %), PhH, rfl 1 h (71%)

stereospecifically in both products. The condensation of **1256** with 3,4-dimethoxyaniline proceeded quite regioselectively and provided tricycle **1261** in 71% yield. Importantly, the presence of a chiral center in starting aldehyde has profound impact on the product stereochemistry; reaction of the racemic aldehyde **1257** with *meta*-anisidine afforded regioisomers **1262a** and **1262b** in yields 76 and 11%, respectively, which may be accounted for by the cyclization *via* a transition state **1258b** with the methyl group in equatorial position.

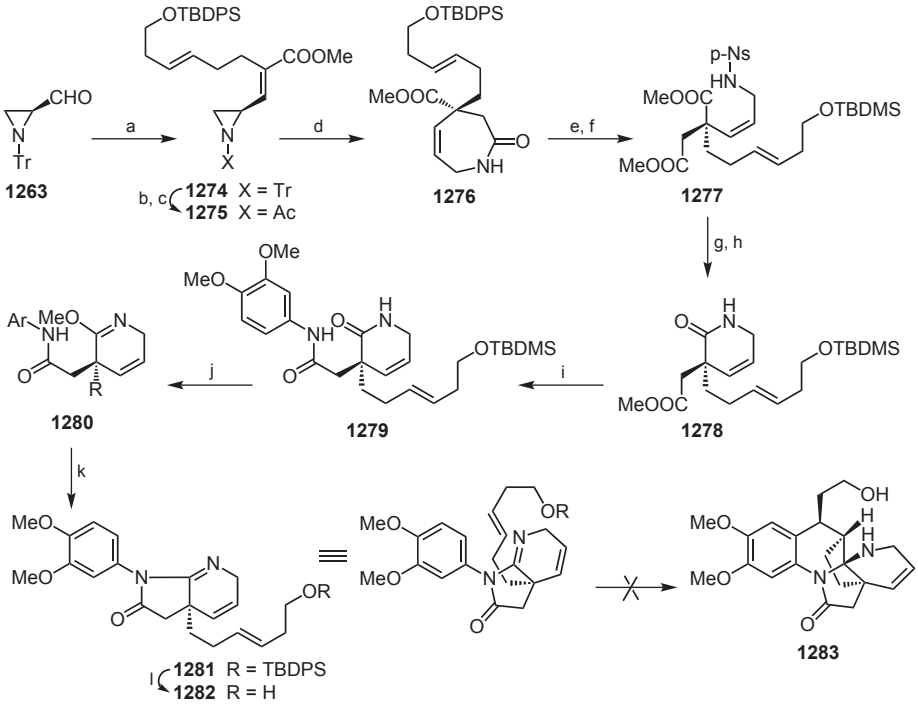


SCHEME 47

Reagents and conditions: a) CH_2=CHCH=$CHCH_2CH_2CH$(COOMe)$PO(OEt)_2$, $Ba(OH)_2$ (1 eq), THF/H_2O (40:1), rt 30 min, then **1263** (1 eq), rt 5 h (**1264** 88%; *E*:*Z* 11:1). b) Et_3SiH (4 eq), TFA (4 eq, dropwise), CH_2Cl_2, 0 °C 20 min (71%). c) Ac_2O (5.3 eq, dropwise), DMAP (cat), Et_3N, 0 °C 5 min (90%). d) **1265**, LiHMDS (2 eq, dropwise), PhMe, –78 °C 20 min → 100 °C 10 min → rt (77%, ee 97%). e) Dibal-H, PhMe, –78 °C 20 min (59%). f) 3,4-Dimethoxyaniline (1.2 eq), TsOH (0.1 eq), PhMe, rfl 30 min (**1269a**:**1269b** 10:1; **1269a** 70%). g) 9-BBN (5 eq), THF, 0 °C → rt 1 d, then H_2O, 0 °C, then H_2O_2, NaOH, 2 h (55%). h) TBDPSCl (1.2 eq), DMAP (1 eq), Et_3N, CH_2Cl_2, rt 3 h. i) Boc_2O, DMAP, Et_3N, CH_2Cl_2, rt 30 min (66%, 2 steps). j) NaOMe (2 eq), MeOH, 0 °C 30 min (**1271** 39% + **1272** 49.5%)

