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Bioinspired Synthesis

It All Began with an Error: The Nomofungin/Communesin Story**

Peter Siengalewicz, Tanja Gaich, and Johann Mulzer**

alkaloids · biosynthesis · nomofungin · perophoramidine · total synthesis

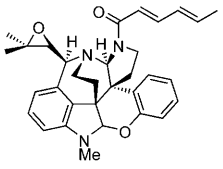
Dedicated to Professor Reinhard W. Hoffmann on the occasion of his 75th birthday

The communesin/nomofungin/perophoramidine story is an impressive example of how biogenetic considerations can lead to the correction of structural misassignments and inspire synthetic chemists with new, fruitful ideas. Intensive studies by a number of research groups culminated in the total synthesis of perophoramidine by the Funk research group in 2004. In 2007, Qin and co-workers completed the first total synthesis of a communesin.

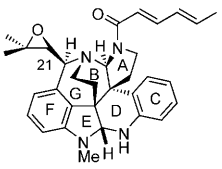
1. Introduction

In 2001, Hemscheidt and co-workers reported the isolation and structural elucidation of an alkaloid **1** from an unidentified fungus growing on the bark of *Ficus microcarpa* in Hawaii.[1a] The fungus died soon after this isolation and could not be recovered again. Therefore, compound **1** was given the very appropriate name "nomofungin" for "no more fungus". "Nomofungin" exhibited moderate cytotoxicity (LoVo, MIC = 3.9 μM; KB, MIC = 8.8 μM; MIC = minimal inhibitory concentration) and was shown to disrupt microfilaments in cultured mammalian cells. Its unusual structure, in particular the N,O-acetal moiety, attracted the attention of numerous synthetic research groups. No wonder that it aroused a sensation when the research groups of Stoltz and Funk discovered independently that the structure of **1** was wrong![2] They revealed that the compound was in reality identical to the known alkaloid communesin B (**2**; Figure 1), which Numata et al. had isolated together with the related compound communesin A (**3**) in 1993 from a strain of *Penicillium sp.* that had grown on the marine alga *Enteromorpha intestinalis*,[3] although the configuration at C21 and the absolute configuration had not been determined. Communesin B exhibited moderate cytotoxicity against P-388 lymphocytic leukemia cells and thus a similar biological activity to that of "nomofungin".[1a] In the light of these findings, Hemscheidt and co-workers retracted their original publication on "nomofungin".[1b]

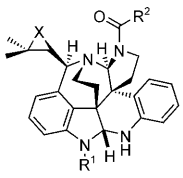
Stoltz and co-workers revealed the identity of **1** and **2** by comparing their ^{1}H and ^{13}C NMR spectroscopic data, which matched almost perfectly.[2a] Crawley and Funk provided additional chemical evidence from synthetic model studies (Schemes 1 and 2):[2b] They prepared the ketal acid chloride **11** from dihydroxyester **10** and connected it with the indole derivative **13** to give amine **14**. On thermolysis, **14** eliminated acetone in a formal retro-hetero-Diels–Alder reaction to generate the orthoquinone methide **15**, which underwent an in situ intramolecular hetero-Diels–Alder reaction to form the nomofungin analogue **16** as a 10:1 *endo*/*exo* mixture. The ^{1}H and ^{13}C NMR spectroscopic data for the key position 7a were clearly different for *endo*-**16** and **1**. To corroborate this result, the aminal analogue **20** was prepared through a similar route, which began with the addition of amine **13** to epoxide **17**. The resulting benzoate **18** eliminated benzoic acid on heating to provide the quinone methide imine **19**, which cyclized to **20**.



1, nomofungin



2, communesin B



3 R^1 = R^2 = Me, X = O, communesin A
4 R^1 = H, R^2 = 2,4-pentadienyl, X = O, communesin C
5 R^1 = CHO, R^2 = 2,4-pentadienyl, X = O, communesin D
6 R^1 = H, R^2 = Me, X = O, communesin E
7 R^1 = R^2 = Me, X= H, communesin F
8 R^1 = Me, R^2 = Et, X = O, communesin G
9 R^1 = H, R^2 = *n*-propyl, X = O, communesin H

Figure 1. Structures of the communesins and "nomofungin".

