

Structure, Bioactivity and Synthesis of Natural Products with Hexahydropyrrolo[2,3-*b*]indole

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Research on natural products containing hexahydropyrrolo[2,3-*b*]indole (HPI) has dramatically increased during the past few years. Newly discovered natural products with complex structures and important biological activities have recently been isolated and synthesized. This review summarizes the structures, biological activities, and synthetic routes for natural compounds containing HPI, emphasizing the different strategies for assembling this motif. It covers a broad gamut of molecules, from small alkaloids to complex peptides.

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4. Summary and Outlook

1. Introduction

From the lushest forests to the deepest oceans, from the simplest organisms to the most complex, nature is replete with compounds containing either a hexahydropyrrolo[2,3-*b*]indole (HPI) unit, or the corresponding 2-carboxylate or 2-carboxamide (both abbreviated HPIC) (Figure 1). Biosynthetically, the simplest of these compounds stem from the amino acid Trp, whereas the more complex ones derive from Trp-containing peptides. Some HPI and HPIC-containing compounds contain two Trp or more units.

2. Structure and bioactivity

The first structures reported to contain HPI or HPIC were alkaloids; however, advances in the isolation and characterization of natural products later enabled identification of medium-sized cyclic peptides containing HPI or HPIC and exhibiting myriad biological activities. Some of these products are very small and are based around an HPI core, for example, (+)-alline (**1**),^[1,2] a small alkaloid with a hydroxyl group at C^{3a} and a methyl group at N¹. (–)-Physostigmine (**2**), isolated from the seeds of the Calabar bean plant (*Physostigma venenosum*) is a cholinesterase inhibitor. (–)-Physostigmine is currently used to treat myasthenia gravis, glaucoma, Alzheimer's disease and delayed gastric emptying, and has recently been employed to treat orthostatic hypotension.^[3] Further examples of these compounds alkylated at C^{3a} include the flustramines A-M (**3-7**), a family of alkaloids isolated from the marine organism *Flustra foliacea*,^[4-9] the flustramides A, B (**8**), and E,^[10,11] dihydroflustramine C (**9**),^[12] (3aR*,8aS*)-6-bromo-3a-[(2E)-3,7-dimethyl-2,6-octadienyl]-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indol-7-ol,^[13] debromoflustramines B^[8] and H,^[9] five recently discovered alkaloids isolated from the plant *Selaginella moellendorfii*,^[14] the flustraminols A and B,^[6] both part of the flustramines family and characterized by a hydroxyl group at C^{3a}; and (–)-pseudophrynaminol (**10**), extracted from the Australian frog *Pseudophryne coriacea*^[15] (Figure 1). The HPIC unit is found in products such as the okaramines A-Q (**11**), isolated from the fungus *Penicillium simplicissimum*.^[16-22] In okaramines the HPIC is condensed to a diketopiperazine (DKP) unit formed from a second amino acid. Leptosins D-F (**12-14**),^[23] gliocladines C-E (**15-17**),^[24] gliocladins A-C,^[25] plectosphaeroic acids A-C (**18, 19**),^[26] (+)-asperazine (**20**),^[27] and nasesezazines A and B^[28] have an analogous DKP unit containing an extra indole, bound between C³ and C^{3a} (except for in the case of (+)-asperazine and the nasesezazines, in which the indole binds *via* C⁷ and C⁶ respectively). Brevicompanines A-H (**21, 22**), *allo*-brevicompanine B and fructigenine B^[29-31] are also alkylated at C^{3a}; as is ardeemin, isolated from a strain of *Aspergillus fischeri*,^[32] roquefortines C, D (**23**), F and G,^[33-36] and aszonalenin (**24**).^[37] Brevianamide E (**25**),^[38] the sporidesmins^[39-42] and notoamide D^[43] are all hydroxylated at C^{3a} (Figure 1).

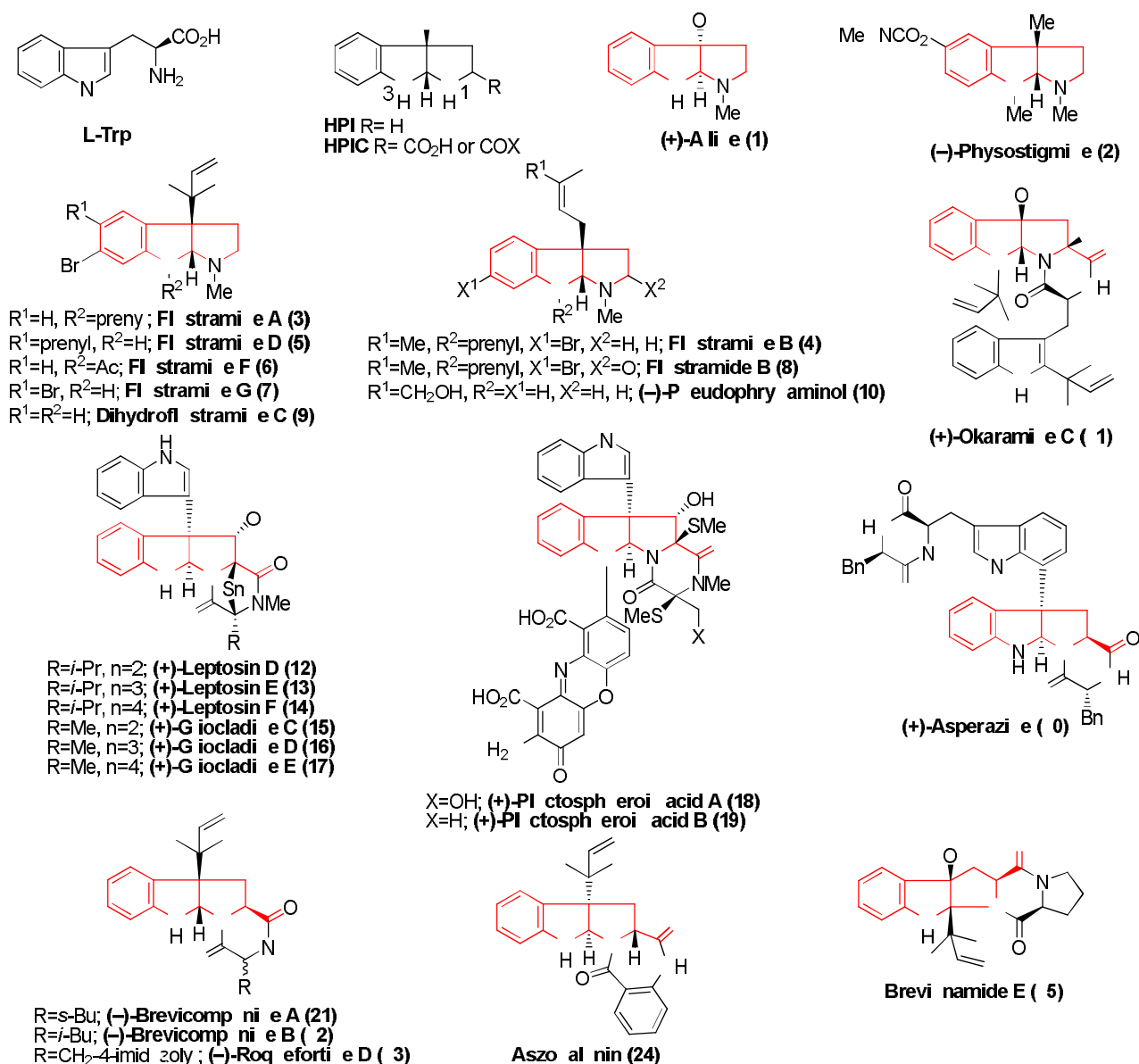


Figure 1. Natural products containing a single HPI or HPIC unit (shown in red)

Natural compounds containing two or more HPI or HPIC units are shown in Figure 2. These include amauromine (**26**) and gypsetin (**27**), dimeric alkaloids in which two HPIC units are condensed through a DKP. Amauromine, obtained from the culture broth of *Amauroascus* sp, has vasodilating activity,^[44,45] and gypsetin is an inhibitor of acyl-CoA.^[46,47] Natural products containing two HPI units comprise the botanical compound (-)-chimonanthine (**28**)^[48-51] or its optical antipode, (+)-chimonanthine, found in the skin of the Colombian poison dart frog, *Phyllobates terribilis*^[49] and in *Psychotria colorata* flowers.^[52] Chimonanthines are dimeric HPIs linked between the C^{3a} of each unit. Related compounds include (*meso*)-chimonanthine,^[53] (-)-chimonanthidine (**29**),^[51] (-)-calycanthidine (**30**),^[51] *N*^b-desmethyl-(*meso*)-chimonanthine,^[50] and the antifungal agent (-)-folicanthine (**31**)^[54] which was isolated from both *Calycanthus floridus*^[55,56] and the seeds of *Chimonanthus praecox*.^[51] The absolute configuration of (-)-**31** was determined by chemical

correlation with (–)-**28**^[51] and the total synthesis of its enantiomer (+)-**31**.^[57] Furthermore, psycholeine,^[58] (*meso*)-pseudophrynamine A^[15] and the recently isolated flustramines O (**32**) and P (**33**)^[9] each have two HPI units (Figure 2).

Natural compounds containing more than two HPI units comprise idiospermuline (**34**)^[59] and the hodgkinsines (**35**),^[50,52,60,61] with three HPI units; psychopentamine^[62] and quadrigemines A, B, C (**36**), and I,^[50,52,58,61,63] with four. Quadrigemine C is a weak antagonist of the SRIF (somatostatin) receptor, like psycholeine and (*meso*)-pseudophrynamine A. Isopsychotridines A and B (**37**)^[61] and psychotridine, with five,^[50,61] oleidine,^[50] with six; and caledonine,^[50] with seven.

Another important group comprises dimeric HPICs linked by the C^{3a} of each unit, each of which contains a DKP. These include the neurokinin antagonists (+)-WIN64821 (**38**) and (+)-WIN64745 (**39**), both isolated from a strain of *Aspergillus* sp.,^[64-66] (–)-ditryptophenaline (**40**), obtained from *Aspergillus flavus*,^[67] the anti-viral agent (+)-asperdimin (**41**), isolated from extracts of *Aspergillus niger*,^[68] chaetocin (**42**), isolated from the fermentation broth of *Chaetomium minutum*,^[69] verticillins A (**43**), B, and C, obtained from *Verticillium* sp., exhibit antimicrobial activity against Gram positive bacteria and potent antitumor activity in HeLa cell lines,^[70-72] gliocladines A (**44**) and B (**45**),^[24] 11,11'-dideoxyverticillin A and 11'-deoxyverticillin A,^[24,73] melinacidins,^[74-76] Sch52900 and Sch52901,^[24] and some leptosins A (**46**), B (**47**), and C (**48**).^[23] Leptosins C and F, isolated from the marine fungus *Leptoshaeria* sp., have inhibitory activity against topoisomerases I and II^[77] (Figure 2).

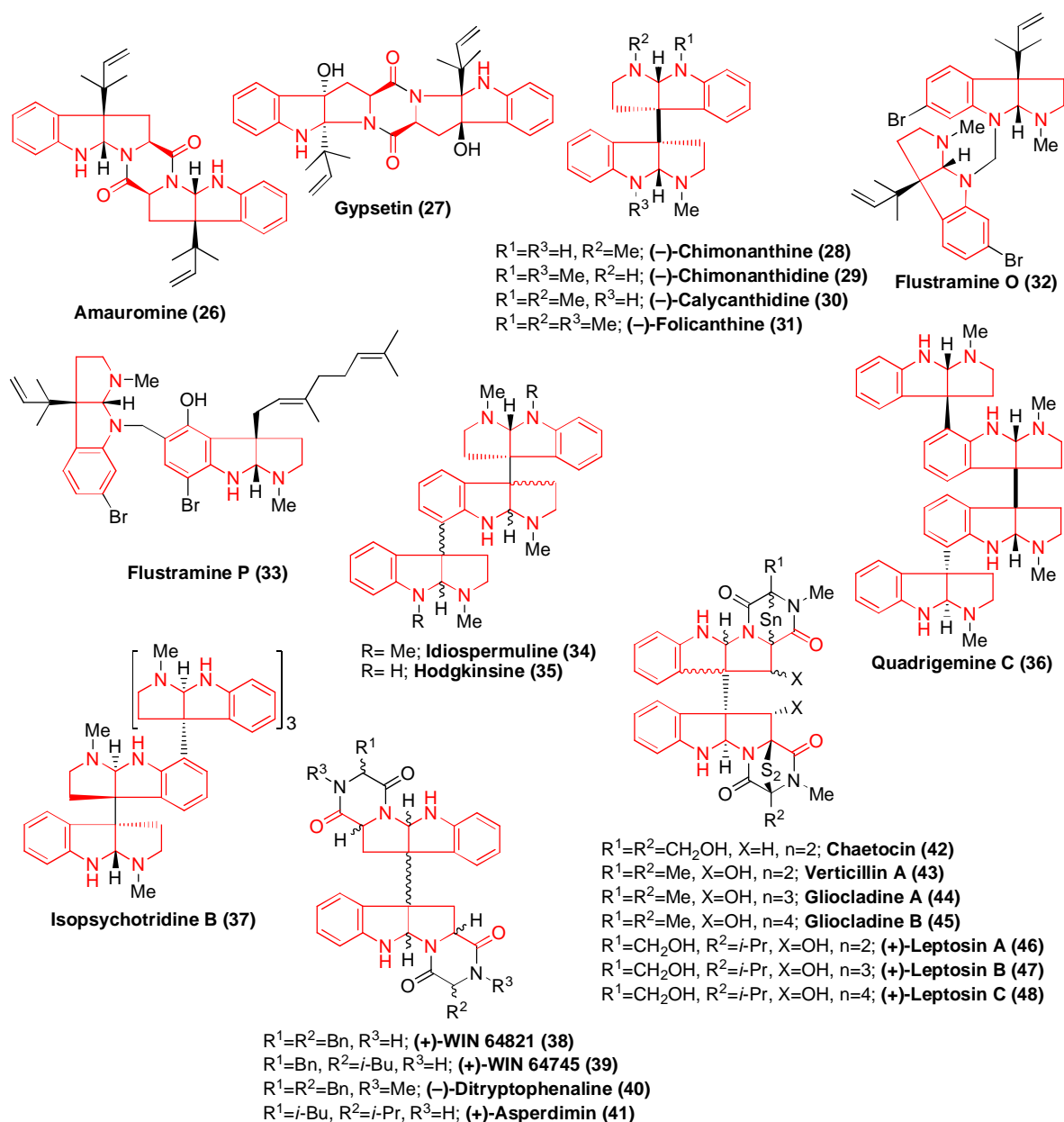


Figure 2. Natural products containing two or more HPI or HPIC units (shown in red)

Several recently isolated products feature a bond between the C^{3a} of an HPI or HPIC unit and the N^{ind} of a modified tryptamine or Trp, such as that found in the alkaloid psychotrimine (**49**).^[62] Another noteworthy example is the epipolythiodioxopiperazine family, whose members exhibit numerous bioactivities, including antitumor, antimicrobial, antinematodal and cytotoxicity; notable members include the chetomin (**50**), chaetocochins A (**51**), B (**52**), and C, and dethio-tetra(methylthio)chetomin, all isolated from the solid-state fermented rice culture of the fungus *Chaetomium cochliodes*.^[78-84] An extra degree of complexity is shown in kapakahines C (**53**) and D (**54**), which are macrocyclic peptides formed through a bond between the N⁸ of an HPIC located at the N-terminal of the linear structure and the C^{4a} of an α -carboline unit, located close to the C-terminal.^[85]

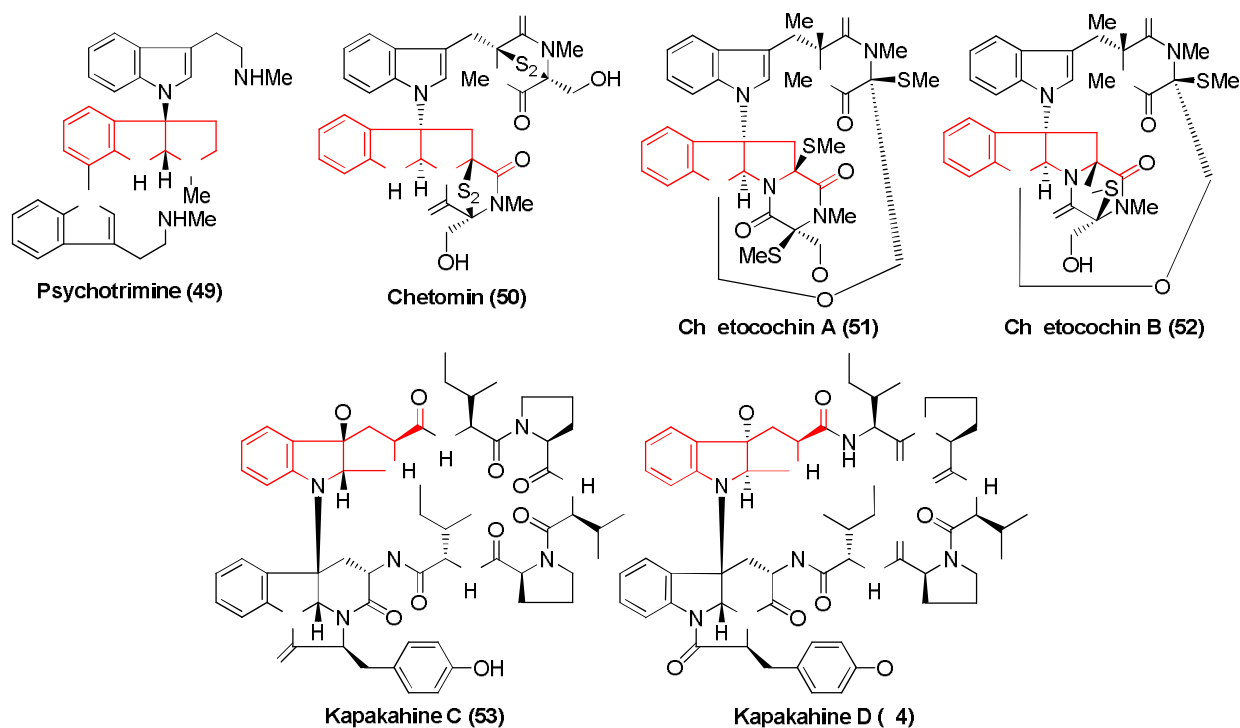


Figure 3. Natural products containing an HPI or HPIC unit (show in red) bound through C^{3a} to the N of an HPIC unit, tryptamine or Trp

Natural products with an HPIC integrated into the peptide chain include omphalotins B-I (55),^[86,87] phakellistatin 3 (56) and isophakellistatin 3;^[88] himastatin (57), in which the HPIC is part of a depsipeptide-chain,^[89,90] its structure and stereochemistry was revised after the total synthesis.^[91,92] Other similar natural products are chloptosin (58);^[93] NW-G01, an antibiotic isolated from *Streptomyces alboflavus*;^[94] and kutznerides 1-9 (59)^[95,96] (Figure 4).