With the efficient cyclization procedure at hand, Magomedov and Zhou have developed two approaches[108] to prepare optically active isoschizogamine using a highly stereoselective aza-Claisen rearrangement to construct advanced intermediates in both cases. Enantiopure aldehyde (*R*)-**1263** was subjected to Horner–Wadsworth–Emmons olefination with the phosphonate (*E*)-CH_2=CH·CH=CH·CH_2CH_2CH(COOMe)PO$(OEt)_2$ and $Ba(OH)_2$ as a base to give the acrylate (–)-**1234** (88%; *E*:*Z* 11:1) in the first synthesis, Scheme 47. After a change of the *N*-protecting group in **1264** to acetyl, the compound (–)-(*R*)-**1265** was metallated with LiHMDS at –78 °C for 20 min. It has been shown that the rearrangement in **1266** was, due to high activation energy, best effected in toluene by a brief heating to 100 °C (10 min). (+)-(*R*)-Caprolactam **1267** thus obtained (77%, ee 97%) was reduced with Dibal-H to aldehyde **1268** (59%). The crucial TsOH-catalyzed cyclization of the latter with 3,4-dimethoxyaniline proved to be highly diastereoselective (dr 10:1), permitting the isolation of advanced intermediate (+)-**1269a** in 70% yield. The vinyl group in **1269a** was then transformed to protected hydroethyl (→ **1270**) in 3 steps. Exposure of the caprolactam **1270** to sodium methoxide provided the Boc-protected amino ester (–)-**1271** (39%) accompanied by amine **1272** (49.5%), which could be reprocessed. Unfortunately, all attempts to selectively dehydrogenate tetrahydroquinoline **1271** to dihydroquinoline **1273** have failed due to instability of the latter.

In the second approach[108], the (*R*)-aldehyde **1263** was transformed to caprolactam **1276** by the above discussed 4-step method (39% overall); the aza-Claisen rearrangement was as stereoselective as above and yielded (–)-(*R*)-**1276** with ee 98% (55%), Scheme 48. The caprolactam **1276** was *N*-nosylated prior to methanolysis with sodium methoxide in MeOH (71%, 2 steps). Lactamization in diester (+)-(*R*)-**1277** was highly ring-size selective and required rather forcing conditions in order to occur (DBU in refluxing acetonitrile). The lactam thus formed (82%) was *N*-denosylated with potassium thiophenoxide (→ **1278**; 92%) before being converted to anilide (–)-(*R*)-**1279** upon reaction with 3,4-dimethoxyaniline in the presence of trimethylaluminum (96%). Lactam **1279** was converted to imino ether (–)-(*R*)-**1280** with Meerwein reagent in the presence of cesium carbonate in 82%. The following formation of bicyclic amidine (+)-**1281** was effected with dimethylaluminum chloride (68%). Unfortunately, subsequent treatment of **1281** with up to 5 equivalents of triflic acid at room temperature only caused deprotection and the alkene amidine **1282** did not cyclize to **1283** even under forcing conditions (TfOH in refluxing toluene).