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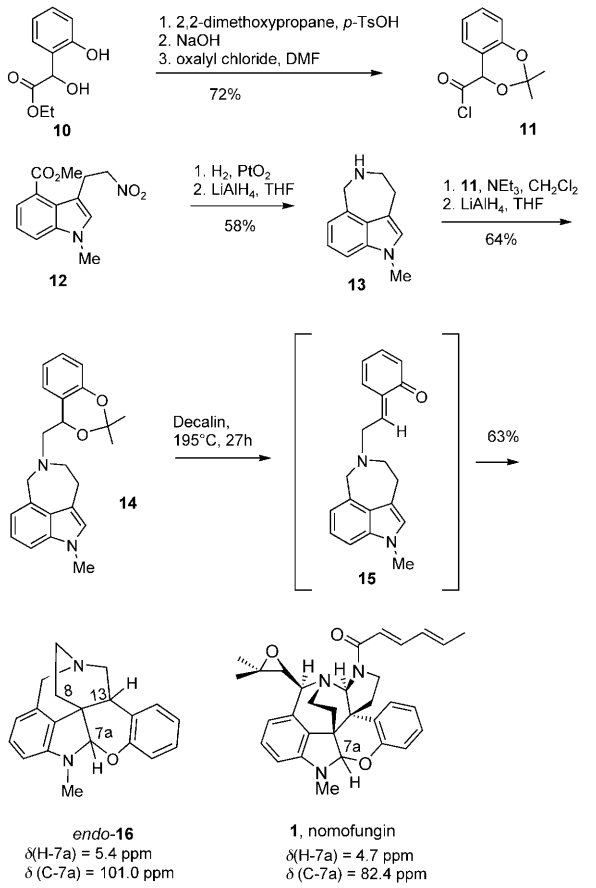
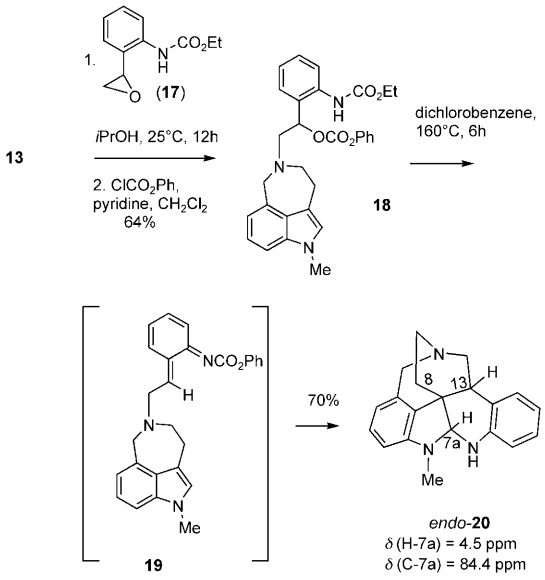


Scheme 1. Model synthesis of "nomofungin" by Funk and Crawley. DMF = *N*,*N*-dimethylformamide, Ts = toluenesulfonyl.



Scheme 2. Model synthesis of communesin B by Funk and Crawley.

The pertinent NMR spectroscopic data of *endo*-**20** were in accord with those of **1** and **2** (Scheme 2).

Remarkably, communesins A and B had not received much attention before the discovery by Stoltz, Funk, and their co-workers. These compounds then shot to fame within a couple of months, and recent isolations have led to an increase in the communesin family to eight members, named communesins A–H (**3**–**9**).[4] Communesin B (**2**) is considered the most biologically active compound in terms of cytotoxicity and insecticidal properties (Figure 1).

Johann Mulzer was born in 1944 in Prien, Germany. He completed his PhD in 1974 under the supervision of Rolf Huisgen at Ludwig-Maximilians-Universität in Munich and then joined the research group of E. J. Corey at Harvard University as a post-doctoral fellow. Between 1982 and 1996 he held professorships at the University of Düsseldorf, Freie Universität Berlin, and Frankfurt University. Since 1996 he has been a full professor at the University of Vienna. His main research interests lie in the total synthesis of structurally and physiologically interesting natural products.