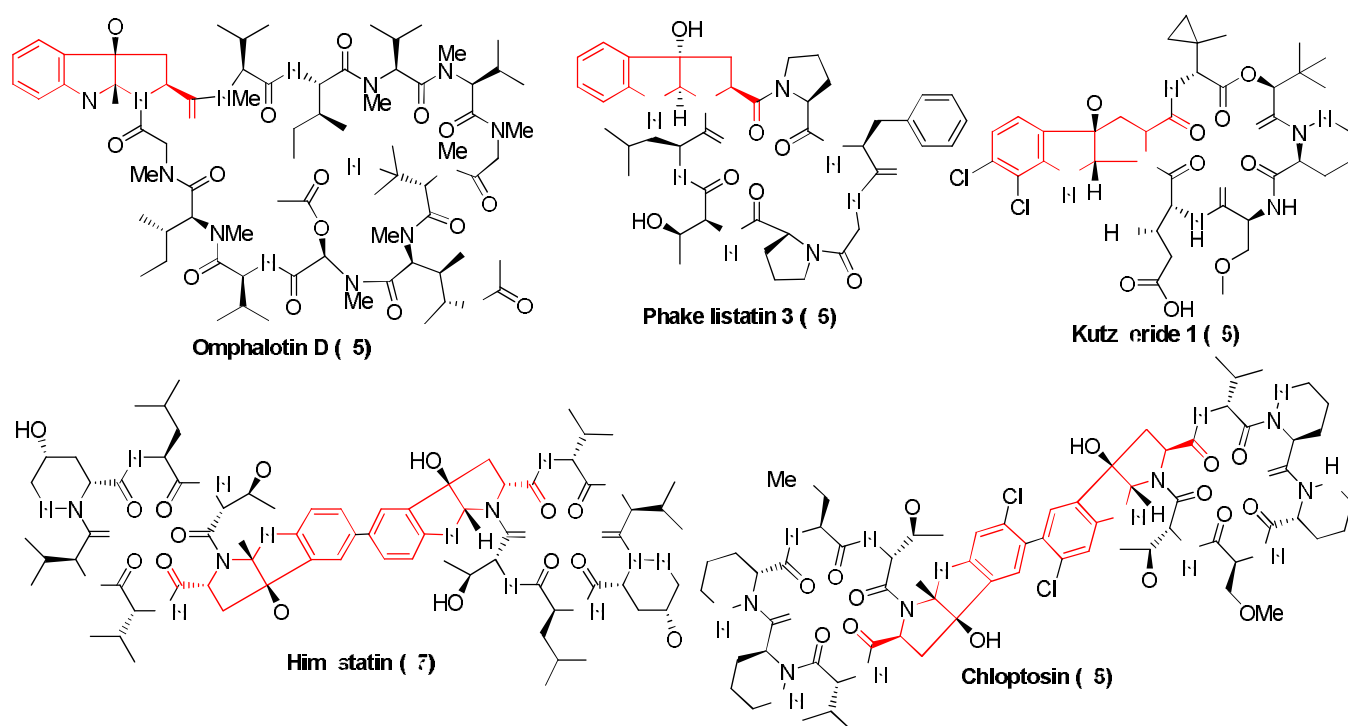


Figure 4. Natural products containing HPIC (shown in red) as part of a peptide chain

Most of these complex structures have only recently been isolated. The literature contains a few reviews, although these cover only specific aspects of these compounds. These include works by Schmidt and Movassaghi,^[97] on biosynthetic hypotheses; Steven and Overman,^[98] on syntheses of poly-HPI compounds; and Crich and Banerjee,^[99] on the stereochemistry of HPI containing-compounds, as well as classical publications on the Calabar bean alkaloids,^[100,101] phenserine,^[102] chimonanthine and related natural products,^[103,104] chaetocin and related natural products,^[105] and the chemistry of cyclic tautomers of tryptamines and Trp.^[106,107]

This article provides an exhaustive overview of the structure, synthesis and bioactivity of HPI and HPIC containing natural products from all of the aforementioned structural classes, emphasizing the synthetic routes to polycyclic compounds of this type published until December 2009. Alkaloids containing a poly-HPI linked at the quaternary carbons, such as quadrigemine C, have been omitted here because they have already been covered in an excellent report by Steven and Overman.^[98]

3. Syntheses of natural products containing HPI or HPIC

Several procedures have been developed for the synthesis of HPI and HPIC units, chiefly in the context of natural product syntheses. Figure 5 illustrates known routes to tricyclic HPI and HPIC.

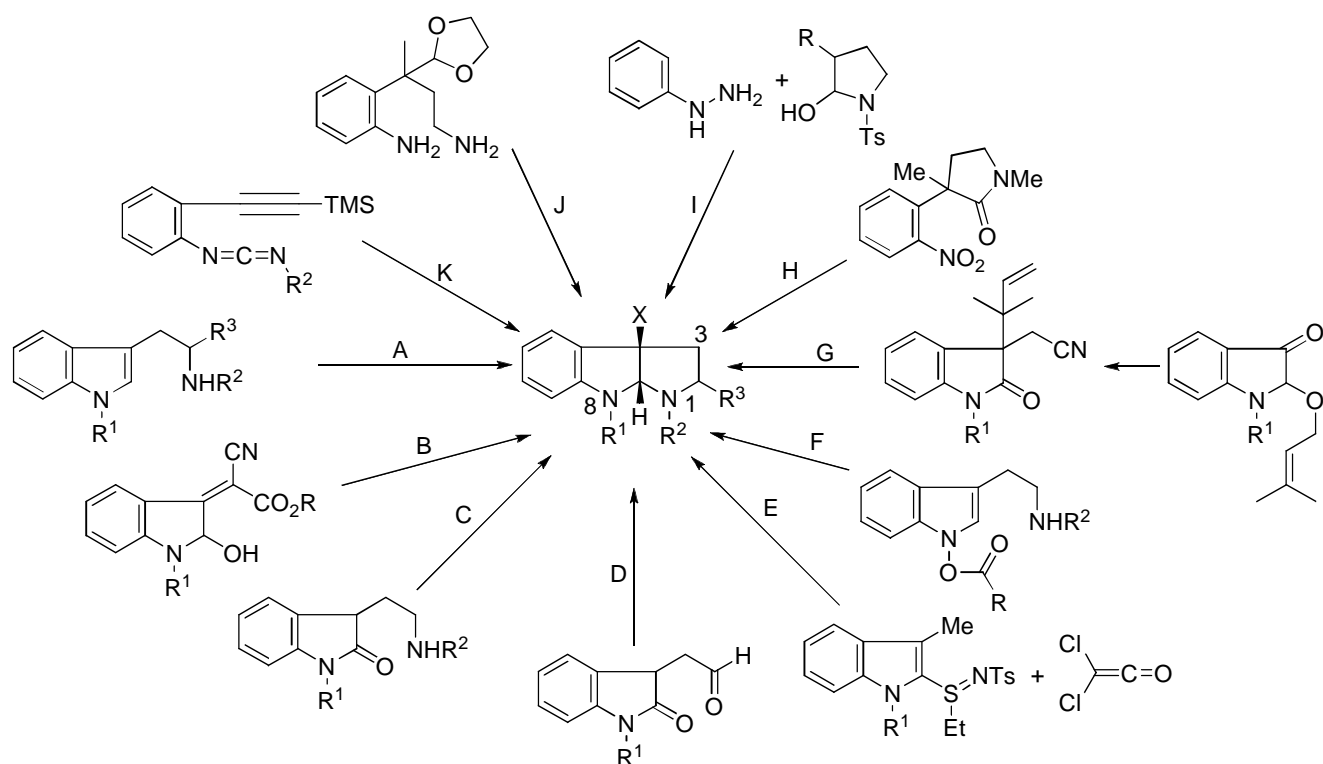


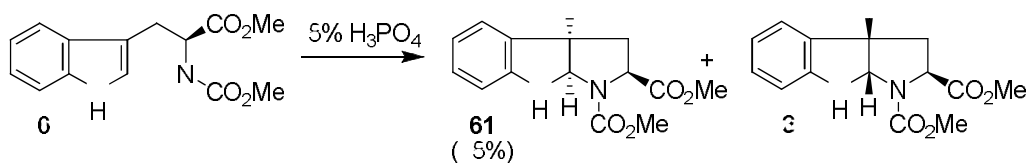
Figure 5. Synthetic strategies for constructing tricyclic HPI and HPIC

The most widely used starting materials for the synthesis of tricyclic HPI and HPIC are functionalized indoles (or oxidized indoles), tryptamines or Trp's (see Fig. 5). Routes A through C comprise bond formation between N^1 and C^{3a} . In Route D, the bonds $C^{3a}-N^1$ and C^2-N^1 are formed from a diketo-derivative of indole. Route E entails introduction of C^2 by formation of the bonds N^1-C^2 and C^2-C^3 , using dichloroketene and an indolyl sulfylimine. In Route F, HPI is performed by reductive cyclization. Route G affords HPI after the rearrangement of an acyloxy group. Route H involves bond formation between N^8 and C^{3a} from a 3-(nitrocyclohex-1-enyl)pyrrolidin-2-one. Route I comprises Fischer indolization, namely, *via* condensation of phenylhydrazines with latent aldehydes. Route J involves simultaneous formation of the bonds N^8-C^{3a} and N^1-C^{3a} . Lastly, Route K, in which HPIC is assembled *via* formation of the bonds $C^{3a}-C^{3a}$ and N^1-C^2 , is based on the aza-Pauson-Khand reaction (APKR).

3.1. Acid catalyzed cyclization

In Route A (Figure 5), HPIC ring closure is acid catalyzed. This involves protonation of indole at C^3 , followed by capture of the resulting indoline by the protected amine of the lateral chain. This procedure has been extensively used, starting from protected tryptamine, Trp or even more complex compounds.

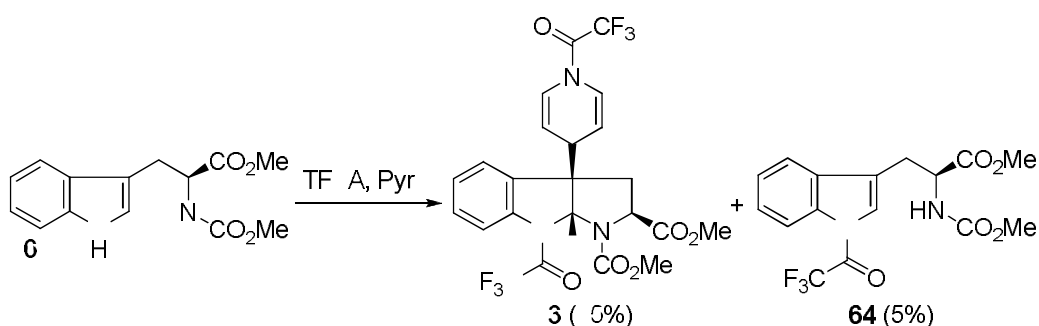
The Trp derivative **60** cyclized in 85% H_3PO_4 to yield two diastereomers of the corresponding HPIC in a thermodynamic ratio of 9:1 (**61:62**, *endo:exo*).^[108] However, if these products are not stabilized in solution by acylation or sulfonylation of N^β , they degenerate back to the starting material (Scheme 1).^[106]



Scheme 1. Acid-catalyzed cyclization of *N*-protected-L-Trp **60**.^[108]

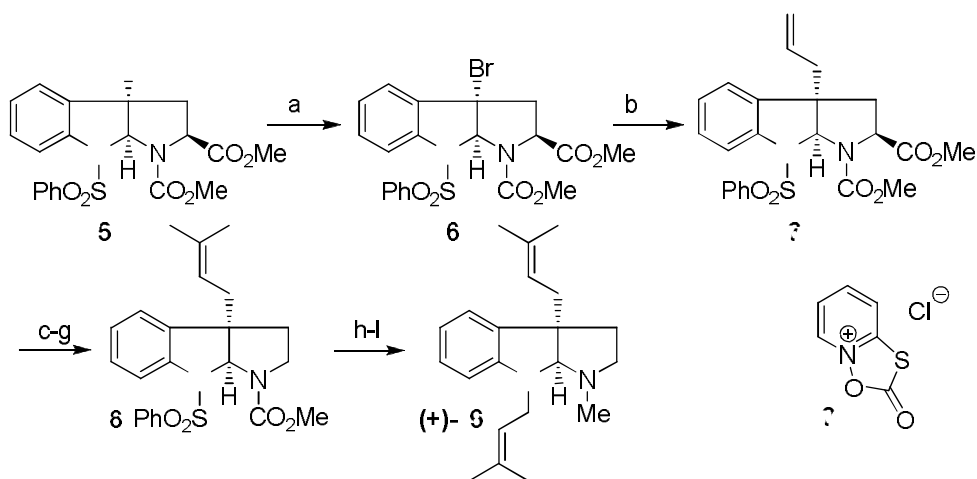
A solution of N^β -methoxycarbonyl-L-Trp **60** in trifluoroacetic acid (TFA) gave, after equilibration, mainly the *endo*-HPIC **61** plus minor amounts of the *exo*-HPIC **62** and starting material. Addition of trifluoroacetic acid anhydride (TFAA) to the solution afforded the two corresponding trifluoroacetyl analogs.^[109]

Treatment of **60** with TFAA in dry pyridine afforded a complex mixture. The main constituents were the adduct **63** (50%) and the N^{ind} -trifluoroacetylated Trp **64**.^[110] The exact structure of **63**, including the stereochemistry of its three stereogenic centers, were unequivocally established by X-ray analysis (Scheme 2).^[111]



Scheme 2. Cyclization of protected *N*-protected-L-Trp **60**.^[110]

Crich described a diastereoselective synthesis of the non-naturally occurring (+)-debromoflustramine B (**69**) and related compounds from the L-Trp-derived HPIC **65**.^[112] Diastereomerically and enantiomerically pure sulfonamide **65** obtained by phenylsulfonylation of **61** was used to prepare HPI alkaloids. The main transformations comprised functionalization and C-C bond formation at C^{3a} ; Barton^[113] reductive decarbomethoxylation at C^2 ; and sequential selective deprotection and alkylation of the two nitrogen centers (Scheme 3).



