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

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This first part of a planned review on developments in the field of total and formal total synthesis of the post-secodine indole alkaloids concentrates on primary alkaloid types. It reviews the synthesis of secodine, aspidospermane, pseudoaspidospermane and ibogane alkaloids; andranginine is also included. It covers the literature from 1992–1993 up to approximately May 2004. A review with 179 references.

Keywords: Indole alkaloids; Secodines; Aspidospermanes; Pseudoaspidospermanes; Vindoline; Ibogane; Aspidophytine; Total synthesis; Synthetic methodologies; Natural products.

1. INTRODUCTION

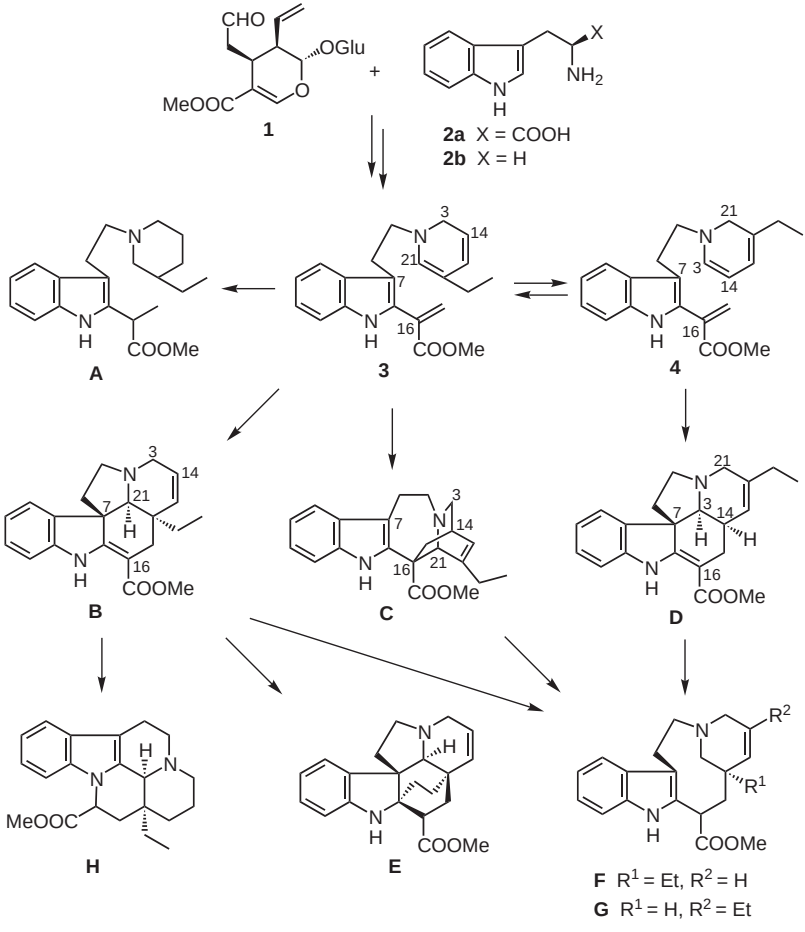
The monoterpenoid indole alkaloids represent an alkaloid family of unprecedented structural complexity, especially in view of their origin from just two rather simple building blocks, i.e. secologanin (**1**) and tryptophan/tryptamine (**2**)[1], Scheme 1. The progress in this field was regularly reviewed by J. Edwin Saxton in *Natural Products Reports*; the last covered the year 1996[2]. Just one review has appeared in *Nat. Prod. Rep.*[3] since his retirement, covering the literature published during 1997. Simultaneously, the topic was reviewed twice in *The Chemistry of Heterocyclic Compounds*, Vol. 25, Part 4: *Monoterpenoid Indole Alkaloids*; edited again by J. E. Saxton[4], the second one dealing with the literature until approximately 1993[5]. The purpose of this review is to provide, at least in part, an update to these excellent books by discussing the literature on synthesis of the post-secodine indole alkaloids of from 1992–1993 up to May 2004.

Secodine represents a crucial intermediate in the biogenesis of the “late” indole alkaloids, Scheme 1. Alternative intramolecular [4+2] cycloaddition reactions of didehydrosecodine (**3**) give rise to both aspidospermane (**B**) and ibogane (**C**) alkaloids; similar process with isomeric didehydrosecodine (**4**) may lead to pseudoaspidospermanes (**D**). Formation of additional rings in **B** leads to aspidofractinines (**E**), kopsanes etc. On the other hand, a rupture of C7–C21 bond/reduction in aspidospermanes (**B**) provides alkaloids

of the quebrachamine/velbanamine type (**F**); a similar process in iboganes (**C**) or pseudoaspidospermanes (**D**) opens the way to cleavamines (**G**).

The feature of crucial importance stems from the inherent planarity of the secodines: It should be noted that, in contrast to pre-secodine alkaloid groups, the post-secodine alkaloids can be formed, in dependence on the enzymatic apparatus of the particular species, in both enantiomeric series. This is illustrated by selected references to isolation of the discussed alkaloids (one per alkaloid, usually a recent one).

The numbering of alkaloid skeletons used in this review is the biogenetic one proposed by Le Men and Taylor[6], see Scheme 1.



SCHEME 1
An overview of the principal types of the post-secodine indole alkaloids

Part I covers the synthesis of aspidospermane (**B**), pseudoaspidospermane (**D**) and ibogane alkaloids (**C**). Included in this review is also the alkaloid andranginine, which seems to be derived from a cycloaddition reaction in the presumed 15,18,19,21-tetradehydrosecodine.

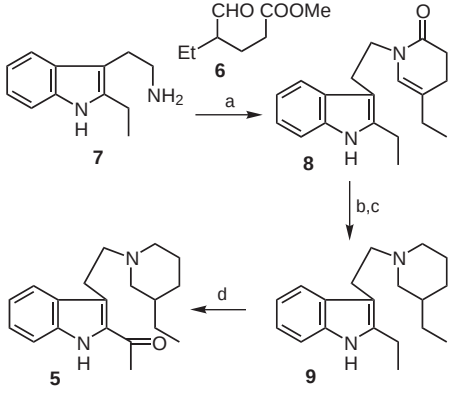
Part II will deal with the alkaloid types originating from the basic skeletons **B** to **D** through the formation (e.g. **E**) as well as the scission (→ **F**, **G**) of C–C bonds or a combination thereof. Some interesting alkaloid transformations will also be included.

Part III of the review will cover the synthesis of the post-secodine alkaloid groups that originate from those discussed here by some kind of skeletal rearrangement (e.g. eburnanes (**H**))[7].

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 room temperature for another 3 h.

2. SECODINES

Reduced secodines (**A**) are occasionally isolated from plant material, substantiating thus biogenetic considerations. A simple, straightforward synthesis of racemic crooksidine (**5**), an alkaloid isolated as (+)-enantiomer from *Haplophyton crooksii*[8], was described[9], Scheme 2. The key step consists in a condensation of methyl 4-formylhexanoate (**6**) with 2-ethyltryptamine (**7**). Reduction of the resulting dihydropyridone **8** gave rise to piperidine **9**

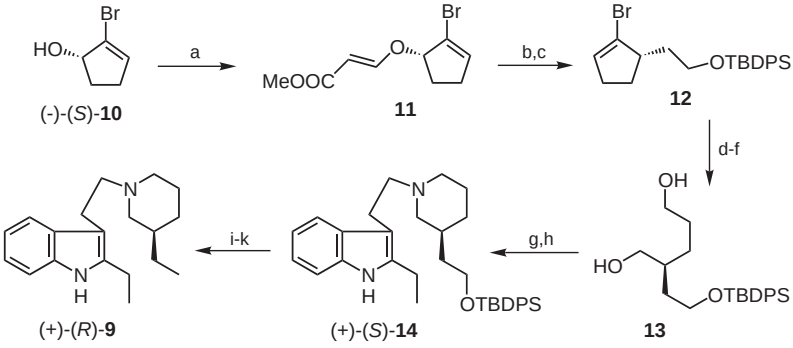


SCHEME 2

Reagents and conditions: a) PhH, rfl 1 h (85%). b) H_2, 10% Pd/C, EtOH, rt 5 h (90%). c) $LiAlH_4$, Et_2O, rt 4 h (91%). d) DDQ, THF aq, 50 °C 1 h (33%)

(or 16-de(methoxycarbonyl)-15,16,17,20-tetrahydrosecodine), the (+)-enantiomer of which is a natural base from *Tabernaemontana cumminsii*[10], which was finally subjected to DDQ oxidation to furnish (±)-crooksidine (**5**).

The absolute configuration of the former alkaloid **9** was determined[11] to be (+)-(*R*) on the basis of its enantioselective synthesis from (–)-(*S*)-**10**, itself obtained by porcine pancreatic lipase (PPL) mediated esterification of (±)-**10** with vinyl acetate, Scheme 3. Claisen rearrangement of the derived alkoxy acrylate **11**, followed by $NaBH_4$ reduction afforded alcohol (–)-(*S*)-**12**.

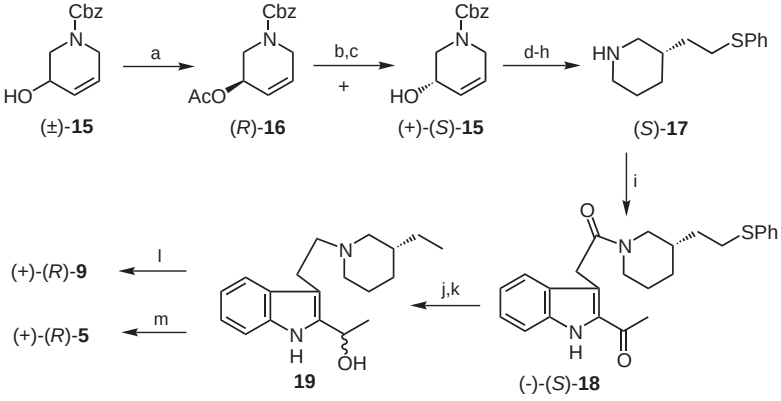


SCHEME 3

Reagents and conditions: a) HCC.COOMe, *N*-methylmorpholine, Et_2O, rt. b) LiI, DMF, 140 °C (sealed). c) $NaBH_4$, rt (76% overall). d) TBDPSCl, i-Pr_2NEt, CH_2Cl_2, rt. e) BuLi, –90 °C → 0 °C, then 1 M $(COOH)_2$ aq (quant.). f) O_3, MeOH, –78 °C, then Me_2S, then $NaBH_4$. g) MsCl, Et_3N, CH_2Cl_2. h) **7**, LiI, 12-crown-4 (cat), i-Pr_2NEt, MeCN, rfl. i) TBAF, THF, rt. j) 2-Nitrophenyl selenocyanate, Bu_3P, THF, rt. k) $NaBH_4$, $NiCl_2$, MeOH, THF, rt (66% from **14**)

Debromination, ozonolysis and subsequent reduction gave diol (–)-(*S*)-**13**, the dimesylate of which was reacted with 2-ethyltryptamine (**7**) to give (+)-(*S*)-**14**. Removal of oxygen functionality from C-18 completed the synthesis of the alkaloid (+)-(*R*)-**9**, $[\alpha]_D$ +11.8 (*c* 0.35, $CHCl_3$). This product should be enantiopure or nearly so, and thus the only reported[12] specific rotation, $[\alpha]_D$ +90, is almost with certainty erroneous. This assumption is confirmed by another synthesis[13], Scheme 4. Ogasawara et al. resolved allylic alcohol **15** again using the PPL procedure, where the Mitsunobu protocol applied to acetate (*R*)-**16** afforded another quantity of (+)-(*S*)-**15**. The Johnson–Claisen rearrangement, followed by manipulation of the ethoxycarbonyl group gave rise to amine **17**, converted to amide (–)-**18** by DCC method. Reduction of **18** provided an alcohol **19**, which was then transformed into both the alkaloid (+)-(*R*)-**9**, $[\alpha]_D$ +11.3 (*c* 0.17, $CHCl_3$), and (+)-crooksidine (**5**), $[\alpha]_D$ +7.8 (*c* 0.6, $CHCl_3$), determining thus the absolute

configuration of the latter as (+)-(*R*). The optical rotation of this alkaloid was again much lower as compared with the value reported for the natural alkaloid[8], $[\alpha]_D$ +27.6 (*c* 0.205, $CHCl_3$).



SCHEME 4

Reagents and conditions: a) Lipase PS, $AcOCH{=}CH_2$, CH_2Cl_2, 40 °C 29 h ((+)-**15** 48%, (–)-**16** 47%). b) K_2CO_3, MeOH, 40 °C (95%). c) 4-$O_2NC_6H_4COOH$, $(=N.COOi\text{-}Pr)_2$, Ph_3P, THF, 0 °C → rt, then NaOMe, MeOH, rt (96%). d) $MeC(OEt)_3$, *t*-BuCOOH (cat), 148 °C (83%). e) H_2, PtO_2, AcOEt (91%). f) $LiBH_4$, THF (95%). g) PhSSPh, Bu_3P, py (92%). h) 50% KOH, EtOH, 110 °C. i) (2-Acetylindol-3-yl)acetic acid, DCC, THF. j) $LiAlH_4$, dioxane, rfl (82%). k) Na, NH_3 (l) (82%). l) $NaBH_3CN$, $BF_3{\cdot}OEt_2$ (82%). m) Dess–Martin oxidation (67%)

3. ASPIDOSPERMANE AND PSEUDOASPIDOSPERMANE ALKALOIDS

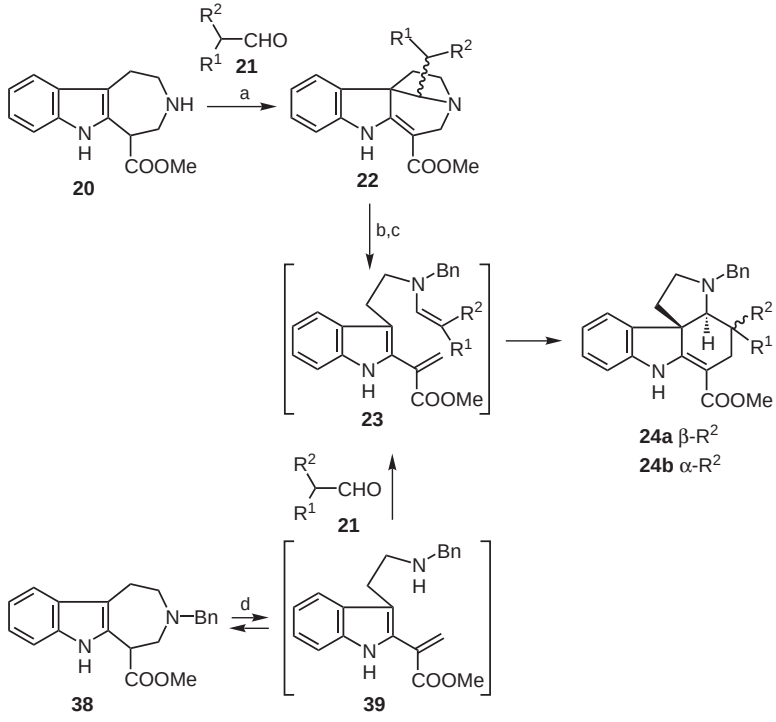
Aspidospermane (**B**) and pseudoaspidospermane (**D**) alkaloids are discussed together due to similarity in synthetic approaches. The reader can thus gain a general idea about the synthesis of these bases with the same pentacyclic skeleton (note the difference in the numbering, which reflects the biosynthesis). J. E. Saxton has published reviews on Aspidosperma alkaloids in 1998 [14,15].

3.1. β-*Anilinoacrylate Alkaloids*

3.1.1. Kuehne's Approach

Kuehne's biomimetic approach to the synthesis of a diverse array of the post-secodine alkaloids, including iboganes (**C**, Chapter 4.1) and cleavamine derivatives[7] (**D**), has developed over the years into the most general synthesis in the field and became a true classics. In a variant of the ap-

proach, a comparative study of two alternative ways to D-nor bases has been published by Kuehne and collaborators[16], Scheme 5. The older procedure consists in a condensation of secondary azepine base **20** with aldehydes **21** to give a bridged azepine **22** (diastereoisomeric mixture), which is quaternised with benzyl bromide. Exposure to base causes fragmentation and leads, through a thermally induced [4+2] cycloaddition in the secodine-like enamine acrylate **23**, to the desired tetracyclic base **24**. An important feature rests upon the fact that, with monosubstituted acetaldehydes **21** (R^2 = H), the procedure leads to (*E*)-enamines **23** (R^2 = H) selectively. Consequently, the overall process is highly stereoselective and affords a single stereoisomer **24a**.



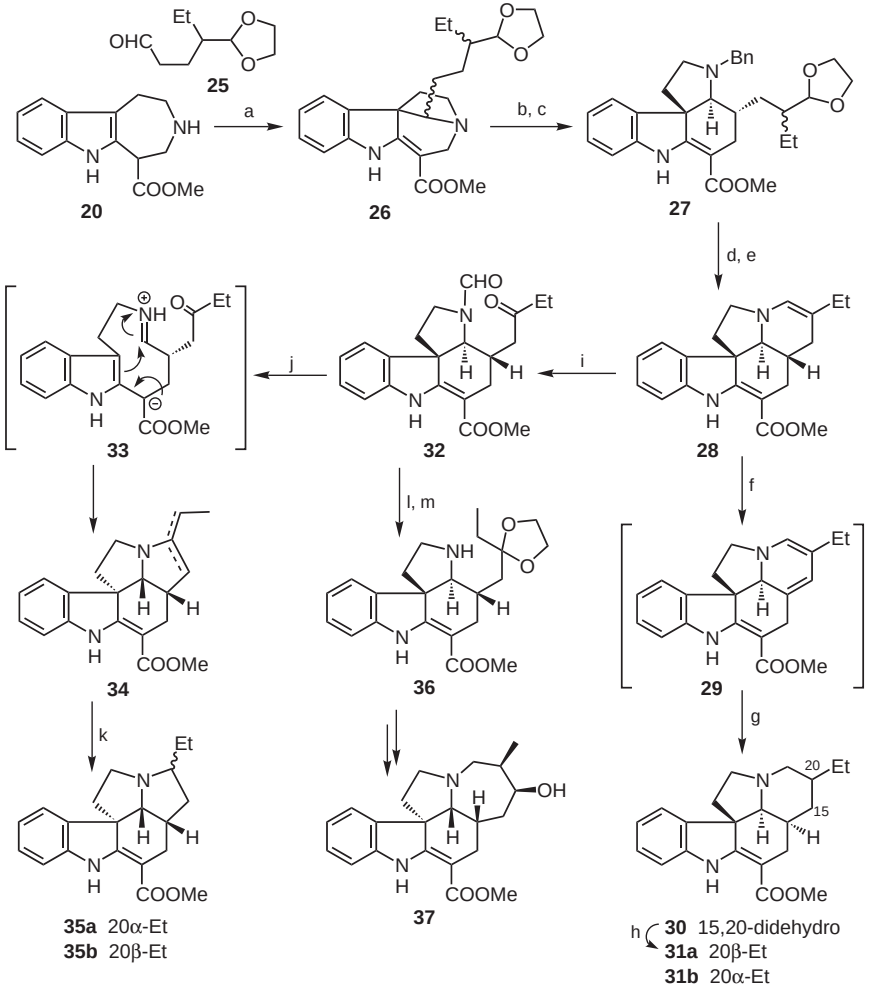
SCHEME 5
Reagents and conditions: a) solvent. b) BnBr. c) Base. d) PhMe, rfl

The procedure is illustrated here by the synthesis of pseudoaspidospermane alkaloids[17], Scheme 6. Reaction of azepine **20** with dialdehyde monoacetal **25** provided stereoisomeric base **26** (84%), which was *N*-alkylated with benzyl bromide (98%). Exposure to base caused fragmenta-

tion and led, through a thermally induced [4+2] cycloaddition in the secodine-like (*E*)-enamine acrylate, stereoselectively to the tetracyclic base **27** (81%), obtained as a 4:5 C-20 stereoisomeric mixture (not significant). *N*-Debenzylation and subsequent mild hydrolysis of the ketal resulted in a spontaneous cyclisation and the crucial tetracycle **28** with unnatural D/E *trans*-annelation was isolated in 98% yield! The stereochemistry at C-20 was inverted through oxidation; borohydride reduction of the presumed aminodiene **29** afforded (±)-pseudotabersonine (**30**), albeit in a low yield; (+)-enantiomer *ent*-**30** was reported[18] from *Pandaca caducifolia*. Its stereoselective hydrogenation then afforded one of the (±)-pseudovincadifformine epimers (→ **31a**). Note that (+)-pseudovincadifformine (*ent*-**31a**) is an alkaloid from *Melodinus polyadenus*[19], while a mixture of *ent*-**31a** and *ent*-**31b** is present in *Tabernaemontana eglandulosa*[20].

On the other hand, the photoassisted oxidative cleavage of enamine **28** provided formamide **32** (91%), and opened thus a way to further alkaloids of the pseudoaspidospermane family[17], Scheme 6. Acid hydrolysis of the formamide **32** released an amine, which underwent epimerisation through the retro-Mannich/Mannich-type reaction in **33**; spontaneous cyclisation provided enamine **34** in an almost quantitative yield. Stereoselective hydrogenation proceeded from the less hindered concave β-face and afforded (±)-ibophyllidine (**35a**); (+)-**35a** is isolable from *Tabernanthe iboga* and *T. subsessilis*[21], while both (+)-**35a** and (+)-20-epiibophyllidine (**35b**) were obtained from *Tabernaemontana albiflora*[22]. Alternatively, the formamide **32** was converted into the amine ketal **36** (61%), which was transformed into (±)-iboxyphylline (**37**) as described previously[23]; (+)-enantiomer was isolated from *Tabernanthe iboga* and *T. subsessilis*[21]. The crucial intermediate **27** ("versatiline") was used also[17] in syntheses of bis-indole[7] and ibogane alkaloids (Chapter 4.1).

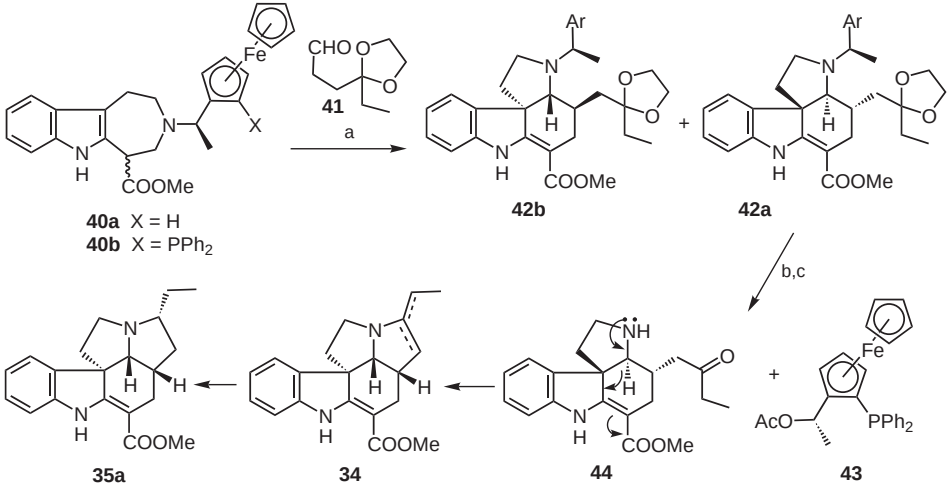
Alternatively, a tertiary azepine (usually benzylated, **38**) is used as starting material, Scheme 5; higher temperatures are necessary in order the reaction to proceed (typically boiling toluene)[16]. It is likely that a fragmentation to the secondary amine acrylate **39** is an initial step; its condensation with monosubstituted acetaldehydes **21** (R^2 = H) is again particularly attractive as it leads to the same (*E*)-enamines **23** selectively. Disubstituted acetaldehydes **21** afford usually, via **23**, stereoisomeric mixtures **24**; for an application in the aspidospermane synthesis, see[17]. Although the two procedures are generally competitive, the important advantage of the latter lies in the possibility of substituting a chiral auxiliary for the benzyl group and running the reaction in an enantioselective mode.



SCHEME 6

Reagents and conditions: a) MeOH, rt 24 h (84%). b) BnBr, Et_2O, rfl 3 days (98%). c) Et_3N, MeOH, rfl 8 h (81%). d) H_2, 10% Pd/C, AcOH, rt. e) 1 M HCl aq/MeOH (2:3), rt 1 h (98%). f) $(PhCOO)_2$, CH_2Cl_2, 20 °C 15 min. g) $NaBH_4$, MeOH, rt 15 min (12%, 2 steps). h) H_2, 10% Pd/C, AcOEt, rt (93%). i) O_2, *hν*, CH_2Cl_2, 0 °C 1 h (91%). j) 1 M HCl aq/MeOH (2:3), 24 °C 36 h (98%). k) H_2, 10% Pd/C, AcOH, rt 2 h (**35a**, 87%). l) $(CH_2OH)_2$, $BF_3{\cdot}OEt_2$ (cat), PhH, rfl (82%). m) NaOMe (cat), MeOH, rfl 2 h

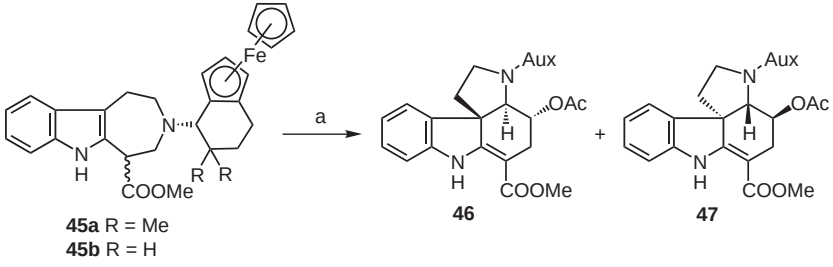
Initially, while developing an enantioselective route to (pseudo)aspidospermane/cleavamine alkaloids, Kuehne et al. have used chiral auxiliaries derived from α-methylbenzyl- and 1-(α-naphthyl)ethylamine, see also[16,24]. The inherent drawback with such chiral synthons rests upon their lengthy preparation, as well as impossibility of regeneration/reuse of chiral amines after the reaction. A solution to these problems has brought by a new generation of chiral auxiliaries of the 1-ferrocenylethyl type, in particular those bearing the diphenylphosphino group in α-position to the ferrocene moiety[25]; for a more detailed discussion and application in cleavamine type alkaloids, see[7]. The ferrocenyl-derived chiral auxiliaries found use in syntheses of both the aspidospermane and pseudoaspidospermane alkaloids[26]; a simple synthesis of (+)-ibophyllidine (**35a**) is shown in Scheme 7. The condensation of (–)-azepine **40b** with aldehyde **41** gave tetracyclic base **42** in 90% yield as a 5:1 mixture of diastereoisomers. The major isomer **42a** (75% isolated yield) was subjected to acidic ketal hydrolysis (99%), followed by a release of the chiral auxiliary through acetolysis (→ **43**). The secondary base **44** underwent an immediate epimerisation at C-3 and C-7 through intermediary iminium compound **34**, and subsequent pentacyclic enamine formation. Hydrogenation then completed the synthesis of the alkaloid (+)-**35a** (>98% ee, 60% from **44**).



SCHEME 7

Reagents and conditions: a) **40b**, PhH, rfl (90%; **42a** 75%). b) 10% HCl aq, THF/MeOH (1:1), rt 4 h (99%). c) AcOH, 70 °C 10 min, then H_2, 10% Pd/C, AcOH, rt 4 days (60% from **44**)

To make the picture complete it should be pointed out that the worst diastereoselection in condensations of the indoloazepines **40** is encountered with 2-acetoxyacetaldehyde. While the azepine **40a** produced a 1:1 mixture of bases, the ratio was slightly improved by the use of **40b**. Recently, a new generation of the more rigid ferrocenyl auxiliaries **45** was introduced[27]. The highest stereoselectivity was achieved with indoloazepine **45a**, Scheme 8. Even with acetoxyacetaldehyde the ratio of 97:3 was reached (the minor component may not be **47**); the acrylate **46** (76%) is an advanced intermediate in synthesis of the strychnane alkaloid (–)-mossambine. Thus, an enhanced rigidity and bulkiness caused an additional diphenylphosphino substituent unnecessary. It is worth noting that, in a variant of the VLB synthesis, the less bulky azepine *ent*-**45b** reacted with still high diastereoselectivity[27] (7–9:1), see[7].



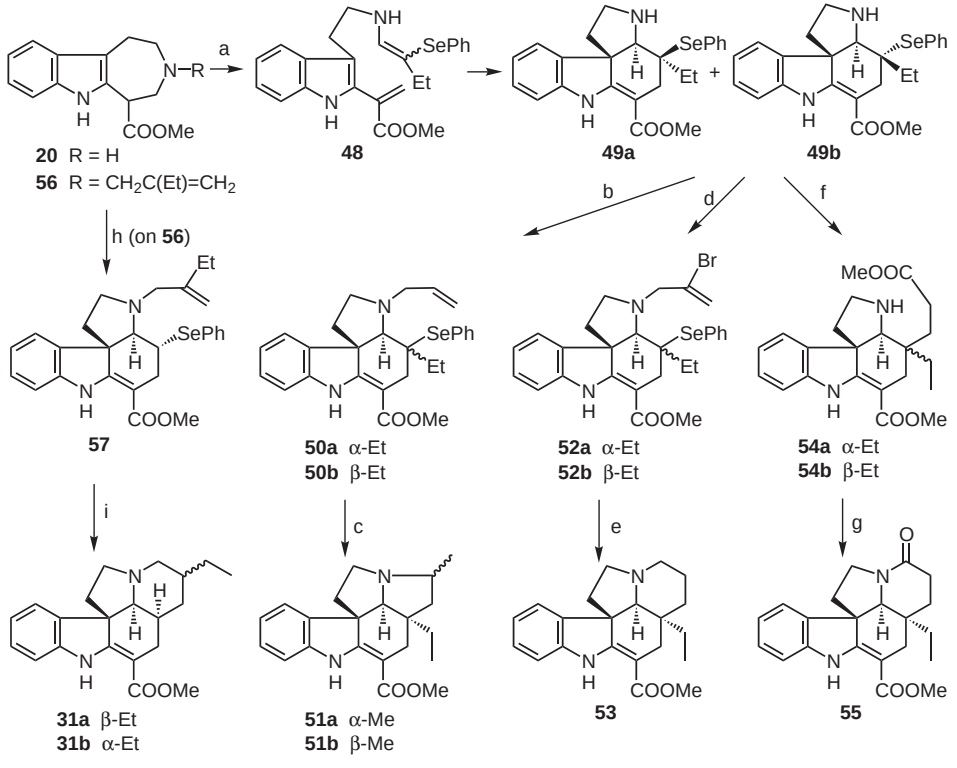
SCHEME 8
Reagents and conditions: a) **45a**, $AcOCH_2CHO$, PhH, rfl 22 h (**46** 76%)

Radical chemistry has been implemented in the synthesis of β-anilinoacrylate aspidospermanes[28], Scheme 9. It does not matter in this methodology that the [4+2] cycloaddition in the secodine-type intermediates **48** gives rise to a diastereoisomeric mixture, as both of them afford on radical cyclisation one and the same alkaloid with "natural" relative stereochemistry. Thus, the condensation of indoloazepine **20** with 2-(phenylselenyl)butanal gave a mixture of tetracyclic bases **49a** and **49b**, which were separately alkylated.

In model experiments, the alkylation of **49a** and **49b** with allyl bromide (or propargyl bromide, not shown) provided tertiary amines **50a** and **50b**, respectively, which, on exposure to tributyltin hydride, afforded via 5-*exo*-trig cyclisation the ibophyllidine analogue **51** as a C-20 epimeric mixture (2.6:1), Scheme 9. An analogous alkylation of **49a** and **49b** with 2-bromoallyl bromide, followed by exclusive 6-*endo*-trig cyclisation in **52a** and **52b** gave (±)-vincadifformine (**53**) as a single stereoisomer in both cases and in

comparable yields (85 and 71%, respectively). Vincadifformine is a widespread alkaloid: Racemic form was isolated from *Vinca difformis*[29], (–)-**53** comes from *Aspidosperma pyrifolium*[30] and (+)-*ent*-**53** is present in *Amsonia tabernaemontana*[31].

