Synthesis of Variolins, Meridianins, and Meriolins

Subjects: Chemistry, Organic

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Marine natural products are a source of essential significance due to a plethora of highly diverse biological properties. The naturally occurring (aza)indole alkaloids variolin B (**1**), meridianins (**2**), and their synthetic hybrids meriolins (**3**) exhibit potent kinase inhibitory activities.

indole alkaloids marine natural products natural product syntheses variolins meridianins meriolins

1. Syntheses of Variolins

1.1. First Total Synthesis by Morris and Anderson

The first total synthesis of variolin B (**1**) was achieved by Morris and Anderson in 2001 [1]. Later in 2005, they published the full details of their synthetic strategy together with the synthesis of the synthetic analog desoxyvariolin B [2]. They recognized the C2-symmetry of intermediate **8,** which is cyclized to the pyridopyrrolopyrimidine in the following key step. After halogen lithium exchange in the methylthiopyrimidine **4**, the reaction with diethyl carbonate (**5**) gave the symmetric ketone **6**. The reaction with the lithiated pyridine **7**, followed by the key step tandem deoxygenation and cyclization in the presence of triethylsilane and TFA led to the variolin core structure **9**. The introduction of the amino groups was achieved by oxidizing the dimethylthiol **9** with *m*-chloroperbenzoic acid (mCPBA) to the corresponding disulfoxide, which was reacted with *p*-methoybenzylamine (PMB amine) (**10**) to give the bisprotected amine **11**. Demethylation of **11** and removal of the PMB protecting groups gave the trifluoroacetate salt of the title compound, which was neutralized with concentrated ammonia to give variolin B (**1**) in an eight-step synthesis and an overall yield of 11% (**Figure 1**) [1].

