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TRANSITION METAL COMPLEXES IN ORGANIC SYNTHESIS, PART 73.[1] SYNTHETIC ROUTES TO NATURALLY OCCURRING FUROCARBAZOLES

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Abstract – The isolation and the development of total syntheses of naturally occurring furocarbazole alkaloids are described. The diverse synthetic strategies which were elaborated by different research groups are discussed and compared.

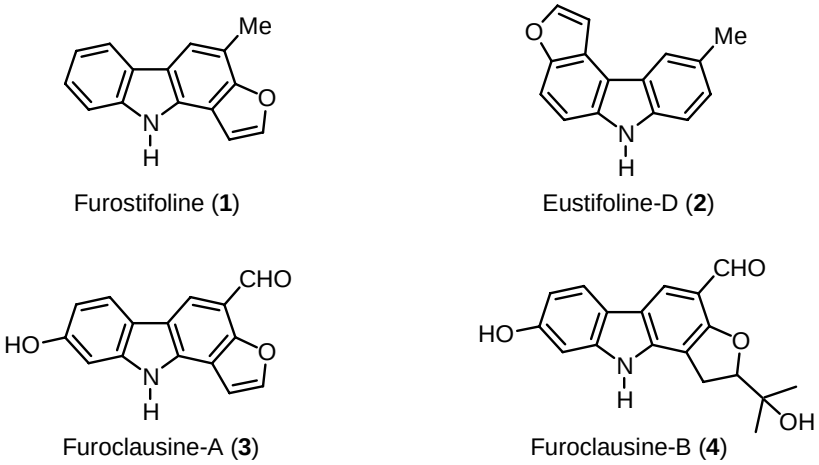
INTRODUCTION

A large number of biologically active carbazole alkaloids has been isolated from natural sources.[2-10] Their useful bioactivities and their interesting structural features attracted the attention of synthetic chemists and led, over the last 15 years, to the development of many different synthetic strategies.[6-20]

Pyrido[4,3-*b*]carbazole alkaloids exhibit antitumor activity[8,21-23] and indolo[2,3-*a*]carbazole alkaloids have a broad range of useful pharmacological activities.[8,24-27] These findings induced a special interest in heteroaryl-fused carbazole alkaloids.[8,28-30] Carbazole alkaloids condensed to a five-membered heteroarene represent a relatively young class of natural products which includes: the furocarbazoles, isolated from terrestrial plants,[31,32] the pyrrolo[2,3-*c*]carbazoles, isolated from Japanese marine sponges of the genus *Dictyodendrilla*,[33] and the imidazo[4,5-*a*]pyrrolo[3,4-*c*]carbazole granulatimide, obtained from the Brazilian ascidian *Didemnum granulatum*.[34]

1 ISOLATION OF FUROCARBAZOLE ALKALOIDS

In 1990 Furukawa at Nagoya described the isolation of the first two furocarbazole alkaloids, furostifoline (**1**) and the isomeric eustifoline-D (**2**), from the root bark of *Murraya euchrestifolia* Hayata, collected in December in the central and southern parts of Taiwan (Scheme 1).[31] In China the extracts of the leaves and bark of *Murraya euchrestifolia* have been used as folk medicine. The variety of carbazole alkaloids from this plant and the pharmacological activity of the plant extracts are dependent on the season.[35]



Scheme 1. Naturally Occurring Furocarbazole Alkaloids.

Wu described in 1997 the isolation and structural elucidation of two further furocarbazole alkaloids, furoclausine-A (**3**) and furoclausine-B (**4**), obtained from the acetone extract of the root bark of *Clausena excavata*.[32] The absolute stereochemistry of the optically active furoclausine-B (**4**) is still unknown. The extracts of the plant *Clausena excavata* are used in traditional folk medicine in China for the treatment of various infections and poisonous snakebites (Figure 1).

Prior to the total synthesis of their naturally occurring counterparts, synthetic derivatives of furocarbazoles were prepared using Fischer indole,[36,37] nitrene insertion,[38] photocyclization,[39] and benzotriazole[40] methodologies. Due to their unprecedented framework and pharmacological potential the

naturally occurring furocarbazole alkaloids became attractive synthetic targets. This review summarizes, in chronological order, the development of different synthetic routes to furocarbazole alkaloids.

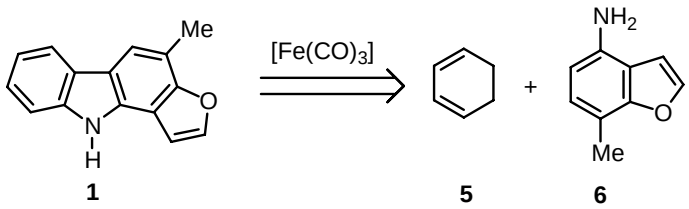
Figure 1. *Clausena excavata* (courtesy of Professor Pei-Fen Lee, National Taiwan University, Taipei, Nature Conservation Network).

2 TOTAL SYNTHESES OF FUROSTIFOLINE

Over the past eight years six total syntheses for the furo[3,2-*a*]carbazole alkaloid furostifoline (**1**) have been reported by several research groups.

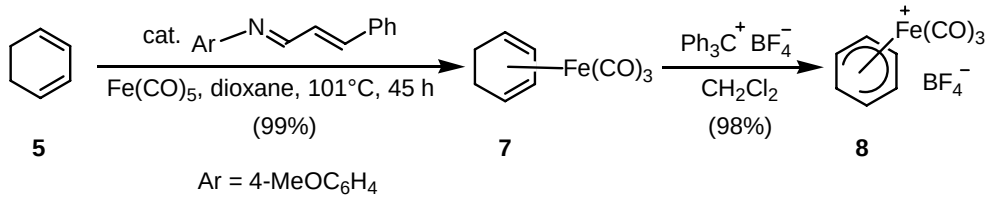
2.1 IRON-MEDIATED SYNTHESIS

In 1996 we described the first total synthesis of furostifoline (**1**) by an iron-mediated construction of the carbazole framework using cyclohexa-1,3-diene (**5**) and 4-amino-7-methylbenzofuran (**6**) as precursors (Scheme 2).[41,42]