On the other hand, the radical addition of **49a** and **49b** to methyl acrylate was not stereoselective; subsequent acid treatment of **54a** and **54b** caused an epimerisation and ring closure, Scheme 9. (±)-3-Oxovincadifformine (**55**) was isolated in moderate yields in both cases (34–36%); note



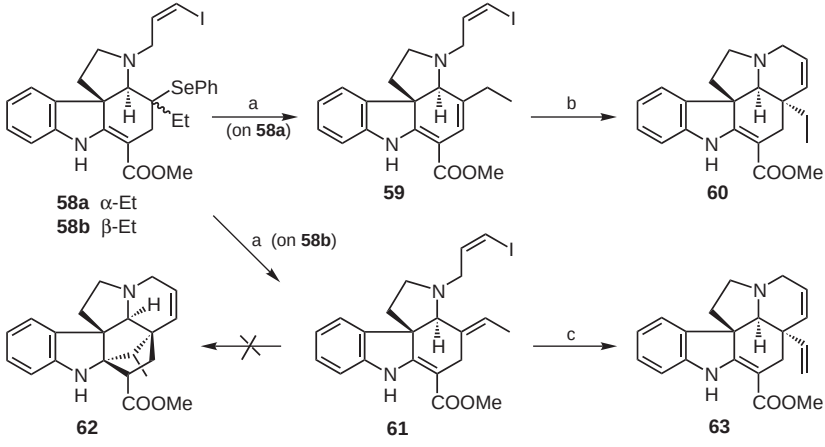
SCHEME 9

Reagents and conditions: a) EtCH(SePh)CHO, PhMe, rfl 18 h (**49a** 49%, **49b** 20%). b) CH_2=$CHCH_2Br$, THF, rt 5 days (**50a** 72%, **50b** 71%). c) Bu_3SnH, AIBN (cat), PhH, 85 °C 12 h (**50a** → **51** 96%, **50b** → **51** 82%; **51a**:**51b** 2.6:1). d) CH_2=$CBrCH_2Br$, THF, rt 5 days (**49a** → **52a** 77%, **49b** → **52b** 80%). e) Bu_3SnH, AIBN, PhH, 85 °C 4 h (**52a** → **53** 85%, **52b** → **53** 71%). f) Bu_3SnH, AIBN, CH_2=CHCOOMe, rt. g) TsOH (1eq), PhMe, rfl 18 h (**49a** → **54a** → **55** 34%, **49b** → **54b** → **55** 36%). h) $PhSeCH_2CHO$, PhMe, rfl 8 h (75%). i) Bu_3SnH, AIBN, syringe pump, 0.015 M in PhH, 85 °C (68%, **31a**:**31b**, 2:1)

that the isomer **54b** has unfavourable stereochemistry and cannot undergo lactamisation to the stereoisomer of **55**. (–)-**55** is available from *Stemmadenia grandiflora*[32].

Alternatively, tertiary indoloazepine **56** was used in a synthesis of racemic pseudovincadifformine[28] (**31a**), Scheme 9. A condensation with (phenylselenyl)acetaldehyde proceeded, as expected, stereoselectively and gave **57** as a single isomer. Its radical cyclisation afforded pseudovincadifformine (**31a**) and its C-20 epimer **31b** in a ratio of 2:1 (68% yield).

Heck reaction permits an easy access to the highly unsaturated aspidospermanes[28]. This is illustrated in Scheme 10 with epimeric iodoalkenes **58a** and **58b**, available from secondary bases **49a** and **49b**. Oxidative generation of the dienic system in **58a**, followed by the Heck reaction in **59** yielded (±)-tabersonine (**60**); (–)-**60** was isolated from *Tabernaemontana heyneana*[33]. With the diastereoisomer **58b** an oxidative elimination took a different course producing the *exo*-olefine **61**. All attempts at transformation of **61** into vindolinine (**62**) using both catalytic and stoichiometric amounts of palladium(II) acetate have failed; instead, (±)-18,19-didehydrotabersonine (**63**) was formed, albeit in only a moderate yield.

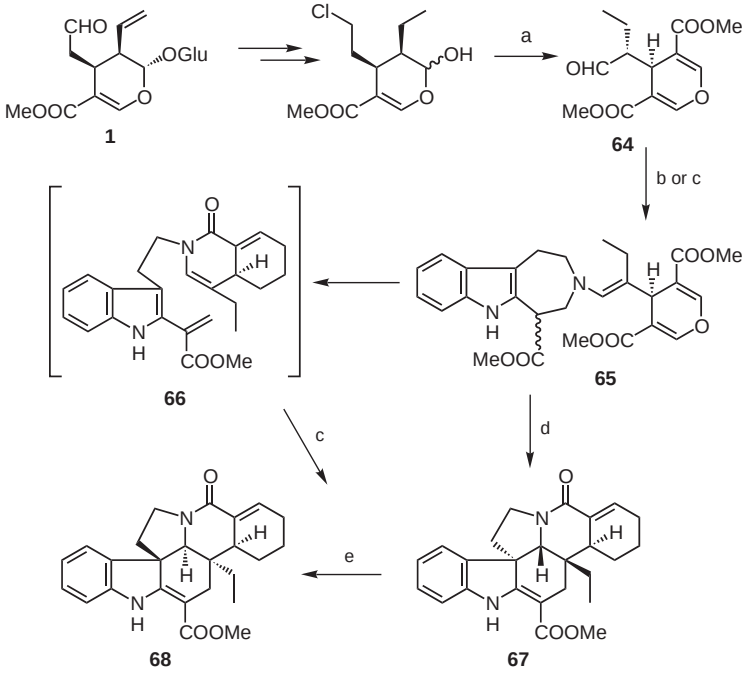


SCHEME 10

Reagents and conditions: a) *m*-CPBA (2.2 eq), CH_2Cl_2, –78 °C 10 min, then –40 °C, Ph_3P, → rt 30 min (**59** 89%, **61** 62%). b) $Pd(OAc)_2$ (0.3 eq), Ph_3P, NaOCHO, Et_3N, MeCN, rfl 12 h (43%). c) $Pd(OAc)_2$ (0.4 eq), Ph_3P, Et_3N, MeCN, rfl 3 h (36%).

An interesting application of the Kuehne's methodology was reported by Brown and Kandasamy[34], Scheme 11. Prolonged reflux (4 days in MeOH) of aldehyde **64**, derived from secologanin (**1**), with the indoloazepine **20** afforded directly through *exo*-cycloaddition of **66**, a mixture of hexacycles **67**

and **68** in a ratio of 2:1. A shorter reaction time (2 days) allowed isolation (15%) of the (*E*)-enamine **65** instead of the usual bridged azepine **22** (see Scheme 5). On standing in chloroform, **65** was quantitatively converted to the kinetically favoured lactam **67**. This could be slowly transformed to the apparently thermodynamically more stable **68**.



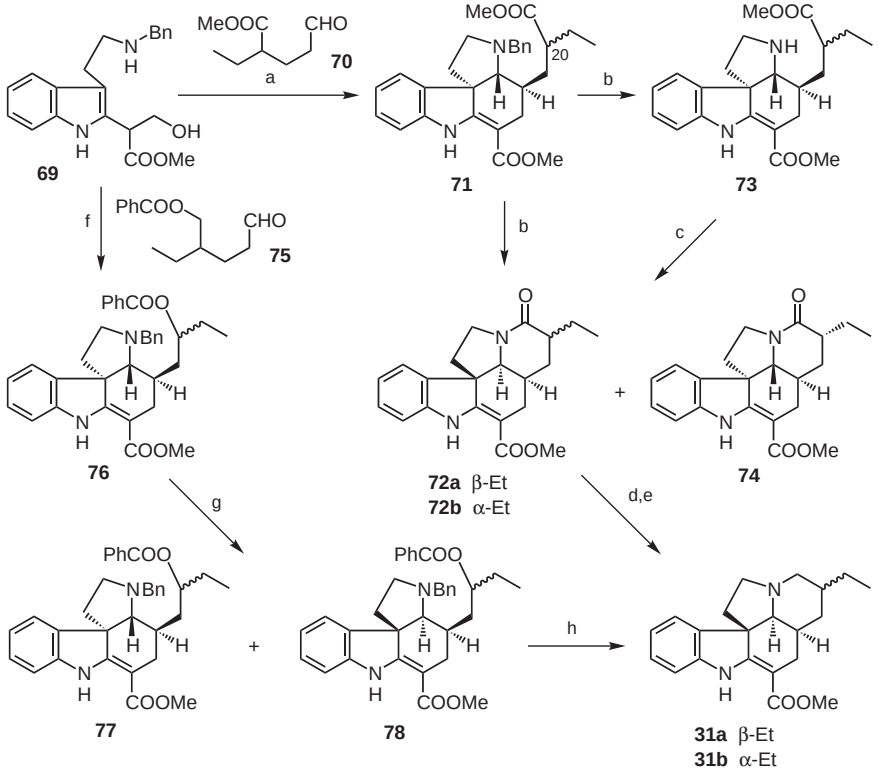
SCHEME 11
Reagents and conditions: a) Me_2CO aq, pH 7, 37 °C 3 days. b) **20**, MeOH, rfl 2 days (**65** 15%). c) **20**, MeOH, rfl 4 days (**67** 10%, **68** 20%). d) $CHCl_3$, rt 7 days (**67** quant). e) MeOH, rfl 6 days

3.1.2. Szántay's Syntheses

A useful alternative to generating the secodine-type species was developed by Szántay and collaborators[35]. (*N*-Benzyltryptaminyl)hydroxypropanoate **69** is allowed to condense with aldehyde with concomitant acidic dehydration. The generated secodine-like intermediate then undergoes cycloaddition as in the Kuehne's synthesis (vide supra).

The strategy was applied to both the aspidospermane[36] and pseudoaspidospermane alkaloid synthesis. The latter procedure is illustrated by the synthesis[37] of (±)-pseudovincadifformine (**31a**), Scheme 12. Condensation

of the amine alcohol **69** with 4-formylbutanoate **70** afforded the tetracyclic amine **71** resulting from (*E*)-configured enamine, as a C-20 epimeric mixture (32%). Hydrogenolysis of benzyl group with partial epimerisation resulted in a mixture of pentacyclic lactams **72** and a secondary *trans*-amine ester **73** (62%), as the latter is much less prone to lactamisation. However, a prolonged reflux with TsOH continued to isomerise **73** (presumably via a species similar to **33**, cf. Scheme 6) and allowed isolation of **72** in a higher yield, together with a minor quantity of the *trans*-lactam **74**. Lactams **72a** and **72b** were transformed via thiolactams into (±)-pseudovincadifformine (**31a**) and its C-20 epimer **31b**, respectively. Analogously, the amine alcohol **69** gave on condensation with aldehyde **75** C-20 epimeric tertiary bases

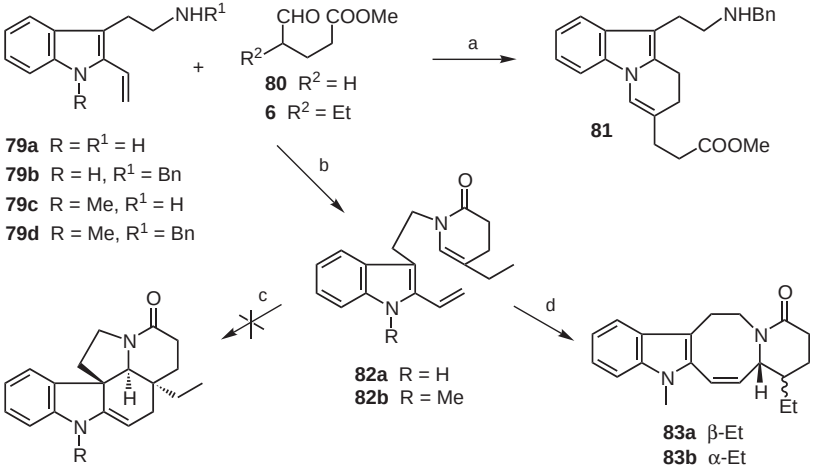


SCHEME 12

Reagents and conditions: a) TsOH·H_2O (cat), PhMe, rfl 48 h (32%). b) H_2, 10% Pd/C, AcOH, 40 min (**73** 62% + some **72**). c) TsOH·H_2O (cat), PhMe, rfl 16 h (**72a** 27%, **72b** 21%, **74** 10%). d) P_4S_{10}, THF, rt 1 day (76–81%). e) Ra-Ni, THF, MeOH, rt overnight (**72a** → **31a** 80%, **72b** → **31b** 75%). f) **75** (2.2 eq), TsOH·H_2O (cat), PhMe, rfl 24 h (38%). g) H_2, 10% Pd/C, AcOH, 2 h (81%, **77**:**78** 1:2). h) KI, DMSO, 145 °C 3.5 h (**31b** 22%)

76. Hydrogenolysis/partial epimerisation afforded a mixture of *trans*- and *cis*-amines **77** and **78**. Surprisingly, heating in dimethyl sulfoxide gave (±)-20-*epi*-pseudovincadifformine (**31b**) as the only isolated product (22%).

An activation of 2-vinylindole by the methoxycarbonyl group is of crucial importance in order for the [4+2] cycloaddition to proceed, as demonstrated by the Szántay group[38]. A series of 2-vinyltryptamines **79** was subjected to condensation with aldehyde esters **6** and **80**, Scheme 13. While no defined product could be isolated from the condensation of **79a** with aldehyde **80**, as well as from amine **79d** and aldehydes **6** and/or **80**, the reaction of secondary amine **79b** with aldehyde **80** led to tricyclic amine **81**. Thermal reaction of primary amines **79a** and **79c** with aldehyde **6** afforded dihydropyridones **82** in 63 and 71%, respectively. Although **82a** resisted all attempts at cycloaddition (to form aspidospermane ring system), similar treatment of **82b** gave the diastereoisomeric azocines **83**.



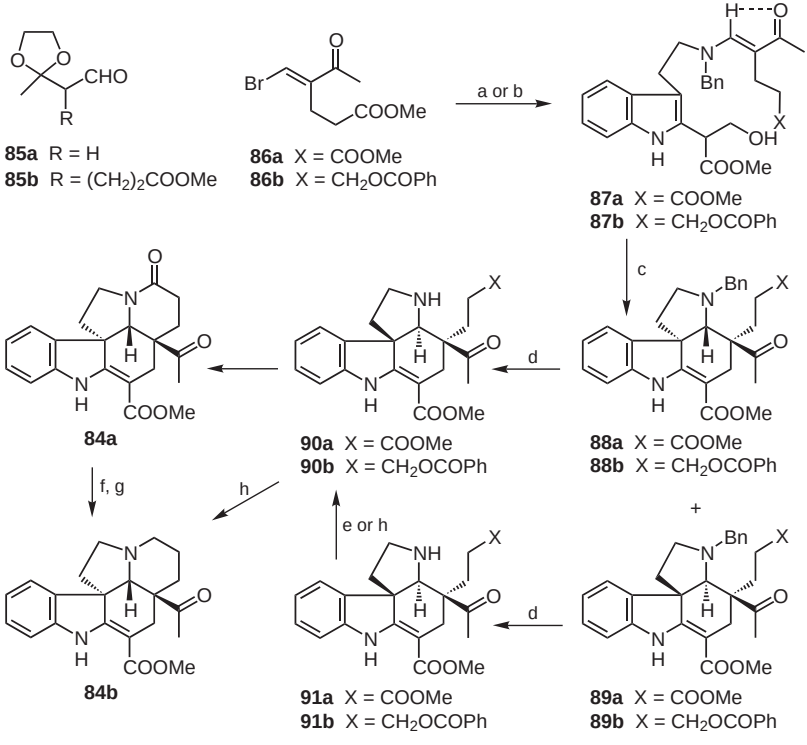
SCHEME 13

Reagents and conditions: a) **79b**, **80**, PhMe, rfl 4 h (**81** 48%). b) **6**, PhH, rfl 2.5 h (**79a** → **82a** 63%, **79c** → **82b** 71%). c) **82a**, PhMe, or $PhMe_2$, or decalin (TsOH), rfl. d) **82b**, TsOH, PhMe, rfl 3 h (**83a**:**83b** 25%:9%)

Efforts aimed at the total synthesis of (±)-3-oxominovincine (**84a**), the (+)-enantiomer of which is an alkaloid from *Tabernaemontana riedelii*[39], have eventually brought success. While use of aldehydes **85** did not allow completion of the synthesis[40], with **85b**, due to a loss of the acetyl group during the condensation, a reaction of bromovinyl ketone **86a** with amine alcohol **69** gave rise to an internally hydrogen-bonded enamino ketone **87a** (70%)[41], Scheme 14. The acid-catalysed dehydration/[4+2] cycloaddition

then led to a 1:1 mixture of diastereoisomers **88a** and **89a**, which were separately transformed into the target alkaloid (±)-**84a**: While the *N*-debenzylation in **88a** gave rise directly to (±)-**84a** via **90a**, a similar reaction of **89a** produced secondary base **91a**, which was transformed into (±)-**84a** only after acid treatment that probably caused epimerisation to **90a** prior to the lactam formation. Alkaloid (±)-**84a** was, finally, converted to (±)-minovincine (**84b**); (+)-**84b** was also isolated from *T. riedelii*[39], while (–)-enantiomer occurs in *Vinca minor*[42].

In a variant of the methodology[43], bromovinyl ketone **86b** was reacted with **69** to give, via **87b** (30%), again a separable 1:1 mixture **88b** and **89b** in 45% yield, Scheme 14. The derived secondary bases **90b** and **91b** (both

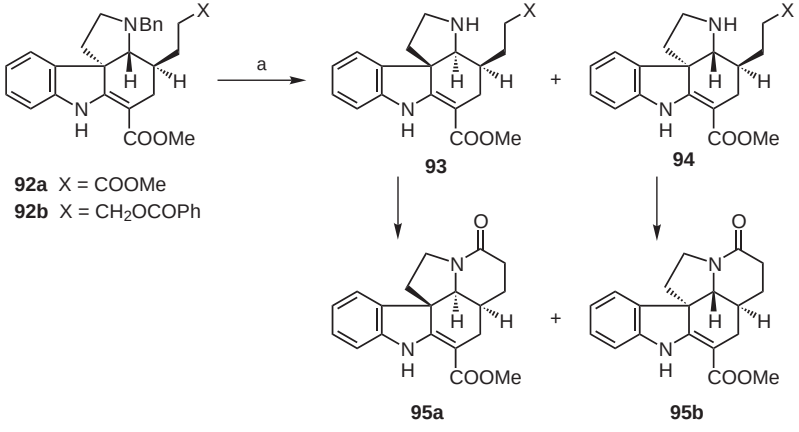


SCHEME 14

Reagents and conditions: a) **86a**, **69**, Et_3N, MeOH, rt 24 h (**87a** 70%). b) **86b**, **69**, i-Pr_2NEt, MeOH, rt 48 h (**87b** 30%). c) **87a** or **87b**, TsOH·H_2O (cat), $PhMe_2$, rfl 24 h (**88a** 19% + **89a** 19%; **88b** 22% + **89b** 23%). d) H_2, 10% Pd/C, AcOH, rt (**88a** → **84a** 64%, **89a** → **91a** 73%; **88b** → **90b** 95%, **89b** → **91b** 95%). e) **91a**, TsOH·H_2O (cat), PhMe, rfl 1 h (**84a** 43%). f) P_4S_{10}, THF, rt 1 h (91%). g) Ra-Ni, THF, MeOH, H_2O, rt (93%). h) **90b** or **91b**, KI, DMF, rfl 2–4 h (**84b** 34%)

sufficiently stable) were then transformed into the target (±)-minovincine (**84b**) by a treatment with potassium iodide in hot DMF (34% both), through a process that with **91b** must have again involved epimerisation.

A study, also by Szántay et al., of the *N*-debenzylation in tetracyclic bases **92** has revealed that the stereochemical consequences of the reaction depend primarily on the reaction temperature, which is not surprising[44], Scheme 15. Thus, while the hydrogenolysis in **92a** at room temperature resulted in roughly 1:1 mixture of pentacyclic lactams **95a** and **95b**, the debenzylation at 85 to 90 °C led to the exclusive formation of the *cis* isomer **95a** with natural C/D stereochemistry. Similarly, the *N*-debenzylation of benzoate **92b** gave rise to a mixture with strongly predominating unwanted isomer **94b** at room temperature, compared with the 4:5 ratio at 85–90 °C. The difference in behaviour of **92a** vs **92b** can be explained by much smoother lactam formation in **93a**, which helps shifting the equilibrium, a process that does not occur in benzoates **93b** and **94b**; for a related epimerisation study on tetra- and pentacyclic skeletons including deuteration, see[45].

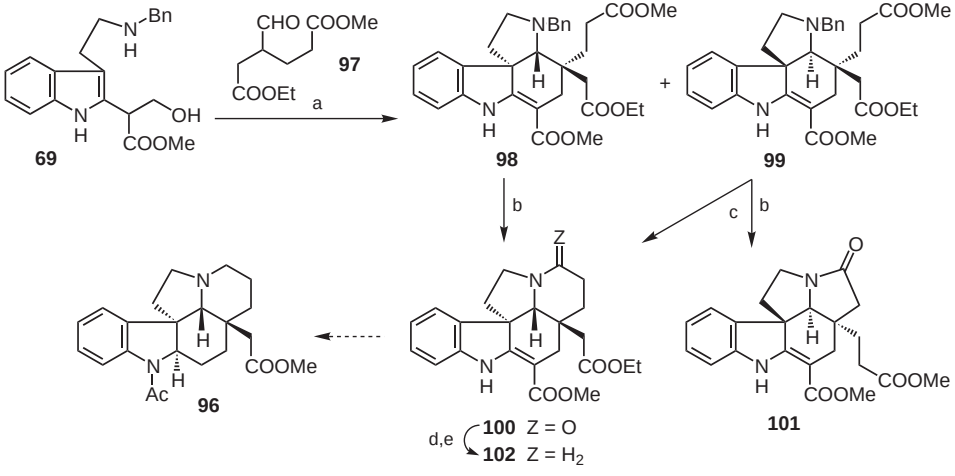


SCHEME 15

Reagents and conditions: a) **92a**, H_2, 10% Pd/C, AcOH, rt (**95a** 33%, **95b** 36%), 70–75 °C (**95a** 58%, **95b** 8%), 85–90 °C (**95a** 62%). b) **92b**, H_2, 10% Pd/C, AcOH, rt (**93b** 7%, **94b** 68%), 70–75 °C (**93b** 23%, **94b** 41%), 85–90 °C (**93b** 23%, **94b** 29%)

The tendency of "naturally" configured tetracyclic aminoesters to undergo preferential lactam formation is further illustrated by Szántay et al.[46] with their formal total synthesis of (±)-*N*-acetyl-12-demethoxycylindrocarine (**96**), whose (–)-enantiomer is contained in *Tabernaemontana*

amygdalifolia[47], Scheme 16. A condensation of the indole amine **69** with aldehyde diester **97** afforded the diastereoisomeric diesters **98** and **99**, which were separated and subjected to the catalytic *N*-debenzylation. Although there are two modes of lactam formation in each of the secondary amines possible, both of them afforded exclusively the expected products **100** and **101**, respectively. Note that the debenzylation of **99** at 100 °C caused partial epimerisation giving rise to the 1:3 ratio of **100** and **101**, albeit in a very low yield. Finally, the lactam **100** afforded base **102** in a usual way.

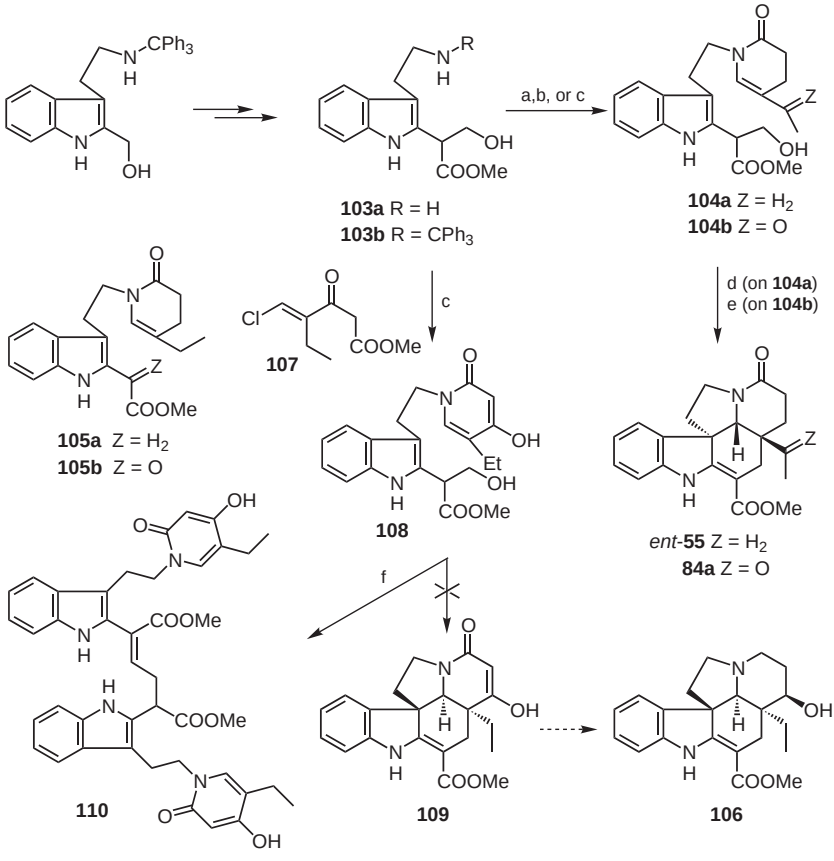


SCHEME 16

Reagents and conditions: a) $TsOH \cdot H_2O$, PhMe, rfl 12 h (**98** 30%, **99** 10%). b) H_2, 10% Pd/C, AcOH, rt (**98** → **100** 20%, **99** → **101** 18%). c) H_2, 10% Pd/C, AcOH, 100 °C (**100** 3%, **101** 10%). d) P_4S_{10}, THF, rt 30 min (80%). e) Ra-Ni, THF, rt 1 h (60%)

Szántay et al. have introduced[48] primary amine **103a** as an alternative to amine **69**, which permitted isolation of the secodine-type intermediates, Scheme 17. Thus, condensation of rather unstable amine **103a**, freshly prepared from the trityl derivative **103b**, with aldehyde ester **6** afforded stable, crystalline lactam **104a** in 79% yield. Its conversion to (±)-3-oxovincadiformine (**55**) was described repeatedly[48,49]; an alternative synthesis from indole acetate **105a** proceeds through **105b**, see[50,51]; Scheme 17. Two procedures for the preparation of stabilised secodine-like intermediate **104b** were implemented in the synthesis of (±)-3-oxominovincine[48] (**84a**), Scheme 17. Condensation of the primary amine **103a** with both the aldehyde ester **85b** (cf. in[40]) and the vinyl bromide **86** afforded lactam **104b** in high yield (76 and 82% from **103b**, respectively). The latter was then transformed by TsOH-assisted thermolysis into the target alkaloid (±)-**84a** (42%). On the

other hand, an attempted synthesis of (±)-15β-hydroxyvincadifformine (**106**) had failed: Although the reaction of **103a** with the conjugated vinyl chloride **107** proceeded as expected and yielded hydroxypyridone **108** in 58% yield from **103b**, it could not be transformed to β-anilinoacrylate **109**; instead, a product of an anomalous dimerisation of the intermediary acrylate was isolated (**110**, 42%).

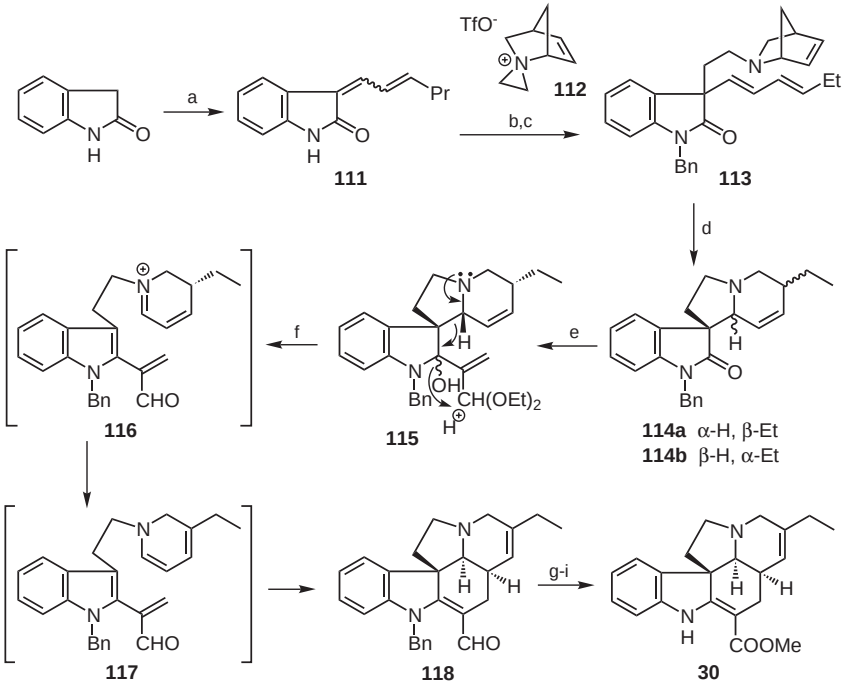


SCHEME 17

Reagents and conditions: a) H_2, 10% Pd/C, MeOH, rt 12 h (**103b** → **103a**). b) PhH, rfl 1 h (**6** → **104a** 79%, **85b** → **104b** 76%). c) H_2, 10% Pd/C, MeOH, rt 12 h, then **86** or **107**, Et_3N, rt 24 h (**86** → **104b** 82%, **107** → **108** 58%). d) Ac_2O, PhMe, rfl. e) $TsOH \cdot H_2O$, xylene, rfl 24 h (42%). f) $TsOH \cdot H_2O$, PhMe, rfl 24 h (42%)

3.1.3. Further Syntheses via Didehydrosecodines

Carroll and Grieco have developed de novo synthesis[52] of pseudoaspidospermanes, which is based on oxindole chemistry, used to generate the secodine-like intermediate, Scheme 18. It did not matter in the initial step that a condensation of (*E*)-hex-2-enal with oxindole provided **111** as a mixture of isomers (65%, *Z*:*E* 1.2:1), as both of them afforded, on exposure to spiroaziridinium triflate **112**/LDA, the same disubstituted oxindole (53%), which was *N*-benzylated (→ **113**). Spiroindolizidine **114**, a masked dihydropyridine, was constructed by a tandem retro-Diels–Alder reaction (which liberated an imine dienophile), and the following aza [4+2] cycloaddition in 61% yield as a readily separable stereoisomeric mixture

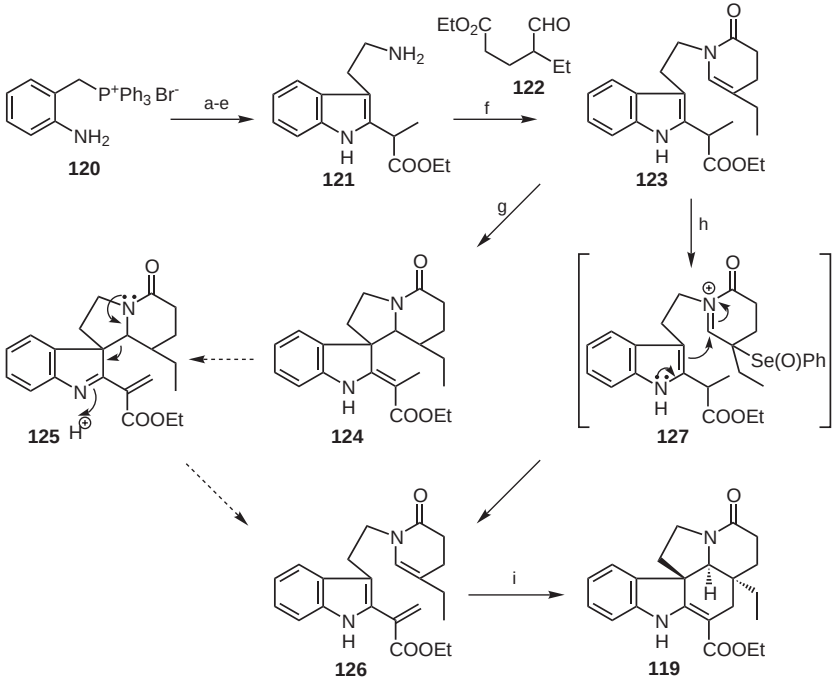


SCHEME 18

Reagents and conditions: a) (*E*)-hex-2-enal, Et_3N/PhMe (1:5), rfl (65%, *Z*:*E* 1.2:1). b) i-Pr_2NK (2 eq), THF, –78 °C, then **112** (1 eq), –78 °C → rt 2 h (53%). c) BnCl, *t*-BuOK, $Bu_4N^+I^-$, THF, 24 h (65%). d) $BF_3{\cdot}OEt_2$ (1.2 eq), 0.02 M in PhMe, 100 °C 2 h (61%, **114a**:**114b** 1:1.5). e) **114b**, 2-lithio-1,1-diethoxyprop-2-ene, THF (95%). f) TsOH (1.1 eq), 0.02 M in acetone, water (20 eq), rt 2 h, then Et_3N (excess), MeCN, 80 °C (50%). g) 2 M HCl aq, 120 °C 1.75 h, then neutral alumina (81%). h) Lithium 4,4′-di-*tert*-butylbiphenylide (30 eq), THF, –5 °C 1 h (87%). i) LDA, THF, –78 °C 30 min → 0 °C 15 min, then ClCOOMe, –78 °C → rt 30 min (35%)

(1.5:1); the configuration at C-20 is, however, of no consequence, as the centre vanishes during the dihydropyridine formation (**116** → **117**). Next, a masked acrylaldehyde moiety was introduced on the carbonyl carbon. Mild acid treatment induced fragmentation in hemiaminal **115** with concomitant liberation of acrylaldehyde. The dihydropyridinium compound **116** thus formed tautomerised to the secodine-like species **117** that underwent the crucial [4+2] cycloaddition in which the 2-vinylindole served exlusively as the diene (50%). The transformation of aldehyde in **118** to methoxycarbonyl group was not straightforward, because the direct oxidation failed. Accordingly, an indirect method consisting of three steps (cf. Chapter 3.1.5) was adopted resulting in the formation of (±)-pseudotabersonine (**30**).