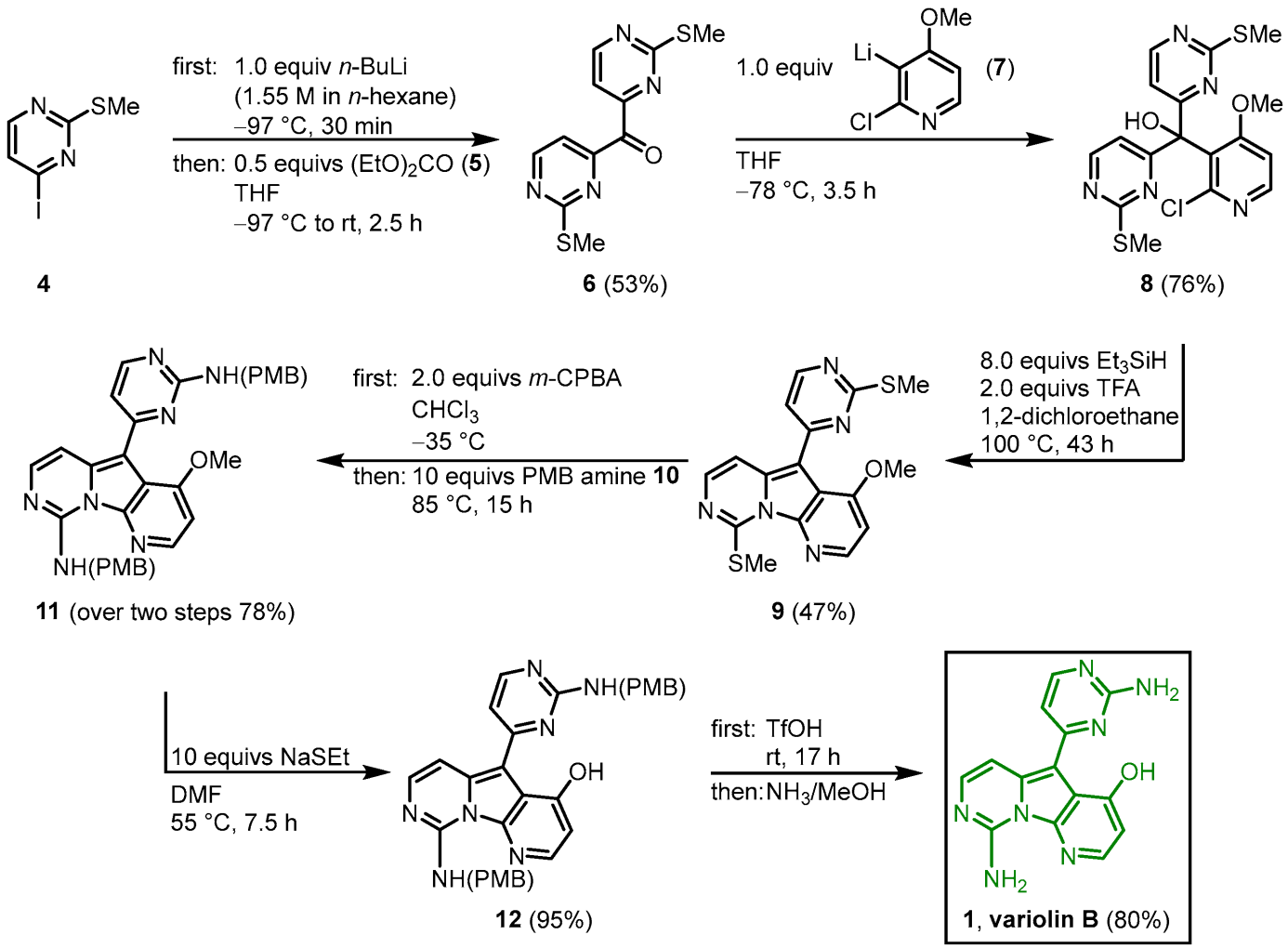


Figure 1. First total synthesis of variolin B (**1**) by Morris and Anderson [1].

1.2. Synthesis by Molina and Fresneda

The next synthetic approach was conducted by Molina and Fresneda, who published their syntheses of **1** in 2002 [3] and a modified synthetic route together with the synthesis of an analog in 2003 [4]. This approach starts with the synthesis of the 7-azaindole **16**. Aldehyde **13** was condensed with azidoacetate **14** and the resulting vinyl azide **15** cyclized to azaindole **16** via a nitrene insertion. After *N*-protection with 2-(trimethylsilyl)ethoxymethyl (SEM), the chloride key intermediate **19** was synthesized in a two-step procedure (**Figure 2**).

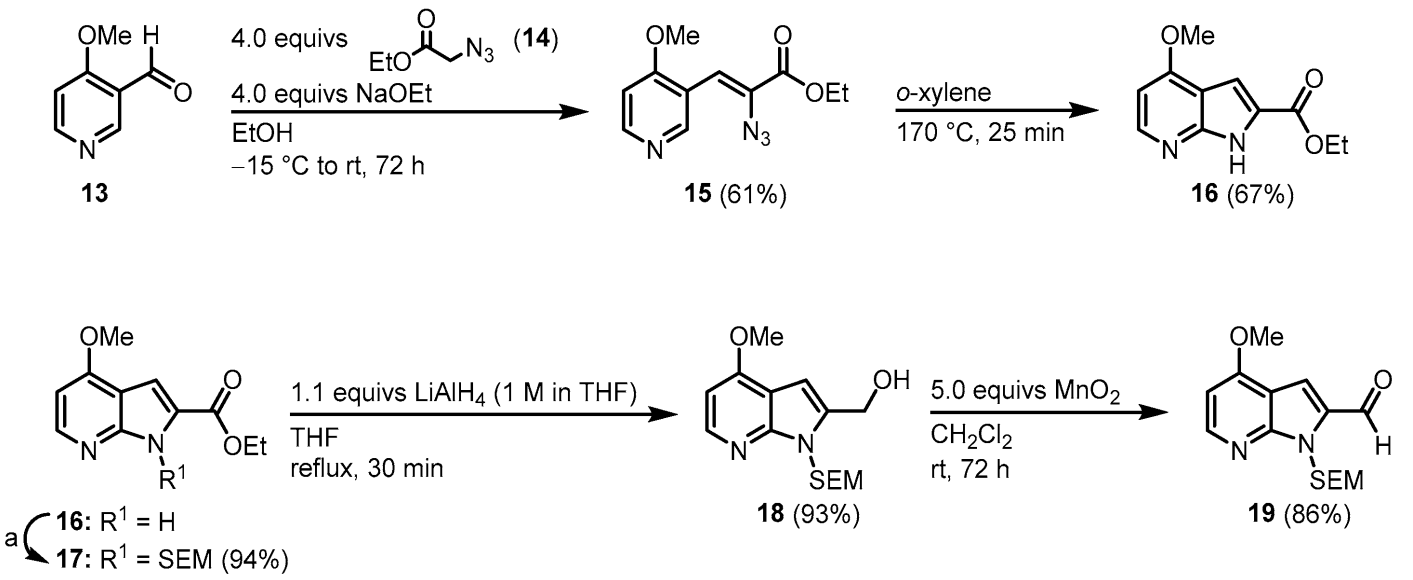


Figure 2. Synthesis of key intermediate azaindole **19**. Reaction conditions for a: first: 1.4 equivs NaH, DMF, rt, 45 min. Then: 1.4 equivs SEM-Cl, rt, 12 h [3].