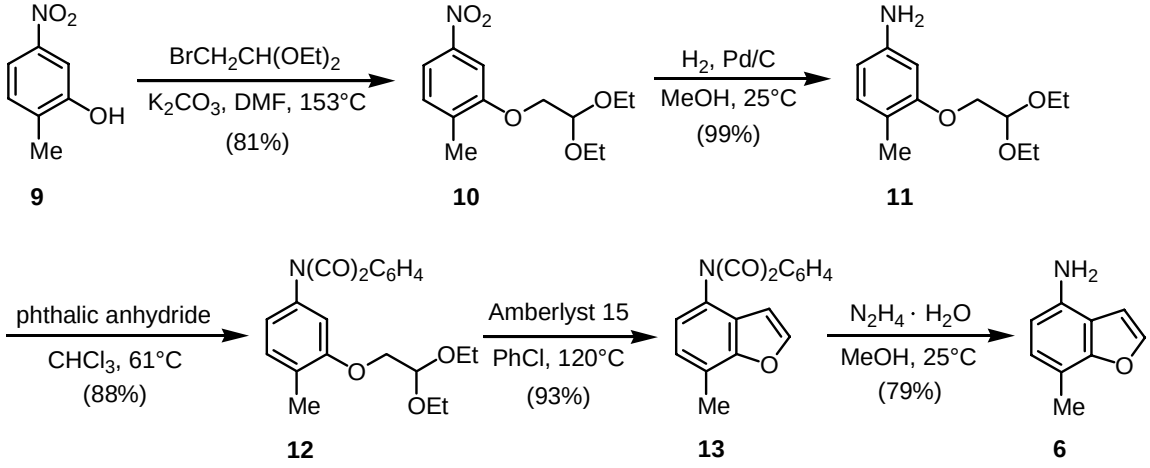
Scheme 2. Retrosynthesis of **1** based on an iron-mediated approach with initial furan cyclization.

The iron complex salt (**8**) is readily available in large quantities by 1-azabuta-1,3-diene-catalyzed complexation of cyclohexa-1,3-diene (**5**) with pentacarbonyliron,[43,44] followed by hydride abstraction using triphenylcarbenium tetrafluoroborate (Scheme 3).[45,46]



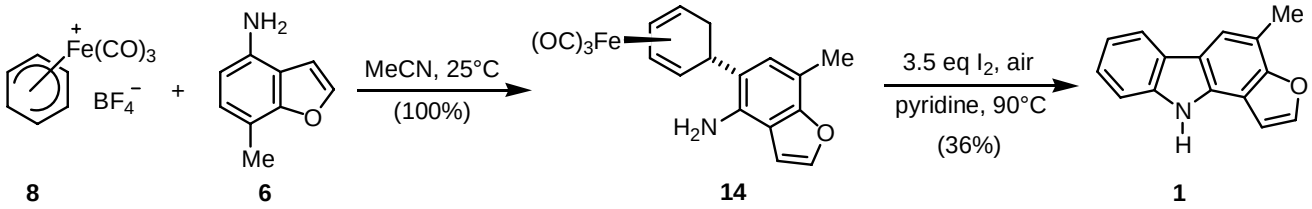
Scheme 3. Preparation of the iron complex salt (**8**).

Starting from the nitrophenol (**9**) an annulation of the furan ring was achieved using bromoacetaldehyde diethyl acetal as a C_2-building block (Scheme 4). The alkylation of **9** with bromoacetaldehyde diethyl acetal provided the aryl ether (**10**). Catalytic hydrogenation of compound (**10**) using palladium on activated carbon afforded the arylamine (**11**). Conversion of the amino group to the phthalimide (**12**) and an Amberlyst 15-catalyzed cyclization provided 7-mehyl-4-phthalimidobenzofuran (**13**). Removal of the phthalimido group afforded 4-amino-7-methylbenzofuran (**6**).[41,42] This five-step sequence provides the 4-aminobenzofuran (**6**) on a multigram scale in 52% overall yield based on the nitrophenol (**9**).



Scheme 4. Synthesis of 4-amino-7-methylbenzofuran (**6**).

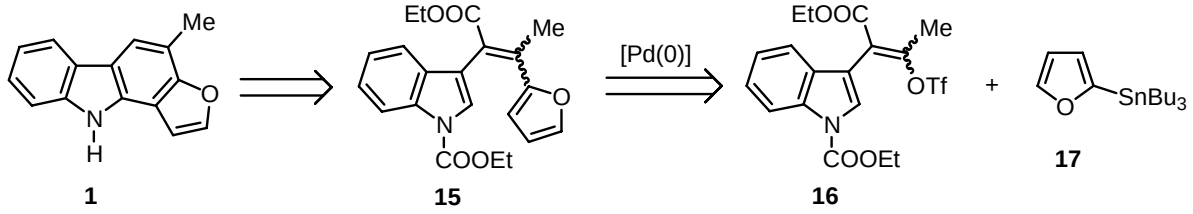
Electrophilic aromatic substitution of the 4-aminobenzofuran (**6**) with the complex salt (**8**) provided quantitatively the iron complex (**14**) (Scheme 5). Cyclization of complex (**14**) by oxidation with an excess of iodine in pyridine at 90°C in the air afforded directly furostifoline (**1**). The first iron-mediated total synthesis provided furostifoline (**1**) in seven steps and 19% overall yield based on the nitrophenol (**9**).[41,42]



Scheme 5. Iron-mediated total synthesis of furostifoline (**1**).