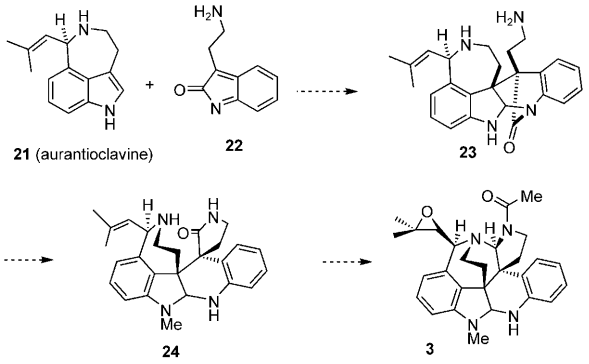
Tanja Gaich studied biology at the University of Salzburg and chemistry at the University of Vienna, where she received her masters degree in 2005. She is currently a PhD student in the research group of Professor Mulzer. Her research is focused on the total synthesis of diterpenes.

Peter Siengalewicz was born in 1973 in Kitzbühel, Austria. He studied chemistry at the University of Innsbruck and the University of Florida, Gainesville, where he obtained his MSc in 2002. He returned to Austria in 2003 and completed his PhD in 2008 under the direction of Professor Mulzer at the University of Vienna with research on the total synthesis of tetrahydroisoquinoline alkaloids.

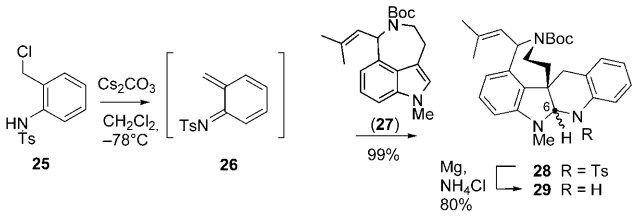
2. Biogenetic Considerations

In their seminal report,[2a] Stoltz and co-workers outlined a biogenetic pathway for **3** that featured a hetero-Diels–Alder addition of the known alkaloid aurantioclavine (**21**) to the quinone methide imine **22** derived from the in situ oxidation of tryptamine. Adduct **23** should then be converted into **3** via lactam **24** (Scheme 3).

In a model study, some evidence was provided for this concept: The quinone methide imine **26** was generated from precursor **25** and added to the aurantioclavine derivative **27** (Scheme 4). This intermolecular hetero-Diels–Alder addition gave the polycycle **29**, which contains communesin rings F, E, D, C, and G, as a diastereomeric mixture. The ^{13}C NMR



Scheme 3. Biomimetic proposal of Stoltz and co-workers for the synthesis of communesin A.[2a]



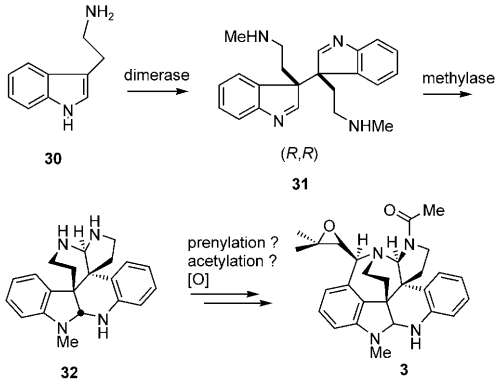
Scheme 4. Biomimetic model study by Stoltz and co-workers.[2a] Boc = *tert*-butoxycarbonyl.

chemical shifts for C6 in both diastereomers of **29** ($\delta = 84.8$ and 83.9 ppm) were in agreement with that observed for communesin B ($\delta = 82.4$ ppm).

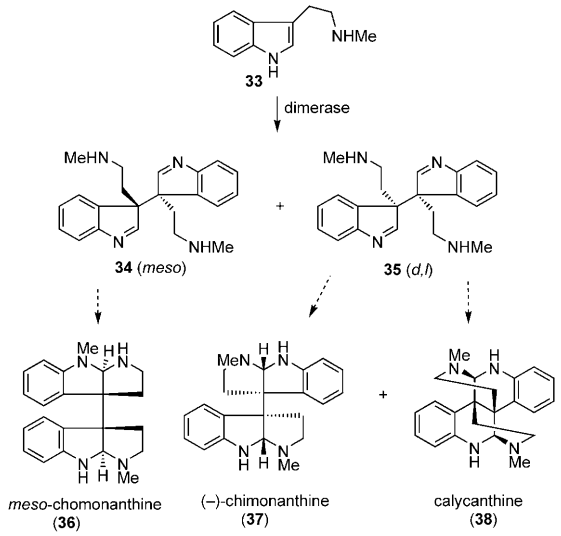
In 2006, Mantle and co-workers reported[5a] that communesins A and B had been isolated under the names of commindolines A and B from *Penicillium commune* in the Pfizer laboratories prior to the publication of Numata et al.[3a] On the basis of labeling experiments, they suggested a new biosynthetic pathway to **3** (Scheme 5), according to which a dimerization of tryptamine (**30**) to give **31** is followed by methylation and demethylation to give metabolite **32**. It remained unclear how **32** should then be transformed into **3**. In 2008, the authors added the comment that aurantioclavine (**21**) could well be a precursor in fungal communesin biosynthesis,[5b] as suggested by Stoltz and co-workers[2a] (Scheme 3).