An oxidative approach to creating the secodine-type intermediate can be seen in the synthesis of (±)-3-oxovincadifformine ethyl ester (**119**) by the Milano group[53], Scheme 19. The amine ester **121** (prepared in 5 steps and

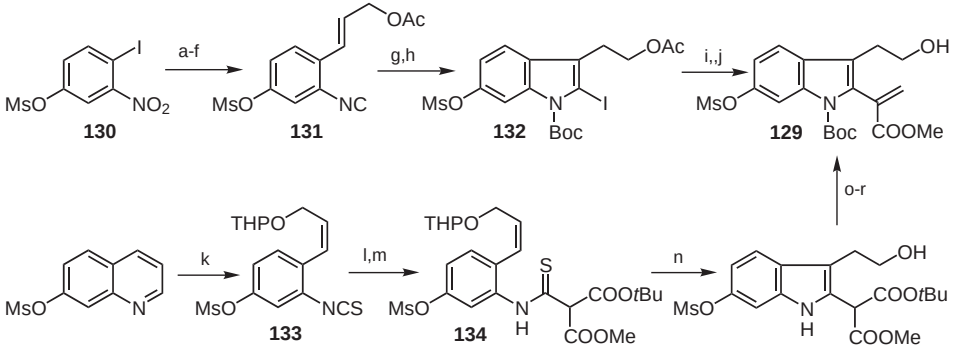


SCHEME 19

Reagents and conditions: a) ClCOCH(Me)COOEt, py, CH_2CH_2, rfl 30 min (97%). b) *t*-BuOK, PhMe, rfl 3 h (64%). c) $Me_2N.CH=CHNO_2$, TFA, CH_2Cl_2, 0 °C 1 h → 20 °C 6 h (64%). d) $NaBH_4$, THF/MeOH (10:1), rt 40 min (93%). e) H_2, PtO_2, EtOH, rt 20 h (80%; overall 30%). f) **122**, PhMe, rfl 2 h → 95 °C 10 h (49%). g) $TiCl_4$, CH_2Cl_2, 0 °C 30 min → rt 72 h (66%). h) BSA, PhH, rt 1 h → 50 °C 16 h (35%). i) PhMe, 110 °C 8 h (92%)

30% overall yield from phosphonium salt **120**) was condensed with ethyl 4-formylhexanoate (**122**). The resulting dihydropyridone **123** (49%) underwent cyclisation upon treatment with titanium(IV) chloride to form spiromethacrylate **124**. It was anticipated that the direct oxidation should provide indolenine acrylate **125** and subsequently the secodine-type indole acrylate **126**. This assumption, however, did not substantiate but oxidation of the propionate **123** with benzeneseleninic anhydride (BSA) brought finally success. This oxidation, which seems to commence with an electrophilic attack of the reagent at the enamine β-position (→ **127**), gave rise to the stable didehydrosecodine **126** in an acceptable yield (35%). The latter underwent smooth [4+2] cycloaddition in refluxing toluene and the target ethyl (±)-3-oxovincadifforminate (**119**) was isolated in 92% yield.

Fukuyama and collaborators have addressed the synthesis of the β-anilinoacrylate alkaloids in both a racemic (→ (±)-vincadifformine[54] (**53**)) and an enantioselective mode. The latter process is illustrated here by the synthesis of (–)-11-methoxytabersonine[55,56] (**128**), which was isolated from *Melodynus polyadenus*[19]. Scheme 20 shows two alternative ways to the construction of indole acrylate synthon **129** starting from non-indole materials. The first synthesis starts from 4-nitrophenol, which was converted in

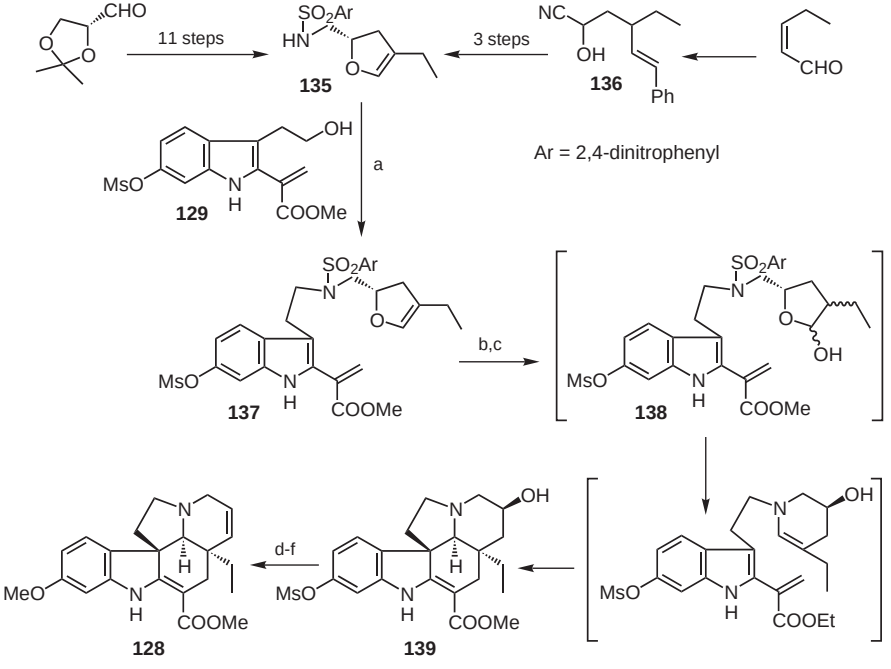


SCHEME 20

Reagents and conditions: a) CH_2=CHCHO, $Pd(OAc)_2$, $BnEt_3N^+Cl^-$, DMF, 50 °C 2 h (83%). b) $NaBH_4$, MeOH, –15 °C 30 min. c) Ac_2O, py, rt 15 min (93%, 2 steps). d) Zn, AcOH, CH_2Cl_2, rt 30 min. e) HCOOH, Ac_2O, CH_2Cl_2, 0 °C 30 min (88%, 2 steps). f) $POCl_3$, py, CH_2Cl_2, 0 °C 40 min (89%). g) Bu_3SnH, AIBN, MeCN, 80 °C 30 min, then I_2, rt 20 min. h) $(Boc)_2O$, DMAP, Et_3N, MeCN, rt 1 h (79%, 2 steps). i) Methyl 2-(tributylstannyl)acrylate, $BnPd(PPh_3)_2Cl$, Ph_3As, CuI, HMPA, DMF, 85 °C 3.5 h. j) Na_2CO_3, MeOH aq, rt 2 h (67%, 2 steps). k) $CSCl_2$, Na_2CO_3, THF aq, 0 °C, then $NaBH_4$, MeOH, 0 °C. l) DHP, camphorsulfonic acid, CH_2Cl_2, rt (65%, 2 steps). m) $MeOOCCH_2COOt$-Bu, NaH, THF, 0 °C. n) Bu_3SnH, AIBN, PhMe, 110 °C. o) Boc_2O, Et_3N, DMAP, CH_2Cl_2, rt (60%, 3 steps). p) H_2, Pd/C, EtOH, rt. q) $Me_2NH{\cdot}HCl$, CH_2O, NaOAc, AcOH, EtOH, rt (72%, 2 steps). r) camphorsulfonic acid, MeOH, rt (99%)

5 steps to iodobenzene[55] **130**. The phosphine-free Heck reaction with acrylaldehyde introduced a three-carbon unit and the product was converted to isocyanide **131**, which underwent radical induced indole formation (Bu_3SnH) and subsequent iodination. Stille coupling with 2-stannylacrylate, followed by alkaline hydrolysis converted **132** to the desired synthon **129**. Starting 7-(mesyloxy)quinoline was converted in 2 steps to isothiocyanate **133** in the second synthesis[56], which was transformed to thioanilide **134** by reaction with *tert*-butyl methyl malonate/base. The radical indole formation afforded, after manipulation of the malonate moiety, the same acrylate **129**.

The other, chirality-bearing synthon **135**, was made accessible either from (*R*)-glyceraldehyde in 11 steps[54], or more efficiently from (*Z*)-pent-2-enal, Scheme 21. The latter was converted to (*S*)-cyanohydrin **136** using enzymatic hydrolysis of the corresponding racemic acetate[56], and further to



SCHEME 21

Reagents and conditions: a) DEAD, Ph_3P, PhH, rt 30 min (89%). b) TFA, CH_2Cl_2, rt 15 min. c) Pyrrolidine, MeOH/MeCN (5:1), rt 5 min → rfl 4 h (65%, 2 steps). d) Ph_3P, CCl_4, MeCN, 70 °C 30 min (88%). e) KOH, MeOH, 80 °C 45 min. f) *t*-BuOK, MeI, *t*-BuOH, THF, 0 °C 90 min (92%, 2 steps)

2,4-dinitrobenzene-1-sulfonamide (*S*)-**135** in 3 steps. The indole ethanol **129** was attached to it using the Mitsunobu reaction (89%). The sulfonamide **137** gave rise, after treatment with TFA followed by removal of sulfonamide group by pyrrolidine, to the intermediary amine lactol **138**, which cyclised spontaneously via a secodine-type intermediate to (–)-14-hydroxy-11-(mesyloxy)tabersonine (**139**) in an overall yield of 65% from **129**. The latter was then transformed to (–)-11-methoxytabersonine (**128**), an intermediate in the authors' synthesis of (–)-vindoline (see Chapter 3.3.2).

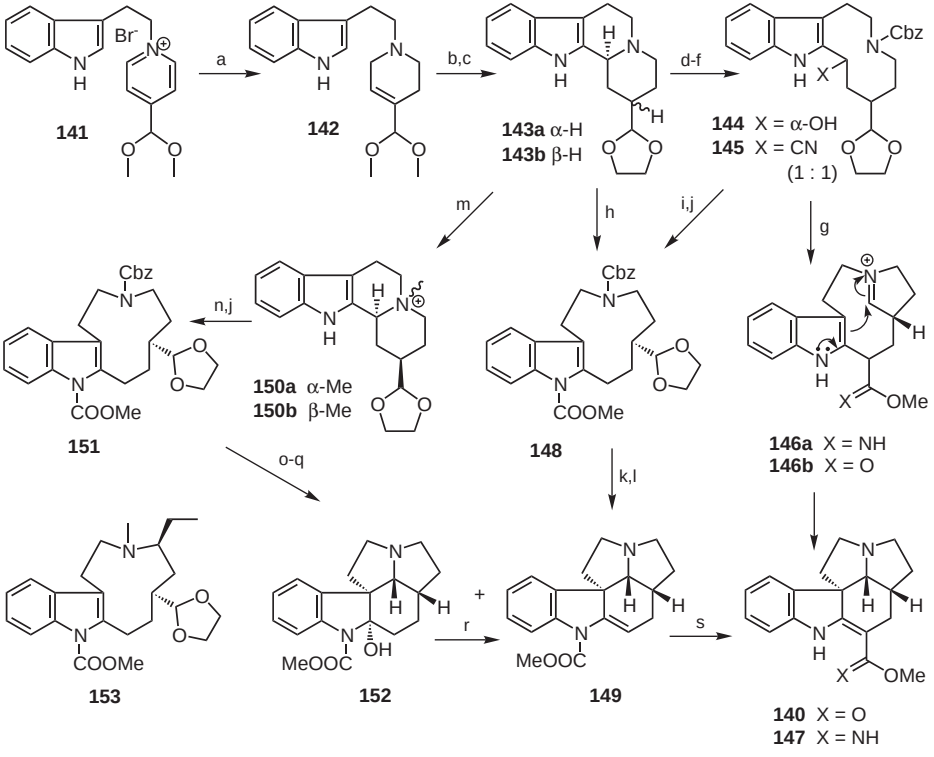
3.1.4. Through Medium-Size Rings

The Barcelona group have reported on two alternative syntheses of (±)-20-desethylibophyllidine (**140**), which are based on transannular cyclisations of the medium-sized intermediates (referred to as "a criss-cross-type annulation"), Scheme 22 [57,58]. The synthesis commences with the quaternisation of 4-(dimethoxymethyl)pyridine with tryptophyl bromide. Quaternary salt **141** was then reduced to tetrahydropyridine **142**, the acid-catalysed Pictet–Spengler cyclisation of which gave, after acetalisation, the ethylene acetal **143** as a mixture of separable isomers (48 and 13%). Chloroformate-induced fragmentation of **143** afforded via **144**, and after introduction of the missing carbon, nitrile **145** as a 1:1 mixture (88%). The crucial cascade cyclisation was accomplished by an acid treatment of the epimeric **145** with HCl/MeOH, followed by water. (±)-20-Desethylibophyllidine (**140**; 30%) was accompanied by the corresponding imidate **147** (29%), which could not be transformed into **140** (the proportion of products thus probably reflects the ratio of intermediates **146a** and **146b**). Note that (+)-**140** is an alkaloid from *Tabernaemontana albiflora*[22].

In an alternative synthesis[58], the major isomer **143a** was subjected to reductive fragmentation (27%); the same product could also be obtained by reduction ($NaBH_3CN$, AcOH) of the benzylic alcohol **144** (53%). Introduction of COOMe group onto the indole nitrogen (→ **148**) was followed by a low-yield removal of the Cbz group. Much more vigorous condition (TFA in refluxing toluene) had to be adopted due to deactivation of the indole ring for the final cyclisation cascade to proceed, which eventually afforded **149** in 90% yield. For rearrangement of **149** to **140**, see Chapter 3.1.5.

The conversion of the acetal **143a** to aspidospermidine derivative **149** could also be initiated by quaternisation with methyl iodide[58], Scheme 22. The salt (90%, **150a**:**150b** 58:32) afforded, after reduction and introducing COOMe onto indole nitrogen, the azecine **151**. This was transformed by a

one-pot method, consisting of *N*-demethylation and TFA-induced cyclisation, to a mixture of **149** and **152** in a 59% combined yield; a prolonged treatment of the hydroxyindoline **152** with TsOH in refluxing benzene provided olefine **149** in 92% yield. It should be noted that a similar ring closure in ethyl analogue **153**, which was synthesised following essentially the

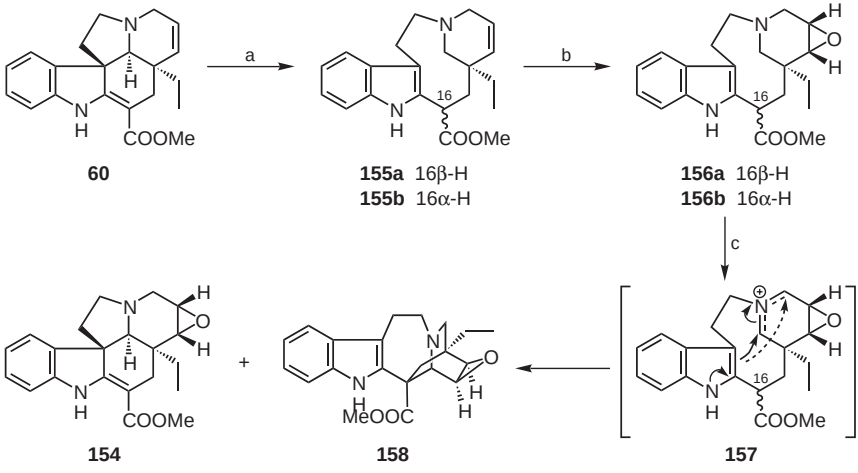


SCHEME 22

Reagents and conditions: a) $NaBH_4$, MeOH, rt 6.5 h (quant). b) 30% AcOH aq, rfl overnight (80% overall). c) $HOCH_2CH_2OH$, $BF_3{\cdot}OEt_2$, AcOH, 35–40 °C → rt 15 min (**143a** 48%, **143b** 13%). d) ClCOOBn, Na_2CO_3, THF, 0 °C 1 h → rt 1 h, then H_2O 50 °C 3 h, then repeat the addition of reagents, 50 °C 2 h (73%). e) Ac_2O, DMAP, py, CH_2Cl_2, rt 2 h (92%). f) NaCN, NaI, DMSO, 90–100 °C 7 h (88%, 1:1). g) HCl/MeOH (satd), 4 °C 16 h, then H_2O, rt 1.5 h (**140** 30%, **147** 29%). h) **143a**, ClCOOBn, THF, –78 °C 1 h, then $NaBH_3CN$, –78 °C 1 h → rt 16 h (27% + **143a** 20%). i) **144**, $NaBH_3CN$, AcOH, TFA, –78 °C → rt 15 min (53% + **144** 11%). j) LDA, THF/HMPA (10:1), –78 °C → rt 30 min, then NC.COOMe, –78 °C 2 h → rt overnight (**148** 95%; **151** 94%). k) H_2, $Pd(OH)_2$, MeOH, rt 3 days (35%). l) TFA, PhMe, rfl 9 h (90%). m) **143a**, MeI, MeOH/CH_2Cl_2 (1:1), 65 °C 30 min (**150a** 58%, **150b** 32%). n) Li, NH_3 (l), EtOH, THF, –78 °C 15 min → rt (60%, dihydro deriv. 20%). o) $ClCOOCHClCH_3$ (neat), 130 °C 6 h. p) MeOH, rfl 8 h. q) TFA, MeOH, rfl overnight (**149** 29%, **152** 30%, **151** 11%). r) TsOH (1.1 eq), PhH, rfl 1 day (92%). s) *hν* (125 W medium pressure Hg lamp), MeOH, rt 2.5 h (**140** 50%)

last-mentioned route, gave rise to cyclised product in only 8% yield as a 1:9 mixture of diastereoisomers.

Intermediate of type **146** has been also implemented by the Szántay group[59] in their synthesis of (–)-lochnericine (**154**) from (–)-tabersonine (**60**), Scheme 23. As an epoxidation of aspidospermanes was shown to lead exclusively to β-epoxides, (–)-**60** was first reduced to a C-16 diastereoisomeric mixture **155** (68%), which afforded, on treatment with *t*-BuOOH/TFA, α-epoxide **156** (62%). The latter was then subjected to the "classic" dehydrogenation[60] with mercury(II) acetate in acetic acid, and the iminium compound **157** underwent spontaneous cyclisation to give (–)-lochnericine (**154**) (35%), accompanied by an alloibogane-type side-product **158** (8%); (–)-**154** was isolated[61] from *Catharanthus roseus*.

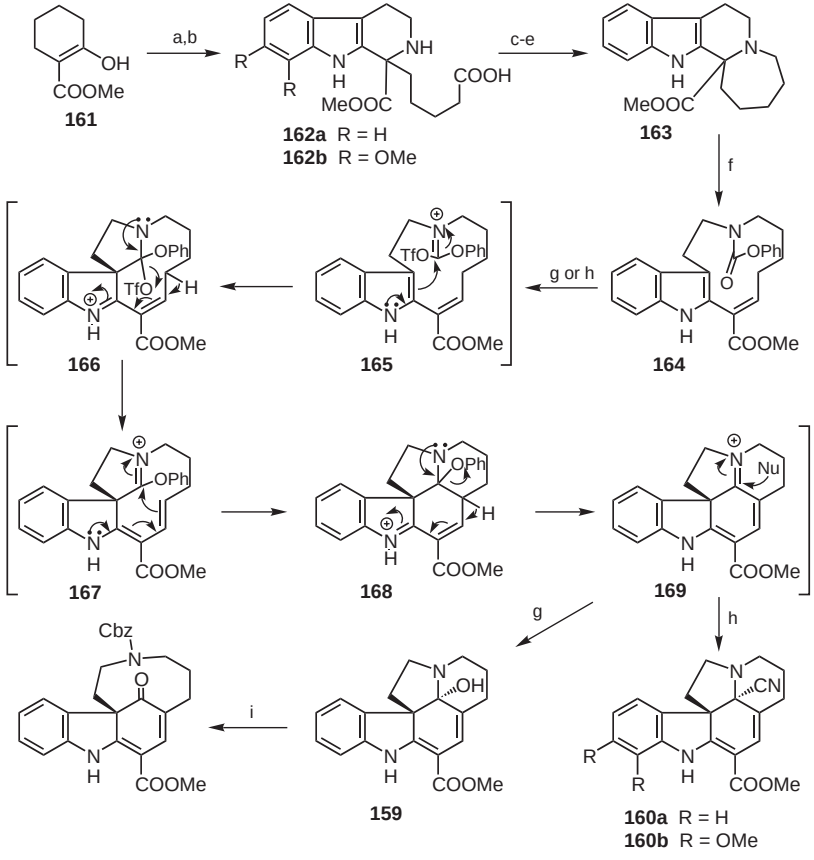


SCHEME 23

Reagents and conditions: a) $NaBH_4$, AcOH, 90 °C (68%, **155a**:**155b** 55:45). b) *t*-BuOOH, TFA, THF, 0 °C → rt 10 h (62%). c) $Hg(OAc)_2$ (excess), AcOH, rt 2 h (**154** 35%, **158** 8%)

Recent synthetic endeavours by Magnus et al. in the field of oligocyclic aspidospermane and related alkaloids have resulted in the development of a brand new approach[62,63], which was enabled by an efficient access to the diene esters **159** and **160**, Scheme 24. 2-Oxoheptanedioic acid ester derived from scission of cyclohexanone carboxylate **161** was condensed with tryptamine (**2b**) affording the β-carboline derivative **162**, which was transformed to the tetracyclic base **163** through the corresponding lactam and thiolactam. Transannular fragmentation induced by exposure to chloroformate provided the medium-sized carbamate **164**.

The following cascade cyclisation is initiated by an attack of triflic anhydride on the carbamate group. Strongly electrophilic iminium **165** suffers an intramolecular attack by the indole β-carbon generating the spirocyclic indoleninium **166**. Regenerated iminium **167** is attacked transannularly by the simultaneously generated dienamine, forming thus a pentacyclic core



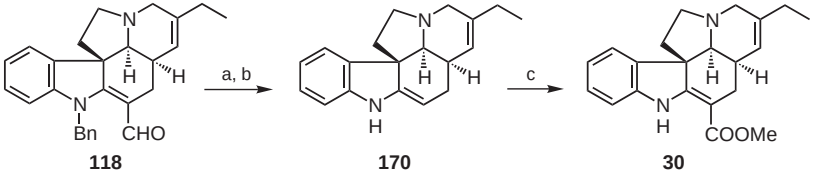
SCHEME 24

Reagents and conditions: a) O_3, CH_2Cl_2, –78 °C 3.5 h, then Me_2S, –78 °C → rt 18 h (87%). b) Tryptamine (**2b**), dioxane/PhH (1:1), rfl 24 h. c) 1–Hydroxybenzotriazole monohydrate, EDCI, Et_3N, DMF, 0 °C 1 h → 23 °C 20 h (67%, 2 steps). d) Belleau's reagent, THF, 0 °C 10 min → 23 °C 6 h (100%). e) Ra-Ni (W-2), THF, 23 °C 10 min (100%). f) ClCOOPh, $ClCH_2CH_2Cl$, rfl 24 h (66%). g) Tf_2O, DMAP (3 eq), CH_2Cl_2, 0 °C 10 min → 23 °C 10 min → rfl 24 h, then $NaHCO_3$ aq satd, rt 30 min (46%). h) Tf_2O (5 eq), DMAP (3 eq), CH_2Cl_2, 0 °C → 23 °C → rfl 22 h, then TMSCN, DMAP, 23 °C (68%). i) ClCOOBn, proton sponge, CH_2Cl_2, 0 °C 8 h → 23 °C 18 h (95%)

of the aspidospermanes. The following indoleninium-to-dienamine isomerisation in **168** induces the formation of a highly conjugated iminium **169**. In the event, treatment of **164** with Tf_2O resulted quickly in a deep purple solution, an aqueous quench of which gave rise to the yellow hemiaminal **159** (yields varying from 46 to 72%), while exposure to TMSCN afforded the more stable aminonitrile **160a** (68%). This fascinating transformation, consisting essentially of two Bischler–Napieralski transannular cyclisations, serves to convert an azacycloundecene **164** to the C/D/E rings of the aspidospermane skeleton (→ **169**), Scheme 24. Compound **160a** was used in syntheses of complex alkaloids of the aspidospermane type (see[7]), like the corresponding 11,12-dimethoxy analogue **160b**, which was synthesised essentially by the above discussed procedure from 6,7-dimethoxytryptamine[63,64].

3.1.5. From Aspidospermidine Intermediates

β-Anilinoacrylate alkaloids can be obtained also by placing a methoxycarbonyl group at C-16 of the (pseudo)aspidospermane skeleton. This method had to be adopted by Carroll and Grieco[52] in their synthesis of (±)-pseudotabersonine (**30**), cf. Scheme 18, Chapter 3.1.3. The acrylaldehyde **118** was deformylated and *N*-debenzylated to give enamine **170**, Scheme 25. The methoxycarbonyl group was then introduced by metallation (LDA) and treatment with excess methyl chloroformate (35%). Generally moderate yields in this procedure are a result of nonregioselectivity and a significant proportion of the *N*-acylated product formation. This was once again proved by Rawal et al.[65] during their synthetic efforts on the aspidospermane alkaloids (cf. Chapter 3.2.2.4, and also 3.2.2.1), who have transformed by this protocol 1,2,14,15-tetradehydro-

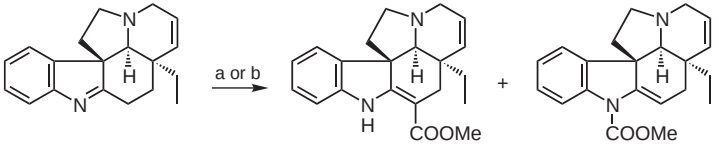


118 **170** **30**

SCHEME 25

Reagents and conditions: a) 2 M HCl aq, 120 °C 1.75 h, then neutral alumina (81%). b) Lithium 4,4′-di-*tert*-butylbiphenylide (30 eq), THF, –5 °C 1 h (87%). c) LDA, THF, –78 °C 30 min → 0 °C 15 min, then ClCOOMe, –78 °C → rt 30 min (35%)

aspidospermidine (**171**) into (±)-tabersonine (**60**) in 37% yield, accompanied by a significant amount of **172**, Scheme 26. On the other hand, the use of a softer Mander's reagent (NC.COOMe) raised the yield of (±)-**60** to 70–80% [65,66]. This is the final step of the most efficient synthesis of both racemic and optically active alkaloid **60** to date.



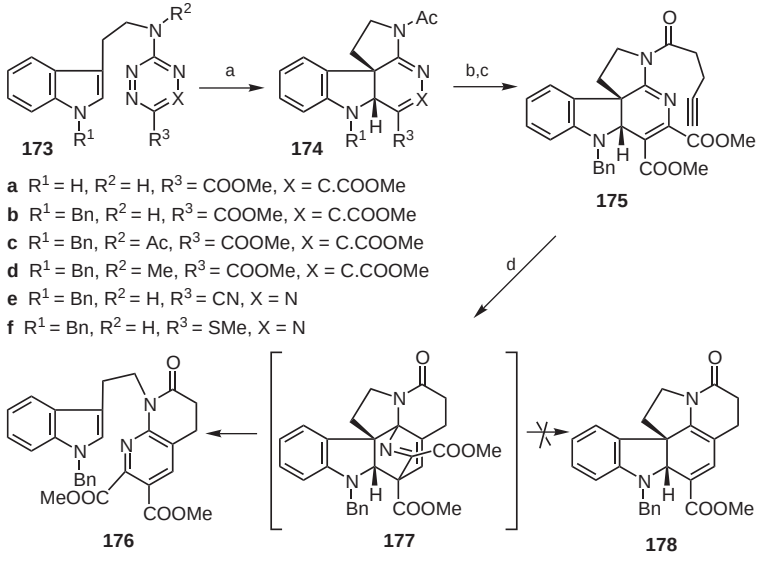
171 **60** **172**

SCHEME 26
Reagents and conditions: a) LDA, THF, –78 °C, then ClCOOMe (37% + **172** significant amount). b) LDA, THF, –70 °C → –20 °C (1 h), then NC.COOMe, –70 °C (80%)

Another method is based on the photo-Fries rearrangement of an ene carbamate[67]. This protocol was used by Bonjoch et al. as a final step in their synthesis of (±)-desethylibophyllidine[58,68,69] (**140**), Scheme 22 (cf. Chapter 3.1.4). The photochemical rearrangement of **149** afforded (±)-**140** in 50% yield.

3.1.6. Model Studies

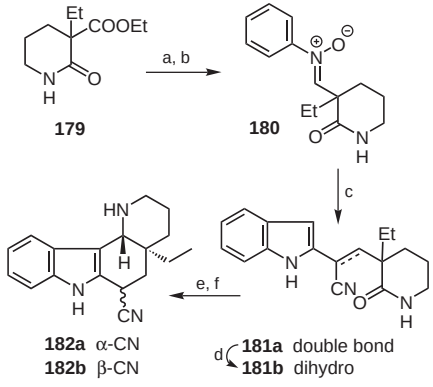
A straightforward approach to synthesis of tetracyclic alkaloid intermediates was published by Snyder et al.[70,71]. The key step rests upon the intramolecular inverse-electron demand Diels–Alder reaction in which the indole 2,3-double bond serves as a dienophile, Scheme 27. Both aminotriazines **173a**–**173c** and -tetrazines **173e**, **173f** gave rise upon exposure to refluxing acetic anhydride to the tetracyclic acetamides **174** in high yields (80–95%); the presence of a free aniline N–H, whose acylation helped in lowering the electron density of heterocyclic dienes, was obligatory – tertiary amine **173d** did not undergo the cycloaddition. Unfortunately, all attempts at closure of the remaining ring failed. Thus, for example the alkyne **175** derived from acetamide **174b** afforded on refluxing in triisopropylbenzene exclusively the 1,8-naphthyridine derivative **176** (31%). Obviously, the [4+2] cycloaddition in **175** took place, but the initial product **177** suffered a retro-Diels–Alder reaction (→ **176**) rather than a loss of the cyanoformate to give the pentacyclic aspidospermane structure **178**.



SCHEME 27

Reagents and conditions: a) Ac_2O, rfl 1–5 h (**173a** → **174a** 89%, **173b** → **174b** 95%, **173c** → **174b** 92%, **173d** no reaction, **173e** → **174e** 87%, **173f** → **174f** 80%). b) **174b**, K_2CO_3, MeOH, rt 4 h (98%). c) $[HC{\equiv}C(CH_2)_2CO]_2O$, rt 18 h (98%). d) 1,3,5-Triisopropylbenzene, rfl 12 h (31%)

A model study published by Blechert and collaborators features a synthesis of the tetracyclic nitrile[72] **182**, Scheme 28. Reduction of ester **179** followed by condensation with phenylhydroxylamine afforded the nitrone



SCHEME 28

Reagents and conditions: a) DIBAL-H, PhMe, –78 °C 3 h. b) PhNHOH, MeCN, rt 36 h (50%, 2 steps). c) CH_2=C=CH.CN, EtOH, rt 5 days (50%). d) Mg, MeOH, rt 2 h (70%). e) $POCl_3$, PhMe, rfl 3.5 h. f) $NaBH_4$, MeOH, 0 °C → rt 1 h (48%; **182a**:**182b** 1:3)

180 (50%), which underwent a reaction with cyanoallene to give acrylonitrile **181a**. Saturation of the double bond gave **181b** as a 1:1 mixture of stereoisomers. Cyclodehydration and subsequent reduction ($NaBH_4$) completed the synthesis of C/D *trans* tetracycle (48%), which was obtained as a mixture of stereoisomers **182a** and **182b** (1:3).