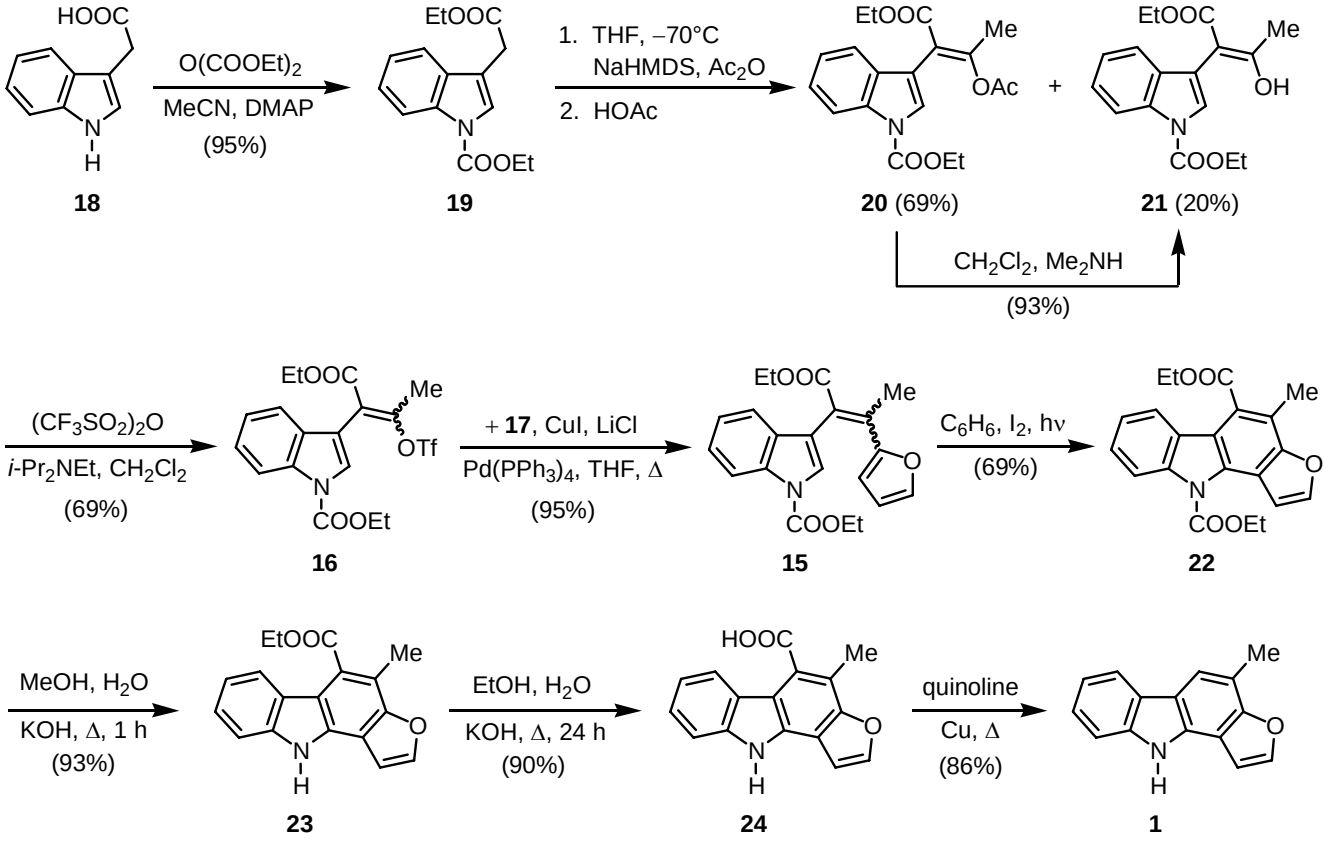
2.2 OXIDATIVE PHOTOCYCLIZATION OF A 3-SUBSTITUTED INDOLE

In 1998 Beccalli and co-workers reported a total synthesis of furostifoline (**1**) by using an oxidative photocyclization of the 3-substituted indole (**15**) (Scheme 6).[47] Retrosynthetic analysis of the indole (**15**) led to the vinyl triflate (**16**) and 2-(tributylstannyl)furan (**17**) as synthetic precursors.



Scheme 6. Retrosynthesis of **1** based on the oxidative photocyclization of a 3-substituted indole.

Reaction of indole-3-acetic acid (**18**) with diethyl dicarbonate in the presence of 4-(dimethylamino)pyridine (DMAP) led to the 1-ethoxycarbonyl derivative (**19**) (Scheme 7). Deprotonation of compound (**19**) with sodium bis(trimethylsilyl)amide (NaHMDS) followed by reaction of the resulting anion with acetic anhydride afforded a 3.5:1 ratio of the enol acetate (**20**) and the enol (**21**) in 89% total yield. The enol acetate (**20**) was converted to the desired enol (**21**) in 93% yield by treatment with dimethylamine in dichloromethane (two steps, 84% overall yield of **21**).[47]

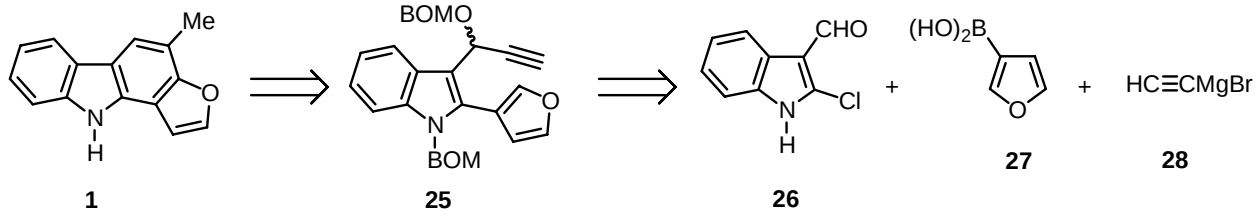


Scheme 7. Synthesis of furostifoline (**1**) by oxidative photocyclization of the 3-substituted indole (**15**).

Alternatively, deprotonation of **19** with lithium diisopropylamide (LDA) and subsequent reaction with acetic anhydride led to the enol (**21**) as the sole product in 68% yield. The reaction of the enol (**21**) with trifluoromethanesulfonic anhydride gave the triflate (**16**) as an inseparable 1:1 mixture of diastereoisomers. Stille coupling of the triflate (**16**) with 2-(tributylstannyl)furan (**17**) afforded the vinylfuran (**15**) in a 1:1 diastereoisomeric ratio. Oxidative photocyclization of the vinylfuran (**15**) in the presence of iodine provided the furo[3,2-*a*]carbazole (**22**). Alkaline hydrolysis of **22** gave the acid (**24**) *via* the *N*-deprotected furo[3,2-*a*]carbazole (**23**). The decarboxylation of compound (**23**) afforded furostifoline (**1**).[47] This synthesis provides furostifoline (**1**) in nine steps and 26% overall yield based on compound (**18**).