In 2006, May and Stoltz[6] developed a more general, detailed biosynthetic concept, with which they not only attempted to explain the formation of the communesins but also that of a number of related alkaloids from common precursors (Scheme 6). More specifically, it was postulated that the dimerization of *N*-methyltryptamine (**33**) should give the *meso* and *d*,*l* dimers **34** and **35**, which could cyclize to the known alkaloids **36**–**38**.

Similarly, the dimer (*R*,*R*)-**39** could undergo two cyclization steps in a cascade process via intermediates **40** and **41** to form the hexacyclic structure **42**, the N-prenylation of which to give **43** could be followed by oxidative conversion into **7** (Scheme 7). An analogous sequence starting from *meso*-**39** would give **44**, which could reasonably serve as a precursor to the known alkaloid perophoramidine (**45**). Remarkably, a similar biogenesis of calycanthaceous alkaloids from tryptamine dimers was suggested by Robinson and Teuber[7] and



Scheme 5. Proposed biosynthesis of the communesins.[5]

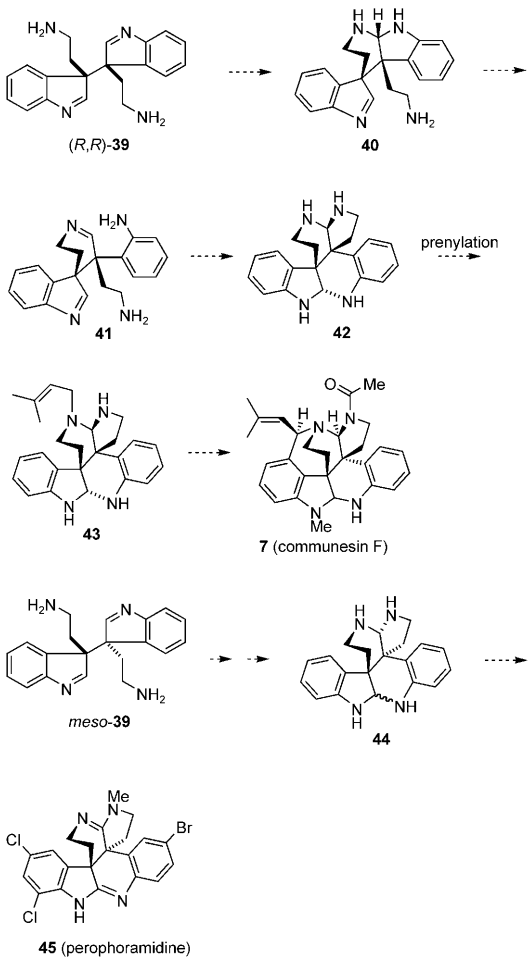


Scheme 6. Proposed biosynthesis of related natural products.[6]

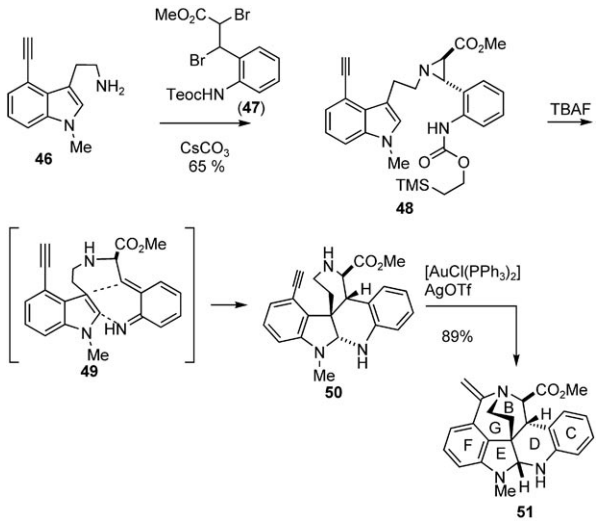
Woodward et al.[8] about 50 years ago. In fact, the gross structure of perophoramidine was anticipated correctly; the only differences were that aminal moieties were assumed to be present instead of amidine functionalities, and the halogen substituents were omitted. The presumed structure was later synthesized by Hendrickson et al.[9]