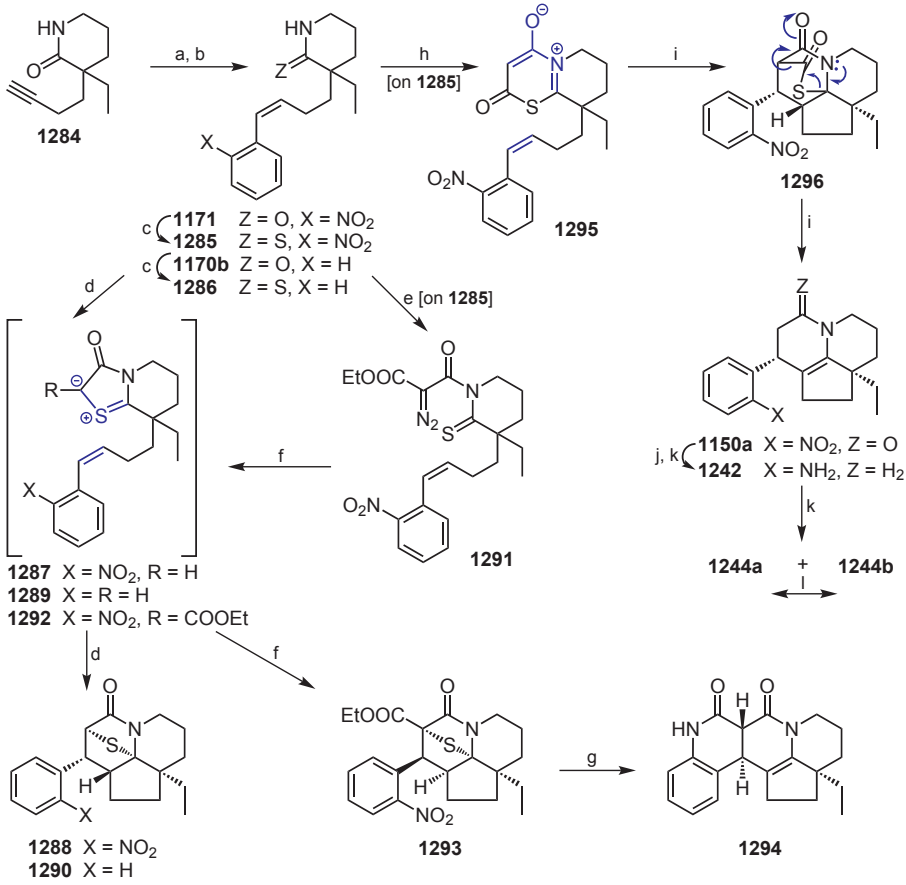


SCHEME 48

Reagents and conditions: a) $TBDPSOCH_2CH_2CH{=}CHCH_2CH_2CH(COOMe)PO(OEt)_2$, $Ba(OH)_2$ (1 eq), THF/H_2O (40:1), rt 30 min, then **1263** (1 eq), rt 5 h (**1274** 85%). b) Et_3SiH (4 eq), TFA (4 eq, dropwise), CH_2Cl_2, 0 °C 20 min (86%). c) Ac_2O (1.1 eq, dropwise), DMAP (0.1 eq), Et_3N (2 eq), 0 °C 5 min (95%). d) **1275**, LiHMDS (1.44 eq, dropwise), PhMe, –78 °C 20 min → rfl 10 min → rt (55%, ee 98%). e) NaHMDS (1.18 eq, during 10 min), THF, –78 °C 20 min, then 4-nitrobenzenesulfonyl chloride (1.34 eq), –78 °C 3 h (80%). f) NaOMe (2 eq), MeOH/THF (1:1), rt 30 min (89%). g) DBU (1.5 eq), MeCN, rfl 1 h (82%). h) PhSH (1.2 eq), K_2CO_3 (3 eq), DMF, rt 1 h (92%). i) 3,4-Dimethoxyaniline (2 eq), $AlMe_3$ (2 eq), CH_2Cl_2, rt 1 h (96%). j) $Me_3O^+BF_4^-$ (1.5 eq), Cs_2CO_3 (3 eq), CH_2Cl_2, rt 1 h (87%). k) Me_2AlCl (5 eq), CH_2Cl_2, rt 2 days (68%). l) TfOH, CH_2Cl_2, rt

14.3. Padwa's Approach

Padwa and collaborators have published[100,109–111] their strategies for construction of the isoschizozygane skeleton using intramolecular [3+2] and [4+2] cycloaddition reactions (for general reviews see[69–79]). Lactams **1171** and **1170b** were synthesized[81,82,100,109–111] essentially as described in Chap. 13.1.2. (see Scheme 35), Scheme 49. Thus, 3,3-disubstituted piperidone **1284** was obtained in 4 steps from δ-valerolactam (**752**) *via* **1167** (60%



SCHEME 49

Reagents and conditions: a) 2-I-$C_6H_4NO_2$ (1.2 eq), [$PdCl_2(PPh_3)_2$] (2.6%), CuI (5.1%), *i*-Pr_2NH (excess), THF, rt 12 h (**1169** 85%). b) [$Pd_2(dba)_3$] (2.5%), $(2\text{-MePh})_3P$ (5.2%), AcOH (1 eq), PhH, 25 °C 1 min, then 1,1,3,3-tetramethyldisiloxane (1 eq), 25 °C 1 h (**1171** 83%). c) Lawesson's reagent (0.55 moleq), PhMe, rfl 1 h (**1171** → **1285** 87%; **1170b** → **1286** 93%). d) $BrCH_2COCl$, xylene, 25 °C overnight, then Et_3N, rfl 1 h (**1285** → **1288** 0%; **1286** → **1290** 85%). e) **1285**, EtOOC·$C(N_2)$·COCl (1.48 eq), Et_3N (2.96 eq), CH_2Cl_2, rt 10 min (72%). f) $Rh_2(OAc)_4$ (2.2 mole %), xylene, rfl 3 h (**1293** 85%). g) $Mo(CO)_6$ (excess), AcOH, rfl overnight (83%). h) **1285**, O=C=C=C=O, –78 °C → 25 °C 5 h (72%). i) PhMe (sealed tube), 120 °C 3 h (66%). j) H_2 (4 atm), Pd/C, rt 15 h. k) $LiAlH_4$, THF, 0 °C → rfl 20 h (**1244a** 48% + **1244b** 35%). l) **1244a** or **1244b**, AcOH, rt 2 h (**1244a**:**1244b** 1:6)