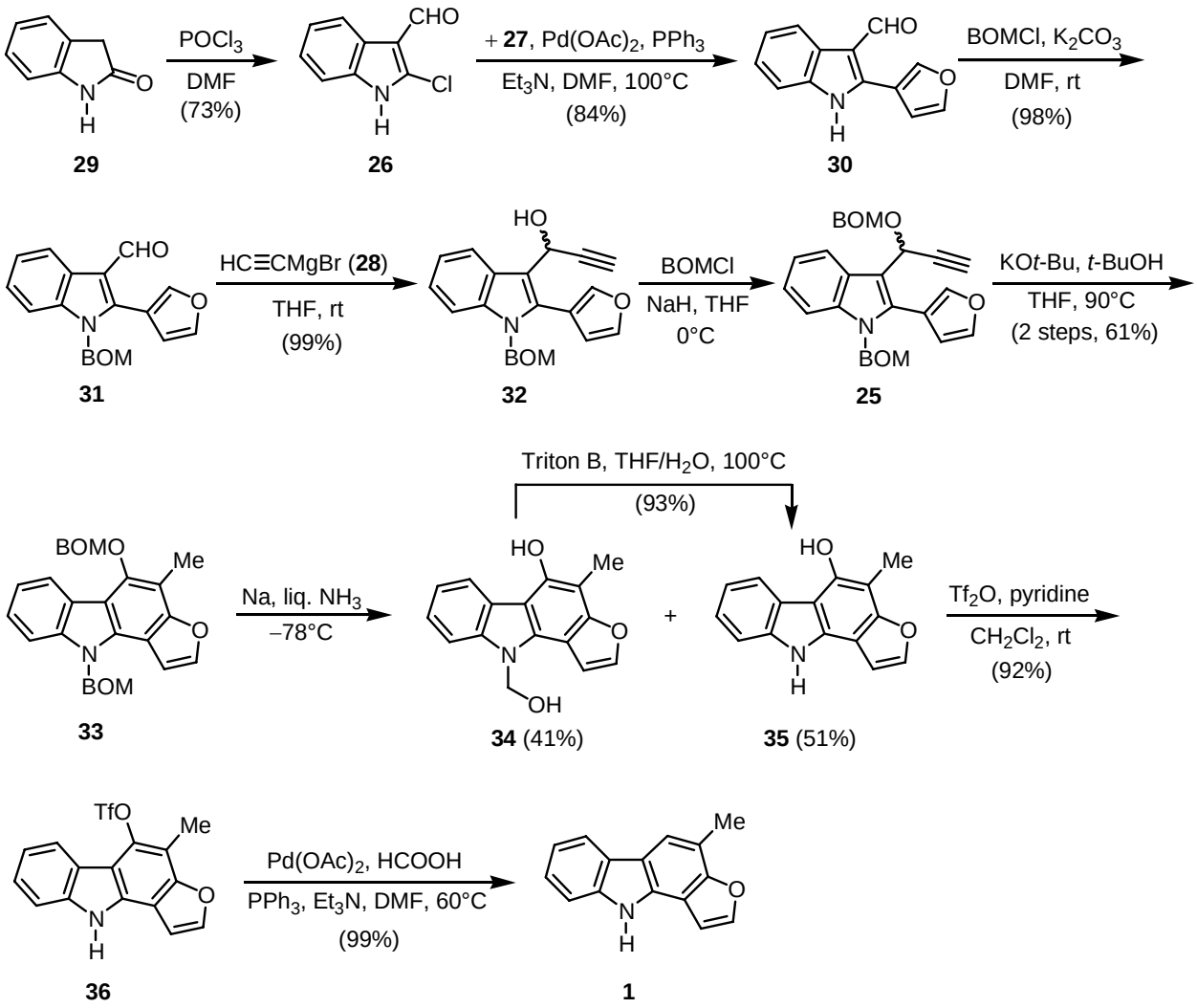
2.3 THERMAL ELECTROCYCLIZATION OF A 2,3-DISUBSTITUTED INDOLE

In the same year Hibino described a total synthesis of furostifoline (**1**) employing a new type of thermal electrocyclic reaction.[48,49] The cyclization proceeds *via* a 2-alkenyl-3-allenylindole intermediate which derives from the 2-(fur-3-yl)-3-propargylindole (**25**) (Scheme 8). Compound (**25**) is prepared from 2-chloroindole-3-carbaldehyde (**26**), furan-3-boronic acid (**27**), and ethynylmagnesium bromide (**28**).



Scheme 8. Retrosynthesis of **1** based on the thermal electrocyclization of a 2,3-disubstituted indole.

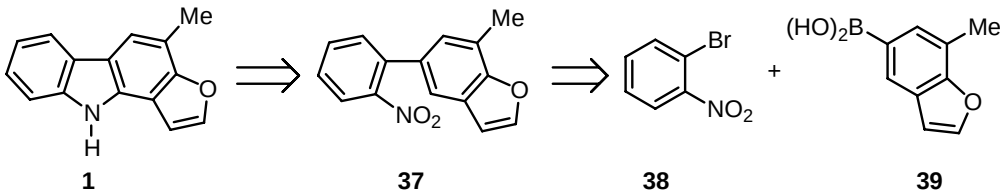
Vilsmeier reaction of oxindole (**29**) afforded 2-chloroindole-3-carbaldehyde (**26**) (Scheme 9).[50] Suzuki coupling of compound (**26**) with furan-3-boronic acid (**27**), followed by protection of the indole nitrogen of **30** with benzyloxymethyl (BOM) chloride provided 1-BOM-2-(fur-3-yl)indole-3-carbaldehyde (**31**). Addition of ethynylmagnesium bromide (**28**) to compound (**31**) and BOM-protection of the propargyl alcohol (**32**) afforded the 2-(fur-3-yl)-3-propargylindole (**25**). Thermal electrocyclic reaction of the indole (**25**) in the presence of potassium *t*-butoxide gave the 5-oxygenated furo[3,2-*a*]carbazole (**33**). Removal of the *N*,*O*-BOM groups of the furo[3,2-*a*]carbazole (**33**) led to the 10-(hydroxymethyl)furo[3,2-*a*]carbazole (**34**) (41%) and 5-hydroxy-4-methyl-10*H*-furo[3,2-*a*]carbazole (**35**) (51%). Compound (**34**) was converted to the furo[3,2-*a*]carbazole (**35**) by treatment with Triton B (93% yield). Removal of the 5-hydroxy group by reductive elimination of the intermediate triflate (**36**) provided furostifoline (**1**).[48,49] The synthesis by Hibino and co-workers affords furostifoline (**1**) in ten steps and 29% overall yield based on oxindole (**29**).