Reagents: a. NBS, Cl_4 , Δ , 60-70%; b. $\text{Bu}_3\text{SnCH}_2\text{CH}=\text{CH}_2$, Δ , 0%; c. NaIO_4 , OsO_4 , 3%; d. $\text{Ph}_3\text{P}=\text{CMe}_2$, 4%; e. KOH , MeOH , 9%; f. H_2 , Et_3N ; g. $t\text{-BuOCl}$, $h\nu$, 61% (2 steps); h. KOH , MeOH , Δ , 9%; i. NaBH_3CN , HCHO , AcOH ; j. KOH , MeOH , 9% (2 steps); k. NaI ; l. prenyl bromide, 7% (2 steps)

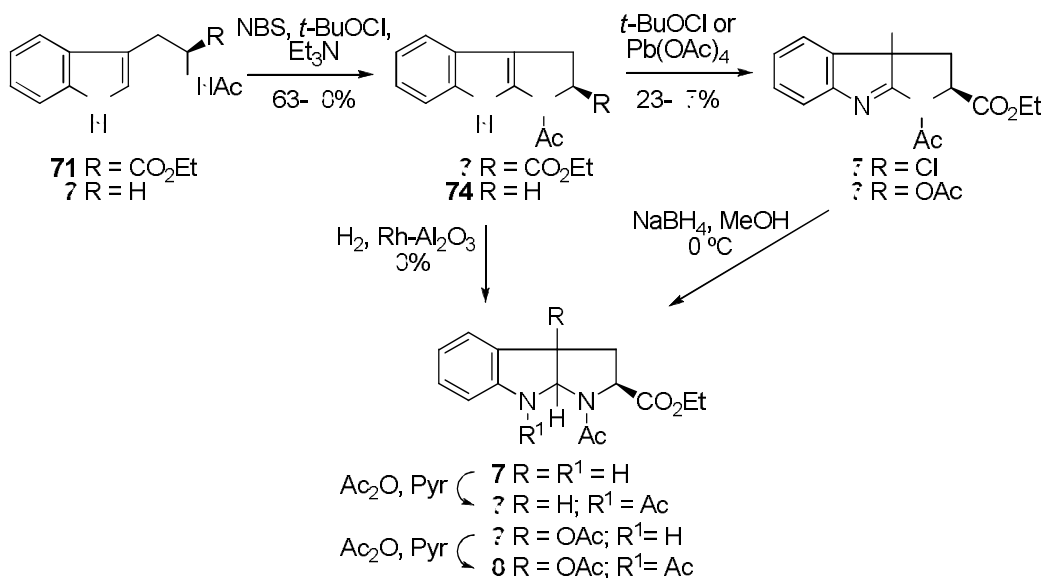
Scheme 3. Synthesis of (+)-debromoflustramine B (69) by Crich^[112]

3.2. Sequential oxidation-cyclization (A, Figure 5)

This methodology exploits the reactivity of compounds such as tryptamine or Trp at their 3-substituted indole position to oxidants such as 2,2-dimethyldioxirane (DMDO), *N*-bromosuccinimide (NBS), and phenylselenenyl chlorides, whereby the resulting imine or iminium salt intermediate is captured by the lateral nitrogen.

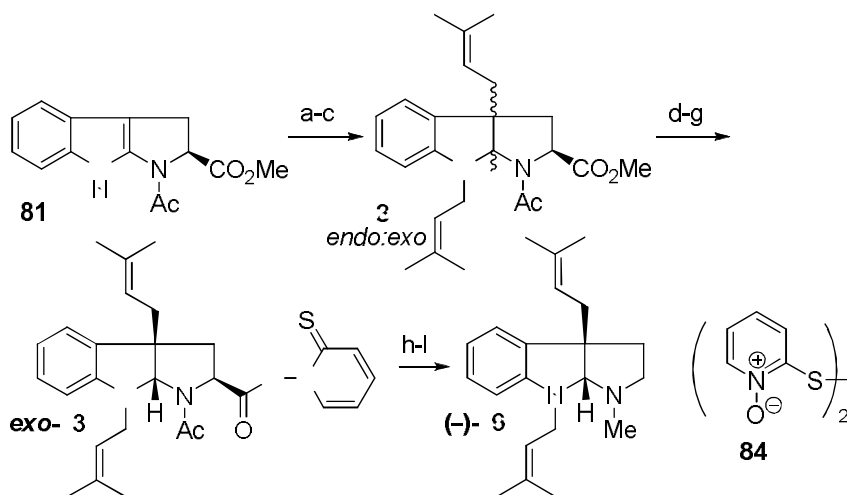
3.2.1. Bromination-cyclization

Witkop *et al.* prepared the tricyclic pyrrolo[2,3-*b*]indoles **73** and **74** by reacting Trp **71** and tryptamine **72**, respectively, with NBS at pH 9.2 in a very dilute solution at room temperature.^[114,115] Compound **73** was slowly reduced over $\text{Rh-Al}_2\text{O}_3$ (as catalyst) in EtOAc to yield HPIC **77**, which was then acetylated with Ac_2O in pyridine to give **78**. Reaction of $t\text{-BuOCl}$ with **73** gave the unstable 3a-chloroindolenine **75**. Analogously, oxidation of **73** with $\text{Pb}(\text{OAc})_4$ in DCM gave the 3a-acetoxyindolenine **76**, which was rapidly reduced by NaBH_4 in MeOH to the 3a-acetoxyindoline **79**, which in turn was converted to the corresponding diacetyl derivative **80** for structural characterization (Scheme 4).



Scheme 4. Cyclization of tryptamine and Trp by Witkop *et al.*^[114]

Lobo and Prabhakar reported a total synthesis of (-)-debromoflustramine B (**69**) from the Witkop HPIC **81** (Scheme 5).^[116,117] Their route starts with consecutive C^{3a} -allylation of **81**, followed by reduction and N^8 -allylation to afford a diastereomeric mixture of *endo* and *exo* methyl esters. These esters had to be transformed into the corresponding Barton esters^[118] for separation. Oxidative removal of 2-carboxylate from *exo*-**3** using $\text{Sb}(\text{SPh})_3$, followed by reduction, N^1 -deprotection and methylation furnished (-)-**69**. Likewise, *endo*-**3** gave (+)-**69** (not shown).



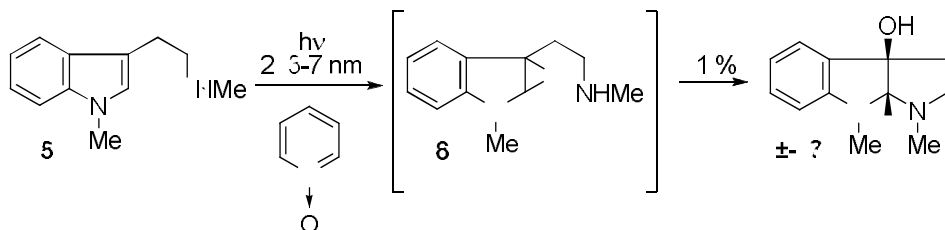
R agents: a. NaH, DMF, prenyl bromide, 60%; b. NaBH_3CN , MeOH, 5%; c. K_2CO_3 , CH_2Cl_2 , 0 °C, 71%; d. NaOH, aq. MeOH; e. H_3O^+ ; f. **84**, Pu_3 , CH_2Cl_2 , 0 °C, 3% (3 steps); g. diastereomer separation; h. $\text{Sb}(\text{SPh})_3$, O_2 , Et_2O , 0 to 18 °C, 4%; i. xylene, Δ , 3%; j. 4.7M NaMeO, MeOH, H_2 , H_2O , Δ , 54%; k. LiAlH_4 , Et_2O , 0 °C, 70%; l. NaH, MeI, CH_2Cl_2 , 3%

Scheme 5. Total synthesis of (-)-debromoflustramine B (**69**)^[116]

Using Br₂ or NBS without base enabled bromination-cyclization of protected Trp or derivatives. Danishefsky *et al.* pursued NBS cyclization^[91,119] in preliminary studies on the total synthesis and structural characterization of himastatin. In the total synthesis of (+)-11,11'-dideoxyverticillin A, Movassaghi *et al.* used bromine and acetonitrile to obtain 3a-bromo-HPIC.^[120] De Lera *et al.* studied the mechanism and proposed the use of electrophiles such as NBS to obtain the bromocyclized product.^[121]

3.2.2. Synthesis of 3a-hydroxy-HPIC

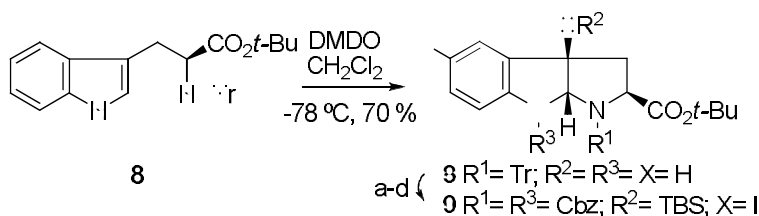
Photochemical oxidation of *N,N*^{ind}-dimethyltryptamine (**5**) in CH₂Cl₂ using pyridine *N*-oxide as oxygen source afforded the HPI (±)-**87**.^[122] The proposed mechanism involves opening of intermediate 2,3-oxide **86** by methylamine residue (Scheme 6).



Scheme 6. Photochemical oxidation of *N,N*^{ind}-dimethyltryptamine (**5**) by pyridine *N*-oxides^[122]

Photocyclization of *N*-methoxycarbonyltryptamine in the presence of (–)-nicotine followed by treatment with triphenylphosphine produced 3-hydroxy-1-methoxycarbonyl-HPI with modest enantioselectivity.^[123] Similar results were obtained using protected Trp.

Danishefsky *et al.* developed a route to 3a-hydroxy-HPIC based on oxidative cyclization of Trp,^[92] in work on the total synthesis of himastatin (**57**). They also revised and confirmed stereochemistry of the natural product. The *tert*-butyl ester of *N*^α-Tr-L-Trp (**88**) reacts with DMDO to give **89**. Protecting groups exchange and iodination at position 5 gave **90** which was later dimerized. (Scheme 7)

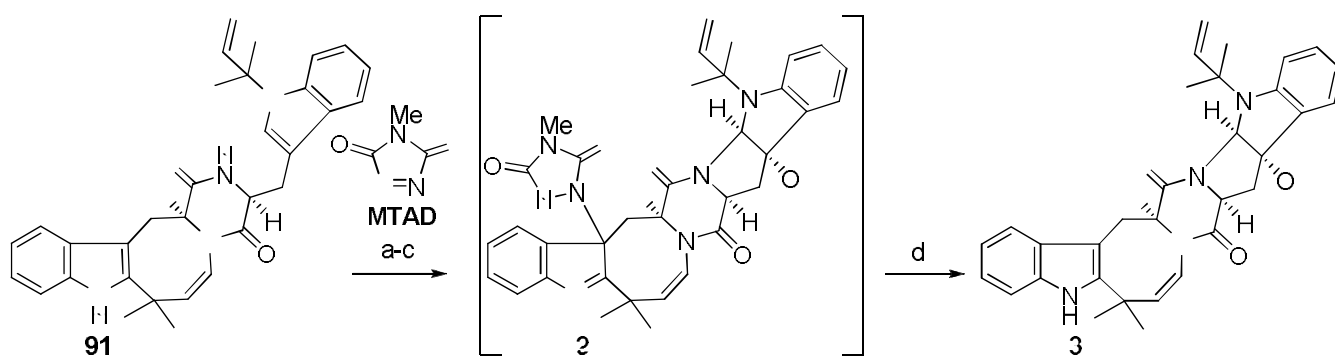


R agents: a. AcOH, MeOH, CH₂Cl₂; b. CbzCl, Pyr, CH₂Cl₂; c. TBSCl, DBU, MeCN; d. ICl, 2,6-di-*tert*-butyl pyridine, CH₂Cl₂, 75%

Scheme 7. Tandem oxidation-cyclization of Trp by Danishefsky *et al.*^[92]

Oxidative cyclization was the key step in the enantioselective total synthesis of the complex alkaloid okaramine N (**93**) by Corey *et al.*^[124] They developed a new method for the selective

differentiation of the two indole subunits of **91**. The commercially available reagent *N*-methyl-1,3,4-triazoline-2,5-dione (MTAD) was used in a novel application: reversible blocking of the *N*-unsubstituted indole subunit, which enabled oxidative ring-closure between the DKP and the *N*-substituted indole ring. The bisindole **91** underwent highly selective reaction with MTAD to form exclusively the ene product at C³ of the *N*-unsubstituted indole subunit. Subsequent photooxidation, employing methylene blue as photosensitizer under sunlamp irradiation, followed by reduction of the resulting product by Me₂S in MeOH, afforded the hydroxylated octacycle **92** cleanly (with only a minor amount of diastereomer). The blocking group was eliminated by thermolysis of the mixture of **92** and the diastereomer to furnish **93** in good total yield (Scheme 8).

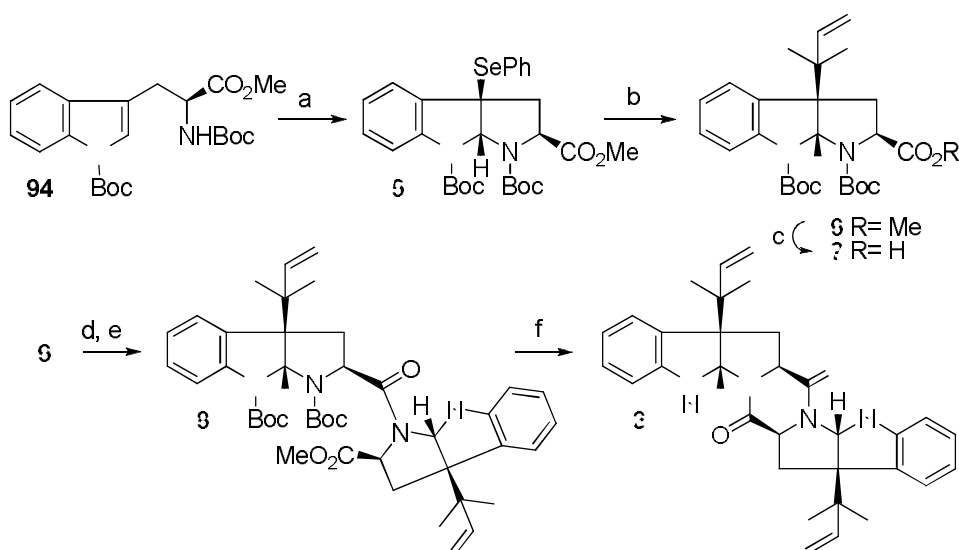


Reagents: a. MTAD, CH₂Cl₂, -5 °C; b. O₂, hv, MeOH, methylene blue, -28 °C; c. SMe₂, MeOH, -28 to -10 °C; d. 10 °C, 70% (4 steps)

Scheme 8. Enantioselective synthesis of okaramine N (**93**)^[124]

3.2.3. Phenylselenocyclization

The total synthesis of amauromine **26** from **95** (Scheme 9) has been reported. The keystone of this approach was kinetic stereoselective synthesis of **95** from *N*,*N*'-diBoc protected L-Trp methyl ester via selenocyclization reaction.^[125] Treatment of protected Trp **94** with *N*-phenylselenophthalimide (*N*-PSP) and pyridinium *p*-toluenesulfonate (PPTS) gave **95**. The synthesis of **95** was the first construction of *exo*-HPIC from a protected Trp in a high diastereoselective manner. Transformation of phenylselanylHPIC **95** with methyl trifluoromethanesulfonate (MeOTf) in the presence of 2,6-di(*tert*-butyl)pyridine and prenyltri(*n*-butyl)tin gave the angular reverse prenyl derivative **97**.