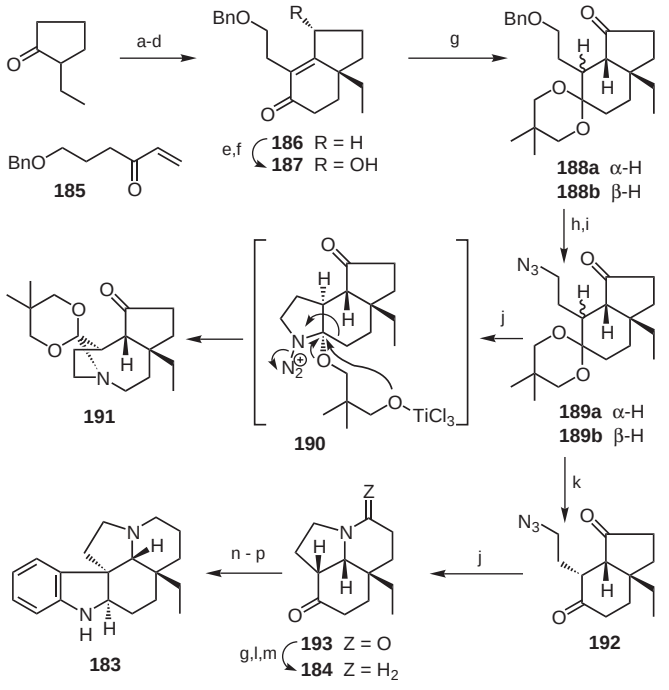
3.2. Aspidospermidines and Pseudoaspidospermidines

3.2.1. Through CDE (Lilolidine) Intermediates

Enantioselective total synthesis of (+)-aspidospermidine (**183**) by Aubé et al.[73] features an intramolecular Schmidt reaction as the key step and proceeds through CDE (lilolidine) ketone **184**, and thus parallels in final stages the first synthesis of (±)-aspidospermine by Stork and Dolfini[74]. The chirality was induced very early by an asymmetric Michael addition (d'Angelo's protocol[75]) of vinyl ketone **185** to ((*S*)-1-phenylethyl)imine derived from 2-ethylcyclopentanone, Scheme 29. The enone **186** was obtained in 49% overall yield and 84–86% ee, which could be raised to 100% by a simple recrystallisation. Allylic hydroxylation was achieved by the oxone oxidation of the derived dienol acetate. The following ketalisation in **187** proceeded with concomitant isomerisation of the allylic alcohol to a ketone, which adjusted also the relative stereochemistry of the future C-21 chiral centre; the ketal was isolated in 65–69% yield and as a mixture of diastereoisomers (**188a**:**188b** 12:1). Uneventful conversion of benzyl ether to the azide (Mitsunobu reaction) set the stage for the crucial Schmidt nitrogen insertion.

Rather surprisingly, an intramolecular insertion in **189** proceeded with participation of the ketal moiety (see **190**) and afforded bridged lactam **191** (53%). As this outcome could have been caused by *trans* orientation of azidoalkyl and cyclopentanone carbonyl, it was reasoned that deketalisation could cause epimerisation, and the Schmidt reaction then could follow the usually preferred δ- to γ-lactam formation. In the event, treatment of **189** with lithium tetrafluoroborate proceeded as expected, and the diketone **192** was obtained (89%) as a 10:1 mixture of α- and β-epimers. Subsequent exposure to titanium(IV) chloride led to the lactam **193** in 82% yield, Scheme 29.

In the light of the preceding evidence[74] the Fischer indolisation was not even tried on **193**, but only on the derived lilolidine ketone **184**. Even in this case the Fischer indolisation/reduction afforded some isomeric indole



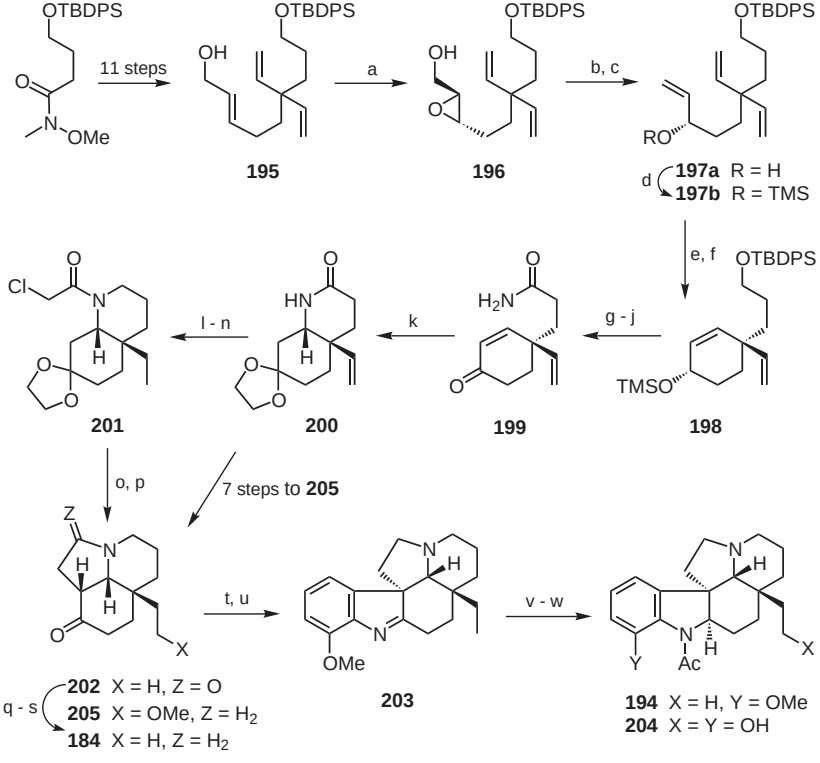
SCHEME 29

Reagents and conditions: a) (–)-(*S*)-1-Phenylethylamine. b) **185**, hydroquinone (cat), $ZnCl_2$, Et_2O, rfl. c) 10% AcOH aq. d) NaOMe, MeOH, rfl (49% overall). e) AcOC(Me)=CH_2. f) Oxone, Me_2CO (88%, 2 steps). g) $Me_2C(CH_2OTMS)_2$, TfOTMS, CH_2Cl_2, 0 °C → rt (**188** 65–69%, **188a**:**188b** 12:1). h) H_2, 10% Pd/C (85%). i) HN_3, Ph_3P, DEAD, PhH, 0 °C → rt (73%). j) $TiCl_4$, CH_2Cl_2 (**188** → **191** 53%, **192** → **193** 82%). k) $LiBF_4$ (89%). l) $LiAlH_4$, THF, rfl. m) $LiBF_4$, MeCN aq, rfl (67%, 3 steps). n) $PhNHNH_2$. o) AcOH, rfl. p) $LiAlH_4$, THF, rfl (**183** 51%, isomer 13%)

(13%), in addition to the desired (+)-aspidospermidine (**183**, 51%), which is an alkaloid from *Melodinus morsei*[76].

An enantioselective synthesis of (–)-aspidospermine (**194**) by Shishido et al.[77] utilises also Fischer indolisation of **184**, the synthesis of which is based on a diastereoselective ring-closing olefin metathesis as the key step, Scheme 30. A lengthy preparation of the allylic alcohol **195** set the stage for Sharpless epoxidation (92%), and the resulting oxirane **196** was converted to alcohol **197a** (91%). As the results in the following step were erratic with alcohol **197a**, it was silylated before crucial ring-closing metathesis: Exposure of **197b** to the Grubbs' ruthenium complex induced a quantitative and highly diastereoselective formation (87:13) of the cyclohexene ring. Cyclohexene **198** (87%!) was transformed into the unsaturated ketone **199** which, upon exposure to toluenesulfonic acid, underwent a diastereo-

selective Michael addition to give lactam **200** (72%). An internal ketone alkylation in the derived chloroamide **201** afforded lactam **202** as a single stereoisomer (72%). Removal of the lactam carbonyl required three more steps and set the stage for the Fischer reaction; cf. with[74]: Reaction of **184** with (2-methoxyphenyl)hydrazine produced indolenine **203**, which was converted to (–)-aspidospermine (**194**) in 22% yield from **184**. Unfortu-



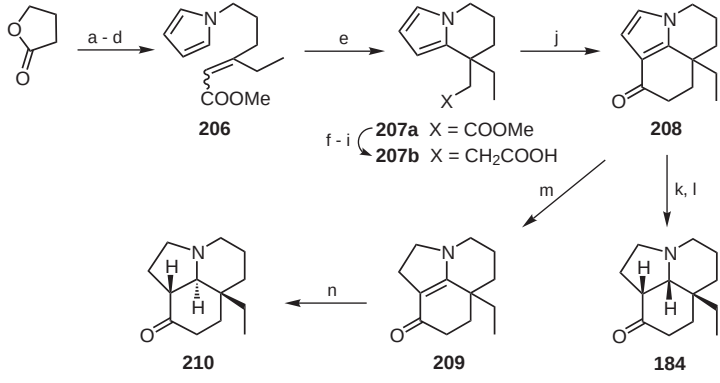
SCHEME 30

Reagents and conditions: a) (+)-DIPT, $Ti(Oi\text{-}Pr)_4$, TBHP, 4 Å MS, CH_2Cl_2, –25 °C 24 h (92%). b) I_2, Ph_3P, imidazole, PhH, rt 35 min (95%). c) Zn, AcOH, 50 °C 30 min (96%). d) TMSCl, Et_3N, CH_2Cl_2, rt 30 min (98%). e) Grubbs' catalyst (0.1 eq), CH_2Cl_2, rt 48 h. f) 1% HCl aq/THF (1:3), rt 30 min (87%, 2 steps). g) TBAF, THF, rt 6 h (94%). h) Jones reagent, Me_2CO, rt 20 min (91%). i) $(COCl)_2$, CH_2Cl_2, rt 2 h. j) NH_3 (g), THF, rt (78%, 2 steps). k) $TsOH{\cdot}H_2O$ (cat), PhH, rfl 14 h, then $HOCH_2CH_2OH$, rfl 6 h (87%). l) H_2, PtO_2, EtOH, rt 12 h (99%). m) $LiAlH_4$, THF, rfl 2 h. n) $ClCH_2COCl$, Et_3N, CH_2Cl_2, rt 30 min (72%, 2 steps). o) 1 M HCl aq/THF (2:1), rfl 2 h. p) *t*-BuOK, PhH/*t*-BuOH (1:1), rt 30 min (79%, 2 steps). q) $TsOH{\cdot}H_2O$ (cat), $HOCH_2CH_2OH$, PhH, rfl 14 h (85%). r) BH_3, THF, rt overnight. s) 1 M HCl aq/THF (3:2), rfl 1 h (84%, 2 steps). t) $2\text{-}MeO.C_6H_4.NHNH_2{\cdot}HCl$, Na_2CO_3, EtOH, rt 3 h. u) AcOH, 95 °C 1 h. v) $LiAlH_4$, THF, rt 24 h. w) Ac_2O, py, rt 3 h (22%, 4 steps)

nately, no information was provided on the regioselectivity of the Fischer process[77]. Note that (–)-**194** is available from *Vallesia glabra*[78], and (+)-enantiomer *ent*-**194** occurs in *Aspidosperma pyrifolium*[79].

The same authors have also accomplished[80] a formal total synthesis of (–)-limaspermine (**204**), Scheme 30: They transformed the olefine lactam **200** into tricyclic lactam (–)-**205**, the racemic form of which was an advanced intermediate in Pearson's synthesis of (±)-**204** [81]. (+)-Limaspermine (**204**) was reported from *Aspidosperma limae*[82].

A synthesis of racemic CDE ketone **184** was reported recently by Banwell and Smith[83], which exploits the nucleophilicity of the pyrrole ring, Scheme 31. The synthesis starts with the known *N*-alkylation of pyrrole with γ-butyrolactone. The product was converted to the acrylate **206** obtained as a 1:1 *E*/*Z*-mixture, which afforded, upon intramolecular Michael addition mediated by excess aluminium chloride, the indolizine ester **207a** (83%), homologated in ordinary way to propionic acid **207b**. The latter underwent an internal Friedel–Crafts acylation induced by aqueous HCl and yielded the lilolidine derivative **208** (72%). A two-step conversion of **208** to the ketone **184**, albeit in a low yield (28%), completed the formal total synthesis of (±)-aspidospermidine (**183**).

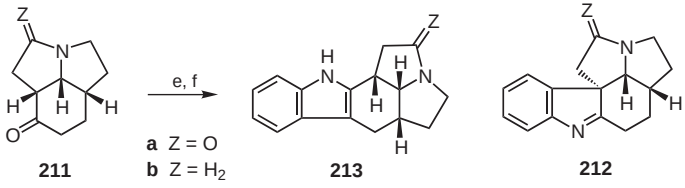


SCHEME 31

Reagents and conditions: a) 160 °C 2 h. b) MeONHMe·HCl, pyridine *N*-oxide disulfide, Bu_3P, CH_2Cl_2, 18 °C 16 h (87%). c) EtMgBr (1.7 eq), Et_2O, 0 °C → rt 2 h, then 0.3 M $KHSO_4$ aq, –40 °C (100%). d) $(EtO)_2POCH_2COOMe$ (2 eq), NaH (2 eq), THF, 18 °C 2 days (77%; *E*/*Z* ca. 1:1). e) $AlCl_3$ (5 eq), Et_2O, 0 °C → 18 °C 5 h (83%). f) DIBAL-H (2 eq), CH_2Cl_2, –78 °C 30 min → 0 °C 1 h (75%). g) MsCl, Et_3N, CH_2Cl_2, 0 °C 5 min → 18 °C 45 min (95%). h) NaCN (5 eq), *N*,*N*′-dimethylpropyleneurea, 18 °C 2 days (91%). i) KOH, MeOH aq, rfl 16 h (88%). j) 5 M HCl aq, 18 °C 1 h (72%). k) H_2, PtO_2 (cat), AcOH, 18 °C 18 h. l) Dess–Martin periodinane (3 eq), 0 °C 30 min → 18 °C 30 min (28%, 2 steps). m) H_2, 5% Rh/Al_2O_3 (cat), AcOH/EtOH (1:49), 18 °C 18 h (80% based on recovered **208**). n) $LiAlH_4$ (excess), THF, 18 °C → rfl 1.5 h (65%)

Unsatisfied with the yield of the above transformation, the authors subjected **208** to milder initial hydrogenation conditions (5% Rh/Al_2O_3 vs PtO_2), which, after $LiAlH_4$ reduction of intermediary enamide **209**, resulted in 51% yield of the epimeric ketone **210**, Scheme 31. Unfortunately, all attempts at Fischer indolisation of this last compound failed, which illustrates subtle factors (vide infra) that govern the outcome of the transformation[83]; see also Chapter 3.2.2.1.

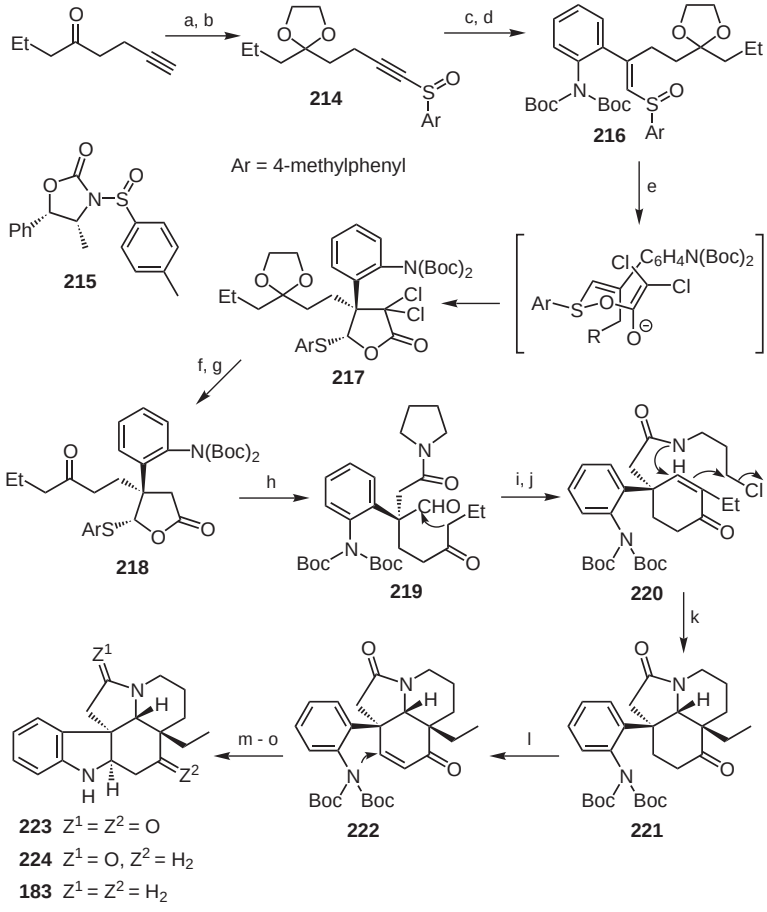
In an attempt to access the ibophyllidine skeleton, Bonjoch et al. have subjected tricyclic ketones **211** to the Fischer reaction[69], Scheme 32. Unfortunately, both the conditions tried (hot AcOH or HCl/EtOH) led uniformly to the exclusive formation of the undesired pentacycles **213**. The failure to form **212** follows probably from a different conformation (as compared to lilolidine derivatives above) such, which prevents formation of an ene hydrazine in the desired direction.



SCHEME 32

Reagents and conditions: a) $PhNHNH_2 \cdot HCl$, Na_2CO_3, EtOH, rfl 1.5 h. b) AcOH, 95–115 °C 1–3 h (**211a** → **213a** 42%; **211b** → **213b** 25%). c) HCl/EtOH (**211a** → **213a** 45%; **211b** → **213b** 40%)

Another fully enantioselective total synthesis of (+)-aspidospermidine (**174**) by Marino et al.[84] features two consecutive internal Michael additions that serve to build-up the aspidospermane skeleton, Scheme 33. Chirality is induced rather early by its transfer from sulfur to carbon during [3,3] sigmatropic rearrangement in a reaction of chiral vinyl sulfoxide with dichloroketene. The synthesis begins with the preparation of the chiral alkynyl sulfoxide (+)-**214** through the reaction of alkynyllithium with Evans' *N*-tolylsulfinyl oxazolidinone (4*R*,5S,R_S)-**215** (84%). Addition of *ortho*-metalated Boc-protected aniline to **214** provided a vinyl sulfoxide (82%), which was converted to the (*E*,R_S)-alkenyl sulfoxide **216**. In a crucial, chirality-inducing step, trichloroacetyl chloride was added to vinyl sulfoxide **216** and Zn–Cu couple at –45 °C; dichlorolactone **217** was obtained in 78% yield, as a single stereoisomer. The derived oxolactone **218** afforded, upon exposure to pyrrolidine, aldehyde **219**. Its aldol condensation provided cyclohexenone ring; a carboxyl was released simultaneously

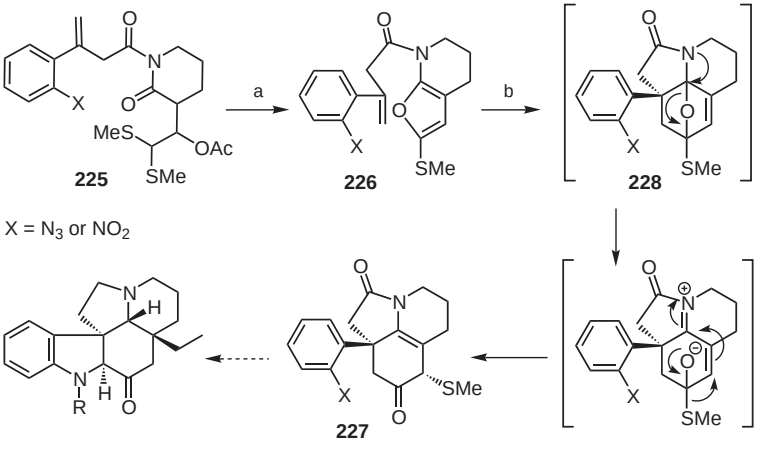


SCHEME 33

Reagents and conditions: a) $HOCH_2CH_2OH$, PhH, TsOH (cat), rfl 24 h (90%). b) BuLi, THF, –78 °C 1 h, then $MgBr_2/Et_2O$, 0 °C → rt 1 h, then (4*R*,5*S*,R_S)-**215**, –78 °C 30 min (84%). c) PhNHBoc, *t*-BuLi (2 eq), –78 °C 1 h → –20 °C 2.5 h, then CuBr.SMe_2, THF, –78 °C → warm, then (+)-**214**, –78 °C 3 h (82%). d) MeLi, THF, –78 °C 2.5 h, then $(Boc)_2O$, –78 °C 1.5 h → 0 °C 2 h (81%). e) Zn(Cu) (20 eq), $Cl_3C.COCl$, THF, –40 °C 15 min (78%). f) Bu_3SnH (2.3 eq), Et_3B (0.3 eq), PhH, 78 °C 15 h (92%). g) TsOH (cat), Me_2CO, rt overnight (96%). h) Pyrrolidine, PhH, rt 12 h (86%). i) Pyrrolidine, i-PrOH, 33% AcOH aq, rt 24 h. j) i-BuOCOCl, Et_3N, THF, 0 °C 5 min, then $ClCH_2CH_2CH_2NH_2 \cdot HCl$, Et_3N, DMF, 0 °C → rt 30 min (61%, 2 steps). k) NaH, DMF, 0 °C 1 h (86%). l) KHMDS (2.2 eq), THF, –78 °C 1 h, then TMSCl, –78 °C 1 h, then evaporate; then O_2, $Pd(OAc)_2$, DMSO, 70–75 °C 16 h (80%). m) 3 M HCl aq/i-PrOH (1:1), rfl 40 min (96%). n) $N_2H_4 \cdot H_2O$, Na, $HOCH_2CH_2OH$, 160 °C 1 h → 190 °C 1 h → 210 °C 3 h (75%). o) $LiAlH_4$, THF, rfl 3 h (90%)

which was converted to the amide **220** (65% in 2 steps). In a crucial ring forming step, exposure of **220** to the base (NaH) induced a stereoselective Michael addition followed by the chlorine displacement with an intermediary enolate; as a result, 7-aryllilolidinedione **221** was isolated in 86% yield! Conversion of **221** to the unsaturated ketone **222** set the stage for the remaining ring closure. An acid deprotection of aniline in **222** and the following closure of ring B by a stereoselective Michael addition provided (+)-aspidospermidine-5,17-dione **223** in 90% yield. Sequential removal of oxygen functionalities via lactam **224** completed the synthesis of (+)-aspidospermidine (**183**).

Recently, Padwa et al. have redesigned their approach to aspidospermane skeletons through intramolecular [4+2] cycloaddition in order to avoid rather harsh conditions required in reactions with indole as the dienophile; a styrene moiety was substituted for the indole[85], Scheme 34. With the straightforward method of synthesis of the 2-amidofurans at hand[86], a treatment of the thioacetal **225** with DMTSF reagent (dimethyl(methylsulfanyl)sulfonium tetrafluoroborate) provided furan **226**, which was heated at 120 °C. The desired pentacyclic ketone **227** was obtained in quantitative yield as a single diastereoisomer through rearrangement of the primary cycloadduct **228**. Work is in progress on the closure of the remaining B ring (Smalley cyclisation); see also Chapter 3.2.3.2.



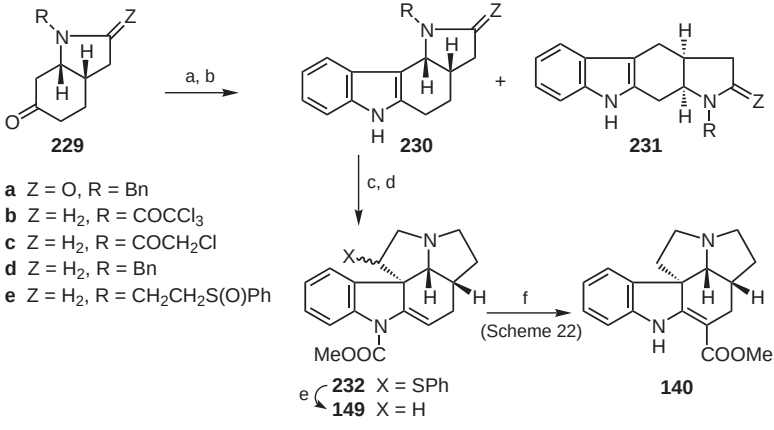
SCHEME 34
Reagents and conditions: a) DMTSF. b) 120 °C (quant)

3.2.2. Through ABCD Intermediates

Apart from an efficient construction of the ABCD ring system, an important goal is the closure of the spirocyclic E ring; here the procedure of Magnus[87], which rests upon trapping of the Pummerer rearrangement-derived thionium ion by the indole C-3, seems to be almost a standard procedure nowadays.

3.2.2.1. Fischer Indole Synthesis

A model study of the Fischer indole synthesis on ketones **229** was reported by Bonjoch and collaborators[69], Scheme 35. It was demonstrated that the regioselectivity of the reaction could be efficiently controlled by hybridisation of the nitrogen, which influenced the conformation of the transient specii. Thus, while the lactam **229a** and amide **229b** yielded only the unwanted tetracycles **231** and amide **229c** gave rise to a mixture of **230c** (23%) and **231c** (20%), the same reaction of the amine **229d** led exclusively to the desired amine **230d** (54%). Encouraged by these results, the authors addressed the synthesis of (±)-20-desethylibophyllidine[68,69] (**140**). The crucial indole formation from amine ketone **229e**, accesible from *O*-methyltyramine in three steps (54% overall), proceeded as expected and gave the tetracyclic indole **230e** as a mixture of sulfur isomers (60% yield), which

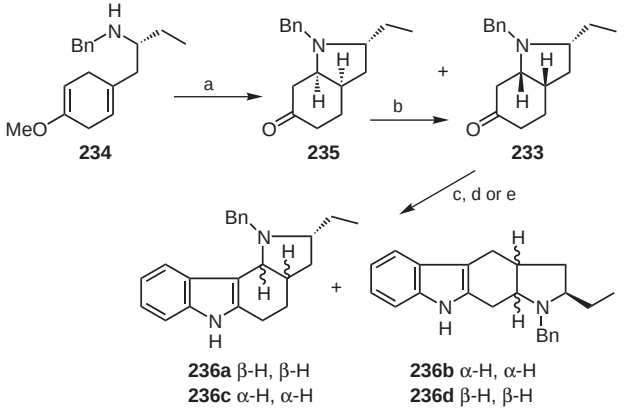


SCHEME 35

Reagents and conditions: a) $PhNHNH_2 \cdot HCl$, Na_2CO_3, EtOH, rfl 1.5 h. b) AcOH, 95 °C 2–3 h (**229a** → **231a** 27%; **229b** → **231b** 30%; **229c** → **230c** 23% + **231c** 20%; **229d** → **230d** 54%; **229e** → **230e** 60%). c) LDA, HMPA/THF (1:6), –78 °C 1 h, then NC.COOMe, –78 °C → rt 2 h (78%, 1:1). d) TFAA/TFA (1:1), PhMe, 80 °C 2 h (63%, 1:1). e) Ra-Ni (W-2), EtOH, rfl 4 h (64%). f) *hν*, MeOH, rt 2.5 h (50%)

was carbamoylated with Mander's reagent (78%). The resulting sulfoxide was subjected to the closure of E ring using Magnus' protocol: Treatment with TFAA/TFA mixture generated a thionium which was triggered by the indole creating thus the remaining spirocyclic ring of **232**, appearing again as a 1:1 mixture of epimers (63%). Removal of sulfur gave **149**, whose transformation into (±)-**140** (50%) was already discussed in Chapter 3.1.5.

A great impact of the structure variation in hydroindoles on the course of the process was demonstrated by the same Laboratory with the Fischer synthesis study of an ethyl analogue[88] (–)-**233**, which has all the chiral centres properly adjusted for the conversion to (+)-ibophyllidine (**35a**), Scheme 36. The amine **233** was obtained as a major product (53%) from diene **234** by its exposure to 3 M hydrochloric acid; minor stereoisomer **235** (7%) afforded on treatment with the same acid a mixture with isomer **233** highly prevailing (9:1). Unlike **229d**, **229e**, the phenylhydrazone of **233** yielded, upon exposure to hot acetic acid, a mixture of four products **236a**–**236d** (49%; 1:2:1:2). The yield of the desired isomer **236a** could not be much improved by the modification of conditions: With trifluoroacetic acid in CH_2Cl_2 the mixture did not contain any of the isomers **236c**, **236d**, but the desired **236a** was still the minor component (12%; 1:4.5).

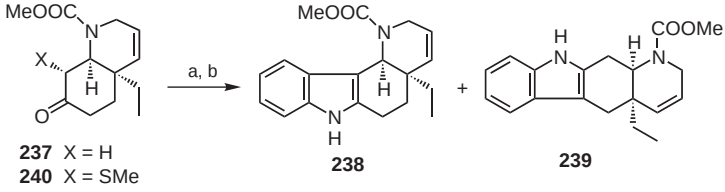


SCHEME 36

Reagents and conditions: a) 3 M HCl aq, 95 °C 5 h (**233** 53%, **235** 7%). b) 6 M HCl aq, 90 °C 18 h (**233**:**235** 9:1). c) $PhNHNH_2 \cdot HCl$, Na_2CO_3, EtOH, rfl 3 h. d) AcOH, 110 °C 4 h (**236a**:**236b**:**236c**:**236d** 1:2:1:2). **e**) TFA/CH_2Cl_2 (1:10), 35–40 °C 17 h (**236a** 12%, **236b** 53%)

The problem of regioselectivity in Fischer indolisation was also studied by Rawall et al.[66] during their synthesis of tabersonine and other aspidospermane alkaloids. The phenylhydrazone of ketone **237** afforded on treatment with hot acetic acid a mixture of indoles (93%), which contained the

desired tetracycle **238** as the minor product (41%), Scheme 37. The ratio of products could not be improved, and the Gassmann indolisation of (methylsulfanyl)ketone **240** failed completely; this prompted the authors to develop a new methodology, see Chapter 3.2.2.4.



237 X = H
240 X = SMe

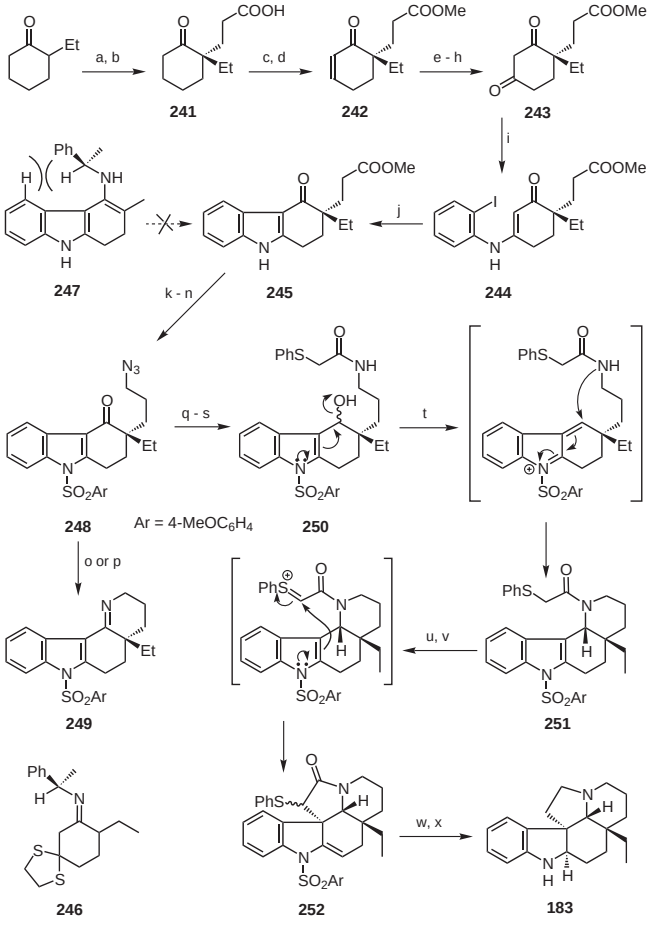
238 **239**

SCHEME 37
Reagents and conditions: a) $PhNHNH_2 \cdot HCl$, Na_2CO_3, EtOH, rfl 1.5 h. b) AcOH, 95 °C 2–3 h (**237** → **238** 41% + **239** 52%)

3.2.2.2. Through 3,3-Disubstituted Carbazolones

Synthesis of (+)-aspidospermidine (**183**) by Desmaële and d'Angelo[89] implements 3,3-disubstituted carbazolone derivatives. The optical activity in this enantioselective total synthesis was induced at the very beginning of the process, Scheme 38. Thus, the enantioselective addition of the enamine derived from 2-ethylcyclohexanone and (+)-(*R*)-1-phenylethylamine to acrylate afforded (+)-(*S*)-**241** in 83% yield and 86% ee, corresponding to 90% asymmetric induction due to 96% optical purity of the starting amine. Cyclohexanone was then transformed via cyclohexenone **242** to the cyclohexane-1,3-dione (+)-(*S*)-**243**. Its exposure to 2-iodoaniline gave the enaminone **244**, which cyclised oxidatively to carbazolone (–)-**245** using copper(I) species (84%). A more direct approach to **243** and **245** from **246** and **247**, respectively, failed completely; in the first case due to the unexpected side reaction, in the latter model case the corresponding imine did not tautomerise to **247**, which would itself fail to react with Michael acceptors due to steric hindrance by branching.