Scheme 9. Synthesis of furostifoline (**1**) by thermal electrocyclization of the indole (**25**).

2.4 REDUCTIVE CYCLIZATION OF AN *o*-NITROBIARYL

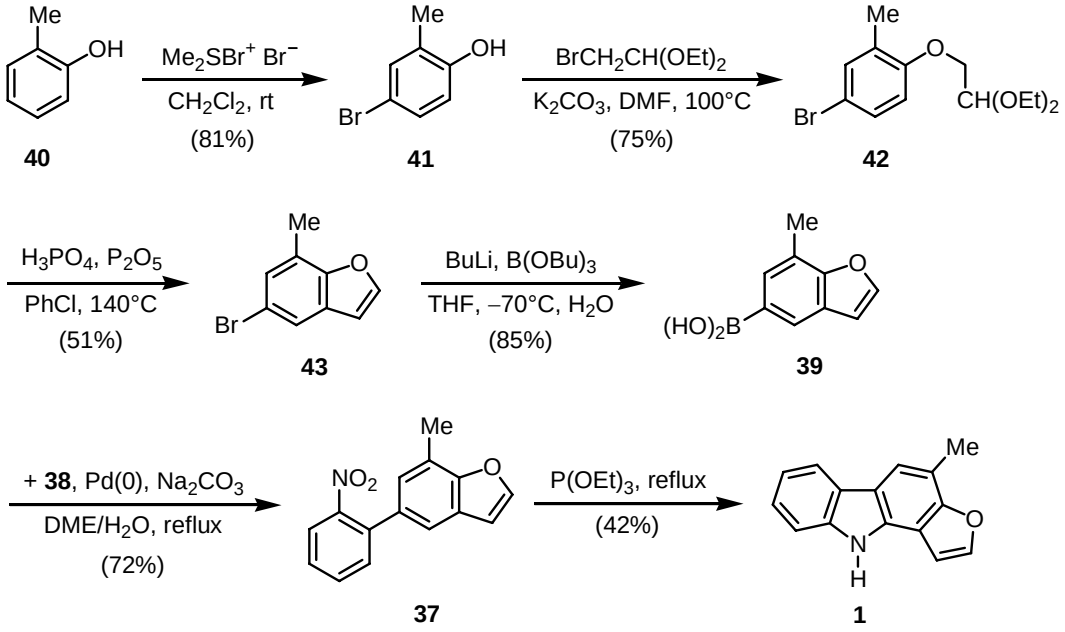
In 1999 Timári and co-workers described a total synthesis of furostifoline (**1**) by cyclization of the *o*-nitrobiaryl (**37**) (Scheme 10).[51] The formation of the carbazole ring is achieved using Cadogan's reductive cyclization of *o*-nitrobiaryls by insertion of an intermediate nitrene.[52] The *o*-nitrobiaryl (**37**) is prepared by Suzuki coupling of 2-bromonitrobenzene (**38**) with 7-methylbenzofuran-5-boronic acid (**39**).



Scheme 10. Retrosynthesis of **1** based on a reductive cyclization of the *o*-nitrobiaryl (**37**).

Bromination of *o*-cresol (**40**) gives 5-bromocresol (**41**) (Scheme 11).[53] Alkylation of 5-bromocresol (**41**) with bromoacetaldehyde diethyl acetal afforded compound (**42**), which on acid-promoted cyclization

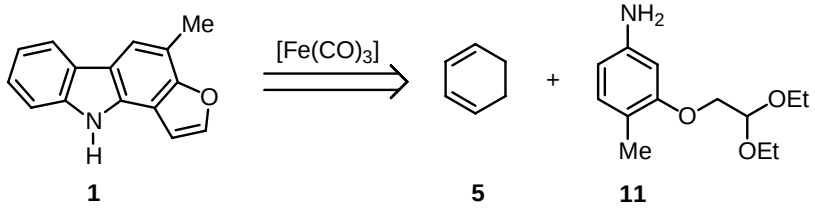
gave 5-bromo-7-methylbenzofuran (**43**). A halogen/metal exchange reaction of **43** with *n*-butyllithium followed by reaction of the intermediate aryllithium with tributyl borate gave the boronic acid (**39**) in 85% yield. The palladium-catalyzed cross coupling of the boronic acid (**39**) with 2-bromonitrobenzene (**38**) provided the *o*-nitrobiaryl (**37**) in 72% yield. Reductive cyclization of the *o*-nitrobiaryl (**37**) with triethyl phosphite afforded by nitrene insertion furostifoline (**1**) in 42% yield.[51] Timári's synthesis provides furostifoline (**1**) in six steps and 8% overall yield based on *o*-cresol (**40**).



Scheme 11. Synthesis of furostifoline (**1**) by Cadogan's reductive cyclization.