3. Total Synthesis of Communesins

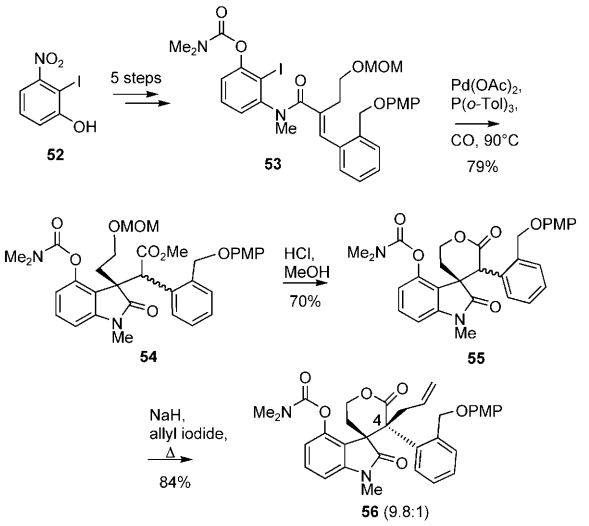
Several model studies towards the communesin skeleton have been carried out. In one such study, Funk and Crawley[10] (Scheme 8) made use of a hetero-Diels–Alder addition of a quinone methide imine to an indole in a similar approach to that used for the model systems **16** and **20** (Scheme 1 and Scheme 2) and that proposed by Stoltz and co-workers (see Scheme 4). The synthesis described by Funk and Crawley involves the aziridine precursor **48**, which is readily accessible from the tryptamine derivative **46** and dibromoester **47**. Fluoride-induced removal of the Teoc group triggers the opening of the aziridine ring to form the quinone methide imine **49**, which cyclizes immediately to the polycycle **50**. This ring system contains rings F–C and B of the communesin



Scheme 7. Common biogenetic origin of the communesins and perophoramidine.



Scheme 8. Approach of Funk and Crawley to the synthesis of the communesins. TBAF = tetrabutylammonium fluoride, Teoc = 2-trimethylsilylethoxycarbonyl, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.[10]



Scheme 9. Synthetic study towards the communesins by Weinreb and co-workers.[11] MOM = methoxymethyl, PMP = *p*-methoxyphenyl.

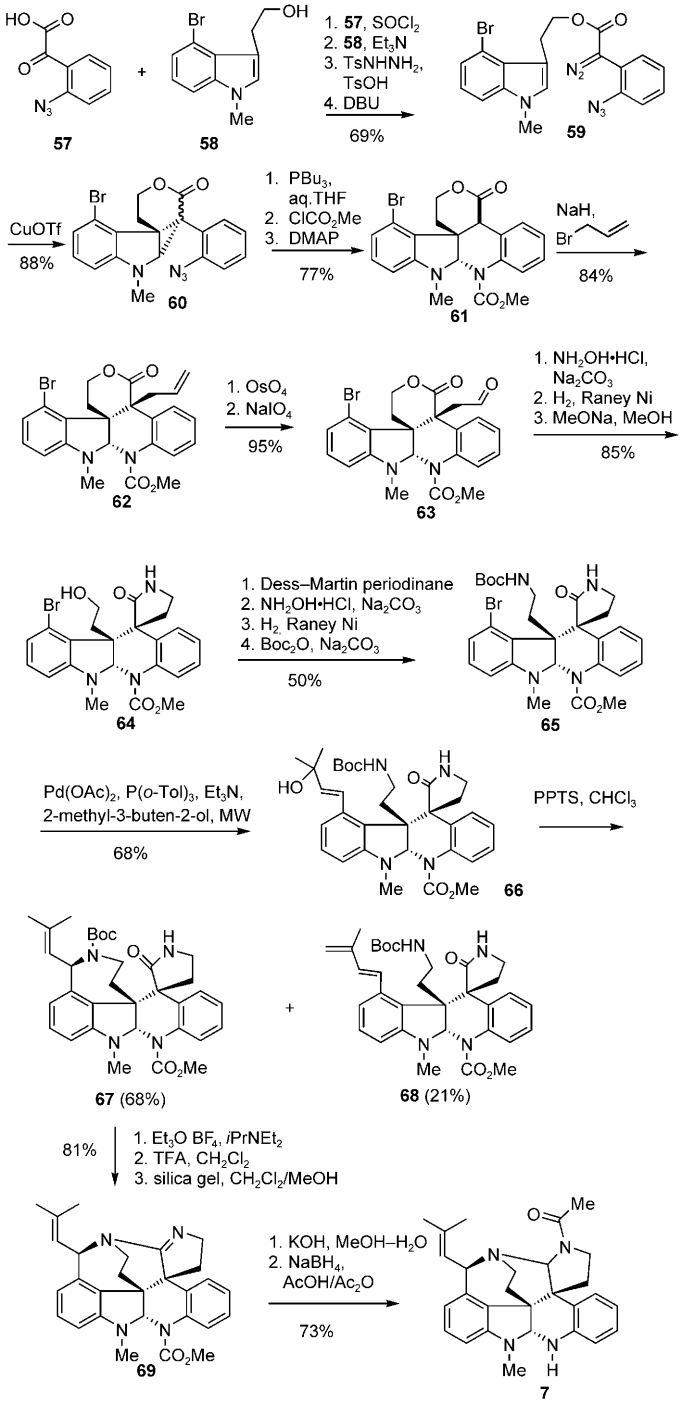
skeleton. Ring G is added in a gold(I)-catalyzed addition of the B-ring amine to the alkyne to form the final product **51**.