A chemoselective reduction of the methoxycarbonyl group in the presence of 4-ketone (88%; in fact a vinylogous amide protected against reduction by *N*-metallation) initiated a conversion of the former group to the azidomethyl (→ **248**). The reduction of the derived tetracyclic imine **249** with a variety of agents led only to the unnaturally *trans*-configured product amines. Hence, an indirect, yet efficient procedure was adopted: Sodium borohydride reduction of the carbonyl group in **248** followed by a manipulation of the azido functionality provided amide alcohol **250**. Its cyclisation induced by TFA gave the tetracyclic amide **251** stereoselectively

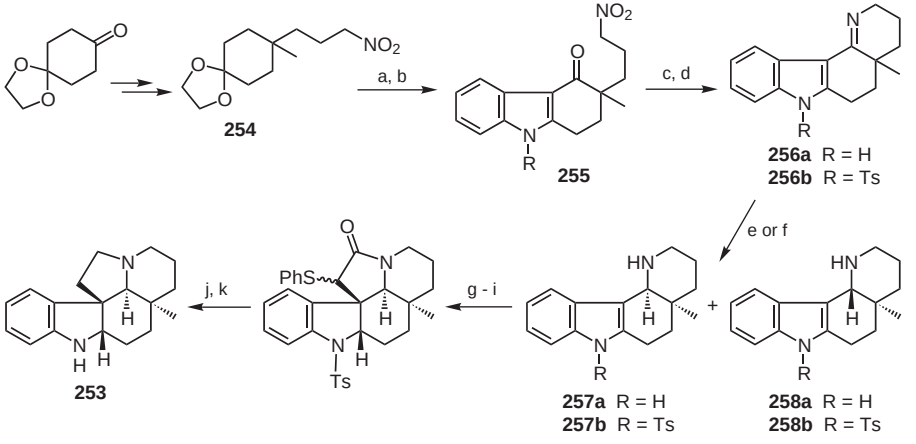


SCHEME 38

Reagents and conditions: a) (+)-(*R*)-PhCH(Me)NH_2 (96% ee), TsOH, PhMe, rfl 12 h. b) CH_2=CH.COOMe, hydroquinone (cat), 65 °C 3 days, then 20% AcOH aq, 20 °C 3 h (83% overall, 86% ee). c) TMSCl, Et_3N, DMF, 100 °C 48 h (97.8% crude). d) DDQ, 2,6-lutidine, PhMe, rt 4 days (80%). e) PhSH, Et_3N, CH_2Cl_2, 0 °C 3 h (93%). f) NCS, CCl_4, 0 °C 5 h (82%). g) NaOMe, MeOH, rfl 2 h (80%). h) 1 M HCl aq/THF (1:2), rt 3 h (74%, optically pure). i) 2-$IC_6H_4NH_2$, TsOH (cat), PhMe, rfl 5 h (94%). j) NaH, HMPA, rt, then CuI, 120 °C 2 h (84%). k) $LiBHEt_3$, THF –40 °C 1 h (88%). l) MsCl, DMAP (cat), Et_3N, CH_2Cl_2/THF (5:1), 0 °C 2 h (99% crude). m) NaN_3, DMF, 80 °C 2 h (86% crude). n) 4-$MeOC_6H_4SO_2Cl$, TBAHS (cat), CH_2Cl_2, 50% NaOH aq, rt 2 h (65% from **245**). o) Ph_3P, THF, rt 18 h (69%). p) H_2 (5 atm), 10% Pd/C, EtOH, AcOH, 20 °C 24 h (91%). q) $NaBH_4$, EtOH, rfl 30 min (92%; 1:1). r) Ph_3P, THF, rt 18 h. s) $PhSCH_2COCl$, CH_2Cl_2, 1 M NaOH aq, rt 30 min (62% overall; 1:1). t) TFA, CH_2Cl_2, 0 °C 15 min (93.5%). u) $NaIO_4$, THF/MeOH (3:1), rt 48 h (88%). v) TFAA, CH_2Cl_2, 0 °C 15 min, then PhCl, 0 °C → 135 °C (30 min) 2 h (89%). w) Ra-Ni (W–2), EtOH, DMF, rt 20 min (56% from **248**). x) $LiAlH_4$, THF, 0 °C → 20 °C 2 days (68%)

and in a high yield of 93.5%! The final stages followed in principle the Magnus' protocol and afforded pentacyclic sulfonamide **252**, the sequential reduction of which with Raney nickel and $LiAlH_4$ afforded eventually the desired (+)-aspidospermidine[89] (**183**).

The problem of a stereochemical outcome of the tetracyclic imine reduction (similar to **249**) was also studied by Urrutia and Rodríguez[90,91] in their total synthesis of racemic 18-nor-aspidospermidine **253**, Scheme 39. Tetrahydrocarbazolone **255**, prepared by Fischer indolisation of the symmetrical ketal **254** and oxidation by DDQ (65% overall), underwent a spontaneous imine formation after the nitro group reduction (→ **256a**; 91%). After an extensive experimentation it was shown that, unlike common hydrides, which afford in most cases the unwanted *trans*-amines, an addition of the Lewis acid ($AlCl_3$) to the $LiAlH_4$ reduction of **256** in low-complexing toluene (with a small amount of THF added to render the mixture homogeneous) favoured the formation of *cis*-amine **257** (70–75:30–25). Amine **257b** was then transformed into the unnatural base (±)-**253** by an application of the Magnus' protocol.

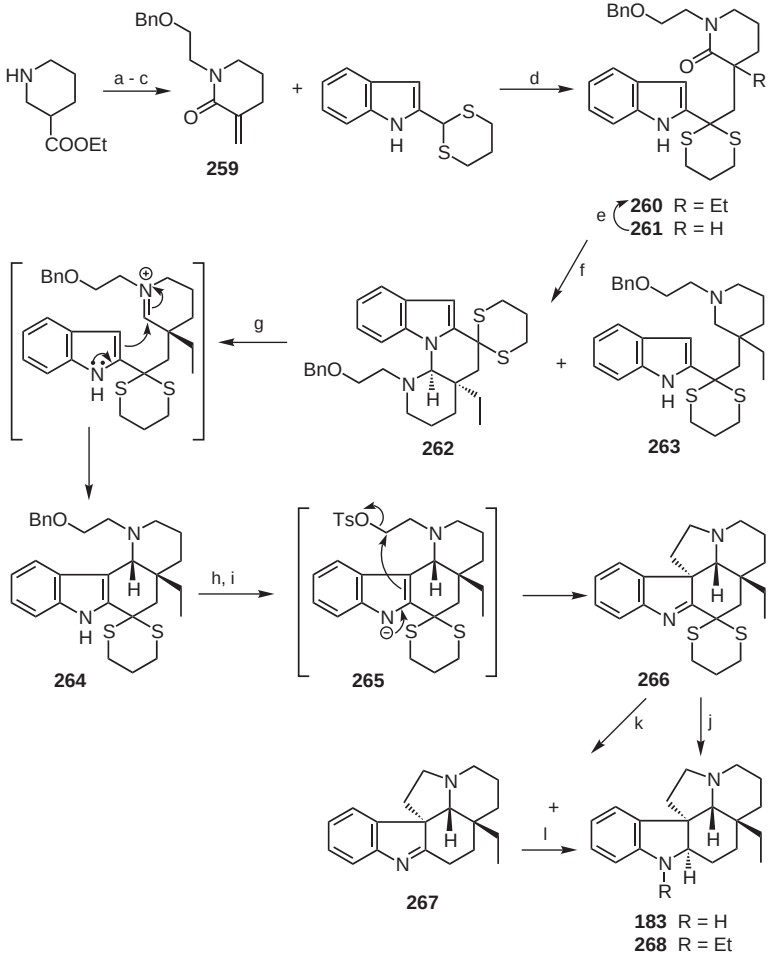


SCHEME 39

Reagents and conditions: a) $PhNHNH_2 \cdot HCl$, AcOH, 100 °C 2 h (81%). b) DDQ, THF, 0 °C 3 h, then K_2CO_3 (s), 2 h (80%). c) $NaBH_4$, $NiCl_2 \cdot 6H_2O$, NaOH (1 eq), EtOH, 80 °C, then $N_2H_4 \cdot H_2O$, 80 °C 4 h (91%). d) TsCl, $Bu_4N^+I^-$, NaOH aq, CH_2Cl_2, 0 °C 5 min (74%). e) **256a**, $AlCl_3$, PhMe/THF (30:1), 0 °C 5 min, then $LiAlH_4$, rt 2 h (97%; **257a**:**258a** 7:3). f) **256b**, $AlCl_3$, $LiAlH_4$, PhMe/THF (30 or 9:1), 0 °C 4 h (93%; **257b**:**258b** 75:25). g) $PhSCH_2COCl$, Et_3N, CH_2Cl_2, rt 18 h (96%). h) $NaIO_4$, THF aq, rt 48 h (72%). i) TFAA, CH_2Cl_2, rt 25 min, then PhCl, rfl 2 h (68%; 7:3). j) Ra-Ni, EtOH, DMF, rt 1 h (82%). k) $LiAlH_4$, THF, rt 48 h (50%)

3.2.2.3. Through Cyclisation of AB-D Iminiums

Rubiralta and coworkers have described a synthesis of (±)-aspidospermidine (**183**), which represents an efficient alternative to the production of N_b-substituted ABCD tetracycles via Fischer indolisation[92], Scheme 40. The syn-



SCHEME 40

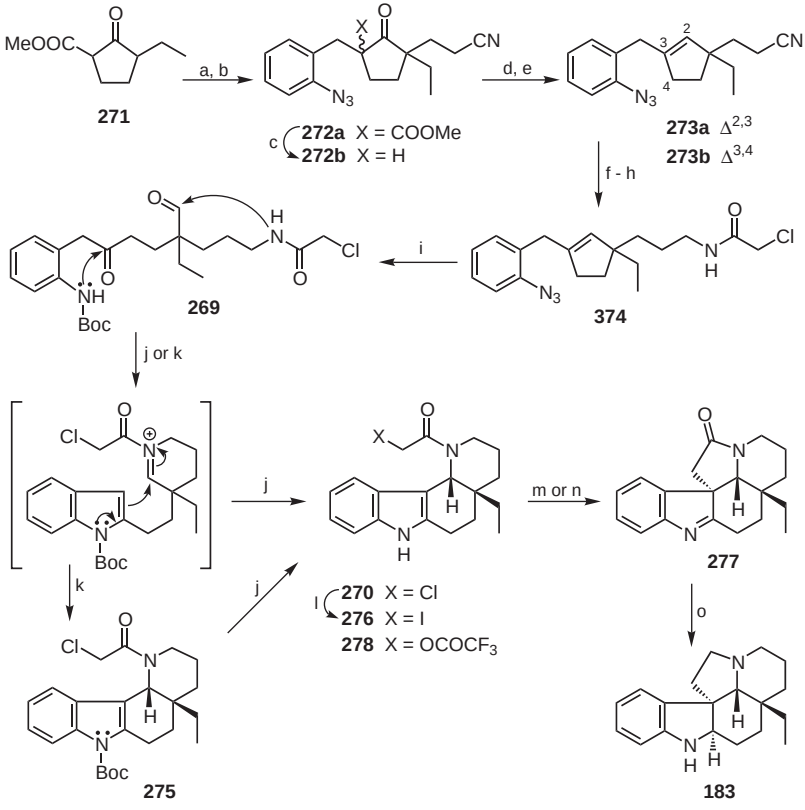
Reagents and conditions: a) $BnOCH_2CH_2Br$, K_2CO_3, PhH, rfl 24 h (89%). b) 6 M HCl aq, rt overnight (quant). c) Ac_2O, rfl 4 h, then → 0 °C, K_2CO_3 aq., 0 °C 4 h (86%). d) BuLi, THF, –78 °C 20 min, then **259**, HMPA, –78 °C 30 min, then EtI, –78 °C 1 h (**260** 53% + **261** 10%). e) *s*-BuLi, THF, –78 °C 20 min, then EtI, HMPA, –78 °C 1 h (quant). f) **260**, DIBAL-H, THF, 0 °C (**262** 73% + **263** 10%). g) 50% AcOH aq, rfl 2 h (90%). h) Me_2S, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 35 °C 2 h (86%). i) *t*-BuOK (3 meq), TsCl (2 meq), rt 1 h (77%). j) Ra-Ni (W-2), EtOH, rfl 30 min (**183** 23% + **268** 25%). k) Ra-Ni (W-2), dioxane, rfl 30 min (**183** 30% + **267** 35%). l) $LiAlH_4$

thesis features an efficient Michael addition of a metalated dithiane to the α-methylidenepiperidone **259**, followed by C-ethylation, which produced ethyllactam **260** (53%) together with lactam **261** (10%); the latter could be quantitatively converted to **260** through metalation/ethylation. Dibal-H reduction of the lactam **260** gave hemiaminal **262** in 73% yield together with an over-reduced piperidine **263** (10%). The former underwent a stereoselective isomerisation to tetracycle **264** upon exposure to refluxing 50% acetic acid in a high yield (90%). *O*-Debenzylation ($BF_3 \cdot OEt_2$; 86%) was followed by a reaction with TsCl and an excess potassium *tert*-butoxide which resulted in a closure via **265** of the remaining E ring (→ **266**; 77%). The latter reaction is thus another efficient procedure for the indolenine formation from tetracyclic ABCD precursor. The following desulfurisation with Raney nickel was best performed in dioxane producing (±)-indolenine **267** (35%) and (±)-aspidospermidine (**183**; 30%); $LiAlH_4$ reduction of the former then raised the overall yield of the desired base **183**. Note that 1,2-didehydroaspidospermidine (**267**) is itself a natural alkaloid – (+)-**267** occurs in *Rhazya stricta*[93], while (–)-enantiomer (*ent*-**267**) is isolable from *Vinca erecta*[94].

Total synthesis of (±)-aspidospermidine (**183**) by Toczko and Heathcock[95] is based on yet another approach to the construction of ABCD synthon and the following closure of the E ring; the ABCD tetracyclic amide **270** was stereoselectively built up through a spontaneous self-assembly in aldehyde ketone **269**, Scheme 41. Cyclopentanone **271** was first alkylated in α-position with 2-azidobenzyl bromide (94%) and then the γ-enolate (again Cs_2CO_3) underwent Michael addition to acrylonitrile giving ester **272a**, which was decarboxylated (→ **272b**; 77% in 2 steps). Borohydride reduction/dehydration with PCl_5 and pyridine afforded a 63% yield of a 4:1 mixture of olefine **273a** and its isomer **273b**, which was carried further without separation. Ozonisation of the derived amide carbamate **274** produced rather unstable aldehyde **269** (31%; 4:1 mixture), which cyclised by exposure to TFA in CH_2Cl_2 (1:1) producing acetamide **270** in 81% yield; this crucial transformation could be run more efficiently without intermediate isolation (37 vs 53%). On the other hand, 0.5 M TFA in CH_2Cl_2 did not split off the Boc-group and afforded carbamate **275** in 76% yield, which was then deprotected with TFA (88%).

The crucial formation of the spirocyclic E ring in the chloroacetamide **270** was best induced by treatment of the derived iodide **276** with silver triflate (→ **277**; 88%); note that the use of silver trifluoroacetate yielded in addition to **277** (46%) an almost equal amount of the substitution product **278**. Lithium aluminium hydride reduction of the indolenine **277** com-

pleted the 13-step synthesis of (±)-aspidospermidine (**183**), with 5.9% overall yield[95].



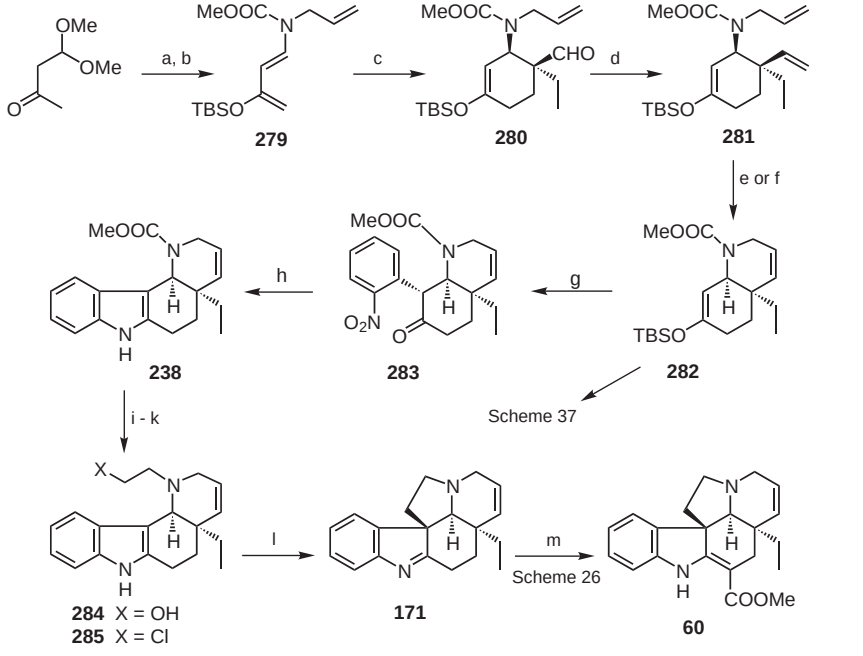
SCHEME 41

Reagents and conditions: a) 2-Azidobenzyl bromide, Cs_2CO_3, NaI, Me_2CO, rt 45 min (94%). b) CH_2=CHCN, Cs_2CO_3 (1 eq), *t*-BuOH, rfl 1.5 h (1:1 diast. mixture). c) KOH, i-PrOH aq, rt 4 h (77%; 1:1 diast. mixture). d) $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C 15 min, then $NaBH_4$, 0 °C. e) PCl_5, py, cool 60 min (63%; **273a**:**273b** 4:1). f) $LiAlH_4$, THF, rfl 4 h (65%; 4:1 diast. mixture). g) $(ClCH_2CO)_2O$, Et_3N, CH_2Cl_2, 0 °C 20–25 min → rt. h) Boc_2O, Et_3N, MeOH, rfl 14 h (67%; 4:1 diast. mixture). i) O_3, CH_2Cl_2, –78 °C, then Me_2S, –78 °C → rt 1 h (31%). j) TFA/CH_2Cl_2 (1:1 v/v), rt 15 min (53%, 2 steps; from **269** 81%, from **275** 88%). k) 0.5 M TFA in CH_2Cl_2 (76%). l) NaI, Me_2CO, rfl 2 h. m) AgOTf, THF, rt 30 min (86%). n) $AgOCOCF_3$, THF (**277** 43% + **278** almost equal yield). o) $LiAlH_4$, THF, rt 30 min → rfl 4 h (82%)

3.2.2.4. Rawal's et al. Syntheses

Rawal and Kozmin have developed de novo both the racemic as well as the enantioselective, synthesis of aspidospermane alkaloids, which turned out to be the most efficient approach to date[65,66]. The synthesis of

(±)-tabersonine (**60**) starts with the preparation of 1,3-diheterosubstituted diene **279**, which then undergoes a highly stereoselective [4+2] cycloaddition with 2-ethylacrylaldehyde via an *endo*-transition state (less than 5% of *exo*-isomer could be detected in the raw mixture), Scheme 42. Aldehyde **280** is obtained in this stereochemistry defining step in a yield of 97%! A conversion to diene **281** then set the stage for the closure of the



SCHEME 42

Reagents and conditions: a) CH_2=$CHCH_2NHCOOMe$, TsOH (cat), $CHCl_3$, rfl 1–2 days (90–45%). b) NaHMDS (1.1 eq), THF, –78 °C 1 h, then TBSCl, –78 °C 2 h (quant). c) CH_2=C(Et).CHO, PhMe, 65 °C 15 h → 85 °C 33 h (97%). d) $Ph_3P^+MeBr^-$, BuLi, THF, –78 °C → rt (85%). e) Grubbs' ruthenium catalyst, CH_2Cl_2, 40 °C 2 h (75%). f) Schrock's molybdenum catalyst, PhH, 60 °C 1 h (88%). g) NPIF, DMSO/THF (2:1), 20 °C 1.5 h (94%). h) $TiCl_3$, NH_4OAc, Me_2CO aq, 20 °C (89%). i) TMSI, CH_2Cl_2, rfl 1 h (91%). j) $BrCH_2CH_2OH$ (10 eq), Na_2CO_3, EtOH, rfl 18 h (100%). k) MsCl, Et_3N, CH_2Cl_2, –20 °C → rt 30 min (90%). l) *t*-BuOK, THF, 20 °C 16 h (87%). m) LDA, THF, –70 °C → –20 °C (1 h), then NC.COOMe, –70 °C (80%)

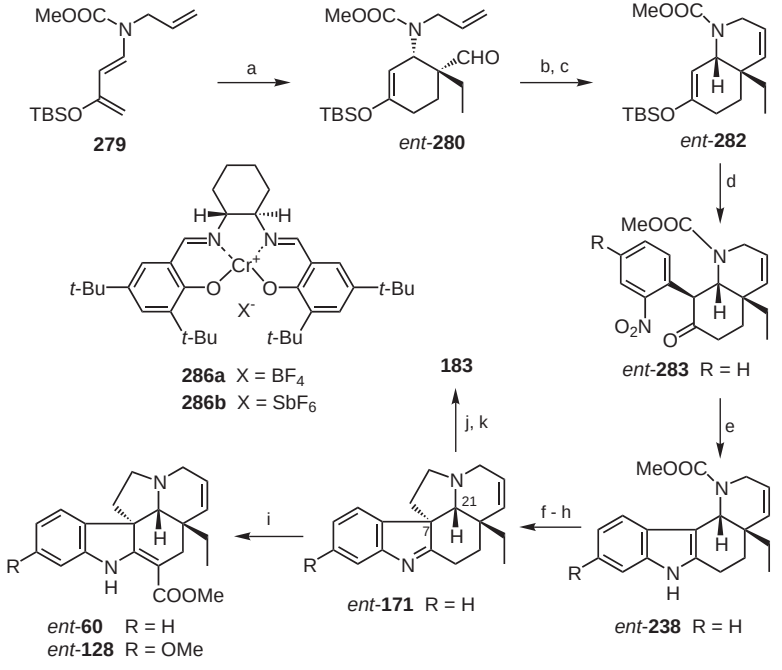
ring through metathesis, which defines future 14,15-unsaturation of the aspidospermane skeleton. The best results were obtained with Schrock's molybdenum catalyst, which afforded **282** in 88% yield. Since conversion of the enol ether **282** to ABCD carbamate **238** through Fischer indolisation did not satisfy the authors due to a low regioselectivity (see Chapter

3.2.2.1), they developed an alternative synthesis by introducing a novel reagent[96] for the transformation of **282** into the substituted ketone **283**: Reaction with (2-nitrophenyl)phenyliodonium fluoride (NPIF) yielded ketone **283** as a single stereoisomer (94%). Titanium(III) chloride reduction led to an aniline, which spontaneously cyclocondensed and gave indole **238** in 89% yield. Removal of COOMe moiety in **238** followed by an introduction of the two-carbon chain by alkylation then afforded the alcohol **284**. Since a direct conversion of the indole **284** to indolenine **171** by using the Rubiralta's protocol led to variable yields of the desired pentacycle (30–50%), the authors used a two-step method consisting of a mesylation, which produced chloro derivative **285** (90%), and subsequent base-catalysed SN2′ alkylation to afford (±)-14,15-didehydroaspidospermidine (**171**) in 89% yield. The conversion of indolenine **171** to (±)-tabersonine (**60**) using Mander's reagent was already mentioned in Chapter 3.1.5. This is the most efficient total synthesis to date, producing base (±)-**60** in an overall yield of about 30%[65,66]!

With the efficient approach to synthesis of the racemic tabersonine at hand, Rawal and collaborators addressed an enantioselective synthesis of aspidospermane alkaloids[66], Scheme 43. On the basis of their discovery that Jacobsen's chiral chromium(III)–salen complex **286** was very efficient in catalysing the [4+2] cycloaddition of 1-amino(silyloxy)butadienes with 2-substituted acrylaldehydes[97,98], the authors performed the cycloaddition of diene **279** with 2-ethylacrylaldehyde in the presence of these catalysts. Enantioselectivity was higher with fluoroantimonate salt **286b**, and with 5 mole % of the catalyst ee as high as 96% was achieved on 1 mmol scale (yield of aldehyde *ent*-**280** 91%), and still 95% at 20 mmol scale. The remaining steps of the synthesis paralleled the racemic procedure with some practical improvements. Thus, the aldehyde *ent*-**280** was converted to the carbamate *ent*-**282** using Grubb's catalyst and further to the α-aryl ketone *ent*-**283** by reaction with the NPIF reagent in an overall yield of 57–62%. The *ent*-**283** was converted via indole *ent*-**238** to indolenine *ent*-**171** and finally to (+)-tabersonine (*ent*-**60**) in 33–39% yield for the reaction sequence on the gram scale.

Unnatural (+)-11-methoxytabersonine (*ent*-**128**) was made accessible[66] using this approach by substituting (4-methoxy-2-nitrophenyl)phenyliodonium fluoride for NPIF reagent in a reaction with the carbamate[66] *ent*-**282**. The remainder of the synthesis paralleled the (+)-tabersonine case, and the ketone *ent*-**283** (R = OMe) was converted to (+)-base *ent*-**128** in 37% overall yield again on the gram scale.

The indolenine *ent*-**171** was also transformed into the natural (+)-aspidospermidine (**183**) using sodium borohydride reduction followed by catalytic hydrogenation (73% yield)[66], Scheme 43.



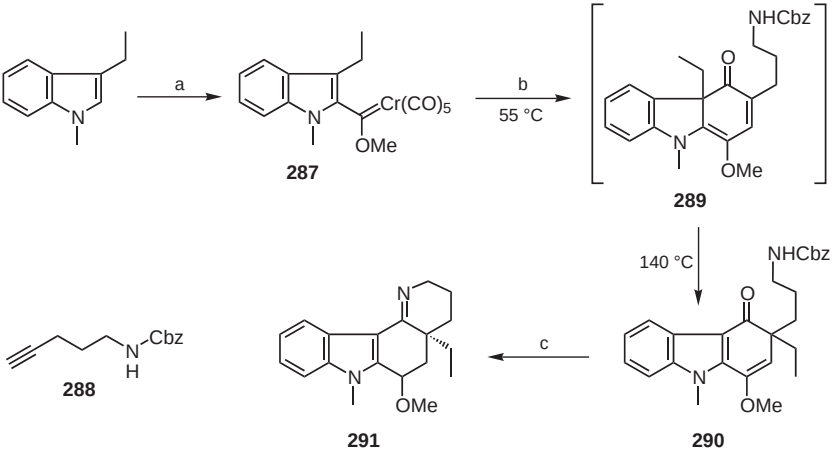
SCHEME 43

Reagents and conditions: a) **286b** (5 mole %), CH_2=C(Et).CHO, 4 Å MS, CH_2Cl_2, –40 °C 2 days (91%, 96% ee/1 mmol; 95% ee/20 mmol). b) $Ph_3P^+Me\ Br^-$, BuLi, THF, –78 °C → rt. c) Grubbs' ruthenium catalyst (4.3–7.5 mole %), CH_2Cl_2, rfl 44 h. d) NPIF, DMSO/THF (2:1), 0 °C → rt 3.5 h (59%, 3 steps). e) $TiCl_3$, NH_4OAc, Me_2CO aq, rt 30 min. f) TMSI, CH_2Cl_2, rfl 1 h. g) $BrCH_2CH_2OH$ (10 eq), Na_2CO_3, EtOH, rfl 15 h. h) MsCl, Et_3N, CH_2Cl_2, –15 °C 30 min, then *t*-BuOK, THF, –15 °C → rt 45 min. i) LDA, THF, –70 °C 40 min, then NC.COOMe, –70 °C 20 min (39% from *ent*-**283**). j) *ent*-**171**, $NaBH_4$, EtOH, 0 °C 30 min → rt 1 h. k) H_2, PtO_2, EtOH, rt 15 h (73%, 2 steps)

3.2.2.5. Model Studies

A model study of the ABCD tetracycle synthesis was reported by Wulff and coworkers[99], featuring a new strategy for the introduction of C-20 ethyl group by [1,5] sigmatropic rearrangement of cyclohexadienones, Scheme 44. Indol-2-ylcarbene chromium complex **287** reacted with terminal alkyne **288** at 55 °C and gave, after insertion of CO and electrocyclisation, the intermediary cyclohexadienone **289**, which underwent at higher temperature

(140 °C) the [1,5] sigmatropic shift of the ethyl group to the future aspidospermane C-20 position. The isomeric cyclohexadienone **290**, isolated in 61% yield, was subjected to transfer hydrogenolysis, which effected splitting off the carbamate group and resulted in the formation of the tetracyclic imine **291** in 92% yield.



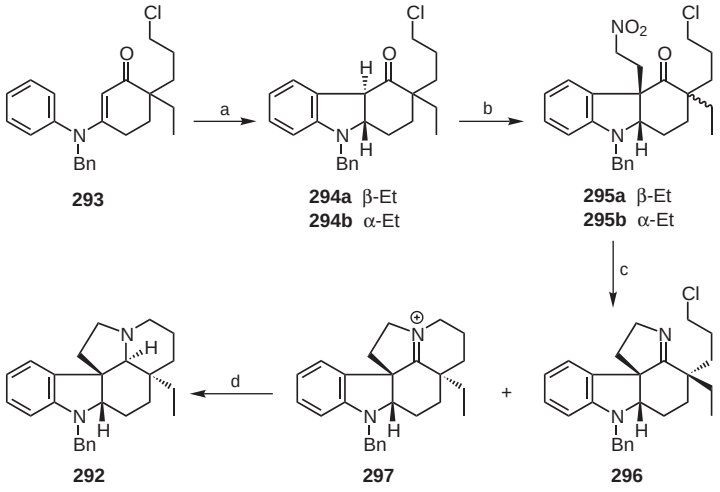
SCHEME 44

Reagents and conditions: a) *t*-BuLi, THF, –78 °C 40 min → rt (1 h), then → –78 °C, $Cr(CO)_6$, –78 °C 4–5 h → rt 18 h, then TfOMe, 0 °C 30 min → rt 1 h (52%). b) **288**, xylenes, 55 °C 1.5 h → 140 °C 1 h (61%). c) $HCOONH_4$, 10% Pd/C, MeOH, rfl 18 h (92%)

3.2.3. Through ABCE Intermediates

3.2.3.1. Carbazolones as Intermediates

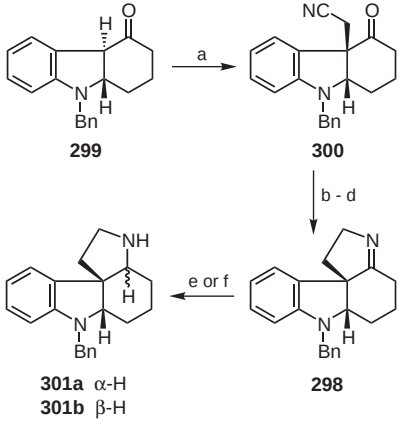
French authors reported[100,101] on a synthesis of (±)-N_a-benzylaspidospermidine (**292**), Scheme 45. The known enaminone[102] **293** underwent a nonoxidative photocyclisation and the resulting *trans*-hexahydrocarbazolone **294**, obtained as a 1:1 epimeric mixture, was used to build up the remaining aspidospermane rings. Thus, LDA-mediated Michael addition to nitroethene gave rise to the *cis*-hexahydrocarbazolone **295** (62%; again 1:1 mixture). Reduction of the nitro group in **295** and an immediate cyclodehydration was followed, in an epimer with "natural" C-7/C-20 stereochemistry, by the spontaneous quaternisation in an intermediary imine. The separated pentacyclic immonium salt **297** (34%) then afforded by stereoselective hydrogenation (±)-N_a-benzylaspidospermidine (**292**) in 70% yield.