2.5 IMPROVED IRON-MEDIATED SYNTHESIS

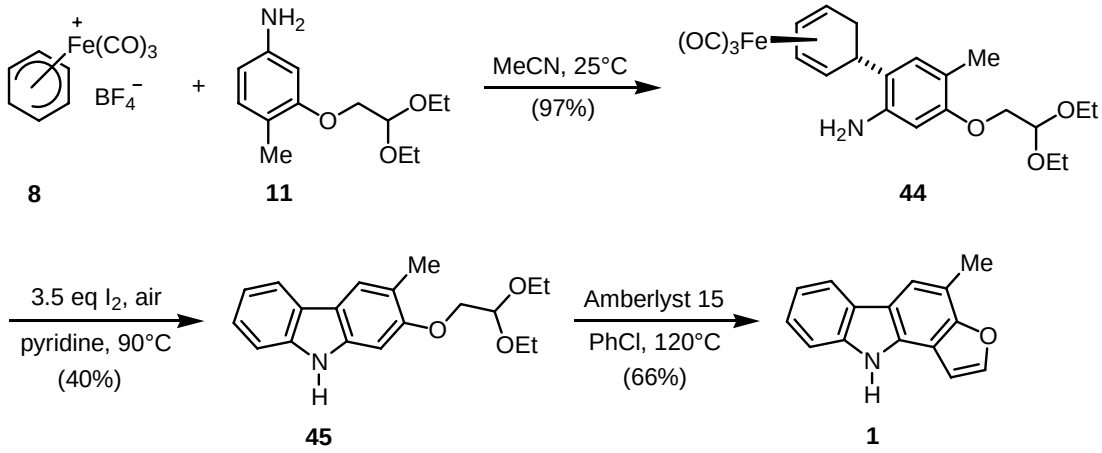
In 2000 we described full experimental details of our first total synthesis of furostifoline (**1**) and a novel approach (Scheme 12).[42] In this alternative route the iron-mediated arylamine cyclization for construction of the carbazole heterocycle is carried out before the annulation of the furan ring. This reversal of the sequence of the two cyclizations leads to a shorter synthesis by avoiding a protection of the amino group. Thus, retrosynthetic analysis leads to cyclohexa-1,3-diene (**5**) and the arylamine (**11**) as the precursors.



Scheme 12. Retrosynthesis of **1** based on an iron-mediated approach with initial carbazole cyclization.

The arylamine (**11**) is available from the nitrophenol (**9**) in two steps and 80% overall yield by alkylation and subsequent catalytic hydrogenation (Scheme 4). Electrophilic substitution of the arylamine (**11**) by

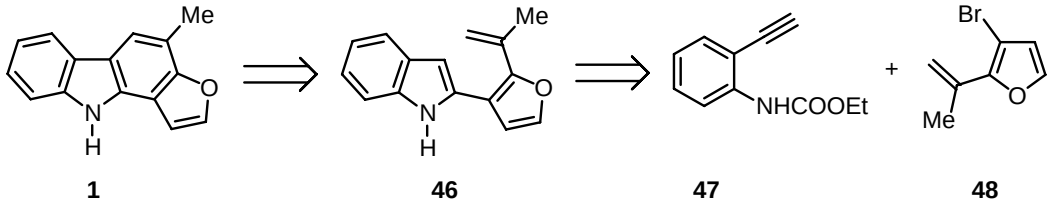
reaction with the iron complex salt (**8**) afforded the iron complex (**44**) (Scheme 13). The iron-mediated arylamine cyclization of complex (**44**) with iodine in pyridine led to the carbazole (**45**) in 40% yield. Annulation of the furan ring by treatment of the carbazole (**45**) with catalytic amounts of Amberlyst 15 in chlorobenzene at 120°C afforded directly furostifoline (**1**) in 66% yield.[42] The improved iron-mediated synthesis leads to furostifoline (**1**) in only five steps and 21% overall yield based on the nitrophenol (**9**). In our first route, we needed seven steps to get a 19% overall yield from the same starting material (Schemes 4 and 5).[41,42]



Scheme 13. Improved iron-mediated total synthesis of furostifoline (**1**).

2.6 OXIDATIVE PHOTOCYCLIZATION OF A 2-SUBSTITUTED INDOLE

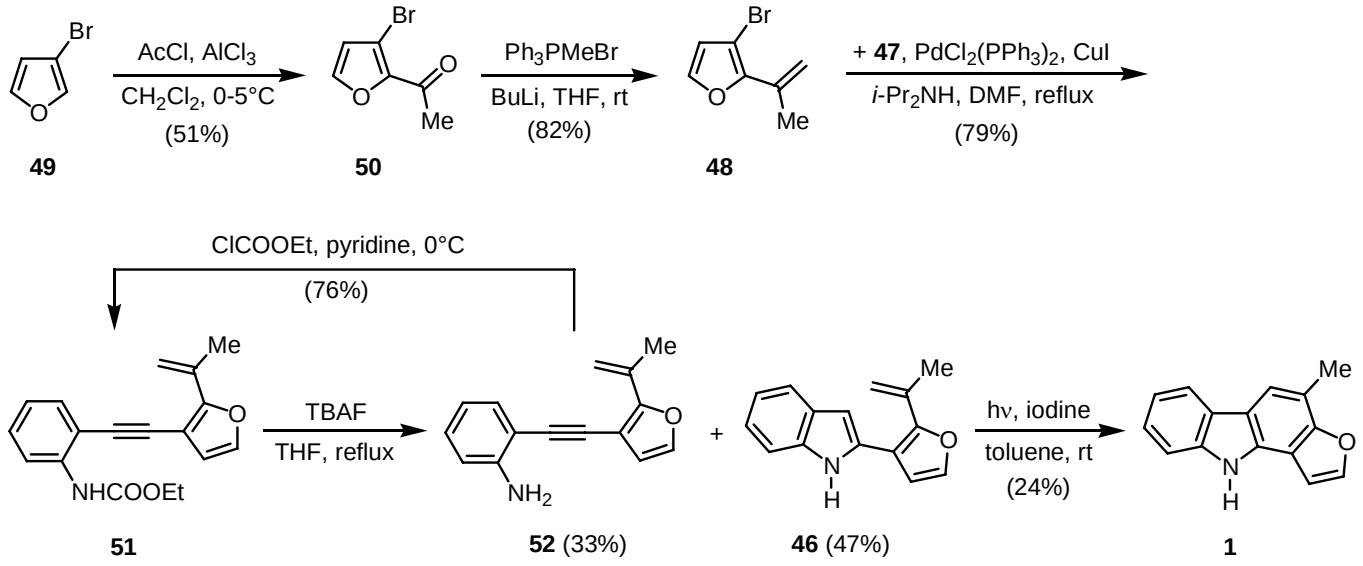
In 2002 Yasuhara *et al.* described a total synthesis of furostifoline (**1**) by oxidative photocyclization of 3-(indol-2-yl)-2-(isopropenyl)furan (**46**), which was obtained by a palladium-catalyzed cross coupling of ethyl 2-ethynylphenylcarbamate (**47**) with 3-bromo-2-isopropenylfuran (**48**) (Scheme 14).[54]



Scheme 14. Retrosynthesis of **1** based on the oxidative photocyclization of a 2-substituted indole.