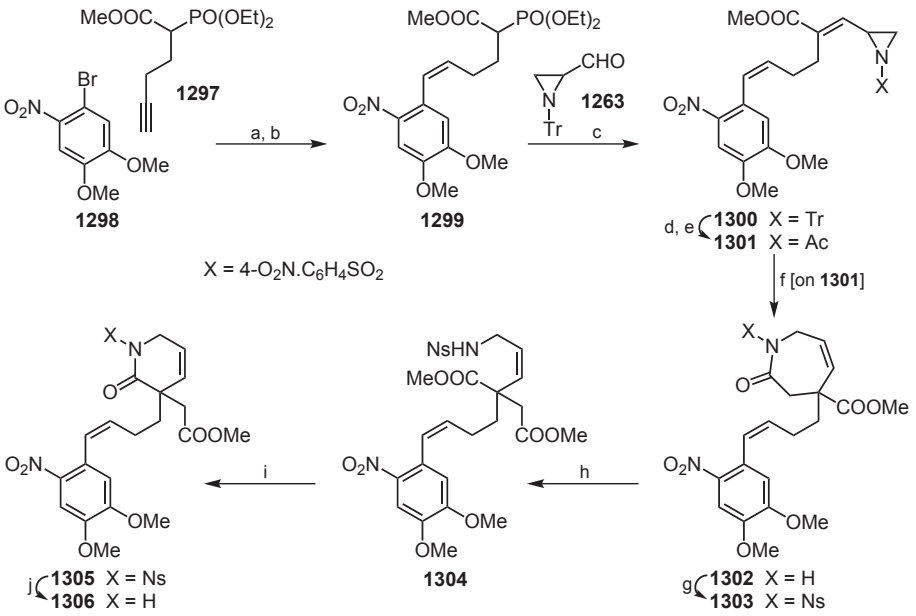
overall) and subjected to Castro–Stephens coupling with 2-iodonitrobenzene upon catalysis with $[PdCl_2(PPh_3)_2]$ and CuI to give a disubstituted alkyne (→ **1169** in Scheme 35; 85%). The latter was reduced by the Trost–Braslau method (1,1,3,3-tetramethyldisiloxane, $[Pd_2(dba)_3]$ (cat), $(2\text{-MePh})_3P$ (cat), AcOH) to alkene **1171** (83%) and then converted to thiolactam **1285** with Lawesson's reagent (87%). Likewise, piperidone **1170b** was converted to piperidine thione **1286** (93%).

Nitro thiolactam **1285** failed[100,109] to give any [3+2] dipolar cycloaddition product **1288** on treatment with bromoacetyl bromide and triethylamine (xylene at 25 °C to reflux), while the cycloaddition of thiolactam **1286** [100,109,111] proceeded smoothly and afforded *via* **1289** stereoselectively the tetracyclic lactam **1290** in 85% yield, Scheme 49. Generation of dipole **1287** was confirmed by isolation of the product of its trapping reaction with *N*-phenylmaleimide (75%). A synthetic potential of the more highly activated dipole **1292** was studied next. The thiolactam **1285** was converted to diazo ester **1291** (72%) which afforded upon treatment with catalytic Rh(II) in boiling xylene the expected cycloadduct **1293** as a single stereoisomer (83%). The following treatment with molybdenum hexacarbonyl was expected to remove the sulfur bridge, however, a simultaneous reduction of the nitro group had also taken place and the pentacyclic lactam **1294** ensued in 83% yield.

Based on these results, the synthetic strategy was changed[100,109,110] to [4+2] cycloadditions, Scheme 49. The thiolactam **1285** was exposed to carbon suboxide and the generated betaine **1295**, which could be isolated (72%), was thermolyzed in boiling toluene; [4+2] cycloaddition had taken place and the cycloadduct **1296** extruded COS to arrive at stereohomogeneous lactam **1150a** (66%). Consecutive reduction of the nitro group and the lactam moiety by lithium aluminum hydride generated the lilolidine **1242** undergoing spontaneous cyclization to the stereoisomeric mixture **1244a** (48%) and **1244b** (35%), which could be equilibrated in acetic acid to a mixture with the desired stereoisomer **1244b** highly predominating (6:1); compare with Chap. 14.1., Scheme 44.