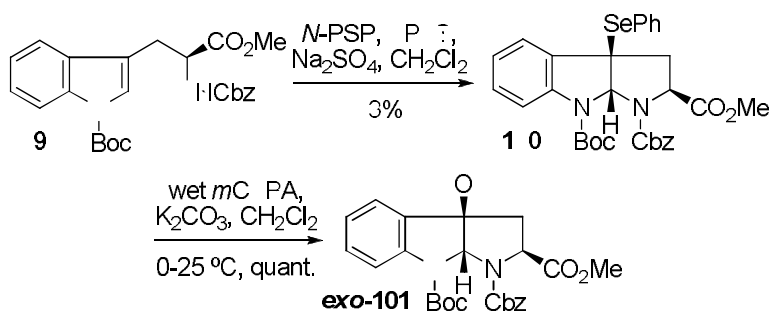


Reagents: a. *N*-PSP, CH_2Cl_2 , P^{\ominus} , 3%; b. MeOTf, 2,6-di(*tert*-butyl)pyridine, $\text{Me}_2\text{C}=\text{CHCH}_2\text{SnBu}_3$, CH_2Cl_2 , -78 °C to reflux, 60% (9:1 *exo-endo*); c. NaOH, MeOH , H_2O , reflux, 5%; d. TMSI, MeCN, 0 °C, 3%; e. P^{\ominus} , BOP-Cl, Et_3N , CH_2Cl_2 , 5%; f. TMSI, MeCN, 0 °C, 5%

Scheme 9. Total synthesis of amaumomine (**26**)^[125]

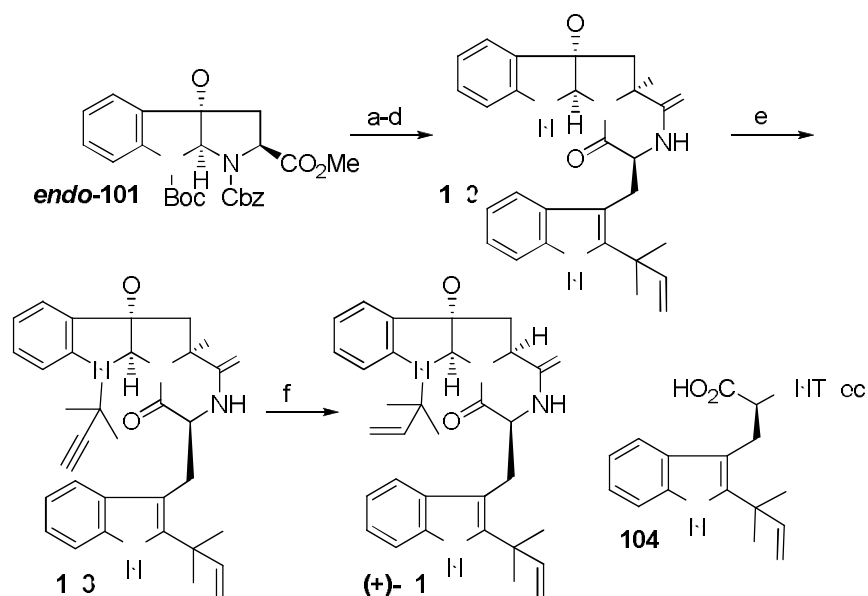
Roquefortine D (**23**) was prepared from the inverse prenylated-HPI **97**, which was reacted with protected His under peptide coupling conditions followed by removal of both *N*-*tert*-butoxycarbonyl (Boc) groups, cyclization, and finally, photolytic elimination of the *o*-nitrobenzyl protecting group (ONB) of the resulting imidazole.^[126,127]

Ley *et al.* described a path to stereocontrolled synthesis of the 3*a*-hydroxypyrrolo[2,3-*b*]indole skeleton (Scheme 10).^[128] The procedure is based on a two-step selenocyclization–oxidative deselenation sequence. Treatment of **99** in the conditions described by Danishefsky^[125] gave **100** as a simple diastereomer with an excellent yield. The following oxidation with *m*-chloroperbenzoic acid (*m*CPBA) gave the desired product *exo*-**101**.



Scheme 10. Two-step route to 3*a*-hydroxy HPIC *exo*-**101** by Ley *et al.*^[128]

The same group later used this two-step sequence in an elegant and concise total synthesis of (+)-okaramine C (**11**) by epimerization at C^2 of **100** to obtain *endo*-**101**, formation of the DKP with the Trp **104** and introduction of isoprenyl on N^{β} (Scheme 11). Isoprenyl group was afforded after partial reduction of the alkyne introduced by N^{β} -alkylation using 2-bromo-2-methylbut-3-yne.^[129]



Reagents: a. H_3PO_4 aq., CH_2Cl_2 ; b. H_2 , Pd/C, MeOH, 3% (2 steps); c. H_2 , Pd/C, MeOH, 3% (2 steps); d. TASF, DMF, 97%; e. $\text{H} \equiv \text{CC}(\text{Me})_2\text{Br}$, CuCl , CH_2Cl_2 , DIEA, rt, 8%; f. Lindlar' cat., H_2 , 9:1 MeOH:Pyr, 5%

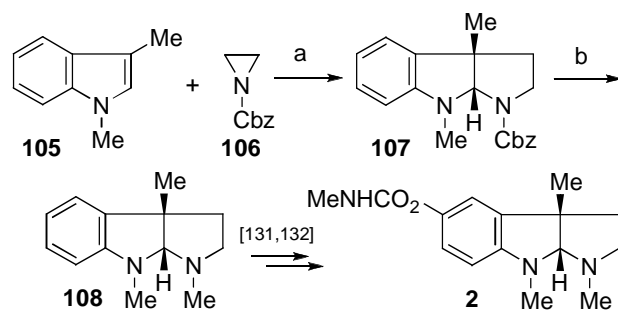
Scheme 11. Total synthesis of (+)-okaramine C (**11**)^[129]

3.3. Alkylative cyclization

3.3.1. Cyclization with electrophiles (A, Figure 5)

This procedure uses the reactivity of indole nucleus of tryptamine or tryptophan with alkylating agents over the substituted 3-position, followed by *in situ* capture of the resulting indoline by the protected lateral amine.

Nakagawa and Kawahara described a concise synthesis of desoxyeseroline (**108**),^[130] a precursor of physostigmine (**2**) (Scheme 12).^[131] Their route was based on a Lewis acid-catalyzed alkylative cyclization of 1,3-dimethylindole with *N*-benzyloxycarbonyl (Cbz) protected aziridine to form compound **107**, which is readily converted into physostigmine. They tested several Lewis acids, finding $\text{Sc}(\text{OTf})_3$ and TMSCl in dichloromethane to be the best conditions.

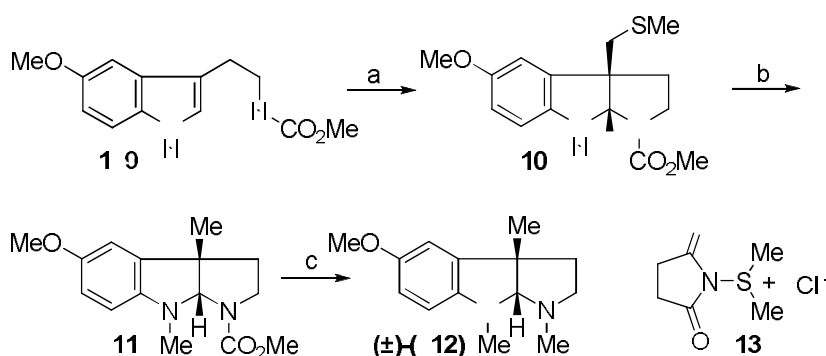


Reagents: a. $\text{Sc}(\text{OTf})_3$, TMSCl , CH_2Cl_2 , $-30\text{ }^\circ\text{C}$, 52%;
b. Red-Al, toluene, reflux, 95%

Scheme 12. Alkylative cyclization of 1,3-dimethylindole^[130]

Reaction of *N*_β-protected tryptamine with allyl bromides afforded the *N*¹-protected 3α,8-bisallyl-HPI,^[133] (±)-debromoflustramides B and E and (±)-debromoflustramines B and E have been prepared using this procedure.^[134]

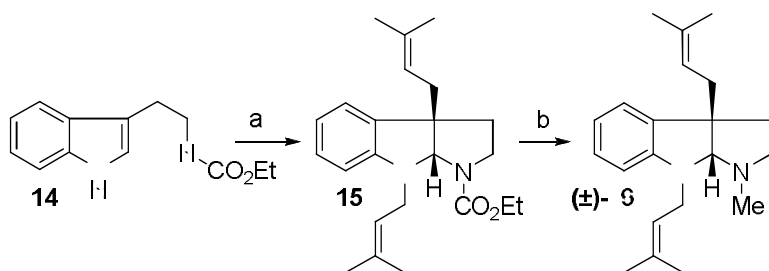
Nakagawa *et al.* synthesized (±)-esermethole (**112**) using an alkylative cyclization.^[135] Reaction of Corey-Kim reagent (**113**) with tryptamine carbamate **109** and *i*-Pr₂NEt gave the HPI **110**. Simultaneous reductive methylation and desulfurization of **110** were achieved by hydrogenation using Raney Ni (W2) and aqueous HCHO to give **111**, which was then reduced with Red-Al to give (±)-**112** in quantitative yield (Scheme 13).



Reagents: a. **13**, *i*-Pr₂NEt, -78 °C, 8%; b. H₂, Ni-Raney (W2), aq. HCHO, EtOH, reflux, 0%; c. Red-Al, toluene, reflux, 96%

Scheme 13. Synthesis of (±)-esermethole (**112**) by Nakagawa *et al.*^[135]

The Ganesan group published a fast and elegant three-step total synthesis of (±)-debromoflustramine B (**69**) via zinc triflate-mediated biomimetic alkylative cyclization from tryptamine (Scheme 14).^[136]

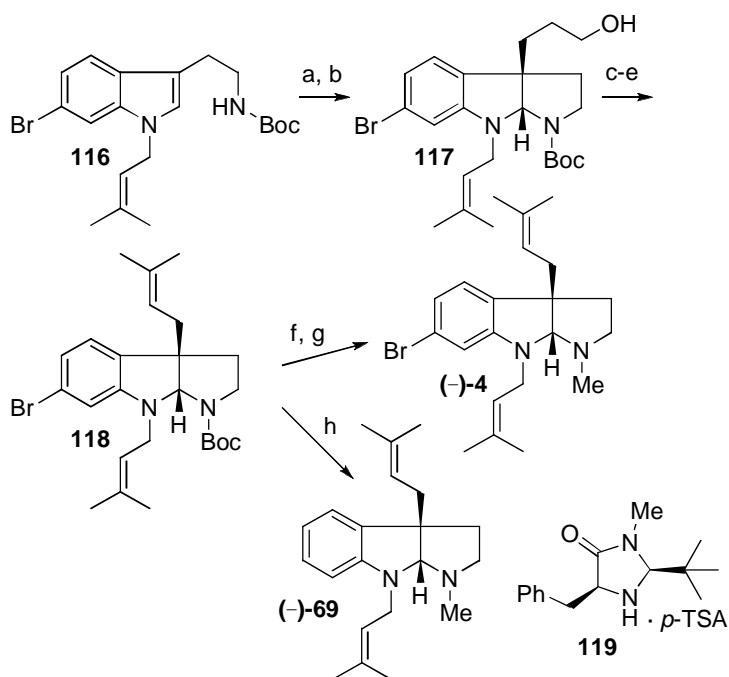


Reagents: a. prenyl bromide (4 equiv), Zn(OTf)₂, Bu₄NI, *i*-Pr₂NEt, toluene, rt, 70%; b. Red-Al, toluene, reflux, 96%

Scheme 14. Total synthesis of (±)-debromoflustramine B (**69**) by Ganesan *et al.*^[136]

(-)-Flustramine B (**4**) and (-)-debromoflustramine B (**69**) were enantioselectively synthesized in routes based on organocatalytic preparation of pyrroloindoline (Scheme 32). Addition of tryptamine **116** to α,β -unsaturated aldehydes in the presence of imidazolidinone catalysts **119** gave the cyclized pyrroloindoline adduct **117** in high yield and with excellent enantioselectivities. Adduct **117**

was transformed into (-)-**4** and (-)-**69** using common synthetic procedures, in excellent yields and with high ee's.^[137]



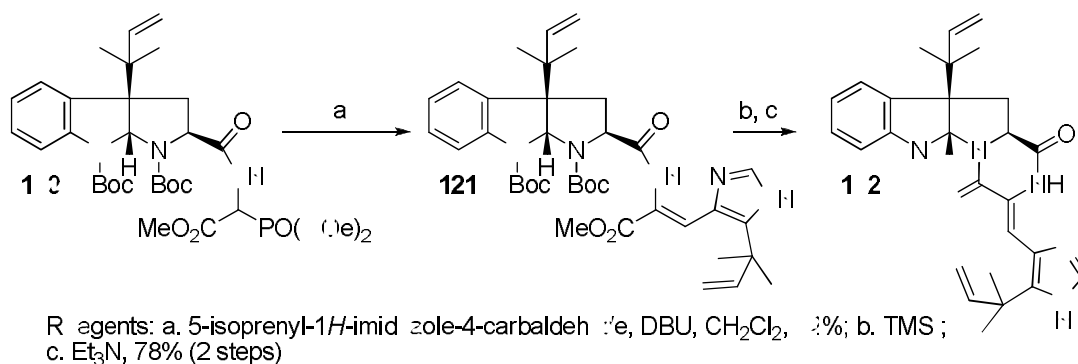
Reagents: a. propenal, **119**; b. NaBH₄, MeOH, 78%, 90% ee (2 steps); c. MsCl; d. NO₂PhSeCN, H₂O₂, 89% (2 steps); e. Grubbs metathesis, 2-methyl-2-butene, 94%; f. TMSI; g. NaBH₄, HCHO, 89% (2 steps); h. LiAlH₄, 91%

Scheme 15. Enantioselective syntheses of (-)-flustramine B (**4**) and (-)-debromoflustramine B (**69**)^[137]

A one-pot synthesis of (±)-deoxypseudophrynaminol^[138] was afforded with moderate yield from the commercially available *N*⁶-methyltryptamine by transformation into the corresponding Grignard reagent, followed by addition of 4-bromo-2-methyl-2-butene, the target in moderate yield.

Similar chemistry was recently exploited to synthesize isoroquefortine C and roquefortine C.^[139]

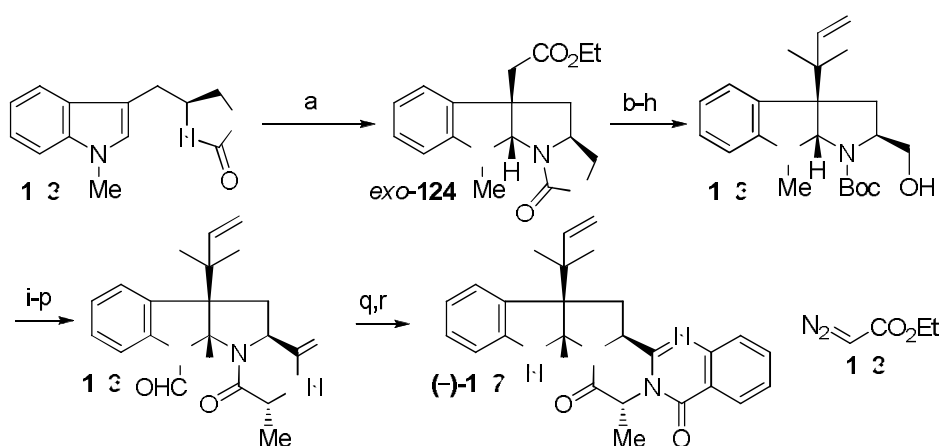
A slightly modified version of this strategy recently enabled preparation of isoroquefortine E (**122**).^[140] A Horner–Wadsworth–Emmons reaction was the key step to building the dehydroamino acid **121**, which was then underwent DKP formation (Scheme 16).



Reagents: a. 5-isoprenyl-1*H*-imidazole-4-carbaldehyde, DBU, CH₂Cl₂, 82%; b. TMSI; c. Et₃N, 78% (2 steps)

Scheme 16. Synthesis of isoroquefortine E (**122**)^[140]

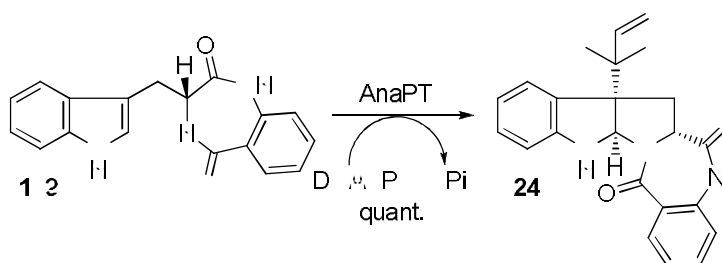
(-)-Ardeemin (**127**) and its *N*-acyl analogs have been synthesized from L-Trp in 20 steps in approximately 2% overall yield (Scheme 17).^[141] One-pot reaction of **123** with the diazoester **128** gave the chiral 3a-substituted HPI **124** containing the proper configuration in three stereocenters. (-)-**127** was prepared from the tetracyclic compound **124** via the following steps: transformation of the ethyl acetate substituent into the corresponding isoprenyl group, hydrolysis of the cyclic carbamate, and orthogonal protection of both amino groups to give **125**, which was converted into the DKP **126**. Finally, formation of the last benzopyrimidone condensed-ring by acylation with *o*-azidobenzoic anhydride followed by cyclization.