2-Acetyl-3-bromofuran (**50**) was prepared by Friedel-Crafts acylation of 3-bromofuran (**49**) (Scheme 15).[55] Wittig reaction of 2-acetyl-3-bromofuran (**50**) afforded 3-bromo-2-isopropenylfuran (**48**), which on Sonogashira coupling with ethyl 2-ethynylphenylcarbamate (**47**) led to the *N*-protected (2-isopropenylfur-3-yl)ethynylaniline (**51**) in 65% yield over two steps. The tetrabutylammonium fluoride (TBAF)-promoted reaction of **51** provided the deprotected aniline (**52**) (33%) and 3-(indol-2-yl)-2-(isopropenyl)furan (**46**) (47%). Compound (**52**) was recycled to the *N*-ethoxycarbonyl derivative (**51**) in 76%

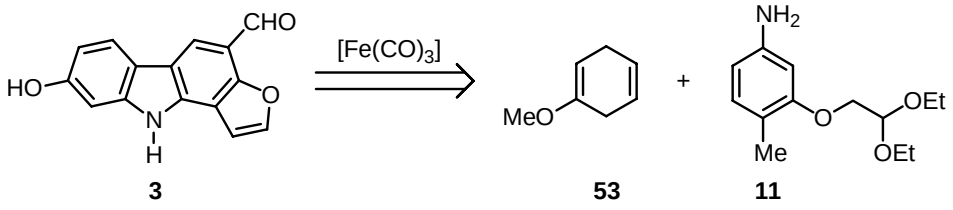
yield by protection of the amino group. The oxidative photocyclization of the 2-substituted indole (**46**) in the presence of a catalytic amount of iodine afforded furostifoline (**1**) in 24% yield.[54] The synthesis reported by Yasuhara and his group provides furostifoline (**1**) in seven steps and 5% overall yield based on 3-bromofuran (**49**).



Scheme 15. Synthesis of furostifoline (**1**) by oxidative photocyclization of the 2-substituted indole (**46**).

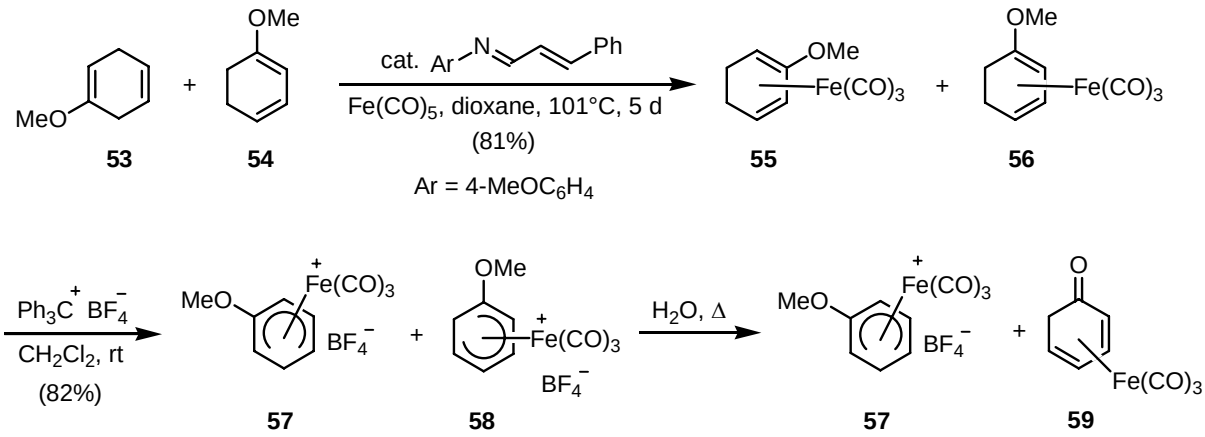
3 IRON-MEDIATED TOTAL SYNTHESIS OF FUROCLAUSINE-A

Recently we reported the first total synthesis of the furo[3,2-*a*]carbazole alkaloid furoclausine-A (**3**).[56] Following the improved protocol developed for synthesis of furostifoline (**1**) (Scheme 13),[42] we projected to achieve the iron-mediated cyclization to the carbazole prior to the annulation of the furan ring. Application of this strategy to the synthesis of furoclausine-A (**3**) led us to 1-methoxycyclohexa-1,4-diene (**53**) and the arylamine (**11**) as precursors.