In an alternative approach by Weinreb and co-workers[11] (Scheme 9), a Heck cyclization was applied as the key step to form ring E in the communesin skeleton. Thus, the aryl iodide **52** was elaborated into the unsaturated amide **53**, which was converted into indolinone **54** under classical Heck cyclization/carbonylation conditions. The formation of lactone **55** was followed by O-allylation of the enolate and stereoselective Claisen rearrangement to give compound **56**, which contains the characteristic two contiguous quaternary stereogenic centers of the communesins.

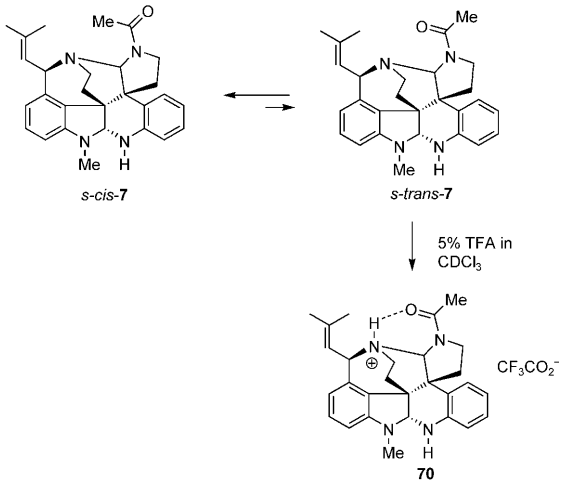
The first synthesis and only synthesis to date of a communesin (communesin F, **7**) was completed by Qin and co-workers[12] in 2007 (Scheme 10). Capitalizing on previous model studies,[13] they installed the crucial vicinal quaternary stereogenic centers by an intramolecular cyclopropanation, which led to cyclopropane **60** as the key intermediate. The synthesis started with the formation of diazoester **59** from keto acid **57** and alcohol **58**. Copper(I)-catalyzed cyclopropanation generated spirolactone **60**, which was transformed into aminal **61** through an S_N1-type ring opening of the cyclopropane. The subsequent allylation to give **62** was based on the approach of Weinreb and co-workers.[11] The formation of aldehyde **63** was followed by a cyclization to give amide **64**. Conversion of the primary alcohol into the Boc-protected amine **65** and a Heck reaction to insert the aromatic prenyl side chain then gave the tertiary alcohol **66**, which underwent cyclization in the presence of PPTS to give the aurantioclavine ring in **67**. Diene **68** was formed as a side product. Compound **66** was transformed into amidine **69**, which was deprotected and reduced to furnish the racemic alkaloid **7** in 23 steps and approximately 3% overall yield. The authors found that **7** was formed as an inseparable mixture of *s-cis* and *s-trans* rotamers, which could be distinguished in the NMR spectra. The rotameric equilibrium was highly dependent on

the solvent (2.6:1 in $CDCl_3$ and 5.1:1 in $[D_6]$DMSO; DMSO = dimethyl sulfoxide). The protonation of **7** with 5% TFA in $CDCl_3$ provided the salt **70** as a single isomer, presumably as a result of intramolecular hydrogen bonding (Scheme 11).