Reagents: a. **123**, Cu(OTf)₂, CH₂Cl₂, -5 °C, 82%; b. LDA, MeI, CH₂F₂, -78 °C to rt; c. LDA, MeI, CH₂F₂, -78 °C to rt, 72% (2 steps); d. LiBH₄, CH₂F₂, MeOH, 0 °C, 61%; e. DMP, CH₂Cl₂, rt, 92%; f. Ph₃PMel, LHMDS, CH₂F₂, -78 °C to rt, 3%; g. K^t-BuO, aq *t*-BuOH, quant.; h. (Boc)₂O, CH₂Cl₂, rt, 5%; i. DMP, CH₂Cl₂, rt, 92%; j. P₂C₅, CH₂Cl₂, rt, 76%; k. NaClO₂, NaH₂PO₄ buffer, rt, quant.; l. ClCO₂*i*-Bu, Et₃N, D-Ala-OMe, CH₂Cl₂, 0 °C, 81%; m. TMSI, MeCN, 0 °C, 3%; n. LiOH, aq. MeOH, 5%; o. ClCO₂*i*-Bu, Et₃N, CH₂Cl₂, 0 °C to rt, 71%; p. diastereomeric separation; q. *n*-BuLi, *o*-azidobenzoic anhydride, CH₂F₂, -78 °C, 2%; r. *n*-Bu₃P, benzene, rt, 3%

Scheme 17. Total synthesis of (-)-ardeemin (**127**)^[141]

Li *et al.* recently devised an innovative route to aszonalenin (**24**) and similar alkaloids structure. They employed the enzyme AnaPT, a prenyltransferase, to catalyze the prenylation of (*R*)-benzodiazepinedione **129** in the presence of dimethyl allyl diphosphate (DMAPP) to afford **24** (Scheme 18).^[142]



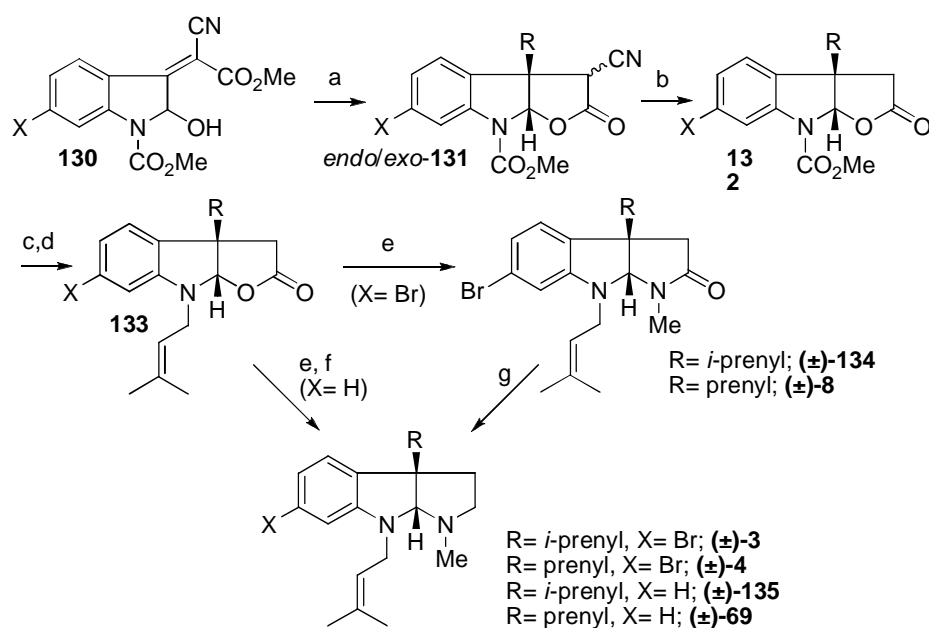
Scheme 18. Enzyme catalyzed synthesis of aszonalenin (**24**) by Li *et al.*^[142]

3.3.2. Cyclization with nucleophiles (B, Figure 5)

This procedure is based on a Michael addition of a nucleophile on the 3-position of 2-hydroxyindolin-3-ylideneacetate followed by *in situ* lactonization.

The Joseph-Nathan group devised total syntheses of (±)-flustramines A (**3**) and B (**4**), (±)-flustramides A (**134**) and B (**8**), and (±)-debromoflustramines A (**135**) and B (**69**) (Scheme 19).^[143,144] A conjugate addition of a prenylmagnesium bromide specie to 2-hydroxyindolenines **130** to give the C³-epimeric lactone **131**. Decyanation of the resulting α-cyano-γ-lactones with wet alumina in refluxing THF, followed by *N*-deprotection and allylation, gave compounds **133**, which, upon *N*-methyl insertion under the appropriate conditions, afforded the desired target natural compounds.

Same procedure was used by for the synthesis of dihydroflustramine C (**9**) and Flustramine E.^[145]



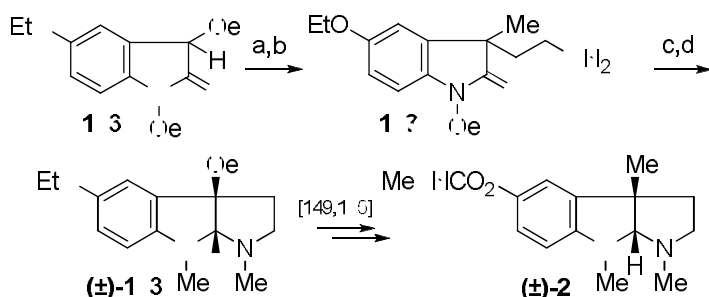
Scheme 19. Total syntheses of (±)-flustramines A (**3**) and B (**4**), (±)-flustramides A (**134**) and B (**8**), and (±)-debromoflustramines A (**135**) and B (**69**)^[144]

3.4. Successive alkylation cyclization of oxoindoles (C, Figure 5)

Pyrrolidine formation of HPIC from 2-oxoindoles consists in an enolate alkylation followed by N¹-C^{8a} reductive bond formation.

Julian and Pilk synthesized (±)-eserethole (**138**),^[146] based on their previous work on HPI assembly.^[147,148] Their approach was actually part of a formal synthesis of physostigmine (**2**).^[149-150]

The route shown in Scheme 20 comprises α -alkylation of the oxindole **136**, followed by reduction of the nitrile, *N*-methylation, and finally, reductive cyclization to give the racemic (\pm)-**138**.

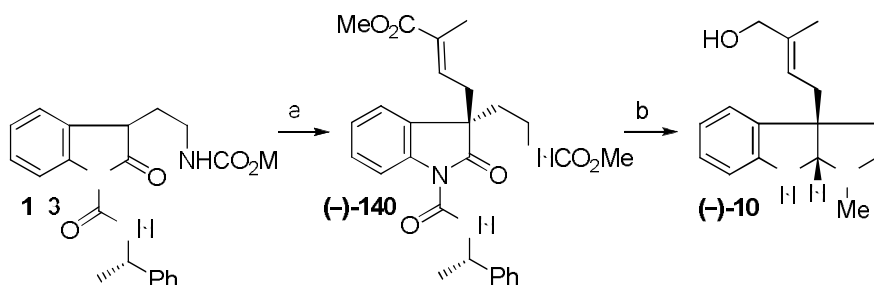


Reagents: a. ClCH_2CN , NaEtO (or Na), 84%; b. H_2 , Pd , 91%; c. PhCHO , then MeI followed by hydrolysis, 86%; d. Na , EtOH , 9%

Scheme 20. Synthesis of (\pm)-eserethole (**138**)^[146]

The Julian and Pilik procedure has been used extensively to prepare Calabar alkaloids. It has been modified to improve the oxindole preparation,^[151-160] adapted to the use of protecting groups,^[161-164] performed with chemical resolution of different intermediates,^[163,165-168] and combined with asymmetric alkylation of oxindole.^[169,170] Furthermore, a modified Julian and Pilik procedure has been used to prepare numerous analogs of physostigmine (**2**) and related alkaloids.^[166,171-175] A. Bossi reported an interesting version^[176] to prepare a 3-aminoethyloxindole from 5-methoxytryptamine.

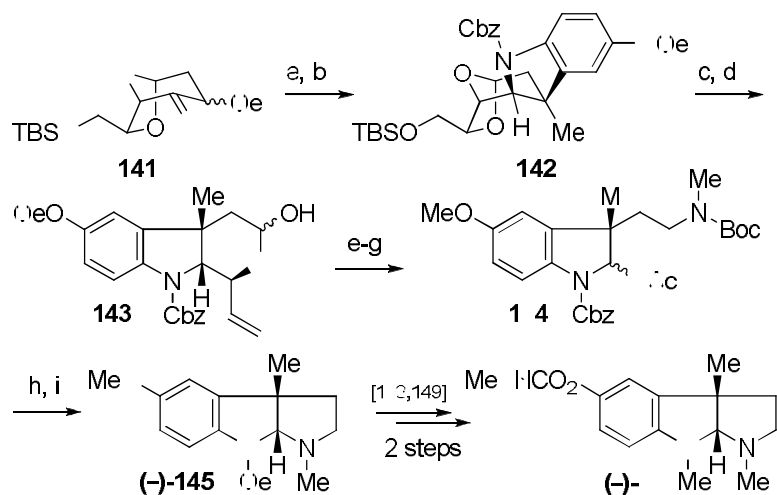
A total synthesis of (–)-pseudophrynaminol (**10**) based on diastereoselective α -alkylation of the chiral oxindole **139** with methyl 4-bromo-2-methylbut-2-enoate (Scheme 21) has been reported.^[177] The yield and diastereoselectivity of the process strongly depend on the solvent and base used. Separation of the two isomers, followed by reduction of (–)-**140** with LiAlH_4 , gave (–)-**10**. The 1-phenylethylcarbamoyl substituent on the oxindole nitrogen not only acts as a protecting group, but also as a prochiral group for asymmetric induction in the diastereoselective alkylation, enabling separation of diastereomer (–)-**140**. Moreover, this group is readily eliminated during reduction of the methyl ester and the carbamate.



Reagents: a. methyl 4-bromotiglate, NaMeO , MeOH , 0°C , 7%, 51% de; b. LiAlH_4 , dioxane, reflux, 76%

Scheme 21. Total synthesis of (–)-pseudophrynaminol (**10**)^[177]

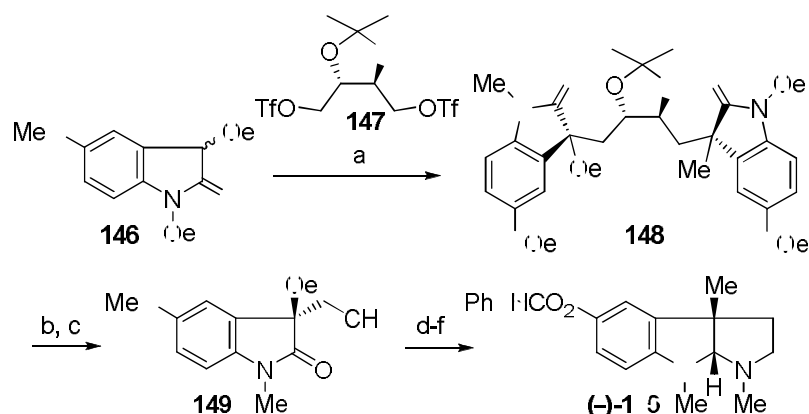
Identical final ring formation for the Calabar alkaloids (–)-physovenine and (–)-**2** was performed using a chiral building block for the diastereocontrolled construction of indoline **142**, a precursor of compound **144** (Scheme 22).^[132,178] The oxidation level of compound **144** obviates reduction after the cyclization to form the HPI skeleton.



Reagents: a. Ar-I-H₂-HCl, Pyr-H₂O (9:1), reflux; b. LiAlH₄, THF, 0° C then Cbz-Cl, aq. K₂CO₃, 70% (2 steps); c. TBAF, THF, 3%; d. Zn, AcOH-EtOH (1:9), 97%; e. Me-I-H₂-HCl, NaBH₃CN, MeOH, 0° C, 3%; f. Boc₂O, NaHCO₃, MeOH, 94%; g. Pb(OAc)₄, benzene, 60° C; h. 10% HCl, Et₂O, reflux, 3% (2 steps); i. H₂, 10% Pd-C, 36% HCHO, MeOH, 3%

Scheme 22. Synthesis of (–)-physostigmine (**2**)^[132,178]

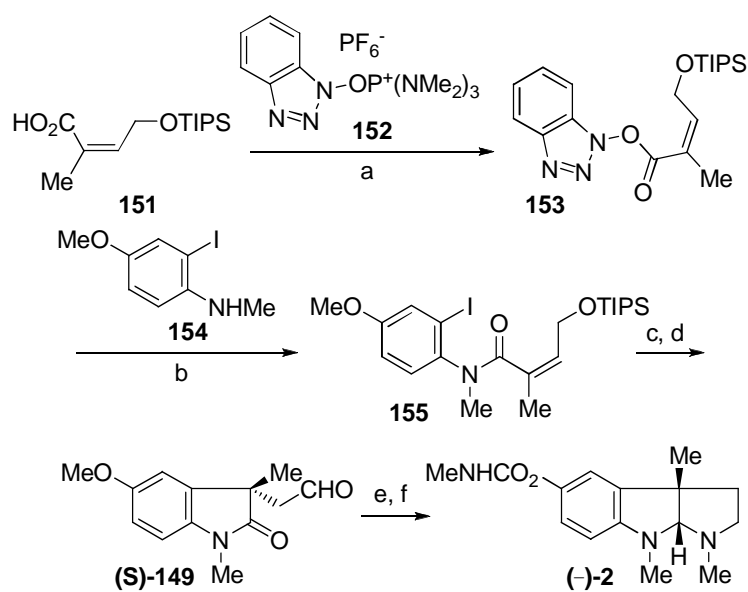
Hayashi employed a similar route oxindole alkylation in the total synthesis of CPC-1.^[179] Overman's group used the same cyclization strategy (D, Figure 5) for an elegant total synthesis of (–)-phenserine (**150**),^[180] in which alkylation of compound **146** with the chiral bistriflate **147** was the key step in the preparation of **149**, in excellent yield and with more than 99% ee (Scheme 23).



Reagents: a. KHMDs, THF-DMPU (3:2), -78° C, 70%; b. *p*-TsOH, MeOH, H₂O; c. NaIO₄, THF, H₂O, 92% (2 steps), > 99% ee; d. Me-I-H₂-HCl, LiAlH₄, MgSO₄, THF, 3%; e. Br₃, CH₂Cl₂, 91%; f. NaH, PhNCO, THF, 82%

Scheme 23. Total synthesis of (–)-phenserine (**150**) by Overman *et al.*^[180]

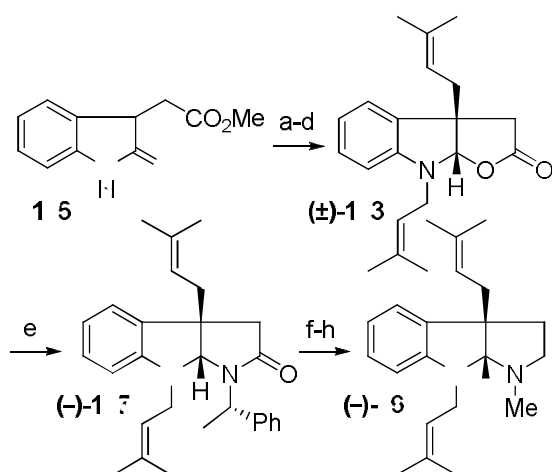
Same last steps (D, Figure 5) were used in an efficient route to either enantiomer of (–)-physostigmine **2**, and their respective congeners, is summarized in Scheme 24.^[181-183] It is based on versatile, asymmetric preparation of HPIs having carbon substituents at C^{3a}, starting from *Z*-butenoic acid **151** and *N*-methyl-*p*-anisidine **154**. The central step is catalytic asymmetric Heck cyclization of (*Z*)-2-methyl-2-butenanilide **155** to form oxindole aldehyde (*S*)-**149**. The same group later prepared several derivatives with aryl substituents at C^{3a} of the HPI.^[184]



Reagents: a. Et₃N, CH₂Cl₂, 23 °C; b. 60 °C, 67% (2 steps); c. 10% Pd₂(dba)₃·CHCl₃, 23% (s)-BINAP, PMP, DMA, 100 °C; d. 3M HCl, 23 °C, 84% (2 steps), 95% ee; e. MeNH₂·HCl, Et₃N, LiAlH₄, THF, reflux, 88%; f. BBr₃, CH₂Cl₂, 23 °C, then Na, Et₂O, MeNCO, 63%

Scheme 24. Asymmetric synthesis of (–)-physostigmine (**2**)^[183]