With the general strategy approved, the authors set out to synthesize[110] the piperidinone **1306** to serve as a precursor of isoschizogamine, Scheme 50, using essentially the strategy of Magomedov (see Chap. 14.2.). Sonogashira coupling of alkyne **1297** with arylbromide **1298** ($[PdCl_2(PPh_3)_2]$ and CuI as catalysts) afforded an alkyne which was reduced by Trost–Braslau method to olefine **1299** (88%), obtained as a 9:1 inseparable (*Z*):(*E*)-mixture. Acrylate **1300** was then secured by Horner–Wadsworth–Emmons olefination of the latter with racemic aldehyde **1263** using barium hydroxide as a base in

76% and with 11:1 ratio of (*E*):(*Z*)-isomers about the newly formed double bond. *N*-Deprotection necessitated some experimentation and, finally, with triethylsilane and TFA proceeded in 71% yield and the product was *N*-acetylated (86%). The following metallation of the resulting acetamide **1301** with LiHMDS set the stage for the aza-Claisen rearrangement which proved somewhat troublesome as it gave a yield of **1302** as low as 10% when run at –78 °C to 0 °C, and which could be raised to 30% at 80 °C. The remaining steps included *N*-nosylation (→ **1303**; 41%), azepinone ring-opening with sodium methoxide (→ **1304**), lactamization induced by DBU (→ **1305**; 77% over 2 steps) and denosylation with $PhSH/K_2CO_3$ which, finally, provided the target piperidone **1306** in 71% yield.



SCHEME 50

Reagents and conditions: a) $[PdCl_2(PPh_3)_2]$ (2.6%), CuI (5%), *i*-Pr_2NH (excess), THF, rt 15 h (62%). b) $[Pd_2(dba)_3]$ (4.1%), $(2\text{-MePh})_3P$ (8.2%), AcOH (1 eq), 1,1,3,3-tetramethyldisiloxane (1 eq), PhH, rt 15 h (88%; *Z*:*E* 9:1). c) $Ba(OH)_2$ (1 eq), THF aq, rt 15 h (76%). d) Et_3SiH (4 eq), TFA (4 eq), CH_2Cl_2, 0 °C 30 min, then *i*-Pr_2NEt, 0 °C 30 min (71%). e) Ac_2O, DMAP, Et_3N, CH_2Cl_2, 0 °C 20 min (86%). f) LiHMDS (1.7 eq), THF, –78 °C 20 min, then 80 °C 20 min (30%). g) NaHMDS (1.5 eq), THF, –78 °C 30 min, then NsCl, –78 °C 2 h (41%). h) NaOMe (2 eq), THF/MeOH (1:1), rt 30 min. i) DBU, MeCN, rfl 1 h (77%, 2 steps). j) PhSH, K_2CO_3, DMF, rt 1 h (71%)

NOTES ADDED IN PROOF

Quite recently, two new total syntheses of racemic meloscine (**956a**) were reported. Strategy of Curran and Zhang[112] is based on radical cascade cyclization in divinylcyclopropane and ring-closing metathesis. Feldman and Antoline[113] inplemented in their synthesis radical cyclization cascade of allenyl azide to construct pyrrolizidine *DE*-ring intermediate.

Preparation of an early intermediate of Fukuyama's synthesis of mersicarpine (**1021**, see Chap. 11.2.2.) was published[114]. Padwa and co-workers[115] have explored possibilities of using dipoles generated from *N*-diazomalonyloxindoles in cycloaddition approach to mersicarpine.