SCHEME 45

Reagents and conditions: a) *h*ν, PhH (degassed) (77% at 55% conversion). b) LDA, THF, HMPA, –78 °C 1 h, then CH_2=$CHNO_2$, –78 °C 1 h → rt (62%, 1:1). c) $HCOONH_4$, 10% Pd/C, MeOH, rt 20 h (67% at 70% conversion; **296** 33% + **297** 34%). d) H_2 (3 atm), 5% Pt/Al_2O_3, EtOH, rt 2 days (70%)

A model study of the reduction of tetracyclic imines **298** en route to the aspidospermidine skeleton has been reported[103,104], Scheme 46. *cis*-(Cyanomethyl) ketone **300**, obtained stereoselectively by alkylation of *trans*-ketone



SCHEME 46

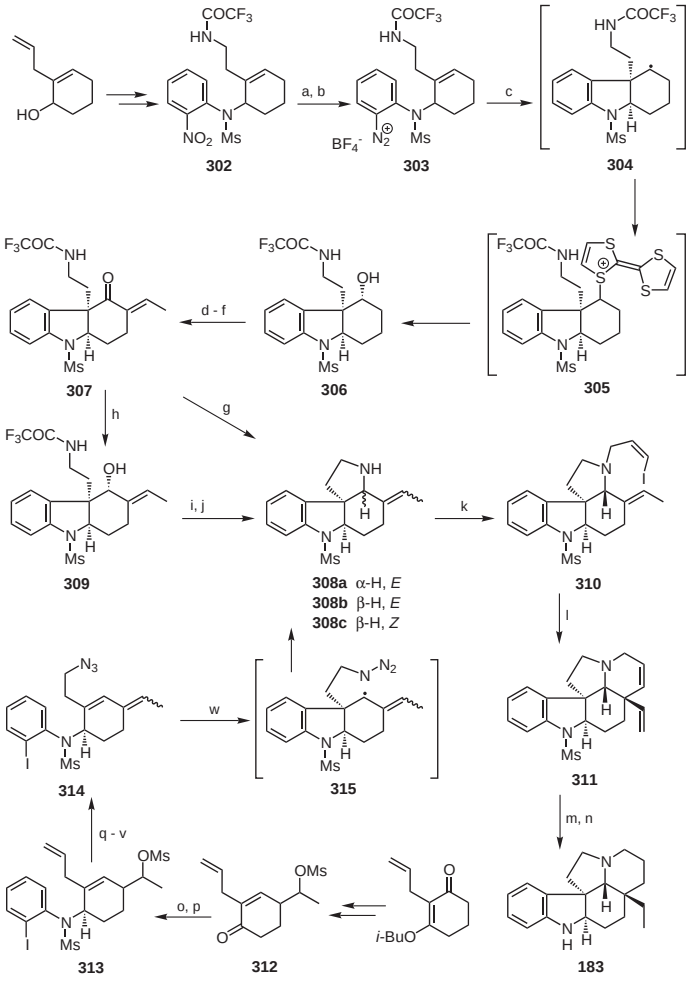
Reagents and conditions: a) KH, THF, rt 5 min, then ICH_2CN, rt 15 min (88%). b) $HOCH_2CH_2OH$, TsOH (cat), PhMe, rfl 3 h (70%). c) $LiAlH_4$, Et_2O, rt 30 min (quant). d) 1 M HCl aq, THF, 0 °C → rt 20 h (93%). e) $NaBH_3CN$, HCl, MeOH, rt 30 min (**301a** 75%). f) H_2 (3 atm), Ra-Ni, rt 4 h (**301a** quant)

299, was converted in three steps into tetracyclic imine **298**. Diastereoisomeric mixtures were mostly formed in its reduction using various reagents, however, with $NaBH_3CN$ in acid medium or Raney nickel in ethanol, the reduction proceeded with complete stereoselectivity and high yields of the desired stereoisomer **301a** could be obtained, see also[105].

Murphy and collaborators have developed two related approaches to the synthesis of (±)-aspidospermidine (**183**), both of them based on radical cyclisation, Scheme 47. The first lengthy synthesis[106,107] rests upon the tetrathiafulvalene (TTF) induced so-called "radical-polar crossover" cascade[108–110], which was used to construct the carbazolone (ABC) synthon. The Mitsunobu reaction with *N*-(2-nitrophenyl)methanesulfonamide initiated the transformation of 2-allylcyclohexenol to sulfonamide **302**, which was then converted to diazonium salt[110] **303**. Its exposure to TTF in moist acetone initiated a cascade of reactions during which an all-*cis* carbazolol **306** was formed. The process presumably proceeds through an intermediary radical **304**, which is converted to sulfonium salt **305**, a displacement giving rise to alcohol **306** stereoselectively in a yield of 45% in 2 steps. The following PCC oxidation and Mukayama aldol reaction/dehydration provided the (*E*)-enone **307**. Unfortunately, its conversion to tetracyclic imine followed by the Luche reduction was intriguing affording exclusively the undesired stereoisomer **308a** (79%). It is worth noting that $NaBH_4$ reduction of the corresponding desethyl analogue provided predominantly (7:3) the naturally configured isomer.

Alternatively, the borohydride reduction of unsaturated ketone **307** leading quantitatively to the *trans*-alcohol **309** was followed by an internal Mitsunobu reaction (99%). A reductive removal of the trifluoroacetyl group then gave the tetracyclic base **308b**, in which the annelation of the D ring was patterned by Kuehne. Thus, alkylation afforded (*Z*)-vinyl iodide **310**, which was subjected to palladium(II)-mediated coupling to yield the pentacyclic diene **311** (37%). The latter was then transformed into (±)-aspidospermidine (**183**) in 2 steps[106,107].

Tris(trimethylsilyl)silane (TTMSS) induced radical cyclisation cascade[111,112] in iodide **314** generating the ABCE spirocycle **308** in the second synthesis by Murphy et al.[113], Scheme 47. Cyclohexenone **312** was converted through the Luche reduction/Mitsunobu protocol to the sulfonamide **313**, which was a mixture of diastereoisomers. The latter was then transformed into a mixture of the (*E*/*Z*) isomeric diene azides **314**, which was treated with TTMSS/AIBN. The thus initiated radical cascade provided, presumably via radical intermediate **315**, the tetracyclic base obtained in this synthesis as a mixture of isomers **308b** and **308c** (40%), whose trans-



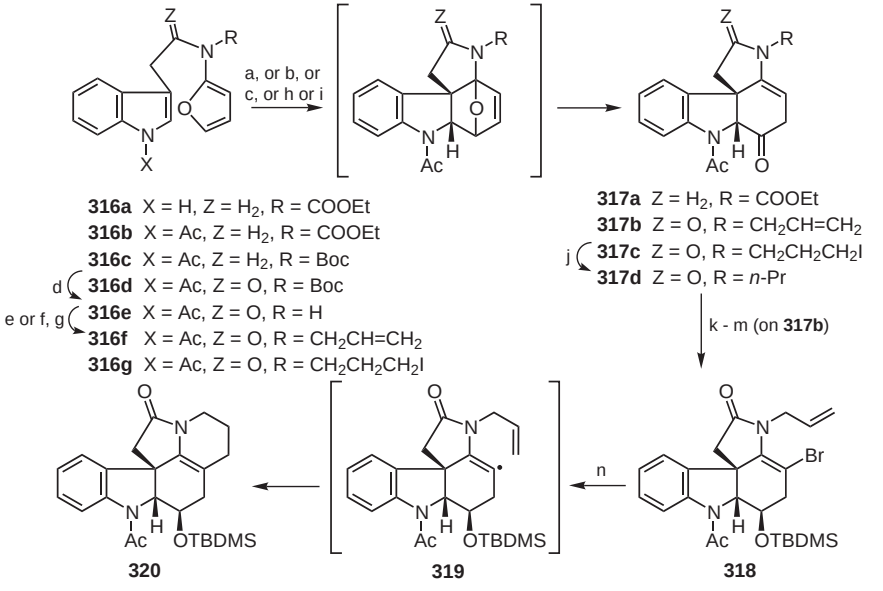
SCHEME 47

Reagents and conditions: a) $NaBH_4$, $Cu(acac)_2$, EtOH, rt 1 h (70%). b) $NOBF_4$, CH_2Cl_2, 0 °C 2 h. c) TTF, Me_2CO, rt 10 min, then H_2O, rt 2 days (45%). d) PCC, SiO_2, CH_2Cl_2, rt 18 h (82%). e) TMSCl, Et_3N, DMF, 80 °C 2 days. f) $(MeCHO)_n$, $TiCl_4$, CH_2Cl_2, –78 °C 30 min → rt (30–40 min) 2 days (51%, 2 steps). g) K_2CO_3, MeOH aq, rt 18 h, then $CeCl_3$, $NaBH_4$, 0 °C 15 min (**308a** 79%). h) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, 0 °C 30 min (100%). i) DEAD, Ph_2PMe, THF, 0 °C 48 h (99%). j) $NaBH_4$, EtOH, 60 °C 24 h (**308b** 82%). k) (*Z*)-CHI=CH.CH_2Br, K_2CO_3, THF, rt 24 h (80%). l) $Pd(OAc)_2$ (0.4 eq), Ph_3P, Et_3N, MeCN, rfl 3 h (37%). m) H_2 (4 atm), 10% Pt/C, EtOH, rt 5 days (58%). n) Red-Al, PhMe, 100 °C 1 h (84%). o) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH (67%). p) DIAD, Me_3P, py, THF (51%). q) OsO_4, NMO, Me_2CO aq, *t*-BuOH (78%). r) $NaIO_4$ aq, Et_2O, EtOH (65%). s) $NaBH_4$, MeOH, rt 20 min (95%). t) DBU, PhMe, rfl (91%). u) MsCl, Et_3N, DMAP, CH_2Cl_2 (78%). v) NaN_3, DMF, 50 °C (72%). w) TTMSS, AIBN, PhH, rfl (**308b** + **308c** 40%)

formation to (±)-aspidospermidine (**183**) paralleled the one described above; for an application of this approach to the formal total synthesis of (±)-vindoline, see Chapter 3.3.3.

3.2.3.2. Indole as a Dienophile

Padwa and coworkers have demonstrated that 2-aminofuran can cycloadd onto the 2,3-indole double bond in intramolecular mode[114] provided the indole nitrogen bears an electron-withdrawing substituent such as an acyl group, Scheme 48. Thus, while indole **316a** did not react at all, 1-acetylindole **316b** afforded upon thermolysis (240 °C, 18 h) the tetracyclic ketone **317a** in 30% yield[114–116]. Note that the *N*-Boc group (as in **316c**) is not compatible with rather harsh reaction condition (240 °C)[114], and amide **316d** splits off the Boc-group at 200 °C to give[115,116] **316e**. The latter result

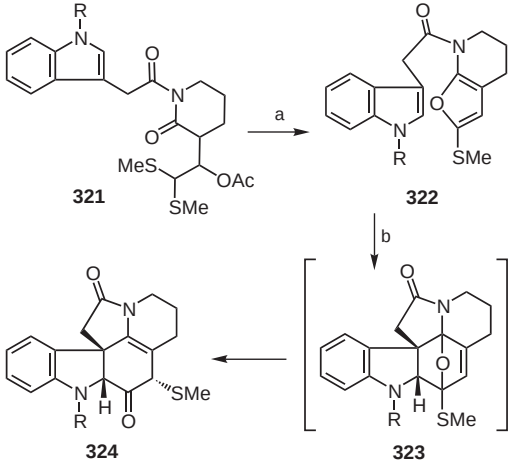


SCHEME 48

Reagents and conditions: a) **316a**, 200 °C (NR). b) **316b**, PhH (sealed tube), 240 °C 18 h (**317a** 30%). c) **316c**, (decomp). d) **316d**, PhH (sealed tube) 200 °C, or $Mg(ClO_4)_2$, MeCN, 45 °C 1.5 h (**316e** 77%). e) **316e**, NaH, DMF, rt 30 min, then CH_2=$CHCH_2I$, rt 30 min (**316f** 50%). f) **316e**, NaH, DMF, rt 30 min, then $ClCH_2CH_2CH_2I$, rt 30 min (54%). g) NaI, Me_2CO, rfl 12 h (**316g** 95%). h) **316f**, PhMe (sealed tube), 200 °C 2 h (**317b** 77%). i) **316g**, PhMe (sealed tube), 200 °C 1.5 h (**317c** 74%). j) **317c**, Bu_3SnH, AIBN, PhH (**317d** 78%). k) **317b**, $NaBH_4$, EtOH, rt 10 min. l) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C 20 min → 25 °C 2 h (60%). m) NBS, CH_2Cl_2, 25 °C 2 h (66%). n) Bu_3SnH, AIBN (cat), PhH (0.01 M), rfl 12 h (91%)

is not surprising in view of the strong preference of secondary amides to adopt an *s-cis* conformation in which the furan ring is too remote from the indole 2,3-double bond. Assuming that the *N*-alkylation could cause the corresponding *s-trans*, and more reactive, conformation (shown in **316**) to be more populated, a series of tertiary amides was prepared from **316e** including *N*-allylamide **316f** and *N*-(3-iodopropyl) derivative **316g**, bearing already the carbons for future installation of the ring D. Both of them furnished on heating (200 °C, 1.5 h) the rearranged cycloadducts **317b** and **317c** in good yields (77 and 74%, respectively)[115,116]. While the latter underwent on attempted radical cyclisation (Bu_3SnH/AIBN) only deiodination (→ **317d**), the *N*-allylamide **317b** was smoothly transformed to vinyl bromide **318** which, on radical cyclisation via **319**, provided a high yield (91%) of the pentacyclic lactam[116] **320**.

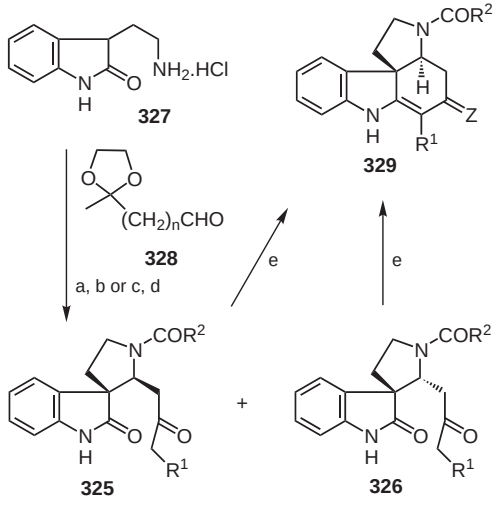
More straightforwardly, tertiary amides **322** containing already the future ring D were tested in the reaction, Scheme 49. Piperidone dithioacetal **321** smoothly cyclocondensed with DMTSF to tertiary amide **322**, which afforded, upon thermolysis and rearrangement in **323**, the lactam **324** containing the complete pentacyclic skeleton of aspidospermane alkaloids[85]. Unfortunately, high temperature was required again in order to effect the [4+2] cycloaddition (260 °C), and the product lactam was isolated in a rather low yield (20%); see also Chapter 3.2.1.



SCHEME 49
Reagents and conditions: a) DMTSF. b) 260 °C (20%)

3.2.3.3. Through ABE(D) Spirocycles

Lévy and collaborators have studied[117] the behaviour of a series of oxindolic spiroketones under the condition of their acid variant of the Ban's iminoether procedure for C ring formation, Scheme 50. Diastereoisomeric ketones **325** and **326** were prepared by the Pictet–Spengler cyclisation/*N*-acylation/deprotection sequence from 2-hydroxytryptamine (**327**) and aldehydes **328** (n = 1, 3), and separately subjected to TsOH in refluxing toluene (no reaction in dioxane or benzene). Ketones **325a** and **325b** afforded tetracyclic amides **329a** and **329b** in much higher yields compared to diastereoisomers **326a** and **326b**, which reflects the necessity of epimerisation prior to condensation in the latter compounds. Much easier epimerisation in **326c** and **326d** accounts for almost the same yields as with **325c** and **325d**; generally, trifluoroacetamides furnish higher yields of tetracycles **329**.

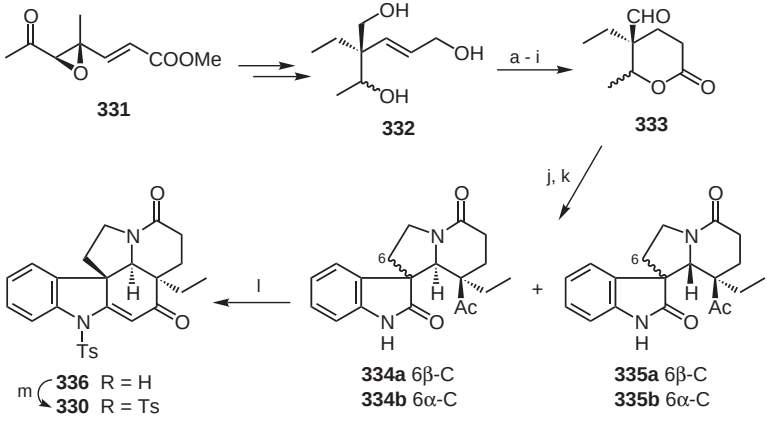


a R^1 = Ac, R^2 = Me, Z = H_2
b R^1 = Ac, R^2 = CF_3, Z = H_2
c R^1 = H, R^2 = Me, Z = O
b R^1 = H, R^2 = CF_3, Z = O

SCHEME 50

Reagents and conditions: a) **328** (n = 3 or 1), NaOH (1.2 eq), MeOH aq, rt 24 h. b) AcCl, DMAP, CH_2Cl_2, then chromatography (60–80%). c) TFAA, Et_3N, CH_2Cl_2, then chromatography (50–70%). d) HCl/MeOH, rt 1 h (96–98%). e) TsOH, PhMe, rfl 18–24 h (**325a** → **329a** 57%, **326a** → **329a** 5%; **325b** → **329b** 79%, **326b** → **329b** 12%; **325c** → **329c** 15%, **326c** → **329c** 11%; **325d** → **329d** 43%, **326d** → **329d** 43%)

A similar acid-catalysed condensation was used by Okada et al.[118] in their enantioselective synthesis of the pentacyclic sulfonamide **330**, an intermediate in the Ban's synthesis of (±)-aspidospermidine[119], Scheme 51. A nine-step transformation of triol[120] **332** (76% ee), derived from epoxyketone **331** of 90% ee, to aldehyde **333** set the stage for the crucial condensation with 2-hydroxytryptamine (**327**). All four possible spirocyclic ketones were isolated following alcohol oxidation with tetrapropylammonium perruthenate (TPAP) in roughly the same proportion. The following closure of the C ring induced by a hot trifluoromethanesulfonic acid was shown to be sensitive to substrate/stereochemistry. Thus, the "naturally" configured stereoisomer **334a** afforded pentacyclic ketone **336** almost quantitatively (98.2%), and isomer **334b** gave ca. 75% yield of **336** after recycling of the unreacted material, which necessitated that an epimerisation had taken place. On the other hand, both stereoisomers **335** were unreactive, reflecting an unfavoured spatial arrangement of the molecules.

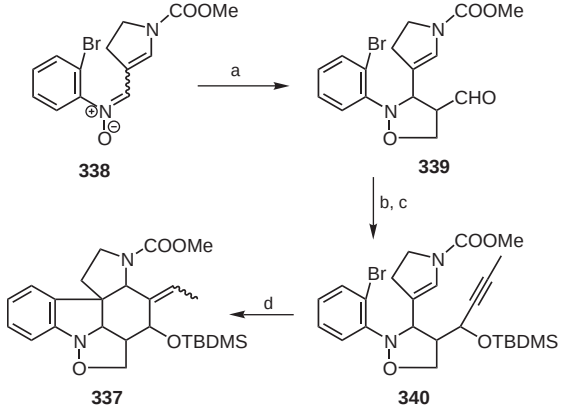


SCHEME 51

Reagents and conditions: a) $Me_2C(OMe)_2$, camphorsulfonic acid (cat), DMF, 90 °C 15 min (99%; 1:1 diast. mixture). b) PCC, CH_2Cl_2, rt 1 h. c) $NaClO_2$, KH_2PO_4, MeC(Me)=CHMe, *t*-BuOH aq, rt 1 h. d) MeI, K_2CO_3, DMF, rt 1 h. e) 1 M HCl/MeOH rt 1 h (77.4%, 4 steps). f) H_2, 10% Pd/C, AcOEt, rt 30 min (87.2%). g) TrCl, py, 90 °C 3 h (98.8%; 1:1 diast. mixture). h) 80% AcOH aq, 60 °C 1.5 h (83.2%). i) SO_3.py, DMSO, Et_3N, CH_2Cl_2, rt 20 min (70%). j) **327**, py, 80 °C 2 h (47.4%). k) TPAP, NMO, CH_2Cl_2, rt 1 h (68.2%). l) F_3CSO_3H, AcOH, 10 °C 3 h (**334a** → **336** 98.2%, **334b** → **336** 78% based on recycled **334b**; **335a** or **335b** → **336** 0%). m)TsCl, Et_3N, CH_2Cl_2, rt 1 h (94.7%)

3.2.3.4. Model Studies

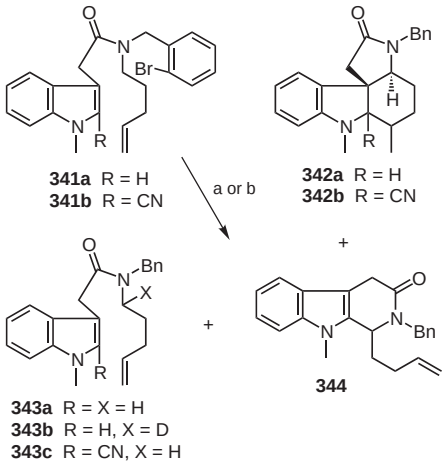
Parsons and coworkers have published the radical cascade approach to synthesis of the ABCE model tetracycles which, among others, resulted in the formation of the pentacyclic carbamate[121,122] **337**, Scheme 52. Dipolar addition of acrylaldehyde to nitrone **338** produced quantitatively the isoxazolidine aldehyde **339** as a diastereoisomeric mixture, which was converted to alkyne **340**. This last compound was subjected to radical cascade cyclisation using Bu_3SnH (Stork's catalytic method) affording pentacycle of an unspecified stereochemistry in a low yield (6%).



SCHEME 52

Reagents and conditions: a) Acrylaldehyde (sealed tube), 90 °C (100%). b) MeCCLi, THF, –78 °C (75%). c) TBDMSOTf, imidazole, CH_2Cl_2 (99%). d) Bu_3SnCl, $NaBH_3CN$, AIBN, *t*-BuOH, rfl (6%)

A model study of the ABCD tetracyclic lactam formation through radical translocation/cyclisation cascade was reported by Jones et al.[123], Scheme 53. Although the treatment of bromide **341a** with Bu_3SnH failed to give any tetracycle **342a** and debromo amide **343a** was the major product (50%), an analogous reaction with Bu_3SnD clearly demonstrated that the radical translocation had indeed taken place: The deuterio lactam **343b** was again the major reaction product. The radical reaction of bromide **341b**, bearing the EWG group at C-2 of the indole ring at ca. 200 °C had resulted in the formation of the desired lactam **342b** (43%) accompanied by the debromo amide **343b**, which was still the major product (50%). The formation of **343b** (or **343a**) is not surprising because the starting amide exists as a mixture of amide conformers (ca. 11:10), and the radical lifetime is generally shorter than the amide bond rotation; only the conformer shown in **341** can effectively participate in the cyclisation process.



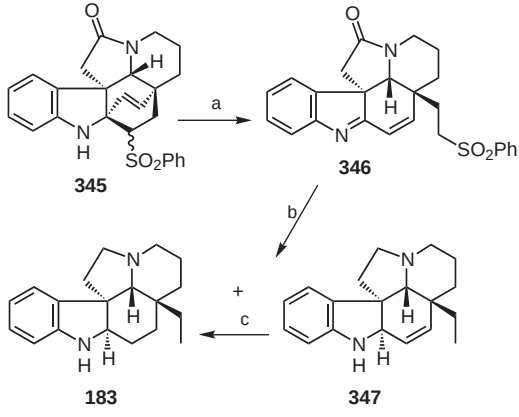
SCHEME 53

Reagents and conditions: a) Bu_3SnH (or Bu_3SnD), AIBN, xylenes (0.02 M), rfl 10 h (**343a** or **343b** 50% + **344** 18% + other products). b) Bu_3SnH (syringe pump), 5-*tert*-butyl-*m*-xylene, rfl 6 h (**342b** 43%; 8:3:2:1 diast. mixture + **343c** 50%)

3.2.4. From Other Skeletons

3.2.4.1. From Hexacyclic Alkaloids

Wenkert and Liu have performed[124] the synthesis of (±)-aspidospermidine (**183**) from an advanced aspidofractinine intermediate **345** (see[7]), Scheme 54. Exposure of **345** to hot potassium *tert*-butoxide caused fragmentation of the



SCHEME 54

Reagents and conditions: a) *t*-BuOK (2 eq), $HOCH_2CH_2OH$, 150 °C 5 h (85%). b) $LiAlH_4$, THF, rfl 18 h (**183** 25% + **347** 49%). c) lit.[125]

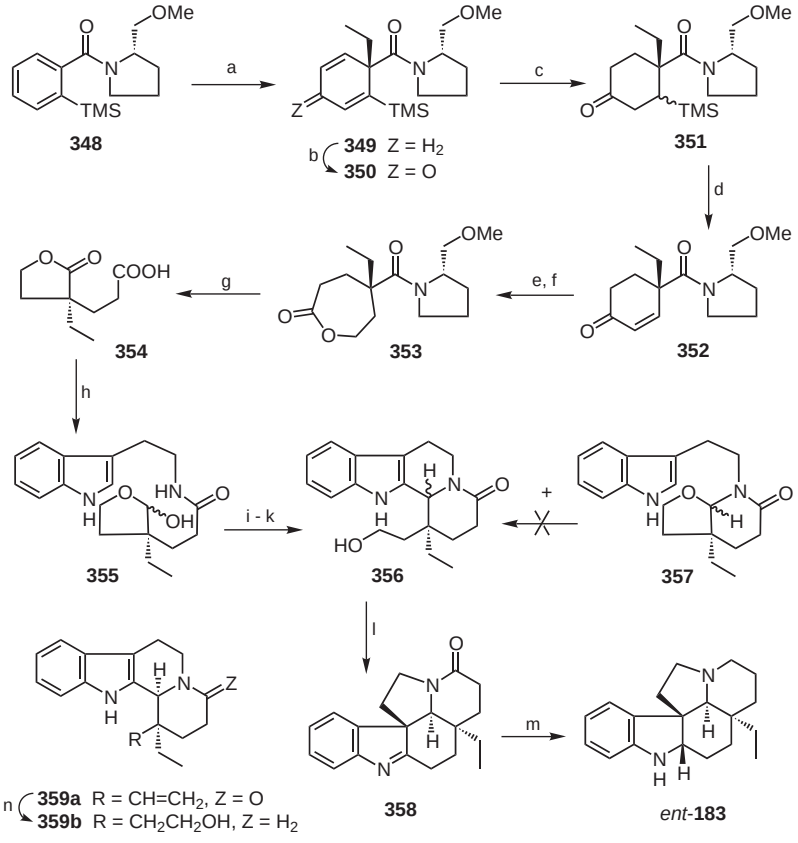
sulfone-bearing ring and pentacyclic sulfone **346** was isolated in 87% yield. Its reduction with lithium aluminium hydride then provided a mixture of olefine **347** (49%) and (±)-aspidospermidine (**183**; 25%). A conversion of the former compound into (±)-**183** as reported previously[125] raised the overall yield of the transformation. This efficient sequence is complementary to the previous Wenkert's approach based on C-20 ethylation[125].

3.2.4.2. From Indolo[2,3-*a*]quinolizines

Schultz and collaborators have implemented in their enantioselective synthesis of (–)-aspidospermidine[126] (*ent*-**183**) the idea of using indolo[2,3-a]-quinolizineethanol in aspidospermane skeleton rearrangement, which was first described by Harley–Mason and Kaplan[127], and was later studied in an optically active series by Fuji et al.[128] (for discussion of the mechanism, see[129]).

The synthesis starts with the chirality introduction through an asymmetric Birch reduction/alkylation sequence in benzamide **348**, in which the TMS group serves as a sufficient desymmetrisation element, Scheme 55. In this way the benzamide **348** derived from (*S*)-prolinol provided almost quantitatively the (–)-cyclohexadiene **349**, which was oxidised by PDC to (+)-(*R*)-dienone **350** in an overall yield of 87% and with 100:1 diastereoisomeric purity. Hydrogenation then gave the saturated ketone **351** as a 2:1 mixture of silyl epimers (94%); oxidative elimination ($CuCl_2$) of the silyl group in **351** proceeded in 93% yield. The overall sequence described here represents a highly efficient route to chiral cyclohex-2-en-1-ones[126].

Upon treatment with trifluoroperacetic acid, generated from TFAA and urea–hydrogen peroxide complex (UHP), enone **352** underwent the Baeyer–Villiger reaction with preferential migration of a vinyl group and afforded, after hydrogenation, lactone **353** in 92% yield, Scheme 55. Hydrolytic removal of the chiral auxiliary produced γ-butyrolactone **354**, which was converted to tryptamide **355** (84% in 2 steps). Its DIBAL-H reduction afforded a 1:1 epimeric lactol mixture, which was subjected to the Pictet–Spengler cyclisation in refluxing acetic acid. The hydroxyethyl lactam was isolated in 65% yield as a 1:1 mixture of epimers **356**; in addition, the bicyclic lactam **357** was also obtained (20%), which could not be converted to **356**. The crucial cyclisation/skeletal rearrangement was induced by hot 40% sulfuric acid; immediate reduction of indolenine **358** with $LiAlH_4$ finally gave (–)-aspidospermidine (*ent*-**183**) in 53% yield based on **356**. It is worth noting that vinyl lactam **359a** could not be converted to **356**, and attempted cyclisation/rearrangement of related amine alcohol **359b** was not successful. This efficient asymmetric synthesis requires 12 steps from the chiral benzamide **348** and affords (–)-aspidospermidine in 19% overall yield[126].



SCHEME 55

Reagents and conditions: a) K, NH_3 (l), *t*-BuOH, THF, –78 °C 10 min, then LiBr, –78 °C 10 min, then piperylene, then EtI, –78 °C 2 h (97%). b) PDC (cat), *t*-BuOOH, celite, PhH, rt 12 h (90%). c) H_2 (63 psi), 10% Pd/C, AcOEt, 5 h (94%). d) $CuCl_2$, DMF, 60 °C 1 h (93%). e) UHP, Na_2HPO_4, CH_2Cl_2, TFAA, 0 °C → rt 4 h, then TFAA, 0 °C → rt overnight (92%). f) H_2, 5% Rh/C, THF, 2 h (100%). g) TsOH·H_2O (1.5 eq), PhH/H_2O (9:1), rfl 48 h. h) Tryptamine (**2b**), Et_3N, THF, 0 °C 10 min, then $(PhO)_2PON_3$, 0 °C → rt overnight (84%, 2 steps). i) DIBAL-H, CH_2Cl_2, –78 °C 45 min (93%; 2:1 diast. mixture). j) AcOH, rfl 48 h. k) 20% NaOH aq, MeOH, rt 30 min (**356** 70% (1:1) + **357** 20%). l) 40% H_2SO_4, 100–110 °C 1.5 h. m) $LiAlH_4$, THF, rfl 1.5 h (53%, 2 steps). n) BH_3·THF, THF, 0 °C → rt 2 h, then H_2O_2, NaOH, 0 °C → 55 °C 1.5 h (86%)

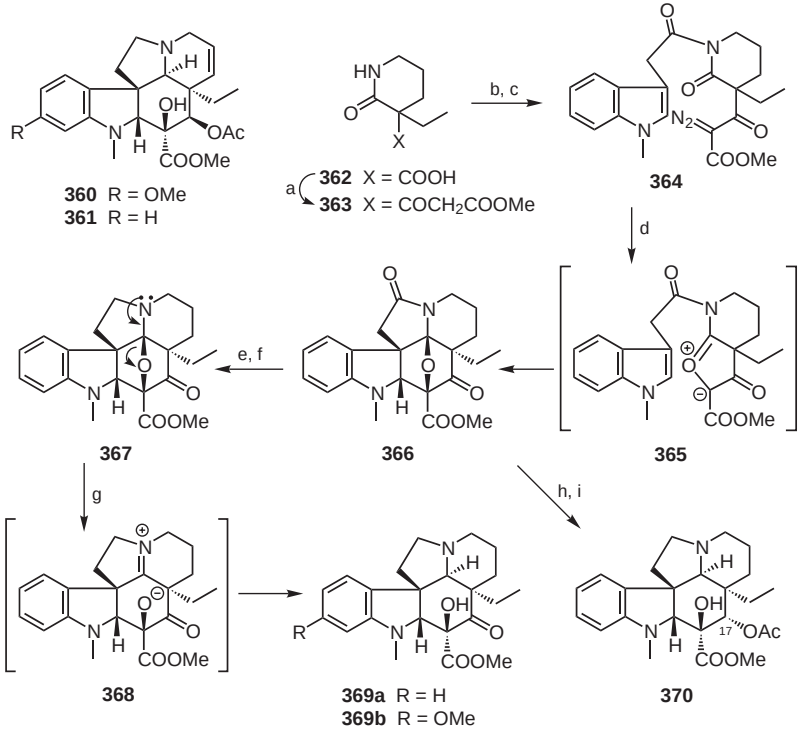
3.3. Vindoline

(–)-Vindoline (**360**) is a constituent of therapeutically important bisindole alkaloids of vincaleucoblastine type. This is why it, and the closely related alkaloid (–)-vindorosine (**341**), continues to be an important synthetic tar-

get, which bears on its central cyclohexane C ring six contiguous chiral centers. Both alkaloids were recently isolated from *Catharanthus roseus*[130].