A related strategy was used by Qin and co-workers in their recent synthesis of the indole alkaloid minfiensine (**75**; Scheme 12).[14] In this case, in a one-pot cascade reaction,



Scheme 10. Total synthesis of communesin F by Qin and co-workers.[12] DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMAP = 4-dimethylaminopyridine, MW = microwave irradiation, PPTS = pyridinium *p*-toluenesulfonate, TFA = trifluoroacetic acid.

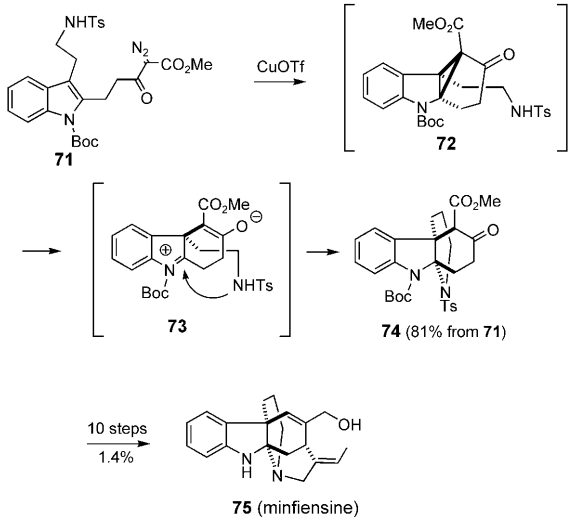


Scheme 11. Tautomeric equilibrium of communesin F.

diazoketoester **71** was first converted into the labile cyclopropane ester **72**, which isomerized to zwitterion **73** under the ring strain. Ring closure and proton migration then generated tetracycle **74**, which was transformed in a lengthy sequence into racemic **75**.

4. Total Synthesis of Perophoramidines

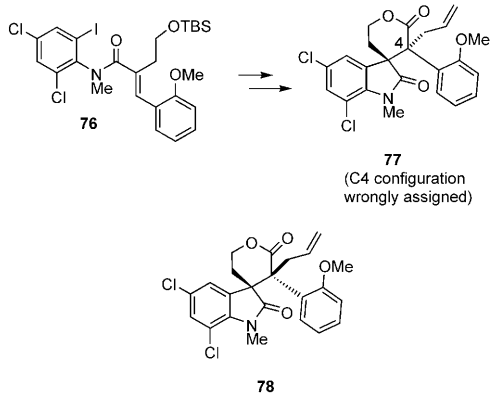
Perophoramidine (**45**) shares the same connectivity as the communesins, but with the opposite configuration at C8. Weinreb and Artman were among the first to tackle a total synthesis of **45**.[15] By using the Heck addition protocol described in Scheme 9, they prepared lactone **77** from aryl iodide **76** (Scheme 13). However, the misinterpretation of NOE effects led to their assignment of the incorrect relative configuration at C4 (C8 in structures **85** and **45**); in reality, the product of the Heck addition was **78**, with the communesin configuration.



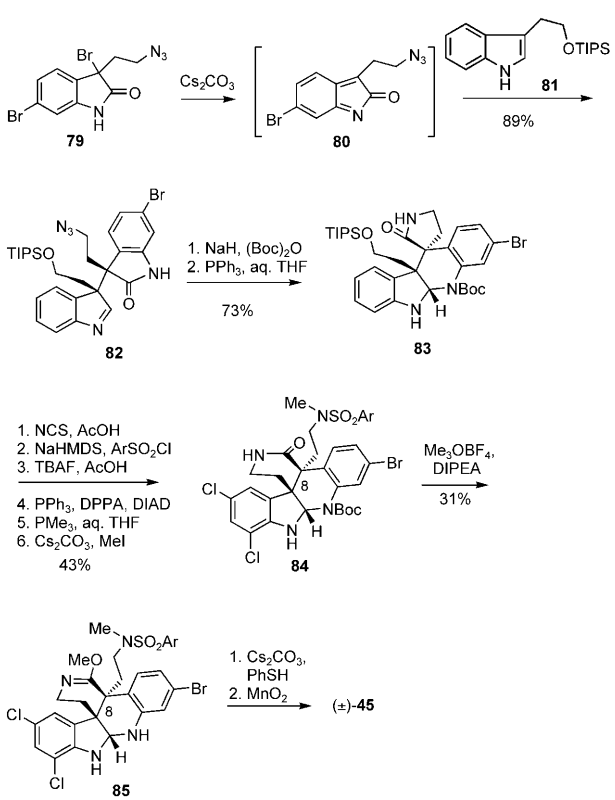
Scheme 12. Synthesis of minfiensine by Qin and co-workers.[14]