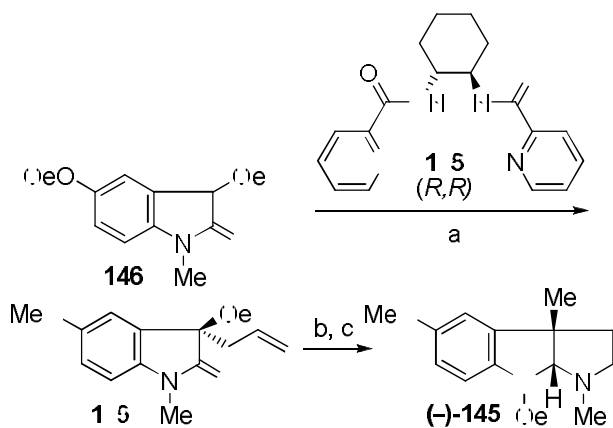
Joseph-Nathan synthesized (–)-debromoflustramine B **69** and its enantiomer *via* the racemic lactone **133** (Scheme 25). Reaction of **133** with (S)-1-phenylethylamine provided the diastereomeric lactams **157**, which were separated, then independently reacted with methylamine and reduced to provide the desired targets.^[185]



Reagents: a. prenyl bromide, 15% aq. NaOH, CH_2Cl_2 , TBAI, -5°C , 7%; b. 15% aq. NaOH, MeOH, $40-50^\circ\text{C}$, 87%; c. NaH, CH_2F_2 , rt; d. LiBHET_3 , CH_2F_2 , $25-30^\circ\text{C}$, 4% (2 steps); e. (*S*)-1-phenylethylamine, 5°C , then diastereomer separation, 3%; f. 5% aq. AcOH, benzene, sealed tube, 110°C , 3%; g. 40% aq. MeI_2 , MeOH, 3%; h. LiAlH_4 , CH_2F_2 , 9%

Scheme 25. Synthesis of (-)-debromoflustramine B (**69**)^[185]

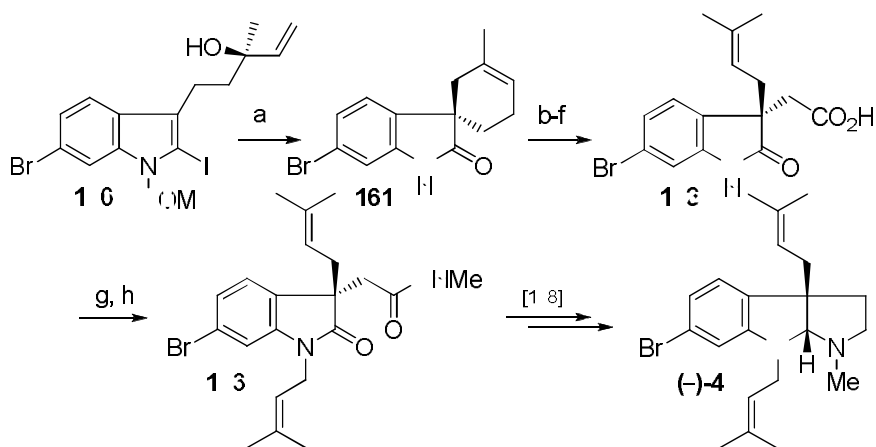
Trost described the earliest examples of molybdenum catalyzed enantioselective allylation of prochiral nucleophiles, reported an interesting route to (-)-esermethole (**145**) based on this chemistry (Scheme 26).^[186] Excellent yields and good-to-excellent enantioselectivities were obtained with a large variety of functionalities at the three positions of the starting oxindole **146**, which provided 3-allyloxindole **159** with 82% ee. Oxidation of the terminal double bond in **159** and reductive cyclization of the resulting aldehyde with methylamine afforded (-)-**145**.



Reagents: a. $\text{Mo}(\text{C}_7\text{H}_8)_3(\text{CO})_3$, $\text{Li}^t\text{-BuO}$, allyl *tert*-butyl carbonate, CH_2F_2 , 3%, 82% ee; b. OsO_4 , N_2 , NaIO_4 , CH_2F_2 , 92%, 82% ee; c. MeI_2 , Et_3N , LiAlH_4 , CH_2F_2 , reflux.

Scheme 26. Synthesis of (-)-esermethole (**145**) by enantioselective allylation of 2-oxindole by Trost^[186]

A total synthesis of (–)-flustramine B (**4**) starting from the spiro compound **161**, enantioselectively prepared *via* one-pot intramolecular Ullmann coupling and Claisen rearrangement of the iodindole **160**, has been reported (Scheme 27).^[187] Compound **161** into **162** was transformed by double-bond oxidation, Wittig reaction and isomerization. *N*-prenylation of the resulting product, and subsequent N¹-C^{8a} bond formation, yielded (–)-**4**.^[188]



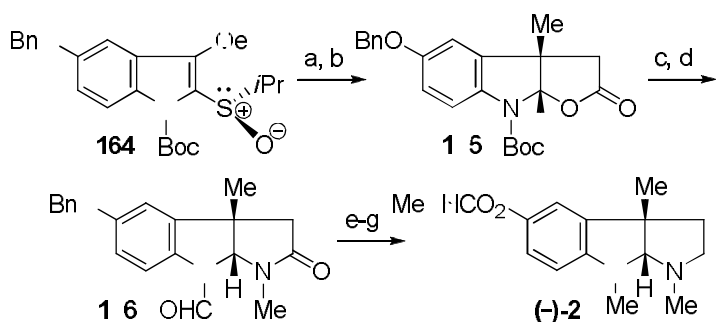
Reagents: a. CuCl, 2-amino pyridine, NaMeO, MeOH, triglyme, 100 °C, 69%; b. OsO₄, NMO, acetone, H₂O, rt; c. NaIO₄, CH₂F₂, H₂O, rt; d. NaClO₂, NaH₂PO₄·2H₂O, 2-methyl-2-butene, *t*-BuOH, H₂O, CH₂F₂, rt, 84% (3 steps); e. Ph₃PMeBr, *n*-BuLi, CH₂F₂, -25 °C to rt; f. H₂SO₄, then MgSO₄, 1,4-dioxane, 60 °C; g. prenyl bromide, K₂CO₃, acetone, reflux, 18% (3 steps); h. aq. MeI₂, MeOH, rt, 75%.

Scheme 27. Total synthesis of (–)-flustramine B (**4**)^[187]

3.5. Synthesis of HPI system by rearrangements processes

3.5.1. [3.3]-Sigmatropic rearrangements (E, F, G, Figure 5)

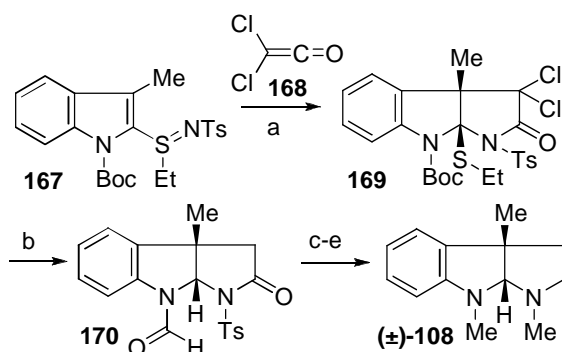
Marino *et al.* showed that 2-(methylsulfinyl)indole reacts with dichloroketene to produce a lactone^[189] useful for assembling an HPI core. The same group later established that lactonization of chiral vinyl sulfoxides with dichloroketene occurs with complete control of the relative and absolute configurations. They employed a then new class of sulfoxylating agents, *N*-(alkylsulfinyl)oxazolidinones, to prepare the starting chiral indolyl sulfoxide. They reported that the size of the alkyl group on the sulfoxide positively correlates with the degree of asymmetric induction.^[190] Lactonization of isopropyl indolyl sulfoxide **164**, followed by desulfonylation and dechlorination, gave **165** (in good enantiomeric excess), which was then transformed into (–)-**2** (Scheme 28).



Reagents: a. Zn/CuCl, Cl₃COCl, -78 °C; b. *n*-Bu₃SnH, AIBN, toluene, reflux, 37% (2 steps); c. HCO₂H, then MeCO₂CHO, 94%; d. MeI, -30 °C to rt, then H₂SO₄ cat., DMF, 15 °C, 68%; e. BH₃·THF, 0 °C to reflux, 43%; f. Ni-Raney (W2), -78 °C, reflux; g. Na cat., MeNCO, 60% (2 steps)

Scheme 28. Enantioselective synthesis of (-)-physostigmine (**2**)^[190]

A close procedure (E, Figure 5) was developed by Padwa for the synthesis of (±)-desoxyeseroline (**108**) using an efficient route to highly functionalized γ -lactams (Scheme 29).^[191] This route comprised reaction of the indolyl sulfylimine **167** with the highly electrophilic dichloroketene to generate a zwitterionic intermediate. Subsequent [3,3]-sigmatropic rearrangement, followed by intramolecular trapping of the Pummerer cation by the amido anion, furnished the γ -lactam product **169** in good yield. Reduction of this compound with Zn and AcOH, followed by treatment with HCO₂H, provided **170**. Removal of the *N*-tosyl group, followed by *N*-methylation and subsequent reduction of the lactam and the formamide, afforded (±)-**108** in good total yield.



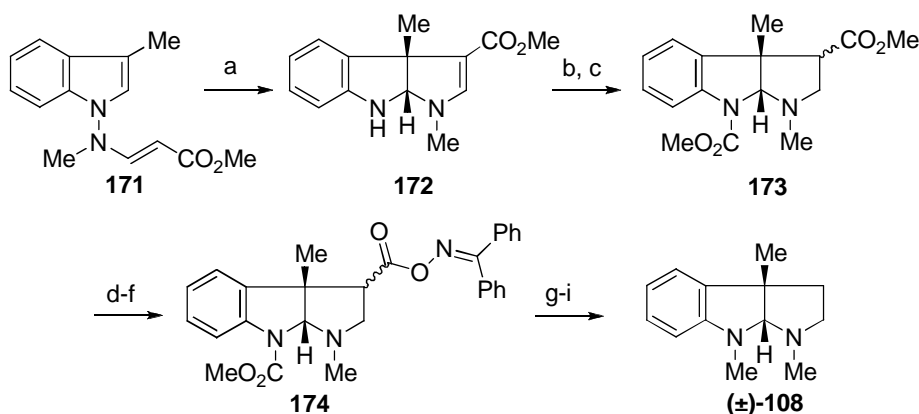
Reagents: a. Zn-Cu, THF, Cl₃CCOCl, 78%; b. Zn, AcOH, TMEDA, EtOH, then HCO₂H, 72%; c. Na, naphthalene, THF, 81%; d. MeI, NaH, THF, 87%; e. BH₃·THF, THF, 80%

Scheme 29. Synthesis of (±)-desoxyeseroline (**108**)^[191]

A formal synthesis of (±)-physostigmine (**2**) via 3,3-rearrangement of a bis-enamine was described by Lobo, Prabhakar *et al.*^[192,193]

(±)-Desoxyeseroline (**108**) was obtained via [3,3]-sigmatropic rearrangement of the *N*-methylvinylamino skeleton of **171** (F, Figure 5). Thermolysis of the enaminoester **171** in *o*-

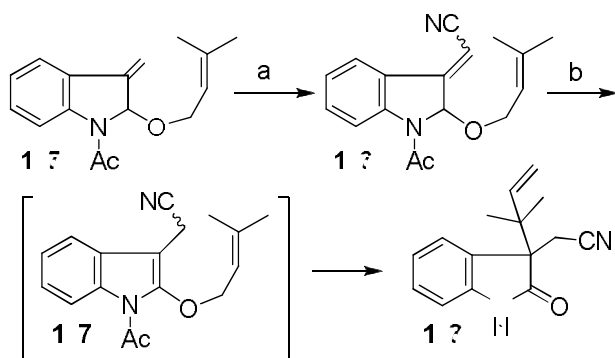
dichlorobenzene gave the tricyclic compound **172** in excellent yield. Compound **172** was easily transformed into the carbamate **173** by a two-step sequence of *N*-methoxycarbonylation and catalytic hydrogenation. The best conditions they found for removing the carboxylic ester at C³ comprised irradiation of the benzophenone oxime ester **174** in a THF-*i*-PrOH mixture containing a large excess of *tert*-butylthiol (Scheme 30).



Reagents: a. *o*-Cl₂C₆H₄, reflux, 91%; b. ClCO₂Me, DMAP, Et₂O, 0 °C to rt, 81%; c. H₂, PtO₂, MeOH, 45 psi, 93%; d. aq. NaOH, MeOH, reflux; e. ClCO₂*i*-Bu, THF, -20 °C; f. Ph₂C=NOH, Et₃N, 75% (3 steps); g. hv, *i*-PrOH, THF, *t*-BuSH, 92%; h. LiAlH₄, THF, reflux, 69%; i. aq. HCHO, NaBH₃CN, 67%

Scheme 30. Synthesis of (±)-desoxyeseroline (**108**) via [3,3]-sigmatropic rearrangement^[193]

There is a utile route to 3-allyl-3-cyanomethylindolin-2-ones which is also amenable to prepare structurally diverse libraries of 3a-allyl-HPI that is based on domino reactions of 2-allyloxyindolin-3-ones of the type **175** (Scheme 31).^[194,195] The process comprises olefination, isomerization, Claisen rearrangement, and deacetylation to give 3-allyl-3-cyanomethylindolin-2-ones of the type **178**. Reductive cyclization enabled preparation of 3a-allyl-HPI-containing alkaloids (G, Figure 5).

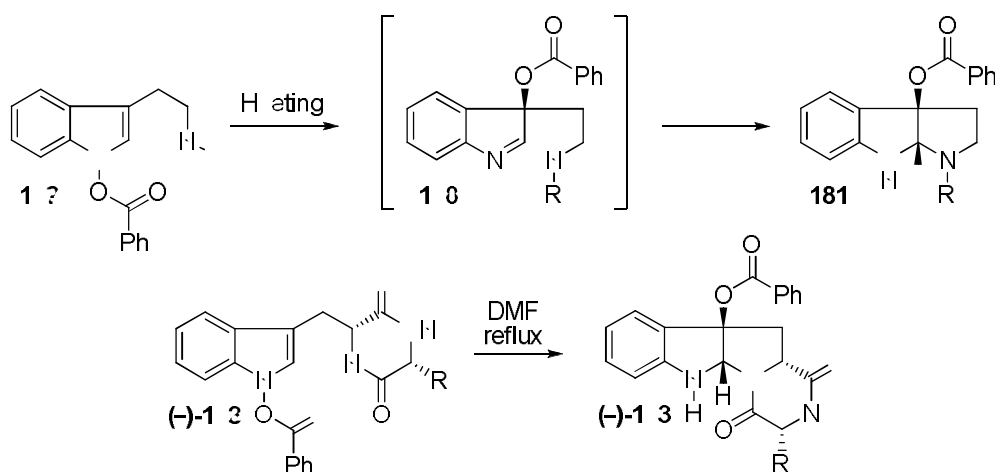


Reagents: a. Ph₃P=CHCN, toluene, reflux, 70%; b. DBU, 0 °C, 7%

Scheme 31. Synthesis of 3-allyl-3-cyanomethylindolin-2-one **178**^[195]

(±)-Flustramines A (**3**) and C, (±)-flustramide A, and (+)- and (-)-debromoflustramine A were ultimately obtained by this route.^[196]

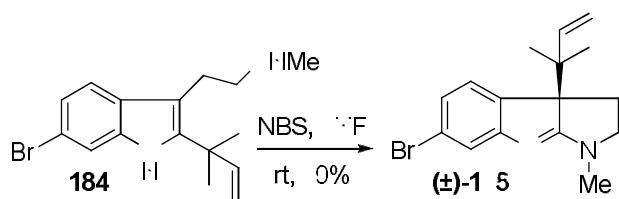
While studying nucleophilic substitution in indoles, the Somei group reacted *N*-methoxyindole derivatives with alkoxides to obtain useful route for the synthesis of (\pm)-debromoflustramine B (**69**).^[197] Further studies of the same authors conducted to the synthesis of 3a-oxygenated HPI C^[198,199] by a rearrangement of the 1-benzoyloxy group of tryptamine **179** followed by cyclization to give the tricyclic system **181** (F, Figure 5). The stereoselectivity of the process was demonstrated by heating ($-$)-**182** in refluxing DMF to produce ($-$)-**183** as the sole product. (Scheme 32)



Scheme 32. Somei's synthesis of 3a-oxygenated HPI **183**^[198]

3.5.2. [1.2]-Rearrangements

(\pm)-Flustramine C (**185**) was synthesized in five steps starting from *N*^b-methyltryptamine. The key step was biomimetic oxidation of the natural product deformylflustrabromine (**184**), causing selective [1.2]-rearrangement of the inverse isoprenyl group and simultaneous cyclization (Scheme 33).^[200]