3.3.1. Cycloaddition Approaches

Padwa's investigations on the intramolecular [4+2] and [3+2] cycloaddition approaches to various natural products[85,131,132], see also Chapters 3.2.1 and 3.2.3.2, have also culminated in a new and highly stereoselective construction of the vindorosine skeleton, in which the indole 2,3-double bond served as a dipolarophile[133,134], Scheme 56.



SCHEME 56

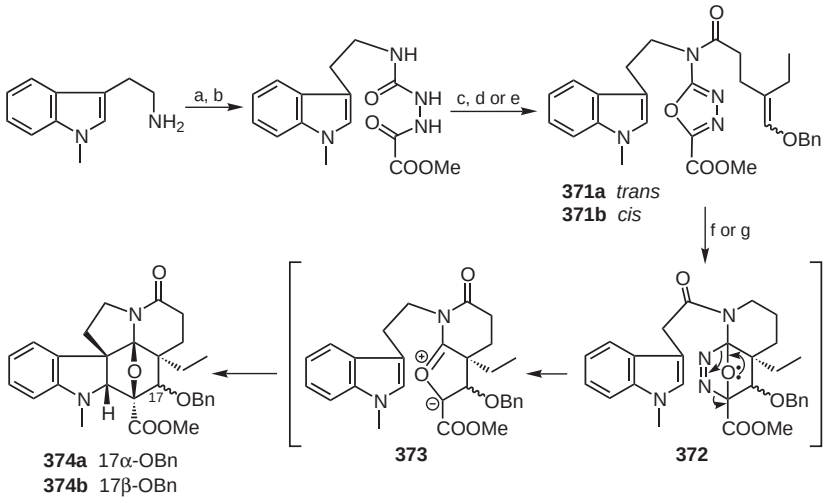
Reagents and conditions: a) $(Im)_2CO$, CH_2Cl_2, rt 12 h, then [$EtOOCCH_2COOH$, i-PrMgCl (3 eq), THF], rt 12 h (58%). b) 1-Methylindole-3-acetyl chloride, CH_2Cl_2, 4 Å MS, rt 12 h (65%). c) Et_3N, MeCN, rt 15 min, then MsN_3, rt 5 h (90%). d) $Rh_2(OAc)_4$ (cat), PhH, 50 °C 4 h (95%). e) Lawesson's reagent, PhMe, 110 °C 5 h (85%). f) Ra-Ni, THF, 65 °C 2 h (96%). g) H_2 (40 psi), PtO_2, HCl aq (cat), MeOH, rt 2 h (94%). h) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, THF, MeOH, rt 4 h (64%). i) Ac_2O, rt 10 min, then AcCl (0.5 eq), rt 8 h (98%)

Piperidonecarboxylic acid **362** was converted into the β-ketoester lactam **363**, which was *N*-acylated with indole-3-acetyl chloride and, on treatment with mesyl azide afforded diazoketone **364** (90%). Subsequently a rhodium(II) catalyst induced formation of a carbene, which was immediately trapped by lactam oxygen; the mesoionic ylide **365** thus formed underwent an *endo* [3+2] dipolar cycloaddition onto the indole double bond and produced hexacycle **366** as a single stereoisomer in an almost quantitative yield (94%!). Removal of the lactam carbonyl (→ **367**) was followed by acid-catalysed iminium formation/reduction in **368**, which yielded hydroxyketone **369a** in a stereoselective manner (94%). Note that the 11-methoxy analogue **369b** has previously been converted to vindoline[135].

On the other hand, expectations that ketone **366** could have adopted a conformation, in which the approach of the reducing agent to the C-17 carbonyl would be favoured from the α-face (leading to the natural 17β-OH configuration) were not fulfilled. Instead, borohydride (Luche) reduction led solely, after acetylation, to 17α-acetate **370**. All attempts at epimerisation at this or later stage proved unsuccessful.

An extensive study of the domino intramolecular cycloadditions in substrates of the general formula **371** was published by Boger and coworkers[136], Scheme 57. The process is initiated by the [4+2] cycloaddition of an olefine with oxadiazole; the primary reaction product **372** loses nitrogen generating the ylide **373** (a dipole), which then undergoes [3+2] dipolar addition to the indole moiety and gives hexacyclic product **374** as a single stereoisomer. During the whole reaction sequence 3 (4) rings are formed including the pivotal C ring, with the sterochemistry of all six chiral centres efficiently controlled.

An obvious advantage here is that the tandem addition allows for the full control over relative stereochemistry of the C-17 hydroxy group (and the C-20 ethyl as well) in the initial cycloaddition (→ **372**). The stereochemical outcome of the dipolar addition over the indole in dipolar intermediate **373**, on the other hand, rests upon exclusive *endo* orientation which is facilitated by the amide/lactam carbonyl; the last group also enhances the reactivity of oxadiazole and is obligatory for a success of the process on the whole; there is no reaction without it. Thus, the *trans*-olefine **371a** gives rise to the 17α-configured product **374a** (79%), while the *cis*-olefine **371b** leads stereoselectively to the "natural" configuration (→ **374b**; 72%)[136]. No doubt, the hexacyclic lactam **374b** represents an advanced intermediate in racemic vindorosine synthesis.

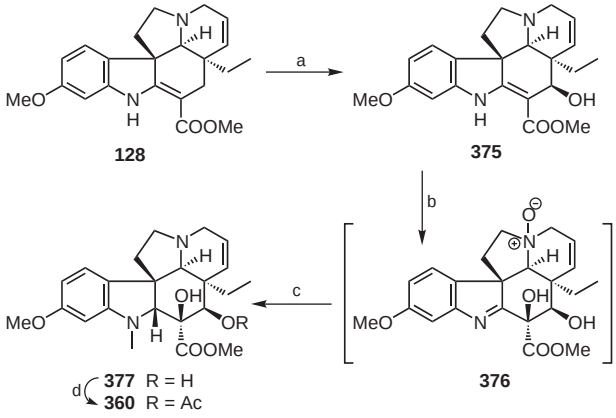


SCHEME 57

Reagents and conditions: a) $(Im)_2CO$, CH_2Cl_2, THF, 0 °C → rt overnight (75%). b) $NH_2NHCOOMe$, AcOH, THF, 40 °C 16 h (65%). c) TsCl, Et_3N, CH_2Cl_2, rt 16 h (65%). d) (*E*)-5-benzyloxy-4-ethylpent-4-enoic acid, EDCI, CH_2Cl_2, 0 °C 5 min, then DMAP, rt 5 h (**371a** 75%). e) (*Z*)-5-benzyloxy-4-ethylpent-4-enoic acid, EDCI, DMAP, CH_2Cl_2, 0 °C → 25 °C 3 days (**371b** 69%). f) **371a**, 1,2-dichlorobenzene, rfl 24 h (**374a** 79%). g) **371b**, 1,3,5-triisopropylbenzene, 230 °C 32 h (**374b** 69%)

3.3.2. Fukuyama's Synthesis

Fukuyama and coworkers have described, en route to VLB [55,137], the most efficient synthesis of (–)-vindoline (**360**) so far[54,137] (see also[138]). The late stages of the synthesis from (–)-11-methoxytabersonine (**128**) (see Chapter 3.1.3) are shown here they are similar to the previous strategy of Danieli et al.[139], Scheme 58. Thus, an allylic oxidation of (–)-**128** with benzeneseleninic anhydride gave the alcohol **375** (88%), which was transformed upon exposure to 3-chloroperbenzoic acid into 16β-hydroxyindolenine with concomitant formation of *N*-oxide (→ **376**). Sequential reduction with cyanoborohydride, first β-selective of the indolenine followed by *N*-methylation of indoline nitrogen completed the build up of the molecule. Removal of the residual *N*-oxygen with hydrogen sulfite completed one-pot transformation **375** → **377** in 64% yield. Finally, the diol **377** was acetylated to give (–)-vindoline (**360**) in an excellent 6% overall yield from 7-(mesyloxy)quinoline.

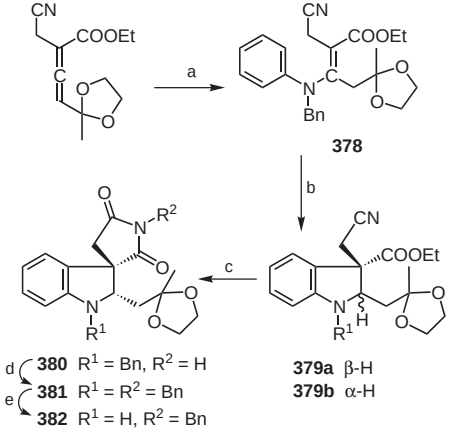


SCHEME 58

Reagents and conditions: a) $(PhSeO)_2O$, PhH, 80 °C 30 min (88%). b) *m*-CPBA, $MeOH/CH_2Cl_2$ (1:9), $NaHCO_3$ aq satd, 0 °C 5 min, then c) 37% CH_2O aq, $NaBH_3CN$, 10% HCl/MeOH → pH 3, 0 °C 5 min, then $NaBH_3CN$, 0 °C → rt 30 min, then Na_2CO_3 → pH 10, then $NaHSO_3$, rt 30 min (64% from **375**). d) NaOAc, Ac_2O, rt 4 h (91%)

3.3.3. Other Studies

An efficient radical approach to the synthesis of the spirocyclic indoline **382** was reported by French authors[140], Scheme 59. Photocyclisation of the easily accessible[141] vinylogous amide **378** was shown to be solvent depend-

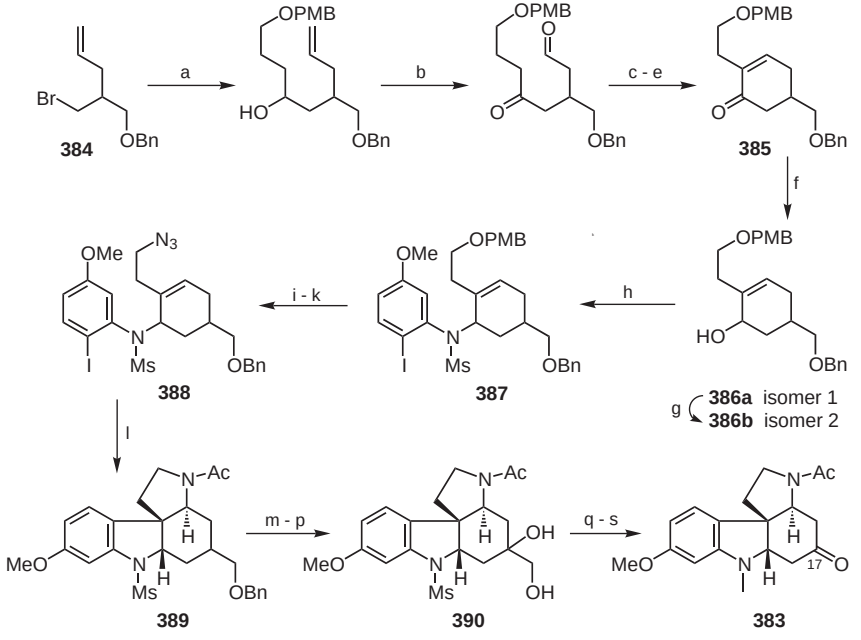


SCHEME 59

Reagents and conditions: a) PhNHBn, PhH, rfl (85%). b) *hν* (400-W medium pressure Hg lamp), MeCN, 0.5 h (**379a** 60%, **379b** 30%). c) **379a**, KOH (s), *t*-BuOH, rfl 3 days (quant). d) DEAD, BnOH, Ph_3P, THF, 0 °C 10 min → rt 12 h (83%). e) $HCOONH_4$, 10% Pd/C, MeOH, rfl 30 min (97%)

ent: Whereas the ratio **379a** to **379b** was 35:55 in benzene, it shifted in acetonitrile to 2:1 in favour of **379a** (90% total yield). Notable is the selective removal of the indoline *N*-benzyl group in **381**, which afforded quantitatively spiroindoline **382**, a valuable intermediate[142] in the synthesis of vindorosine (**361**).

Murphy et al. have extended their approach to aspidospermidine (see Chapter 3.2.3.1) to the preparation of tetracyclic amide[143] **383**, an intermediate in the classic Büchi's synthesis[144] of vindoline (**360**). The necessary functionalisation of C-17 in **383** was provided by the benzyloxymethyl group that was carried through the whole synthesis from the beginning, Scheme 60.

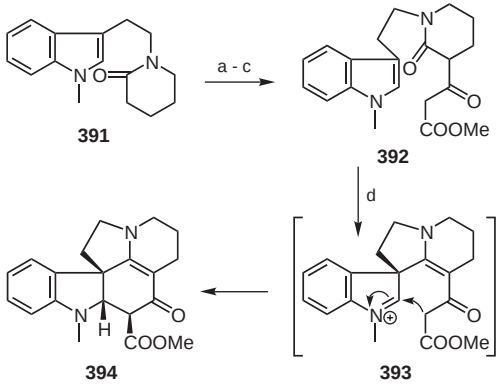


SCHEME 60

Reagents and conditions: a) Mg, THF, then 4-$MeOC_6H_4CH_2OCH_2CH_2CH_2CHO$, rt (85%). b) $(COCl)_2$, Et_3N, DMSO, CH_2Cl_2, –78 °C (90%). c) OsO_4 (0.5%), NMO, Me_2CO aq, rt. d) $NaIO_4$, Me_2CO aq, rt (85%, 2 steps). e) 1% NaOH/i-PrOH aq, rfl (84%). f) $NaBH_4$, $CeCl_3$, MeOH, –15 °C (95%). g) 4-$O_2NC_6H_4COOH$, DEAD, Ph_3P, then NaOH, MeOH (100%). h) 2-I-5-$MeOC_6H_3NHMs$, DEAD, Me_3P, THF, rt (90%). i) DDQ, CH_2Cl_2, H_2O, rt (87%). j) MsCl, Et_3N, CH_2Cl_2, rt (90%). k) NaN_3, DMF, 60 °C (94%). l) TTMSS, AIBN, PhH, rfl, then acetylation (65%). m) H_2, Pd/C, AcOEt, rt (99%). n) 2-$O_2NC_6H_4SeCN$, Bu_3P, THF, rt (95%). o) $NaIO_4$, $NaHCO_3$, MeOH, 50 °C (86%). p) OsO_4 (1%), NMO, Me_2CO aq, rt (91%). q) Na, NH_3 (l), i-PrOH. r) 36% CH_2O aq, $NaBH_3CN$, HCl → pH 3, MeOH, CH_2Cl_2, H_2O (85%). s) $NaIO_4$, Me_2CO aq (84%)

The Grignard reagent derived from bromide **384** was converted in 5 steps to cyclohexenone **385**. The Luche reduction then provided alcohol **386a** with high diastereoselectivity (95:5); whereas its actual stereochemistry was not known, it was shown later that its epimer **386b** obtained by the Mitsunobu protocol (100%) gave much better yield in a radical cyclisation (vide infra). A second Mitsunobu reaction on **386b** with methanesulfonamide afforded sulfonamide **387** (90%). TTMSS induced radical cyclisation in the derived iodo azide **388** followed by *N*-acetylation led stereoselectively to tetracyclic amide **389** in 65% yield; note that the yield dropped to 35% with iodo azide derived from alcohol **386a**. The conversion of benzyloxymethyl group to a carbonyl was addressed next, which proceeded via the osmium tetroxide-mediated dihydroxylation of an exocyclic olefine. After substitution of a methyl for the highly stabilising *N*-mesyl group in **390**, the final diol scission completed synthesis of the tetracyclic ketone **383**, which constitutes a formal synthesis of the racemic alkaloid[143] **360**.

A rapid access to vindoline/vindorosine skeleton was presented by Shannon and collaborators[145], Scheme 61. Piperidone **391** was converted into the tricarbonyl intermediate **392**, which gave rise to pentacyclic ketoester **393** upon exposure to excess trifluoroacetic anhydride: TFAA induced a Bischler–Napieralski reaction, the primary product of which, the indoleninium **393** was then trapped by an internal nucleophile to complete the build up of the skeleton of **394** (51%).



SCHEME 61

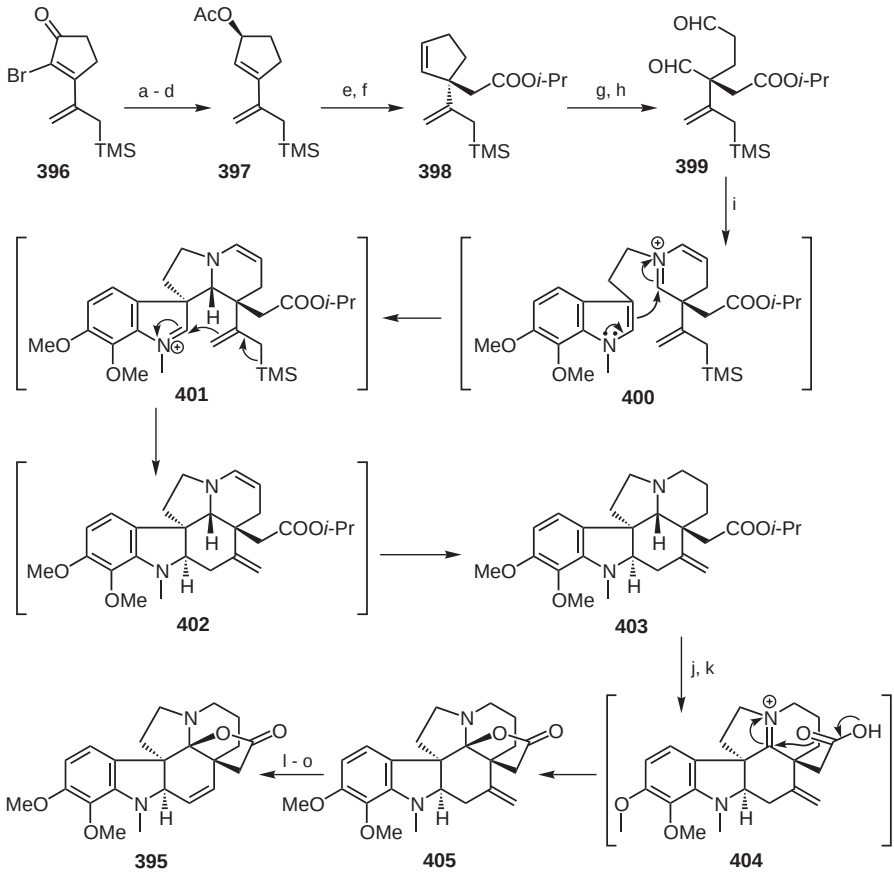
Reagents and conditions: a) LDA, HMPA, THF, –78 °C 30 min, then ClCOOBn, –78 °C 2 h → 0 °C (73%). b) NaH, $MeOCOCH_2COCl$, PhH, rfl 7 h (48%). c) $HCOONH_4$, 10% Pd/C, MeOH, rt 1.5 h (64%). d) TFAA (10 eq), CH_2Cl_2, 20 °C 24 h (51%)

3.4. Aspidophytine

Aspidospermane alkaloids bearing an oxygen bridge between C-18 and C-21 have received rather little attention. However, two carefully designed enantioselective total syntheses of (–)-aspidophytine (**395**), an alkaloid isolated from *Haplophyton cimicidum*[146], were reported by Corey and coworkers[147], and later by Fukuyama's group[148,149], and represent a true highlight in the field.

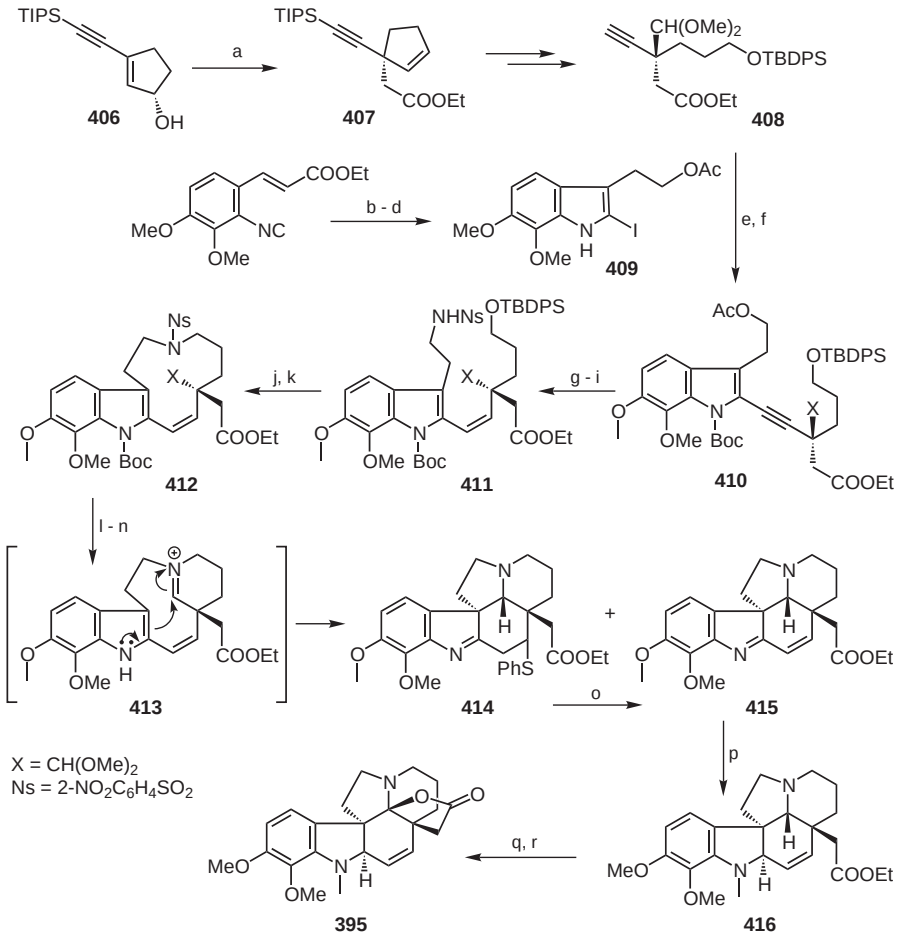
In the Corey's synthesis[147], chirality was introduced early through a CBS reduction of ketone **396**, Scheme 62. The resulting (–)-(*S*)-alcohol (97.4% ee) was subjected to debromination/acetylation sequence to give acetate (–)-(*S*)-**397**, which then underwent an Ireland–Claisen rearrangement of the derived *O*-silyl enolate followed by a conversion to isopropyl ester (+)-(*R*)-**398** with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDCI) and i-PrOH (57%). Selective dihydroxylation of the endocyclic double bond was achieved by a catalytic amount of osmium tetroxide and NMO (57%); $NaIO_4$ induced cleavage then afforded (–)-dialdehyde **399** in an almost quantitative yield. The following cascade of reactions, during which the correct configuration of three contiguous chiral centres (C-21, C-7 and C-2) is induced and the aspidospermane skeleton is being built up, starts with the condensation of 6,7-dimethoxy-N_a-methyltryptamine with aldehyde **399**. In the presence of TFAA, an initially formed dihydropyridinium **400** is attacked by C-3 of the indole moiety from the less hindered α-face generating thus spiroindoleninium **401**. This is immediately attacked from the β-face by an allylic nucleophile. Now that the skeleton is properly constructed, the whole process is terminated by $NaBH_3CN$ reduction of an enamine and/or iminium **402**. The exocyclic olefine **403** is produced in 66% yield from **399**! Five-membered lactone ring is constructed next through hydrolysis of the carboxylic ester (88%) and an extremely efficient regioselective dehydrogenation by $K_3[Fe(CN)_6]$ which is followed by an oxygen addition in the created immonium salt **404** (92%!). Transformation of the sterically hindered *exo*-olefine (–)-**405** to the target molecule was achieved via the derived ketone (71%), whose enol triflate (54%) afforded finally on treatment with Pd(0) and Bu_3SnH (–)-aspidophytine (**395**) in 86% yield[147].

A second synthesis of the (–)-aspidophytine (**395**) was recently reported by Fukuyama et al.[148,149], which utilises essentially the Ban's approach[150] in constructing the aspidospermane skeleton (**412** → **415**), Scheme 63. (–)-(*S*)-Cyclopentenol **406** (>99% ee) derived from cyclopentenone was subjected to the Claisen–Johnson rearrangement, and the unsaturated ester



SCHEME 62

Reagents and conditions: a) $CeCl_3$, THF, rt 3.5 h, then $TMSCH_2C(=CH_2)MgBr$, 0 °C (82%). b) (*R*)-*B*-methyloxazaborolidine (CBS) catalyst, catecholborane, CH_2Cl_2, –78 °C 8 h (93.5%, 97.4% ee). c) 5% Na(Hg), 15–30 °C 2 h (82%). d) Ac_2O, DMAP (cat), Et_3N, rt 1 h (97%). e) LDA, THF, HMPA, –78 °C, then TBDMSCl, –78 °C 15 min → rt 1 h → rfl 3 h. f) EDCI, DMAP (cat), i-PrOH, 40 °C 3 h (57%, 2 steps). g) OsO_4 (0.05 eq), NMO, Me_2CO, 0 °C → rt 6 h (57%). h) $NaIO_4$, THF/H_2O (4:1), rt 35 min (98%). i) 6,7-Dimethoxy-N_a-methyltryptamine, MeCN, rt 5 min, then TFAA, 0 °C 2 h, then $NaBH_3CN$, 0 °C → rt 30 min (66%). j) NaOH aq, EtOH, 75 °C 20 h (88%). k) $K_3[Fe(CN)_6]$, $NaHCO_3$, *t*-BuOH/H_2O (1:2), rt (92%). l) OsO_4 (1 eq), DMAP (2 eq), *t*-BuOH/H_2O (1:2), rt 5–10 min, then Na_2SO_3. m) $Pb(OAc)_4$, AcOH, CH_2Cl_2, –20 °C (71%, 2 steps). n) KHMDS, THF, –78 °C 30 min, then $PhNTf_2$, –78 °C (54%). o) Bu_3SnH (8 eq), $Pd(PPh_3)_4$ (0.2 eq), THF, rt 1 h (86%)



SCHEME 63

Reagents and conditions: a) $MeC(OEt)_3$, *t*-BuCOOH, xylene, rfl 10 h. b) Bu_3SnH, AIBN, MeCN, rfl 1.5 h, then I_2, rt (85%). c) DIBAL-H, PhMe, 10 °C 50 min. d) Ac_2O, py, rt 30 min (85%, 2 steps). e) $Pd(PPh_3)_4$, CuI, Et_3N, 70 °C 2 h (78%). f) Boc_2O, DMAP, MeCN, rt 15 min (94%). g) H_2, Pd/C, EtOH, rt 3.5 h (97%). h) K_2CO_3, MeOH, rt 1 h (96%). i) $NsNH_2$, DEAD, Ph_3P, PhH, rt 5 min (93%). j) TBAF, THF, rt 1 h (93%). k) DEAD, Ph_3P, PhH, rt 5 min (92%). l) TMSBr, CH_2Cl_2, –78 °C 15 min (92%). m) PhSH, Cs_2CO_3, MeCN, 55 °C 20 min. n) TFA, Me_2S, CH_2Cl_2, rt 5 min, then buffer (pH 7.8) (**415** 56% in 2 steps + **414** 29%). o) $Hg(OAc)_2$, EtOH (79%). p) CH_2O, $NaBH_3CN$, buffer (pH 7.0), –70 °C → rt 2.5 h (67%). q) NaOH, EtOH, 70 °C 2.5 h, then → 5 °C, HCl concd (→ pH 8). r) $K_3[Fe(CN)_6]$, $NaHCO_3$, *t*-BuOH/H_2O (1:2), 5 °C → rt 1 h, then $K_3[Fe(CN)_6]$, $NaHCO_3$, 5 °C → rt 15 min (39%)

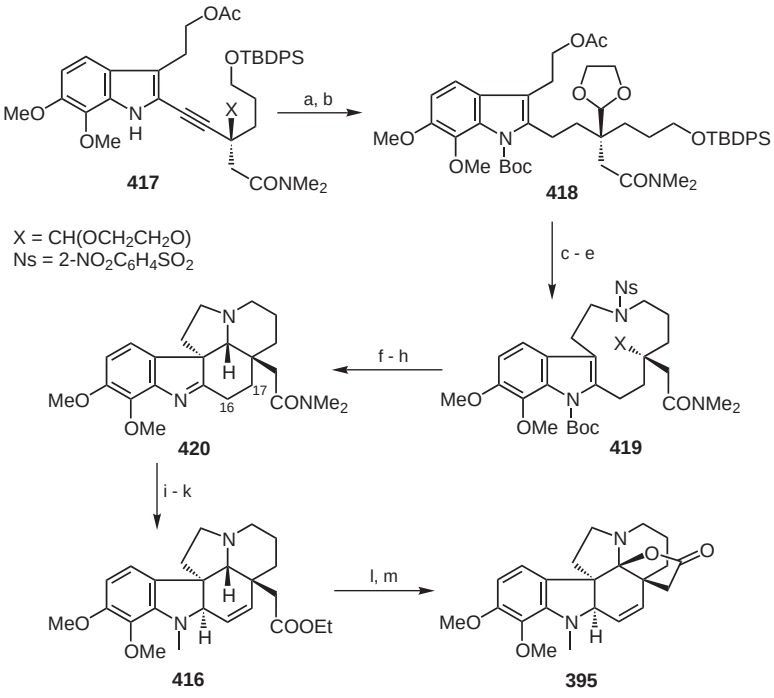
407 was then transformed into acetylene **408**. Sonogashira reaction of the latter with 2-iodoindole **409** provided alkyne (78%) which was Boc-protected (→ **410**); its transformation into the crucial intermediate **411** included a partial saturation of the triple bond (97%) and the Mitsunobu assisted formation of 2-nitrobenzene sulfonamide, which was followed by an internal Mitsunobu-mediated closure of the medium-sized ring (→ **412**, 86% in 2 steps). Sequential removal of protecting groups in **412** induced formation of the cyclic iminium intermediate **413**, an internal attack of which by the indole C-3 provided indolenine **414** (29%) and conjugated indolenine **415** (yield 56% in 2 steps or 79% including **414** to **415** conversion), which was further transformed to indoline **416** by reductive methylation. Total synthesis was completed through an application of the above Corey's procedure to **416**; in this case, however, the yield of (–)-aspidophytine (**395**) was as low as 39%.

The full paper provides also an alternative albeit less efficient variant of the synthesis[149], Scheme 64. In this case, however, partial reduction of alkyne **417** failed even with Lindlar catalyst, so it was converted to alkane. The double Mitsunobu reaction assisted again closure of the 9-membered ring in **418** (48%) and the resulting sulfonamide **419** underwent transformation to indolenine **420** as above (84%). The 16,17-unsaturation was introduced next using benzeneseleninic anhydride (65%); subsequent reduction/reductive methylation as above was followed by the lowest-yield step, conversion of amide to ester functionality (12%). Ester **416** was finally transformed to the target alkaloid (–)-**395** in 29% yield.