15. REFERENCES

1. Hájíček J.: *Collect. Czech. Chem. Commun.* **2004**, *69*, 1681.
2. Hájíček J.: *Collect. Czech. Chem. Commun.* **2007**, *72*, 821.
3. LeMen J., Taylor W. I.: *Experientia* **1965**, *21*, 508.
4. Hugel G., Lévy J.: *J. Org. Chem.* **1984**, *49*, 3275.
5. Hugel G., Lévy J.: *J. Org. Chem.* **1986**, *51*, 1594.
6. Palmisano G., Danieli B., Lesma G., Riva R., Riva S., Demartin F., Masciocchi N.: *J. Org. Chem.* **1984**, *49*, 4138.
7. Takayama H., Sakai S.-I. in: *The Alkaloids: Chemistry and Biology* (Cordell G. A., Ed.), Vol. 50, Chap. 11, p. 415. Academic Press, New York 1998.
8. Saxton J. E. in: *The Alkaloids: Chemistry and Biology* (Cordell G. A., Ed.), Vol. 51, Chap. 1, p. 1. Academic Press, New York 1998.
9. Overman L. E., Robertson G. M., Robichaud A. J.: *J. Am. Chem. Soc.* **1991**, *113*, 2598.
10. Overman L. E., Robertson G. M., Robichaud A. J.: *J. Org. Chem.* **1989**, *54*, 1236.
11. Overman L. E.: *Tetrahedron* **2009**, *65*, 6432.
12. Overman L. E.: *Acc. Chem. Res.* **1992**, *25*, 352.
13. Bernauer K., Englert G., Vetter W., Weiss E.: *Helv. Chim. Acta* **1969**, *52*, 1886.
14. Oberhaensli W. E.: *Helv. Chim. Acta* **1969**, *52*, 1905.
15. Brandes S., Selig P., Bach T.: *Synlett* **2004**, 2588.
16. Selig P., Bach T.: *J. Org. Chem.* **2006**, *71*, 5662.
17. Selig P., Bach T.: *Angew. Chem., Int. Ed.* **2008**, *47*, 5082.
18. Selig P., Herdtweck E., Bach T.: *Chem. Eur. J.* **2009**, *15*, 3509.
19. Bach T., Hehn J. P: *Angew. Chem., Int. Ed.* **2011**, *50*, 1000.
20. Hayashi Y., Inagaki F., Mukai C.: *Org. Lett.* **2011**, *13*, 1778.
21. Rawal V. H., Michoud C., Monestel R. F.: *J. Am. Chem. Soc.* **1993**, *115*, 3031.
22. Denmark S. E., Cottell J. J.: *Adv. Synth. Catal.* **2006**, *348*, 2397.
23. Zhou Y. L., Ye J. H., Li Z. M., Huang Z. H.: *Planta Med.* **1988**, *54*, 315.
24. Denmark S. E., Cottell J. J. in: *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products* (*Chemistry of Heterocyclic Compounds*, Vol. 59, A. Padwa and W. H. Pearson, Eds), Chap. 2, p. 83. Wiley, Chichester 2003.
25. Schultz A. G., Dai M.: *Tetrahedron Lett.* **1999**, *40*, 645.
26. Schultz A. G.: *Chem. Commun.* **1999**, 1263.