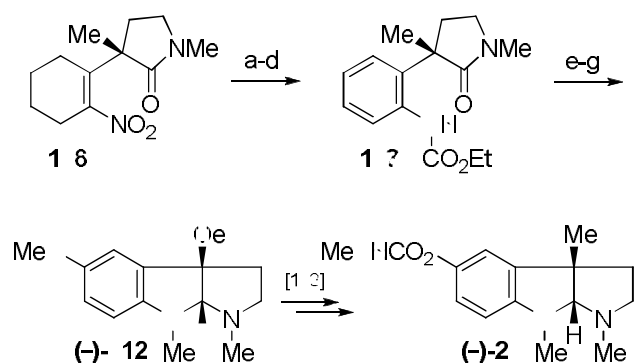
Scheme 33. Synthesis of flustramine C (**185**)^[200]

3.6. Formation of HPI by elaboration of indole heterocyclic ring

3.6.1 Reductive cyclization (H, Figure 5)

A formal total synthesis of ($-$)-physostigmine **2** was accomplished from the chiral nitro olefin **186** (Scheme 34) and stereochemistry of the product was confirmed.^[131] Aromatization of cyclohexene, reduction of the nitro group, and subsequent aniline protection gave **187**, which was submitted to

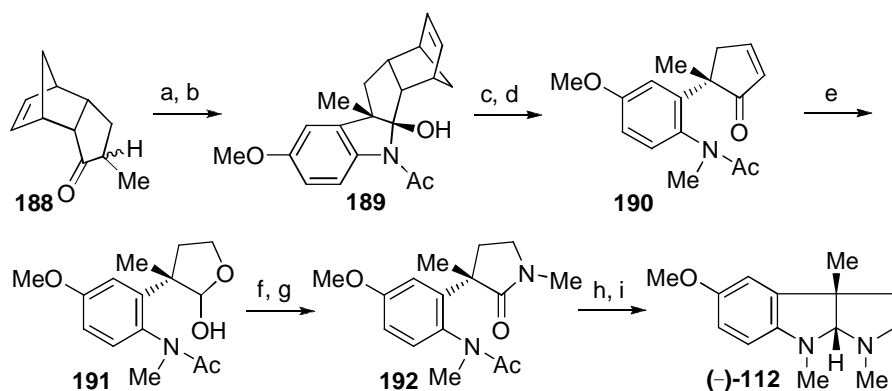
reductive cyclization. Bromination of the aromatic ring, followed by copper-catalyzed methoxy-bromine exchange afforded (–)-esermethole (**112**), which was later converted to (–)-physostigmine. This work constituted the first total synthesis of (–)-**2**.^[132]



Reagents: a. Br₂, K₂CO₃, 3%; b. K₂CO₃, DMSO; c. H₂, PtO₂; d. ClCO₂Et, 29% (3 steps); e. LiAlH₄; f. NBS, 5% (2 steps); g. NaMeO/ CuI, 5%

Scheme 34. Synthesis of (–)-esermethole (**112**)^[131]

(–)-Physovenine and (–)-**2** were enantioselectively synthesized from the optically active enone **188**, which was first transformed into the enone **190** via Fischer indolization and retro Diels Alder chemistries.^[201] Oxidation of **190** to the lactam **192**, followed by reductive cyclization, gave (–)-esermethole (**112**) (Scheme 35). The product was subsequently transformed into (–)-physostigmine via (–)-eseroline in two steps as had previously been described.^[132] The Takano group used the same route to assemble the non-naturally occurring (+)-**2**.^[202]

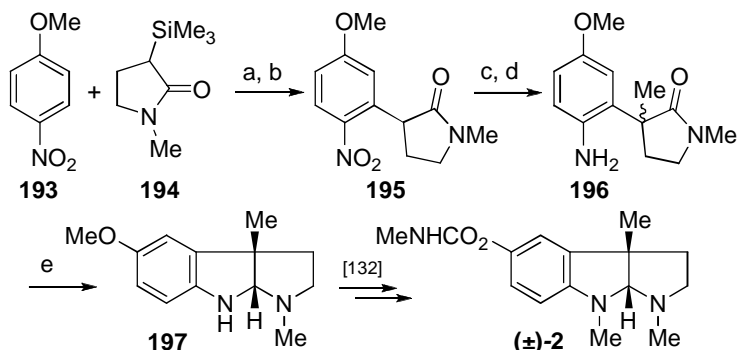


Reagents: a. *p*-MeOC₆H₄NHNH₂·HCl, aq. Pyr (1:10), reflux, 82%; b. Ac₂O, Pyr; c. NaH, MeI, DMF-THF (1:1), 86% (2 steps); d. *o*-Cl₂C₆H₄, reflux, 66%; e. O₃, MeOH, then NaBH₄, -78 °C to rt, 10% HCl then NaIO₄, 62%; f. Ag₂CO₃ on celite, benzene, reflux, 88%; g. 40% aq. MeNH₂, sealed tube, 180°C, 76%; h. *i*-Bu₂AlH, CH₂Cl₂, -78 °C, then NH₄OH; i. LiAlH₄, THF, reflux, 34% (2 steps)

Scheme 35. Enantiocontrolled total syntheses of (–)-esermethole (**112**)^[201]

An efficient formal total synthesis of (±)-physostigmine (**2**) in which a new Vicarious nucleophilic substitution reaction between *p*-nitroanisole and a *C*-silylated derivative of *N*-methylpyrrolidinone was exploited to give **195**.^[203] α -Methylation and reductive cyclization of **195** provided the key

intermediate *N*-demethylesermethole (**197**) in high yield, which was transformed into the (\pm)-**2** as had previously been described (Scheme 36).^[132]

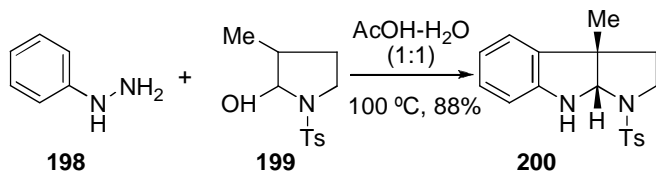


Reagents: a. TASF, THF, -78 °C to rt; b. DDQ, 85% (2 steps); c. MeI, CsOH·H₂O, CH₃Ph, TBAB, rt, 94%; d. H₂, 10% Pd/C, EtOAc, 50 psi, quant. e. LiAlH₄, THF, 60%

Scheme 36. Formal total synthesis of (\pm)-physostigmine (**2**)^[203]

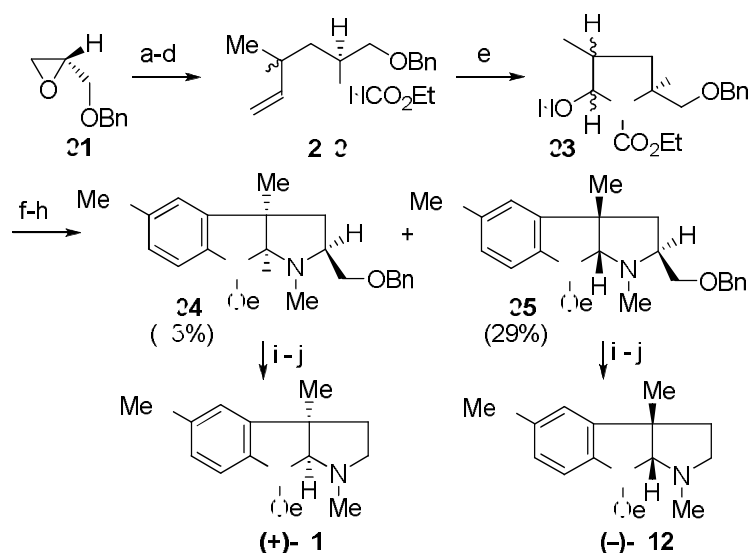
3.6.2. Fischer Indole Synthesis (I, Figure 5)

An efficient method of preparation of HPI system involves the condensation of hydrazines with latent aldehydes to deliver indoline-containing products (Scheme 37) following an interrupted Fischer indolization sequence.^[204] This approach amenable to complex targets was applied with good to excellent yields to several examples.



Scheme 37. Preparation of HPI by Fischer indolization^[204]

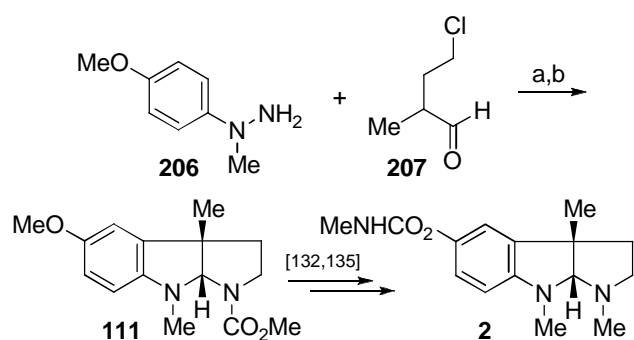
A chiral synthetic route to both enantiomers of esermethole (**112**) was established starting from (*S*)-*O*-benzylglycidol (**201**),^[205] which provided a diastereomeric mixture of hemiacetals **203** in excellent yield (Scheme 38). Fischer indolization of **203** with 4-methoxyphenylhydrazine hydrochloride, followed by dimethylation, gave the HPI derivatives **204** and **205**, which were readily separated. Compounds **204** and **205** were transformed into (+)-**112** and (–)-**112**, respectively, *via* the following sequence: *O*-debenzylation under Birch conditions; removal of the hydroxymethyl group by Swern oxidation of the alcohol; transformation of the resulting aldehyde into a cyanide; and finally, reductive elimination of cyanide from the formed α -aminonitrile.



Reagents: a. $\text{MeCH}=\text{CHCH}_2\text{MgCl}$, $-\text{78}^\circ\text{C}$, 90%; b. phthalimide, Ph_3C , DIAD; c. H_2 , H_2 - H_2O , EtOH, reflux; d. ClCO_2Et , Et_3N , CH_2Cl_2 , 7% (3 steps); e. 2% mol OsO_4 , NaIO_4 , $-\text{78}^\circ\text{C}$ - H_2O (2:1), then NaIO_4 , $-\text{78}^\circ\text{C}$, H_2O , 94%; f. $p\text{-MeOC}_6\text{H}_4\text{NH}_2$, H_2 - HCl , Pyr, reflux, 5%; g. 5% HCHO , NaBH_3CN , MeOH; h. LiAlH_4 , $-\text{78}^\circ\text{C}$, reflux; i. NaOAc , H_3 , 92%-quant.; j. $(\text{COCl})_2$, DMSO, Et_3N , CH_2Cl_2 , then N -methyl- O -sulfonic acid, then NaBH_4 , EtOH, reflux, 2-25%

Scheme 38. Synthesis of (+)- and (-)-esermethole (**112**)^[205]

Nishida *et al.* devised an efficient formal synthesis of physostigmine (**2**) whose key step is a modified Fischer indole synthesis using *N*-methyl-*N*-(*p*-methoxyphenyl)hydrazine and the aldehyde **207** (Scheme 39).^[206] Transformation of **111** into **2** had been previously described.^[135] The authors later made this chemistry enantioselective by using chiral hydrazines, which they readily prepared from commercially available chiral amines.^[207]

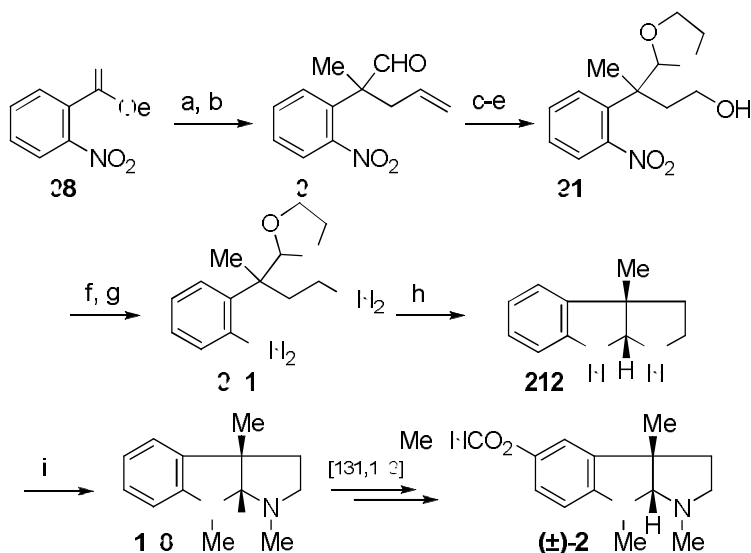


Reagents: a. MeOH, reflux; b. ClCO_2Me , Na_2CO_3 , CH_2Cl_2 , H_2O , 0°C to rt, 80% (2 steps)

Scheme 39. Synthesis of HPI by modified Fischer indole synthesis^[206]

3.7. Synthesis of HPI by simultaneous formation of $\text{N}^1\text{-C}^{8a}$ and $\text{N}^8\text{-C}^{8a}$ bonds (J, Figure 5)

Kulkarni *et al.* recently reported a novel total synthesis of (\pm)-**2** (Scheme 40).^[208] Wittig olefination and posterior Claisen rearrangement of *o*-nitroacetophenone afforded the aldehyde **209**. Protection of the formyl group, oxidation of the double bond, and reduction of the aldehyde in the resulting intermediate afforded the cyclic acetal **210**. Functional group transformation of **210** gave the diamine **211**, whose acetal was hydrolyzed with *p*-TSA to furnish the HPI **212**. Finally, bis-*N*-methylation of **212** and introduction of carbamate on position 5 following a literature protocol^[131] yielded (\pm)-**2**.

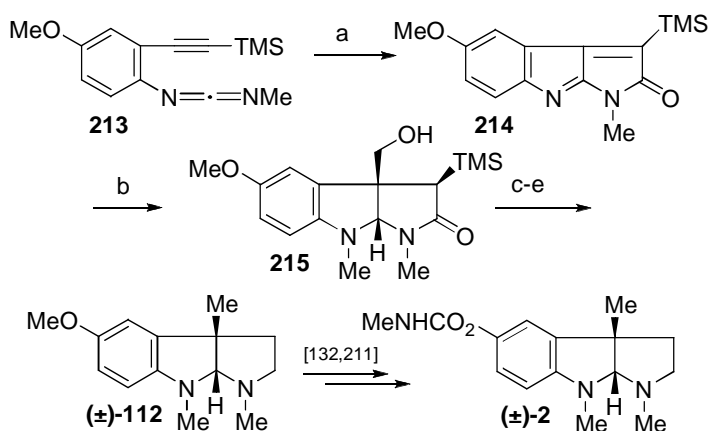


Reagents: a. $\text{CH}_2=\text{CHCH}_2\text{OCH}_2\text{Ph}_3\text{Cl}$, $\text{Na}^+\text{t-BuO}^-$, CH_2F_2 , 0°C ; b. xylene, reflux, 5% (2 steps); c. *p*-TSA, ethylene glycol, toluene, reflux; d. O_3 , SMe_2 , CH_2Cl_2 , 0°C , 8% (2 steps); e. NaBH_4 , aq. CH_2F_2 , 92%; f. DIAD, Ph_3N , phthalimide, CH_3I , H_2 , reflux, 68%; g. Ni-Raney, H_2 , MeOH, 82%; h. *p*-TSA, aq. CH_2F_2 , reflux, 65%; i. aq. HCHO, 10% Pd-C, Et₃N, H_2 , 0°C

Scheme 40. Synthesis of (\pm)-physostigmine (**2**) by Kulkarni *et al.*^[208]

3.8. Aza-Pauson-Khand cyclocarbonylation (K, Figure 5)

(\pm)-Physostigmine **2** has also been synthesized by subjecting an alkynecarbodiimide to an APKR with $\text{Co}_2(\text{CO})_8$ as catalyst (Scheme 41).^[209,210] Under $\text{Co}_2(\text{CO})_8$ -catalyzed cyclocarbonylation conditions, the carbodiimide **213** was transformed into the pyrrolo[2,3-*b*]indol-2-one **214**. One-pot reduction, hydroxymethylation, and *N*-methylation of **214** gave **215** as a single stereoisomer in good yield. Removal of the TMS and hydroxyl groups in **215**, followed by reduction of the resulting lactam, gave (\pm)-esermethole **112** in high yields.