The first and only completed synthesis of **45** to date was reported in 2004 by Fuchs and Funk.[16] In contrast to the communesin approach of the same research group, Fuchs and Funk used an intermolecular version of the biomimetic Diels–Alder addition. Thus, the dibromoindolinone **79** was dehalogenated to give the *o*-quinoid system **80**, which was trapped in situ with the indole derivative **81** to form adduct **82** selectively (Scheme 14). The stereochemical outcome of this addition was interpreted in terms of an *endo* arrangement of the two aromatic moieties in the transition state. A Staudinger reaction of the azide was followed by tandem recyclization to form **83**, which was then converted into perophoramidine (**45**) by a nine-step sequence. Thus, the nonhalogenated aromatic ring was dichlorinated, and the nitrogen atom of the lactam ring was protected as a sulfonamide. The primary alcohol was then converted into an amine, which was used for the formation of δ-lactam **84**. The O-methylation of **84** was accompanied by the removal of the Boc group to form iminoester **85**, which cyclized to the amidine upon cleavage of the sulfonamide. The second amidine functionality was created from the aminal by oxidation with MnO_2.

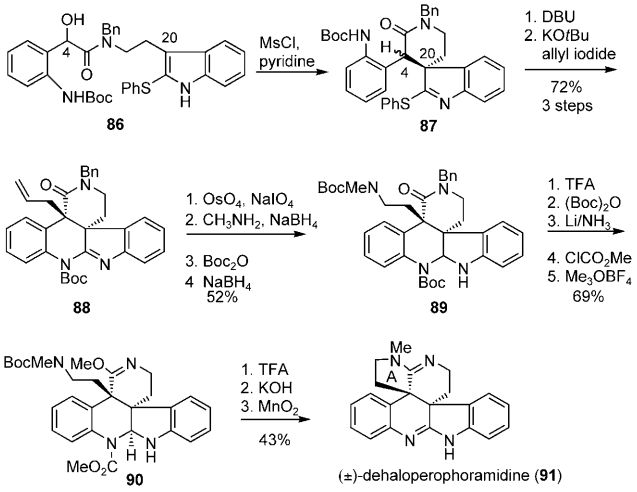
Racemic dehaloperophoramidine (**91**) was synthesized by Rainier and co-workers (Scheme 15).[17] Their approach aimed at the connection of C4 and C20 by an intramolecular enamine alkylation. In fact, the mesylation of alcohol **86** led to the immediate formation of lactam **87**, which was allylated according to the Weinreb protocol (although with the opposite stereochemical outcome!) to give intermediate **88** with the two crucial stereogenic centers C4 and C20 in the correct relative configuration. The alkene was subjected to oxidative cleavage to form the aldehyde, which underwent reductive amination to give the protected amine **89**. Protecting-group manipulation and formation of the iminoester gave intermediate **90**, which was then converted into the bisamidine **91** in a procedure similar to that used by Fuchs and Funk.[16]



Scheme 13. Synthesis of a putative perophoramidine precursor by Artman and Weinreb. TBS = *tert*-butyldimethylsilyl.[15]



Scheme 14. Total synthesis of perophoramidine by Fuchs and Funk.[16] DIAD = diisopropylazodicarboxylate, DIPEA = diisopropyethylamine, DPPA = diphenylphosphoryl azide, HMDS = hexamethyldisilazide, NCS = *N*-chlorosuccinimide, TIPS = triisopropylsilyl.



Scheme 15. Total synthesis of dehaloperphoramidine by Rainier and coworkers.[17] Ms = methanesulfonyl.

5. Conclusion

The fascinating story of the communesin/perophoramidine alkaloids has reached its first climax and is far from completion. It illustrates in a characteristic manner how biosynthetic considerations, unsupported as they may be, can lead to unexpected novel insight and thus pave the way for successful total syntheses. To date, racemic material only has been prepared. Thus, the extension of these studies to asymmetric approaches and the final confirmation of the

absolute configuration of these compounds should be among the next steps to be taken.

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