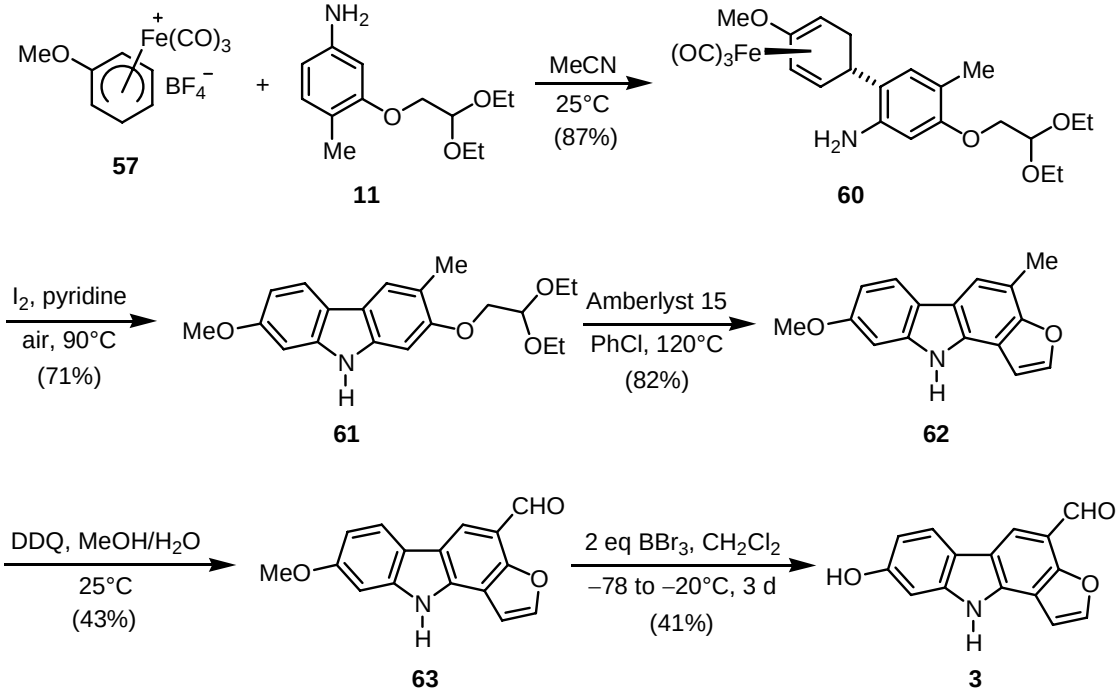
Scheme 16. Retrosynthesis of furoclausine-A (**3**) based on the iron-mediated approach.

Tricarbonyl(η^5-2-methoxycyclohexadienylium)iron tetrafluoroborate (**57**) is prepared on large scale by the 1-azabuta-1,3-diene-catalyzed complexation of the 1-methoxycyclohexadienes (**53**) and (**54**) with pentacarbonyliron to a mixture of the 1-methoxy and 2-methoxy regioisomers (**55**) and (**56**),[44,57] hydride abstraction to the regioisomeric complex salts (**57**) and (**58**), and subsequent hydrolytic separation by chemoselective hydrolysis of the salt (**58**) to tricarbonyl(η^4-cyclohexa-2,4-dien-1-one)iron (**59**).[58]



Scheme 17. Preparation of the 2-methoxy-substituted iron complex salt (**57**).

The arylamine (**11**) was used previously as a starting material for our total synthesis of furostifoline (**1**) and was obtained in two steps and 80% overall yield from 2-methyl-5-nitrophenol (**9**) (Scheme 4). Electrophilic substitution of the arylamine (**11**) by reaction with the iron complex salt (**57**) afforded regio- and diastereoselectively the iron complex (**60**) in 87% yield. Oxidative cyclization of complex (**60**) with iodine in pyridine provided the carbazole (**61**). Annulation of the furan ring by heating the carbazole (**61**) with Amberlyst 15 in chlorobenzene at 120°C afforded 8-methoxyfurostifoline (**62**). Oxidation of **62** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) led to *O*-methylfuroclausine-A (**63**). Cleavage of the methyl ether with boron tribromide provided furoclausine-A (**3**).[56] The iron-mediated synthesis provides furoclausine-A (**3**) in seven steps and 7% overall yield based on 2-methyl-5-nitrophenol (**9**).



Scheme 18. Iron-mediated synthesis of furoclausine-A (**3**).

4 CONCLUSION

From the four known naturally occurring furocarbazole alkaloids so far only two, furostifoline (**1**) and furoclausine-A (**3**), have been obtained by total synthesis. Six total syntheses have been reported for furostifoline (**1**) (Table 1). Three of them, described by Beccalli, Hibino, and Yasuhara, rely on an electrocyclization of an intermediate hexatriene as the key-step of carbazole construction. Beccalli's oxidative photocyclization of a 3-substituted indole and Hibino's thermal electrocyclization of a 2,3-disubstituted indole are quite efficient in the carbazole forming step (69% and 61% yield, respectively). However, these syntheses are comparatively long (nine and ten steps, respectively). Yasuhara's synthesis is shorter and requires only seven steps, but the overall yield suffers from the inefficiency of the oxidative photocyclization of the 2-substituted indole (24% yield). Timári's approach uses Cadogan's nitrene insertion for the carbazole formation and is quite short (six steps). However, the only moderate yields for both annulations (furan ring: 51% yield and carbazole ring: 42% yield) result in a low overall yield (8%). Both of our syntheses apply the iron-mediated oxidative cyclization for the construction of the carbazole ring, which also occurred in only moderate yield (36% and 40%, respectively). However, due to their high convergence, these syntheses are very efficient. In our first approach, the annulation of the furan was performed prior to the carbazole cyclization, which required a protection of the amino group. By reversal of the cyclization sequence the protection was avoided, which led to an even shorter access. This improved version of the iron-mediated synthesis needs only five steps and provides furostifoline (**1**) in 21% overall yield.

Table 1. Comparison of the Different Total Syntheses of Furostifoline (**1**)

Year	Res. group	Method (key-step of carbazole construction)	Steps [a]	Overall yield [a]	Ref.
1996	Knölker *et al.*	Iron-mediated oxidative cyclization	7	19%	41, 42
1998	Beccalli *et al.*	Oxidative photocyclization	9	26%	47
1998	Hibino *et al.*	Thermal electrocyclization	10	29%	48, 49
1999	Timári *et al.*	Reductive cyclization by nitrene insertion	6	8%	51
2000	Knölker *et al.*	Iron-mediated oxidative cyclization	5	21%	42
2002	Yasuhara *et al.*	Oxidative photocyclization	7	5%	54

[a] The number of steps and the overall yields are calculated considering the longest sequence of the synthesis based on a commercial starting material.

Recently, the improved iron-mediated approach to furocarbazoles could be utilized for the first total synthesis of the more highly functionalized furoclausine-A (**3**) (seven steps and 7% overall yield). Further applications of this methodology are under active investigation.

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