27. Coldham I., Burrell A. J. M., White L. E., Adams H., Oram N.: *Angew. Chem., Int. Ed.* **2007**, *46*, 6159.
28. Burrell A. J. M., Coldham I., Watson L., Oram N., Pilgram C. D., Martin N. G.: *J. Org. Chem.* **2009**, *74*, 2290.
29. Goh S. H., Ali A. R. M.: *Tetrahedron Lett.* **1986**, *27*, 2501.
30. Goh S. H., Ali A. R. M., Wong W. H: *Tetrahedron* **1989**, *45*, 7899.
31. Hugel G., Lévy J., Le Men J.: *Tetrahedron Lett.* **1974**, 3109.
32. Abe F., Yamauchi T.: *Phytochemistry* **1994**, *35*, 169.
33. Magolan J., Carson C. A., Kerr M. A.: *Org. Lett.* **2008**, *7*, 1437.
34. Kam T.-S., Subramanian G., Lim K.-H., Choo Y.-M.: *Tetrahedron Lett.* **2004**, *45*, 5995.
35. Nakajima R., Ogino T., Yokoshima S., Fukuyama T.: *J. Am. Chem. Soc.* **2010**, *132*, 1236.
36. Desmaële D., d'Angelo J.: *J. Org. Chem.* **1994**, *59*, 2292.
37. Biechy A., Zard S. Z.: *Org. Lett.* **2009**, *11*, 2800.
38. Bennasar M.-L., Roca T., García-Díaz D.: *J. Org. Chem.* **2007**, *72*, 4562.
39. Randriambola L., Quirion J.-C., Kan-Fan C., Husson H.-P.: *Tetrahedron Lett.* **1987**, *28*, 2123.
40. Takano S., Sato T., Inomata K., Ogasawara K.: *J. Chem. Soc., Chem. Commun.* **1991**, 462.
41. Morales C. L., Pagenkopf B. L.: *Org. Lett.* **2008**, *10*, 157.
42. Yu M., Pagenkopf B. L.: *Tetrahedron* **2005**, *61*, 321.
43. Carson C. A., Kerr M. A.: *Chem. Soc. Rev.* **2009**, *38*, 3051.
44. Bajtos B., Yu M., Zhao H., Pagenkopf B. L.: *J. Am. Chem. Soc.* **2007**, *129*, 9631.
45. a) De Simone F., Gertsch J., Waser J.: *Angew. Chem., Int. Ed.* **2010**, *49*, 5767; b) De Simone F., Waser J.: *Synlett* **2011**, 589.
46. Mizutani M., Inagaki F., Nakanishi T., Yanagihara C., Tamai I., Mukai C.: *Org. Lett.* **2011**, *13*, 1796.
47. Mukai C., Takahashi Y: *Org. Lett.* **2005**, *7*, 5793.
48. Amat M., Lozano O., Escolano C., Molins E., Bosch J.: *J. Org. Chem.* **2007**, *72*, 4431.
49. Lewin G., Schaeffer C., Lambert P. H.: *J. Org. Chem.* **1995**, *60*, 3282.
50. Lewin G., Schaeffer C.: *Nat. Prod. Lett.* **1995**, *7*, 227.
51. Low Y.-Y., Lim K.-H., Choo Y.-M., Pang H.-S., Etoh D., Hayashi M., Komiyama K., Kam T.-S.: *Tetrahedron Lett.* **2010**, *51*, 269.
52. Büchi G., Manning R. E.: *J. Am. Chem. Soc.* **1966**, *88*, 2532.
53. Langlois N., Guéritte F., Langlois Y., Potier P.: *Tetrahedron Lett.* **1976**, 1487.
54. Sapeta K., Kerr M. A.: *Org. Lett.* **2009**, *11*, 2081.
55. Nielsen H. B., Hazell A., Hazell R., Ghia F., Torssell B. G.: *Phytochemistry* **1994**, *37*, 1729.
56. Kam T.-S., Pang H.-S., Choo Y. M., Komiyama K.: *Chem. Biodiv.* **2004**, *1*, 646.
57. Kam T.-S., Sim K.-M., Lim T.-M.: *Tetrahedron Lett.* **2000**, *41*, 2733.
58. Mahboobi v. S., Burgemeister T., Kastner F.: *Arch. Pharm. (Weinheim)* **1995**, *328*, 29.
59. Magolan J., Kerr M. A.: *Org. Lett.* **2006**, *8*, 4561.
60. Reyes-Gutiérrez P. E., Torres-Ochoa R. O., Martínez R., Miranda L. D.: *Org. Biomol. Chem.* **2009**, *7*, 1388.
61. Du D., Li L., Wang Z.: *J. Org. Chem.* **2009**, *74*, 4379.
62. Marion N., Díez-González S., Nolan S. P.: *Angew. Chem., Int. Ed.* **2007**, *46*, 2988.
63. Dickman D. A., Heathcock C. H.: *J. Am. Chem. Soc.* **1989**, *111*, 1528.
64. Heathcock C. H., Norman M. H., Dickman D. A.: *J. Org. Chem.* **1990**, *55*, 798.
65. Brown S. H., Djerassi C., Simpson P. G.: *J. Am. Chem. Soc.* **1968**, *90*, 2445.
66. Laguna A., Novotný L., Dolejš L., Buděšínský M.: *Planta Med.* **1984**, 285.