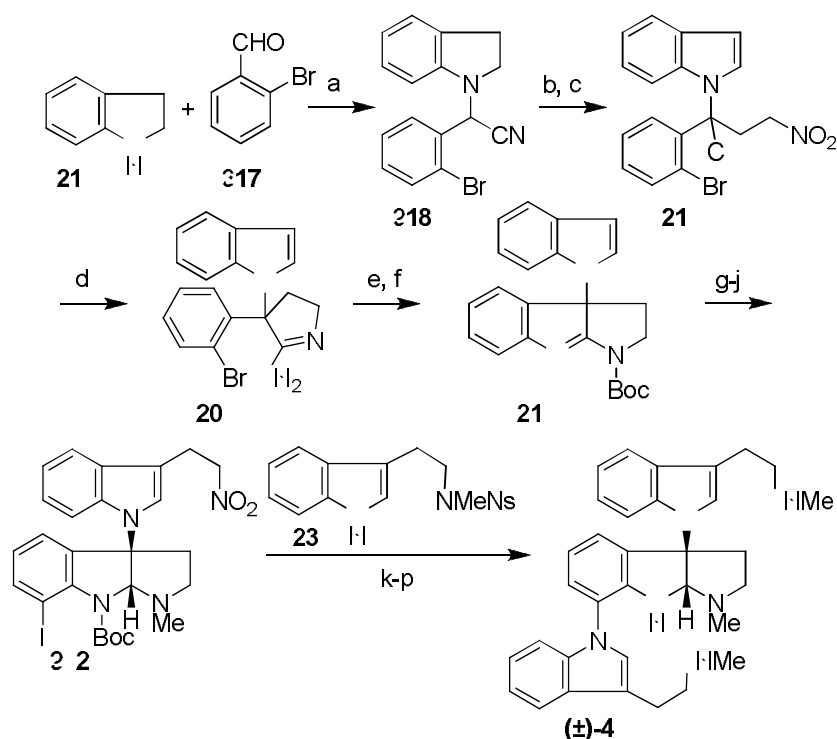
Reagents: a. $\text{Co}_2(\text{CO})_8$, TMTU, benzene, CO (1 atm), 70 °C, 55%; b. NaCNBH_3 , aq. HCHO, AcOH, MeCN, 0 °C, 79%; c. TBAF, THF, reflux, 96%; d. I_2 , PPh_3 , imidazole, CHCl_3 , reflux, 78%; e. LiAlH_4 , THF, reflux, 83%

Scheme 41. Formal synthesis of (±)-physostigmine (**2**) by aza-Pauson-Khand formation of HPI^[210]

(±)-Flustramine B (**4**), (±)-debromoflustramine B (**69**), (±)-debromoflustramide B, (±)-debromoflustramine E, (±)-flustramine E and (±)-debromoflustramide E were prepared^[210] from pyrrolo[2,3-*b*]indol-2-ones *via* APKR of alkynecarbodiimides.

3.9. Synthesis of natural products containing a $N^{\text{ind}}\text{-C}^{3a}$ bond

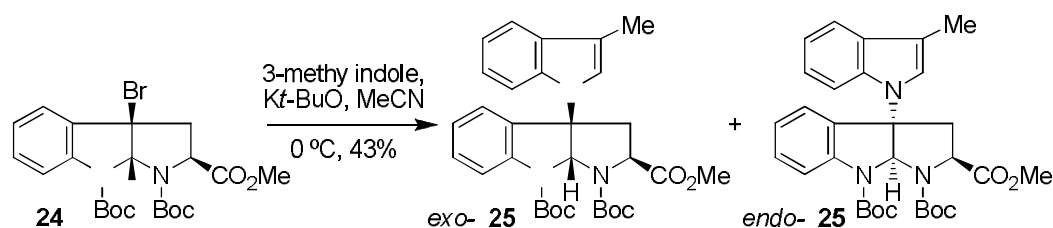
Takayama *et al.* were the first to synthesize a natural product containing a $N^{\text{ind}}\text{-C}^{3a}$ bond characteristic of psychotrimine (**49**).^[212] In fact, the $N^{\text{ind}}\text{-C}^{3a}$ bond was the first bond formed in their sequence (Scheme 42), *via* Strecker reaction of 2-bromobenzaldehyde and indoline to give **218**. Introduction of a nitro-chain alpha to the cyano group of **218**, and oxidation of the indoline, gave compound **219**, containing all the atoms needed for elegant construction of 3a-indolyl-HPI **221**. Reduction of the nitro group in **219** gave the primary amine, which spontaneously cyclized to amidine **220**, whose pyrrolidine nitrogen was then Boc-protected. Finally, copper-mediated intramolecular amination afforded **221**, which was then transformed into **222** via reduction of the Boc-protecting group to methyl, protection of N^{β} , regioselective iodination, and lastly, introduction of nitroethyl at position 3 of the indole. Finally, conversion of the nitro group in **222** into the NMe, followed by copper mediated intermolecular coupling of iodide **222** with tryptamine **223** and subsequent deprotection afforded **49**.



Reagents: a. KCN, aq HCl, MeCN, rt, 92%; b. 1-IMDS, CH₂=CH-IO₂, MeCN, -78 °C; c. DQ, 1,4-dioxane, 0 °C, 90% (2 steps); d. Fe powder, aq HCl, EtOH, reflux; e. Boc₂O, *i*-Pr₂NEt, MeCN, rt, 88% (2 steps); f. CuI, K₃PO₄, DMSO, 0 °C, 91%; g. Red-Al, toluene, 0 to 0 °C, 60%; h. 1-IMDS, Boc₂O, MeCN, -78 to 0 °C; i. *s*-BuLi, TMEDA, I₂, MeCN, -78 to 0 °C, 87% (2 steps); j. InBr₃, CH₂=CH-IO₂, CH₂Cl₂, rt, 86%; k. Fe powder, AcOH, EtOH, dioxane, reflux; l. NsCl, Et₃N, CH₂Cl₂, rt, 93% (2 steps); m. DBU, Me₂SO, DMF, 0 °C, 94%; n. TMSOTf, 2,6-lutidine, CH₂Cl₂, 0 °C to rt, 87%; o. **23**, CuI, K₃PO₄, *N,N'*-dimethylethylenediamine, 1,4-dioxane, 0 °C, 77%; p. Ph-Si, Cs₂CO₃, MeCN, rt, 81%

Scheme 42. Synthesis of (±)-psychotrimine (**49**) by Takayama *et al.*^[212]

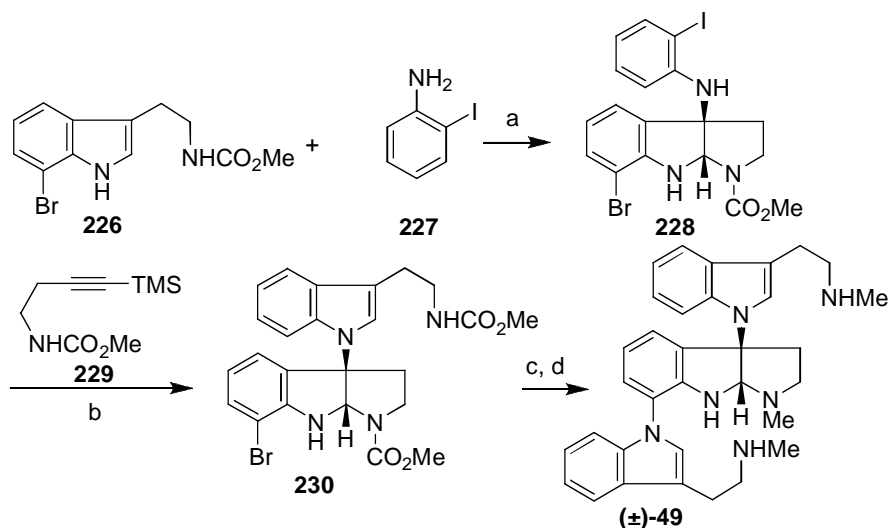
Rainier and Espejo described an alternate strategy to *N*^{ind}-C^{3a} bond formation: reaction of an 3a-bromo-HPIC and an indole derivative.^[213] Compound **224** was subjected to base-catalyzed nucleophilic substitution with indole derivatives, yielding a mixture of diastereomers in which the *endo* product was predominant (Scheme 43).



Scheme 43. Synthesis of 3a-indolyl-HPIC by Rainier and Espejo^[213]

Baran *et al.* prepared psychotrimine (**49**) *via* an elegant synthesis based on the simultaneous formation of the tricyclic system of HPI and the *N*-C^{3a} bond (Scheme 44).^[214] The starting material was bromotryptamine **226**, which was reacted with NIS and 2-iodoaniline to form HPI derivative

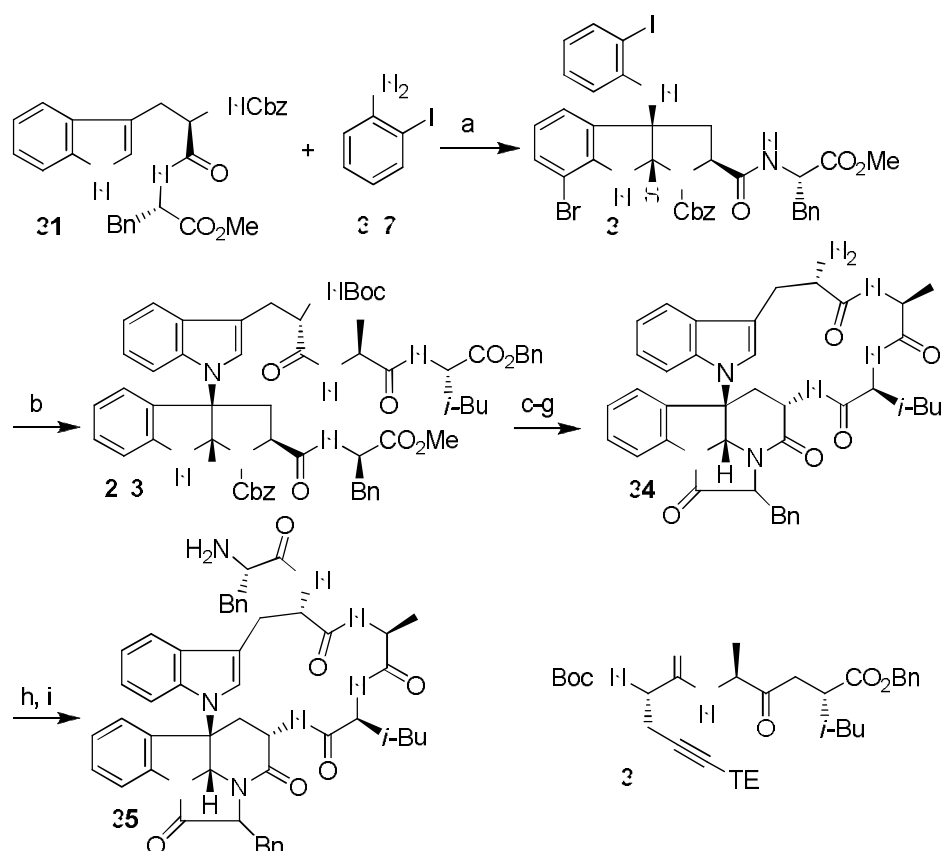
228. Chemoselective Larock annulation^[215] between **228** and an alkyne afforded **230**. Transformation of **230** into (\pm)-**49** follows a similar procedure as that detailed in Scheme 42.



Reagents: a. NIS, Et₃N, MeCN, -45 to 23 °C, 61-67%; b. Pd(OAc)₂, Na₂CO₃, LiCl, DMF, 102 °C, 85%; c. CuI, (\pm)-*trans*-*N,N'*-dimethyl-1,2-cyclohexanediamine, K₂CO₃, *N*^b-(methoxycarbonyl)tryptamine, 1,4-dioxane, 101 °C, 89%; d. Red-Al, toluene, 110 °C, 89%

Scheme 44. Synthesis of (\pm)-psychotrimine (**49**) by Baran *et al.*^[214]

Recently, Baran *et al.* employed a similar strategy to synthesize kapakahines B (**235**) and F (**234**) (Scheme 49).^[216] Reaction of the dipeptide **231** with *o*-iodoaniline and NIS under simultaneous cyclization-amination gave compound **232**. Larock annulation of **232** with the tripeptide **236** gave **233**. Interestingly, the HPIC-opening in this synthesis occurs after the Cbz elimination and the new double-ring closure, to give the α -carboline condensed to an imidazolidinone unit characteristic of kapakahines.



Reagents: a. NIS, MeCN, -45 to -5 °C, 65%; b. Pd(OAc)₂, NaOAc, LiCl, **36**, DMF, 10 °C, 49%; c. 10% Pd/C, H₂, MeOH; d. EDC, HOAt, CH₂Cl₂-DMF (20:1), 70% (2 steps); e. LiOH, HF/H₂O/MeOH; f. (COCl)₂, Et₃N, CH₂Cl₂; g. TFA/CH₂Cl₂ (1:10), 70% (3 steps); h. Boc-Phe-OH, EDC, HOBT, Et₃N, CH₂Cl₂; i. TFA/CH₂Cl₂ (1:10), 81% (2 steps)

Scheme 45. Synthesis of kapakahines B (**235**) and F (**234**) by Baran *et al.*^[216]

4. Summary and Outlook

Since the isolation of physostigmine in 1864, many natural products containing HPI and HPIC have been isolated, above all in the past few decades. Furthermore, a new characteristic trait has been reported in some recently isolated natural products: a bond between the C^{3a} of the HPI or HPIC and the Nnd of a tryptamine or Trp. Some of these compounds are macrocyclic peptides, which contain both the HPIC and the Trp in the peptide chain.

This report has covered synthetic routes to natural products containing one or more HPI and/or HPIC units. The smallest and simplest of these compounds have been prepared via classical indole chemistry, whereas the larger, more complex structures have inspired new synthetic methodologies that exploit a full arsenal of transformations, including oxidative cyclization, Pd-catalyzed reactions as Larock annulations, and enzyme-catalyzed reactions between others. Researchers will undoubtedly harness this new chemistry to further advance work on natural products containing HPICs and/or HPICs.

Many of these natural products present a wide range of biological activities, encompassing acyl-CoA inhibitors, neuropeptide neurotransmitter antagonists, topoisomerase inhibitors, and antibiotics. Thus, it is easy to envisage that in a near future, some of these natural products or their analogs will enter into clinical trials, which will require the need of having bigger quantities. The synthetic routes described in this review should be the base for developing industrial strategies required for these natural products be considered as potential drugs.

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Abbreviations

Ac	acyl
AcOH	acetic acid
AIBN	azobisisobutyronitrile
Anth	9-anthracenyl
APKR	aza-Pauson-Khand reaction
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
BOP	(benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate
BTMAB	benzyltrimethylammonium tribromide
Cbz	benzyloxycarbonyl
mCPBA	<i>m</i> -chloroperbenzoic acid
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
de	diastereomeric excess
DIAD	diisopropyl azodicarboxylate
DIEA	<i>N,N</i> -diisopropylethylamine
DKP	diketopiperazine
DMA	<i>N,N</i> -dimethylacetamide
DMAP	4-dimethylaminopyridine
DMAPP	dimethyl allyl diphosphate
DMDO	2,2-dimethyldioxirane
DMF	<i>N,N</i> -dimethylformamide
DMP	Dess-Martin periodinane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	dimethyl sulfoxide
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	enantiomeric excess
Fmoc	9 <i>H</i> -fluoren-9-ylmethoxycarbonyl
HATU	2-(7-aza-1 <i>H</i> -benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HOAt	1-hydroxy-7-azabenzotriazole
HOBt	1-hydroxybenzotriazole

HPI	hexahydropyrrolo[2,3- <i>b</i>]indole
HPIC	hexahydropyrrolo[2,3- <i>b</i>]indole-2-carboxylate or –carboxamide
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
MOM	methoxymethyl
MTAD	<i>N</i> -methyl-1,3,4-triazoline-2,5-dione
NBS	<i>N</i> -bromosuccinimide
NCS	<i>N</i> -chlorosuccinimide
NHMDS	sodium bis(trimethylsilyl)amide
NIS	<i>N</i> -iodosuccinimide
NMO	<i>N</i> -methylmorpholine- <i>N</i> -oxide
Ns	4-nitrobenzenesulfonyl (nosyl)
ONB	<i>o</i> -nitrobenzyl
PCC	pyridinium chlorochromate
PMP	1,2,2,6,6-pentamethylpiperidine
PPTS	pyridinium <i>p</i> -toluenesulfonate
Pyr	pyridine
<i>N</i> -PSP	<i>N</i> -(phenylseleno)phthalimide
Red-Al	sodium bis(2-methoxyethoxy)aluminum hydride
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAB	tetrabutylammonium bromide
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBAHS	tetrabutylammonium hydrogen sulfate
TBS	<i>tert</i> -butyldimethylsilyl
TBSCI	<i>tert</i> -butyldimethylsilyl chloride
TIPS	triisopropylsilyl
Tf	triflate
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
Teoc	2-trimethylsilylethoxycarbonyl
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
TMSCN	trimethylsilyl cyanide
TMSCl	trimethylsilyl chloride
TMSI	trimethylsilyliodide
TMSOTf	trimethylsilyl trifluoromethanesulfonate
TMTU	tetramethylthiourea
Tr	triphenylmethyl (trityl)
Ts	<i>p</i> -toluenesulfonyl (tosyl)
<i>p</i> -TSA	<i>p</i> -toluenesulfonic acid

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