4. IBOGANE ALKALOIDS

4.1. Kuehne's Syntheses

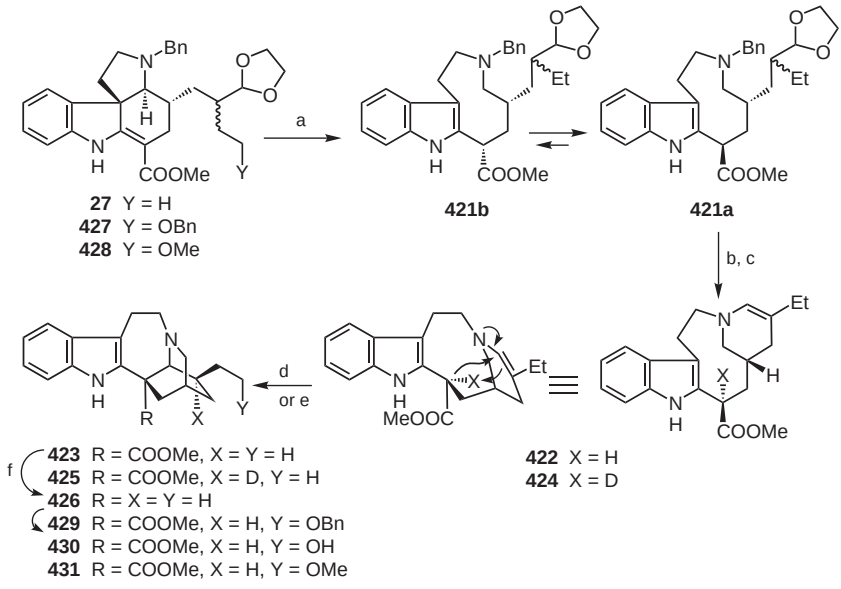
Kuehne and coworkers have previously demonstrated that both aspidospermane and ibogane alkaloid skeletons can be obtained from a common intermediate[151]. Later on they have provided another synthesis of ibogane alkaloids[17], which is based on the use of the common intermediate **27** ("versatiline", see Chapter 3.1.1, Scheme 6), Scheme 65. The tetracycle **27** (separated C-20 isomers, or a mixture) underwent a reduction to the cleavamine-type intermediate **421** (83–88%), appearing as a separable 3:1 mixture of C-16 epimers **421a** and **421b**. Each of them afforded one and the same enamine **422** on sequential hydrogenolysis (89–91%) and acid treatment (98%!); note that with **421b** this must have involved a C-16 epimerisation. The enamine **422** underwent, on standing a week under



SCHEME 64

Reagents and conditions: a) H_2, Pd/C, EtOH, rt 5.5 h. b) Boc_2O, DMAP, MeCN, rt 6 h (93%, 2 steps). c) TBAF, THF, 45 °C 2 h (93%). d) K_2CO_3, MeOH, rt 30 min (85%, 2 steps). e) $NsNH_2$, DEAD, Ph_3P, PhH, rt 10 min (48%). f) PPTS, Me_2CO aq, 70 °C 18 h (quant). g) PhSH, Cs_2CO_3, MeCN, rt 3 h. h) TFA, Me_2S, CH_2Cl_2, rt 5 min, then $NaHCO_3$ aq (84%, 2 steps). i) $(PhSeO)_2O$, PhH, 65 °C 1.5 h (65%). j) CH_2O, $NaBH_3CN$, MeOH, buffer (pH 7.0), rt 1 h (57%). k) $Et_3O^+BF_4^-$, CH_2Cl_2, 40 °C 3.5 h (12%). l) NaOH, EtOH, 70 °C 2.5 h, then → 5 °C, 1 M HCl aq → pH 6 (52%). m) $K_3[Fe(CN)_6]$, $NaHCO_3$, *t*-BuOH/H_2O (1:2), 5 °C → rt 10 min (56%)

high vacuum, a smooth transformation to (±)-coronaridine (**423**) in 95% yield. This stereoselective process was later shown to be induced also thermally[152,153]. The transformation involves a stereoselective hydrogen transfer (or enamine protonation) followed by a Mannich-type closure of the quinuclidine system, as demonstrated by the stereoselective conversion of deuterated intermediate **424** into the 18-deuteriocoronaridine (**425**) by 2-day heating in refluxing toluene. Finally, **423** was converted by the known hydrazinolysis into (±)-ibogamine[152] (**426**). (–)-Coronaridine (**423**) was isolated from *Stemmadenia obovata*[154], while (–)-ibogamine (**426**) is an alkaloid from *Peschiera buchtieni*[155].



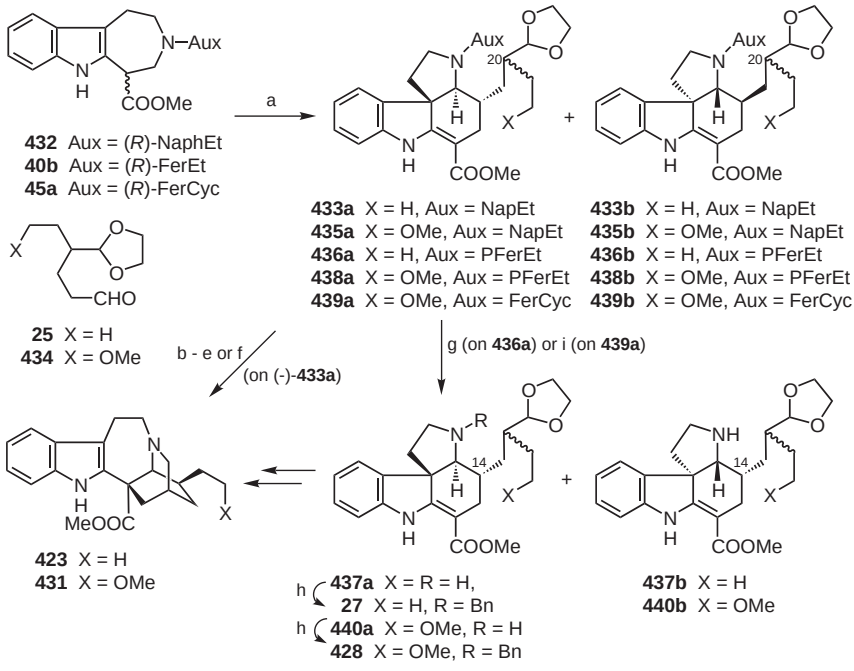
SCHEME 65

Reagents and conditions: a) $NaBH_4$, AcOH, 90 °C 5 min (83–88%, **421a**:**421b** 3:1). b) H_2, 10% Pd/C, AcOH, rt 4.5 h (89–91%). c) 1 M HCl aq/MeOH (1:1), rt 2 h (98%). d) **422** $CHCl_3$, rt 20 min, then evaporate, store 1 week at 0.005 mm pressure (**423** 95%). e) **424**, PhMe, rfl 2 days (**425** 67%, 3 steps). f) N_2H_4

Using essentially this general procedure, and starting from intermediates **427** and **428**, the authors have prepared[153] racemic albifloranine (**430**) whose (–)-enantiomer was isolated from *Tabernaemontana albiflora*[156], and the pharmacologically interesting base (±)-18-methoxycoronaridine (**431**), respectively. In these cases the crucial cyclisation of tetracycles corresponding to **422** was induced thermally (3-h reflux in toluene) and 18-alkoxycoronaridines **429** and **431** were obtained in 70% yields both, Scheme 65.

Kuehne et al. have extended[152] their approach to enantioselective synthesis of (–)-coronaridine (**423**) and unnatural (–)-18-methoxycoronaridine (**431**), using the chiral indoloazepines discussed in Chapter 3.1.1, Scheme 66. Condensation of (*R*)-azepine **432** with aldehyde **25** provided a 89:11 stereoisomeric mixture **433a** and **433b** (80%), each of them as a 1:1 C-20 epimer mixture. The mixtures were separated and individual C-20 epimers (or a mixture thereof **433a**) were transformed to the (–)-coronaridine (**323**) of >99% ee by the procedure used in racemic series; both the thermal (63%) and a vacuum-induced cyclisation in (–)-**422** was applied in the final step. Condensation of (*R*)-azepine **432** with aldehyde **434** worked equally well

and identical 89:11 mixture of **435a** and **435b** was obtained (85%). Unfortunately, minor C-20 epimers **435b** could not be separated and, accordingly, the synthesis yielded (–)-18-methoxycoronaridine (**431**) with 75% ee.



SCHEME 66

Reagents and conditions: a) (*R*)-**432**, **25**, PhMe, rfl 48 h (80%, **433a** (1:1):**433b** (1:1) 89:11); (*R*)-**432**, **434**, PhMe, rfl 12 h (85%, **435a** (1:1):**435b** (1:1) 89:11); **40b**, **25**, PhH, rfl 4 h (**436a** (62%):**436b** 84:16); **40b**, **434**, PhH, rfl 4 h (62%, **438a**:**438b** 87:13); **45a**, **434**, PhH, rfl 22 h (**439a** (87%):**439b** > 99:1). b) **433a**, $NaBH_4$, AcOH, 90 °C 5 min (82%). c) H_2, 10% Pd/C, AcOH, rt 4 h (89%). d) 1 M HCl aq/MeOH (1:1). e) $CHCl_3$, rt 5 h, then evaporate, store 1 week in vacuum ((–)-**423** 68%). f) PhMe, rfl 18 h ((–)-**423** 63%). g) **436a**, AcOH, 70 °C 15 min (**437a** 63%, **437b** 12%). h) BnBr, Et_3N, K_2CO_3, Me_2CO, rt 6 h ((–)-**27** 77%, (–)-**428** 73%). i) **439a**, AcOH, rt 40 min (**440a** 93%, **440b** 3%)

Condensation of (*R*)-azepine **40b** with aldehyde **25** resulted in a slightly worse diastereoselection (84:16). The major C-20 stereoisomers **436a** (ca. 1:1, 62%) afforded on acetolysis secondary base **437a** (63%), accompanied by stereoisomer **437b** (12%) resulting from an isomerisation involving an intermediate similar to **33** in Scheme 6. The separated major isomer **437a** (not necessary, as **437b** has the same C-14 configuration) was benzylated, and the resulting (–)-**27** was then transformed to (–)-coronaridine (**423**) of >99% ee. Analogous condensation of (*R*)-azepine **40b** with aldehyde **434**

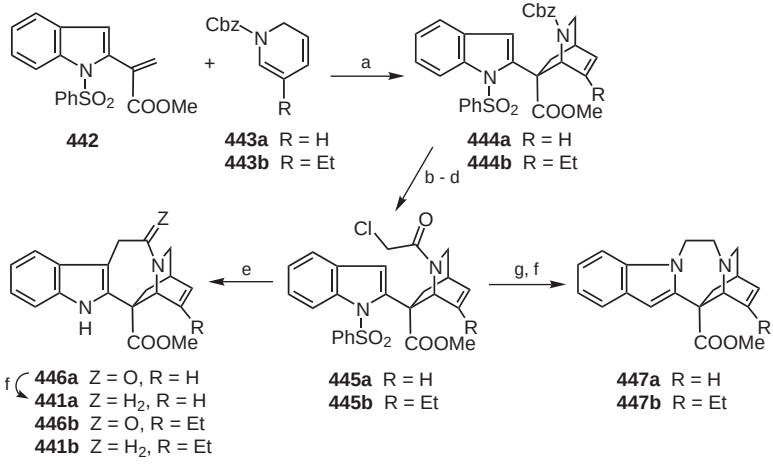
provided an 87:13 inseparable mixture **438** (62%), which was converted analogously via **428** into (–)-18-methoxycoronaridine (**431**) with 65% ee, Scheme 66.

Finally, an efficient synthesis of (–)-18-methoxycoronaridine (**431**) was achieved with azepine **45a**, Scheme 66 [152]. Its condensation with aldehyde **434** was highly diastereo- and enantioselective (**439a**:**439b** >99:1) and afforded pure stereoisomer **439a** in 87% yield. Milder acetolysis condition resulted in lesser extent of isomerisation (**440b** 3%). The major base **440a** (93%) was *N*-benzylated and the resulting (–)-base **428** was then transformed to (–)-18-methoxycoronaridine (**431**) with >99% ee. (–)-**431** is also accessible through the resolution of racemate[157].

4.2. Through Quinuclidine Intermediates

4.2.1. [4+2] Cycloaddition Approaches

Sundberg and coworkers have reported on the improvement[158] of their synthesis of 20-deethylcatharanthine[159] (**441a**), Scheme 67. The protected indolylacrylate **442** underwent [4+2] cycloaddition with dihydropyridine

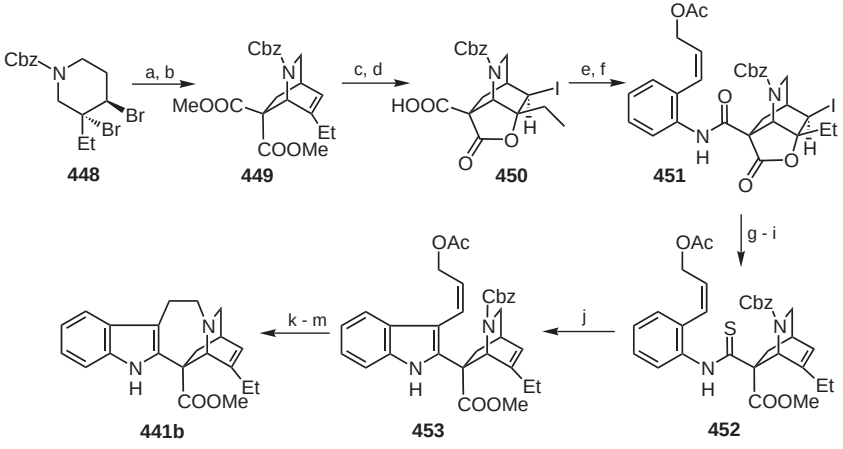


SCHEME 67

Reagents and conditions: a) 100 °C 60 h (**443a** 84%; **443b** 47%). b) TMSI, CH_2Cl_2, 0 °C 1 h → rt 30 min, then HCl/MeOH, rt 1 h (**a** 58%, **b** 61%). c) $ClCH_2COCl$, DMAP, CH_2Cl_2, 0 °C 20 min, then Et_3N, 0 °C 5 h (**a** 70%, **b** 81%). d) *hν* (Pyrex filter), 1,5-dimethoxynaphthalene, ascorbic acid, EtOH, 5 h (**445a** 65%; **445b** 66%). e) *hν* (Vycor filter), $NaHCO_3$, MeOH, 6 h (**446a** 45%; **446b** 25%). f) $NaBH_4$, $BF_3{\cdot}OEt_2$, THF, 0 °C → rt 3 h (**441a** 99.6%; **447a** 37%; **447b** 54%). g) NaH, THF, rt 3 h (**a** 83%, **b** 81%)

443a to give quinuclidine **444a** (84%); the latter was transformed into chloroacetamide **445a**, which on photolysis provided lactam **446a** in 45% yield. Finally, a selective reduction of the lactam carbonyl by in situ generated diborane afforded quantitatively the base (±)-**441a**. Starting with dihydropyridine **443b** the authors also obtained 5-oxocatharanthine (**446b**) by this methodology, which constitutes[160] the formal total synthesis of (±)-catharanthine (**441b**); (+)-enantiomer **441b** was isolated from *Catharanthus roseus*[130]. Ibogane skeletal isomers were also prepared, including bases **447** derived from chloroacetamides[158] **445**.

A new synthesis of (±)-catharanthine (**441b**), which includes build up of the indole moiety, was reported by Fukuyama and collaborators[161,162], Scheme 68. Base treatment of dibromide **448** gave the diene **443b**, which underwent [4+2] cycloaddition with methylidene malonate generated in situ by thermolysis of ethoxymethyl malonate. The resulting diester **449** was converted into acid **450** by hydrolysis and iodolactonisation (67% yield from **448**). Its transformation by the carbodiimide method to anilide **451** (74%) was followed by the reaction with zinc (AcOH), which initiated a re-

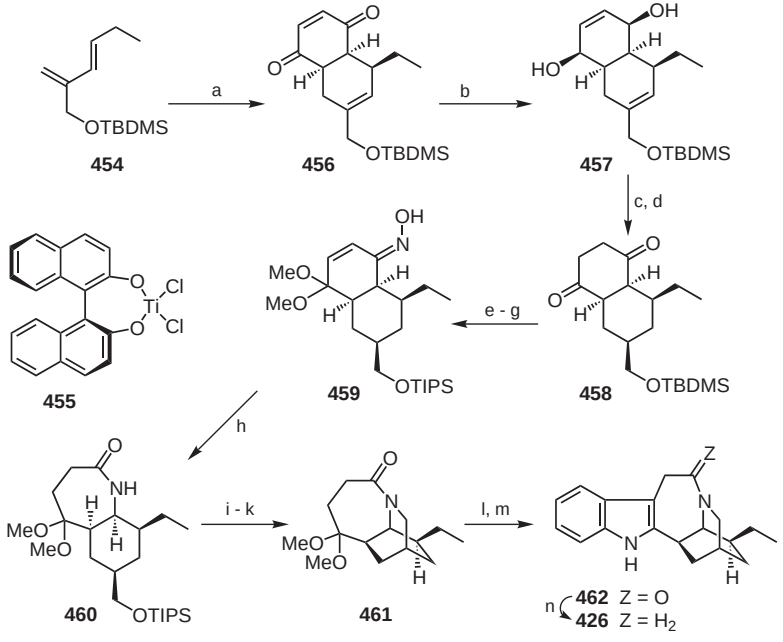


SCHEME 68

Reagents and conditions: a) DABCO, MeCN, rfl 2 h (94% crude). b) $EtOCH_2CH(COOEt)_2$, 100 °C overnight. c) 5 M KOH aq/EtOH (1:1), rfl 2 h. d) I_2, $NaHCO_3$ sat aq, rt overnight (67%, 4 steps). e) (*Z*)-2-$H_2NC_6H_4CH{=}CHCH_2OH$, WSCD, Et_3N, CH_2Cl_2, rt 1.5 h. f) Ac_2O, py, rt 2 h (74%, 2 steps). g) Zn, AcOH, CH_2Cl_2, rt 30 min. h) CH_2N_2, CH_2Cl_2, rt (83%, 2 steps). i) Lawesson's reagent, py, PhMe, rfl overnight (86%). j) 30% H_3PO_2 aq, AIBN, Et_3N, PrOH, 90 °C 45 min (50%). k) K_2CO_3, MeOH, rt 30 min. l) MsCl, Et_3N, CH_2Cl_2, rt 20 min (82%, 2 steps). m) $Pd(OAc)_2$, EtOH, AcOEt, rt 3 min, then Et_3SiH, Et_3N, rt 15 min (96%)

generation of the quinuclidine double bond. A conversion to thioanilide **452** (Lawesson, 86%) set the stage for the radical cyclisation: The treatment with a combination of hypophosphorous acid and AIBN afforded indole carbamate **453** in 40–50% yield. Finally, conversion of acetate to mesylate (82%) and removal of Cbz group allowed internal alkylation to give (±)-catharanthine (**441b**) in 96% yield.

The asymmetric synthesis of (–)-ibogamine (**400**) by White and Choi[163,164], patterned after an early synthesis of Sallay[165], is based on an enantioselective [4+2] cycloaddition of diene **454** with 1,4-benzoquinone in the presence of the titanium complex **455** derived from (*S*)-BINOL, Scheme 69. With 30% of **455** the *endo* addition was complete during 30 min at room temperature and afforded enedione **456** (65%) with 87% ee. Luche reduc-



SCHEME 69

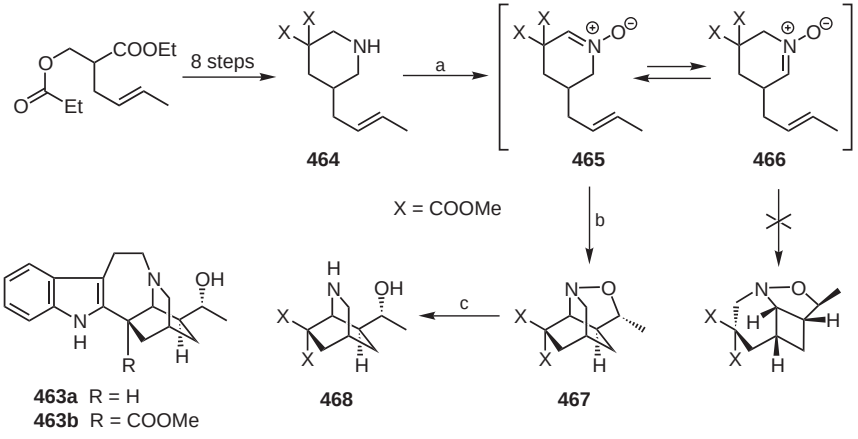
Reagents and conditions: a) 1,4-Benzoquinone, **455** (30 mole %), CH_2Cl_2/PhMe (3:2), rt 30 min. b) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, rt 8 h (62%, 2 steps). c) H_2, Rh/Al_2O_3, AcOEt, rt 24 h (94%). d) PDC, CH_2Cl_2, rt 4 h (88%). e) PPTS (cat), MeOH, 55 °C 3 h (89%). f) TIPSCl, imidazole, DMF, rt 2 h (93%). g) $NH_2OH \cdot HCl$, NaOAc, MeOH, rfl 3 h (81%). h) TsCl, Et_3N, DMAP (cat), CH_2Cl_2, rt 3 h (74%). i) TBAF, THF, rt 1 h (99%). j) TsCl, Et_3N, DMAP (cat), CH_2Cl_2, rt 3 h (100%). k) NaH, THF, 0 °C 1.5 h → rfl 1 h (71%). l) TsOH, Me_2CO, rt 12 h (86%). m) $PhNHNH_2$, AcOH, 50 °C 1 h, then $BF_3 \cdot OEt_2$, 80 °C 12 h (77%). n) $NaBH_4$, $BF_3 \cdot OEt_2$, THF, rt 3 h (78%)

tion then afforded (–)-diol **457**. Stereoselective saturation of both double bonds (Rh/Al_2O_3, 94%) and subsequent oxidation (PDC) gave the dione **458**, which was converted to *anti*-oxime **459**. The following Beckmann rearrangement in the presence of TsCl proceeded regioselectively to give the lactam **460** in 74% yield. The closure of the quinuclidine moiety in the tosylate derived from **460** was induced by the base (NaH, 71%). A release of the ketone function in **461** set the stage for the crucial Fischer reaction, which proceeded quite regioselectively (AcOH, then $BF_3 \cdot OEt_2$) and produced (+)-5-oxoibogamine (**462**) in a high yield (77%). Finally, reduction with diborane as above completed the total synthesis of (–)-ibogamine (**426**) in 14 steps and in 10% overall yield from 1,4-benzoquinone.

Szántay and coworkers have reported on side-products[166–168] of their previously developed desethylcatharanthine[169] and catharanthine[170] syntheses.

4.2.2. [3+2] Cycloaddition Approaches

Borschberg et al. have devised a new approach to ibogane alkaloids[171,172] that allows for the control of stereochemistry in the ethyl side chain, and thus seems to be especially suited for synthesis of alkaloids like (–)-19-hydroxyibogamine (**463a**) and (–)-19-epiheyneanine (**463b**), Scheme 70.

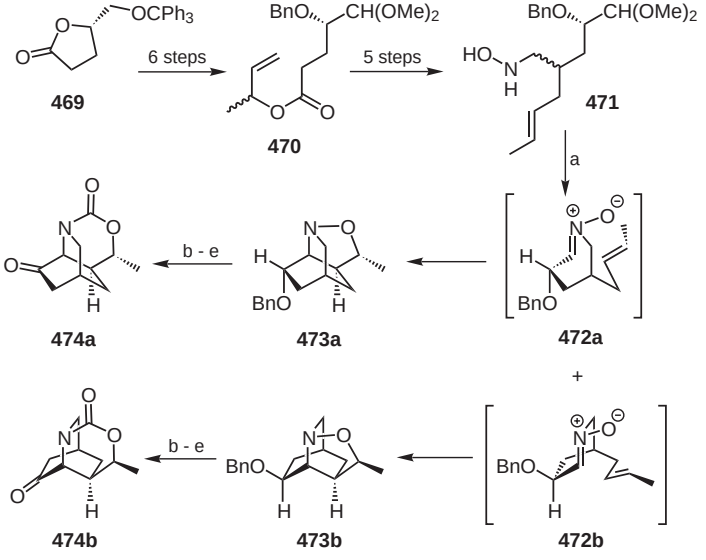


SCHEME 70

Reagents and conditions: a) 30% H_2O_2 aq, Na_2WO_4, MeOH, 0 °C → 25 °C 45 min. b) PhMe, rfl 1 h (**467** 27%, 2 steps). c) Zn, AcOH/MeOH (4:1), 60 °C 1 h (93%)

A tricky, low-yield (15–30%) conversion of piperidine **464** into a mixture of nitrones **465** and **466** (H_2O_2, Na_2WO_4) set the stage for the thermal dipolar cycloaddition. Heating the nitrones resulted in an exclusive formation (10–27% from **464**) of the obviously thermodynamically more stable cycloadduct **467**, a result of reversibility of the reaction and/or equilibrium between **465** and **466**. The conversion of isoxazolidine **467** to the alkaloid skeleton has reached so far the stage of amino alcohol **468**.

A considerably improved, and enantioselective variant of the approach was reported from the same laboratory recently[173], Scheme 71. The lactone **469** derived from (+)-L-glutamic acid was transformed via **470** into the hydroxylamine acetal **471**, obtained as a 1:1 mixture od diastereoisomers that could be partially separated. A treatment with acid induced formation of nitrones **472** (1:1) that underwent an intramolecular [3+2] addition to give the diastereoisomeric cycloadducts in 58% yield (**473a**:**473b** 59:41). These were then separately transformed into the enantiomeric ketones (+)-**474a** and (–)-**474b**.

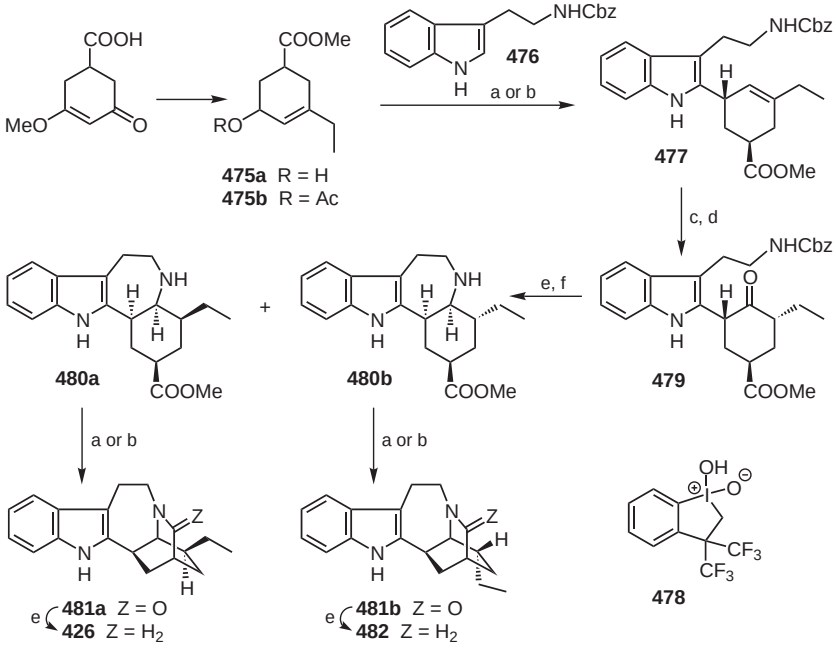


SCHEME 71

Reagents and conditions: a) 1.5 M H_2SO_4 aq/dioxane (1:1), 60 °C 24 h (58.4%, **473a**:**473b** 59:41). b) Zn, AcOH/MeOH (4:1), rt 3 h. c) $(Im)_2CO$, $ClCH_2CH_2Cl$, 75 °C 24 h (60%, 2 steps). d) H_2, 10% Pd/C, EtOH/AcOH (10:1), 23 °C 52 h (71–74%). e) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C 30 min, then Et_3N, –78 °C → 22 °C (72–79%)

4.2.3. Grieco's Synthesis

A conceptually new synthesis of ibogane alkaloids was published by Grieco and collaborators[174], Scheme 72. Allylic substitution with indole **476** in both allyl alcohol **475a** (in $LiClO_4/Et_2O$) and allyl acetate **475b** (lithium cobalt-bis-dicarbollide as catalyst) worked equally well (60%), and the resulting olefine **477** was converted to ketone **479** by sequential hydroboration (68%) and oxidation with Dess–Martin-type oxidant **478** (75%). Removal of the *N*-protecting group followed by reductive amination gave rise to a separable mixture of stereoisomers **480a** and **480b** (1:2.4) in 75% yield. Tetracycle **480a** afforded on pyrolysis 3-oxoibogamine (**481a**), which was reduced to (±)-ibogamine (**426**). Analogously, (±)-20-epiibogamine (**482**) was made accessible from the major isomer **480b** via lactam **481b**.

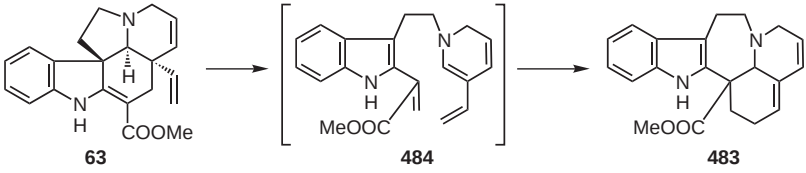


SCHEME 72

Reagents and conditions: a) **475a**, **476** (2 eq), camphorsulfonic acid (cat), 5 M $LiClO_4/Et_2O$, 48 h (60%). b) **475b**, **476** (2 eq), $Li[Co(C_2H_{11}B_9)_2]$ (10 mole %), $ClCH_2CH_2Cl$, rfl 8 h (60%). c) B_2H_6 (3 eq), THF, 0 °C 3 h (68%). d) **478** (2 eq), CH_2Cl_2, rt 4 h (75%). e) Cyclohexene, 10% Pd/C, THF/EtOH (1:1), 80 °C 40 min, then $NaBH_3CN$, TFA, rt 2 h (75%, **480a**:**480b** 1:2.4). f) 220 °C 2 h (**481a** 77%, **481b** 75%). g) $LiAlH_4$, THF, 70 °C 6 h (75%)

5. ANDRANGININE

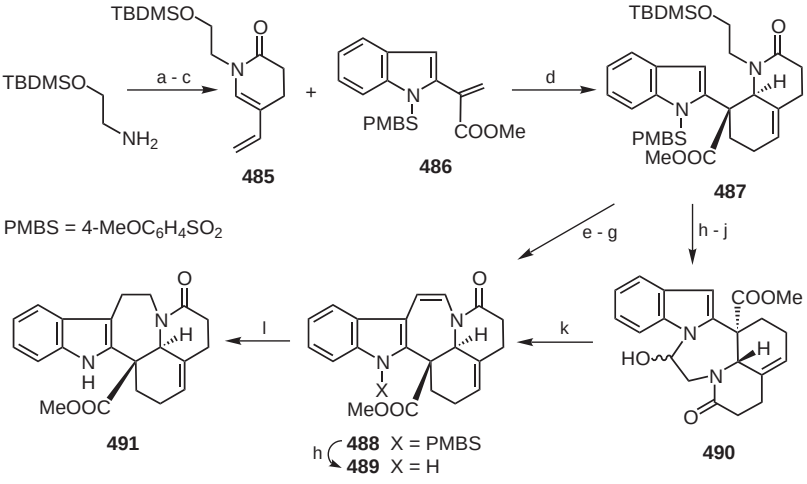
Included in this review is also andranginine (**483**), an alkaloid isolated from *Craspidospermum verticillatum*[175], which seems to be derived from a cycloaddition reaction in the presumed 15,18,19,21-tetradehydrosecodine (**484**), Scheme 73. Note that its formation upon thermolysis from 18,19-didehydrotabersonine (**63**) has been verified[176].



63 **484** **483**

SCHEME 73
Reagents and conditions: a) MeOH, 145 °C 40 h

The Milano group has reported on a synthetic approach to the alkaloid that incorporates an intermolecular [4+2] cycloaddition as the crucial step[177,178], Scheme 74. A reaction of the easily accessible diene **485** with indolylacrylate **486** proceeded both regio- and stereoselectively to give the



485 **486** **487** **490** **491**

SCHEME 74
Reagents and conditions: a) HC≡C.COMe, 0 °C → rt 18 h, then CH_2=CHCOCl, rt → rfl 18 h (48%). b) $NaBH_4$, THF/MeOH (1:2), 0 °C 2 h. c) TsOH (cat), PhMe, 40 °C 30 min (96%, 2 steps). d) PhMe, rfl 72 h (47%). e) TBAF·3H_2O, THF, 0 °C 2 h (99%). f) py.SO_3, Et_3N, DMSO, rt 1 h (94%). g) BF_3·OEt_2, 65 °C 40 min. h) Mg, NH_4Cl, MeOH, rt 6 h (**489** 60%; from **487** 95%). i) TBAF·3H_2O, THF, 0 °C 1 h (84%). j) py.SO_3, Et_3N, DMSO, rt 1 h (**490** 34% + 27%). k) $CHCl_3$, rt 70 h (88%). l) H_2, 5% Pd/C, MeOH (82%)

cycloadduct **487** in 47% yield. The aldehyde derived from silylated alcohol **487** cyclised by the action of a Lewis acid to give the pentacyclic enamide **488**, smoothly converting to indole **489**. Alternatively, if indole nitrogen was deprotected prior to oxidation, intermediary aldehyde was trapped by the indole nitrogen to afford a separable mixture of hemiaminals **490** (34 + 27%), which spontaneously rearranged to **489** upon standing in chloroform (88%). While the selective saturation of the 5,6-double bond proceeded uneventfully (82%), all attempts at transformation of the lactam **491** into the alkaloid have failed.

Note Added in Proof

Recently, Guo and Schultz have reported[179] on a model study aimed at vindoline synthesis. A highly efficient intramolecular azide [3+2] addition is the key feature in a phenyl-substituted CDE tricycle construction.

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