67. Costa P. R. R., Castro R. N., Farais F. M. C., Antunes O. A. C., Bergter L.: *Tetrahedron: Asymmetry* **1993**, *4*, 1499.
68. d'Angelo J., Desmaële D., Dumas F., Guignant A.: *Tetrahedron: Asymmetry* **1992**, *3*, 459.
69. Padwa A.: *Tetrahedron* **2011**, *67*, 8057.
70. Padwa A.: *J. Org. Chem.* **2009**, *74*, 6421.
71. Padwa A.: *Chem. Soc. Rev.* **2009**, 38, 3072.
72. Padwa A. in: *Progress in Heterocyclic Chemistry* (G. W. Gribble and J. A. Joule, Eds), Vol. 20, Chap. 2, p. 20. Elsevier Science, New York 2009.
73. Bur S. K., Padwa A. in: *Advances in Heterocyclic Chemistry* (A. R. Katritzky, Ed.), Vol. 94, Chap. 1, p. 1. Elsevier, New York 2007.
74. Padwa A., Burr S. K.: *Tetrahedron* **2007**, *63*, 5341.
75. Padwa A.: *Helv. Chim. Acta* **2005**, *88*, 1357.
76. Padwa A.: *Pure Appl. Chem.* **2004**, *76*, 1933.
77. Padwa A.: *Pure Appl. Chem.* **2003**, *75*, 47.
78. Padwa A.: *Chem. Commun.* **1998**, 1417.
79. Padwa A., Weingarten M. D: *Chem. Rev.* **1996**, *96*, 223.
80. Padwa A., Hertzog D. L., Nadler W. R.: *J. Org. Chem.* **1994**, *59*, 7072.
81. Padwa A., Harring S. R., Semones M. A.: *J. Org. Chem.* **1998**, *63*, 44.
82. Padwa A., Harring S. R., Semones M. A.: *J. Org. Chem.* **1995**, *60*, 2952.
83. Tanino H., Fukuishi K., Ushiyama M., Okada K.: *Tetrahedron Lett.* **2002**, *43*, 2385.
84. Tanino H., Fukuishi K., Ushiyama M., Okada K.: *Tetrahedron* **2004**, *60*, 3273.
85. Harley-Mason J., Kaplan M.: *J. Chem. Soc., Chem. Commun.* **1967**, 915.
86. Node M., Nagasawa H., Fuji K.: *J. Org. Chem.* **1990**, *55*, 517.
87. Schultz A. G., Pettus L.: *J. Org. Chem.* **1997**, *62*, 6855.
88. Ho T.-L., Chen C.-K.: *Helv. Chim. Acta* **2006**, *89*, 249.
89. Belattar A., Saxton J. E.: *J. Chem. Soc., Perkin Trans. 1* **1992**, 1583.
90. Brennan J. M., Saxton J. E.: *Tetrahedron* **1986**, *42*, 6719.
91. Hájíček J., Trojánek J: *Tetrahedron Lett.* **1981**, *22*, 2927.
92. Hájíček J., Trojánek J: *Tetrahedron Lett.* **1982**, *23*, 365.
93. Renner U.: *Helv. Chim. Acta* **1965**, *48*, 308.
94. Stephens P. J., Pan J.-J., Devlin F. J., Urbanová M., Hájíček J.: *J. Org. Chem.* **2007**, *72*, 2508.
95. Pilarčík T., Havlíček J., Hájíček J.: *Tetrahedron Lett.* **2005**, *46*, 7909.
96. Kuehne M. E., Bornmann W. G., Earley W. G., Marko I.: *J. Org. Chem.* **1986**, *51*, 2913.
97. Hájíček J., Trojánek J: *Collect. Czech. Chem. Commun.* **1986**, *51*, 1731.
98. Pilarčík T., Hájíček J.: Unpublished results.
99. Kuehne M. E., Bohnert J. C., Bornmann W. G., Kirkemo C. L., Kuehne S. E., Seaton P. J., Zebovicz T. C.: *J. Org. Chem.* **1985**, *50*, 919.
100. Robeck D. R., Lee H. I., Flick A. C., Padwa A.: *J. Org. Chem.* **2009**, *74*, 7389.
101. Potts K. T., Rochanapruk T., Padwa A., Coats S. J., Hadjiarapoglou L.: *J. Org. Chem.* **1995**, *60*, 3795.
102. Padwa A., Coats S. J., Semones M. A.: *Tetrahedron* **1995**, *51*, 6651.
103. Hubbs J. L., Heathcock C. H.: *Org. Lett.* **1999**, *1*, 1315.
104. Renner U.: *Lloydia* **1964**, *27*, 406.
105. Hájíček J., Taimr J., Buděšínský M.: *Tetrahedron Lett.* **1998**, *39*, 505.
106. Stephens P., Philip J., Pan J.-J., Devlin F. J., Urbanová M., Julínek O., Hájíček J.: *Chirality* **2008**, *20*, 454.

107. Magomedov N. A.: *Org. Lett.* **2003**, *5*, 2509.
108. Zhou J., Magomedov N. A.: *J. Org. Chem.* **2007**, *72*, 3808.
109. Padwa A., Flick A. C., Lee H. I.: *Org. Lett.* **2005**, *7*, 2925.
110. Padwa A., Bobeck D. R., Mmutlane E. M.: *Arkivoc* **2010**, *vi*, 7.
111. Padwa A., Harring S. R., Hertzog D. L., Nadler W. R.: *Synthesis* **1994**, 993.
112. Zhang H., Curran D. P.: *J. Am. Chem. Soc.* **2011**, *133*, 10376.
113. Feldman K. S., Antoline J. F.: *Org. Lett.*, doi:10.1021/ol203463n.
114. Diao T., Stahl S. S.: *J. Am. Chem. Soc.* **2011**, *133*, 14566.
115. Li H., Cheng B., Boonnak N., Padwa A.: *Tetrahedron* **2011**, *67*, 9829.