Next, two different approaches are reported (**Figure 3**). Aldehyde **19** was similarly condensed as aldehyde **13** to give vinyl azide **20**. After *N*-SEM-deprotection, a Staudinger reaction with triphenylphosphane led to iminophosphorane **21** in a one-pot reaction. Reaction with benzyl isocyanate (**22**) in the key aza-Wittig reaction gave a non-isolable carbodiimide that subsequently cyclized to the desired pyridopyrrolopyrimidine moiety **23**.

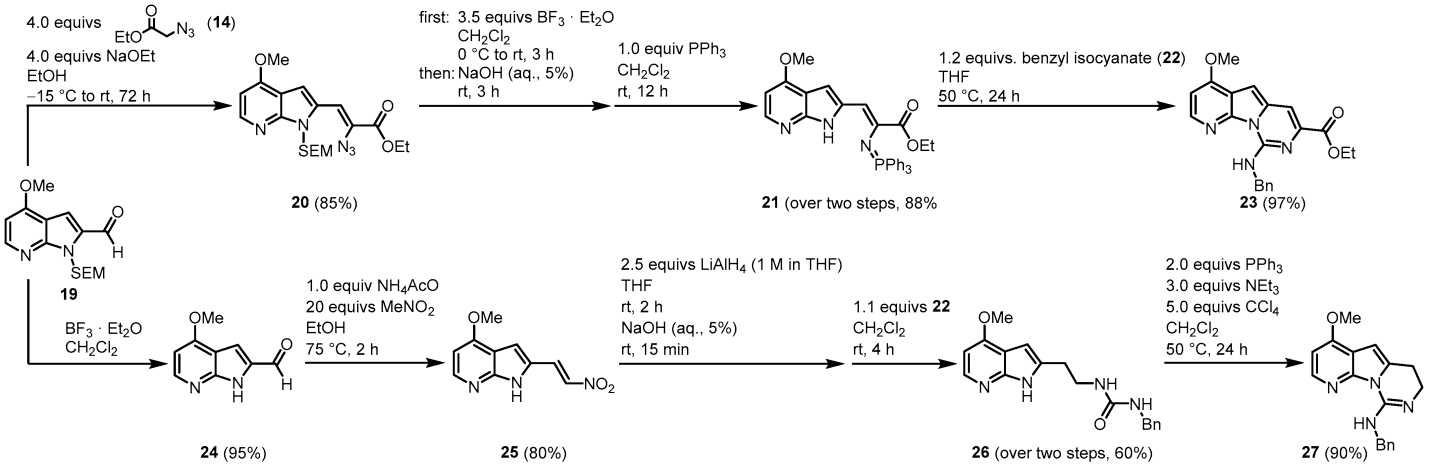


Figure 3. Two approaches to the synthesis of the tricyclic pyridopyrrolopyrimidine structures, **23** and **27** [3].

Molina and Fresneda developed a second approach to obtain the tricyclic variolin core without the ester group at C-7. After the *N*-SEM-deprotection of **19**, a nitroaldol condensation with nitromethane led to the formation of **25**. Treatment with lithium aluminum hydride gave the corresponding 2-(2-aminoethyl)-7-azaindole, which was sequentially converted to the urea derivative **26** with benzyl isocyanide (**22**) without isolation. The **26** was dehydrated to the carbodiimide, which subsequently cyclized to the dihydropyrimidine **27** using the Appel reagent (CCl_4/PPh_3/NEt_3). Applying both synthetic approaches, an oxygen substituent is placed at C-4 and a nitrogen

substituent at C-9. The next step was to introduce the 2-aminopyrimidine ring at C-5, consequently leading both approaches to the acylated intermediate **31**. The reaction of **23** with phosphorus oxychloride and *N*,*N*-dimethylacetamide (DMA) (**28**) allowed the direct introduction of an acetyl group at C-5. Ester hydrolysis led to the carbonic acid **30,** and the thermal treatment forced the formation of intermediate **31** by decarboxylation. The route starting from **27** began with the introduction of a bromine substituent at C-5 and the reaction of bromine **32** with *n*-tributyltin(1-ethoxyvinyl)stannane (**33**) in the presence of dichlorobis (triphenylphosphine)-palladium(II) introduced to the acetyl group at C-5. Oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) gave the intermediate **31** (**Figure 4**).

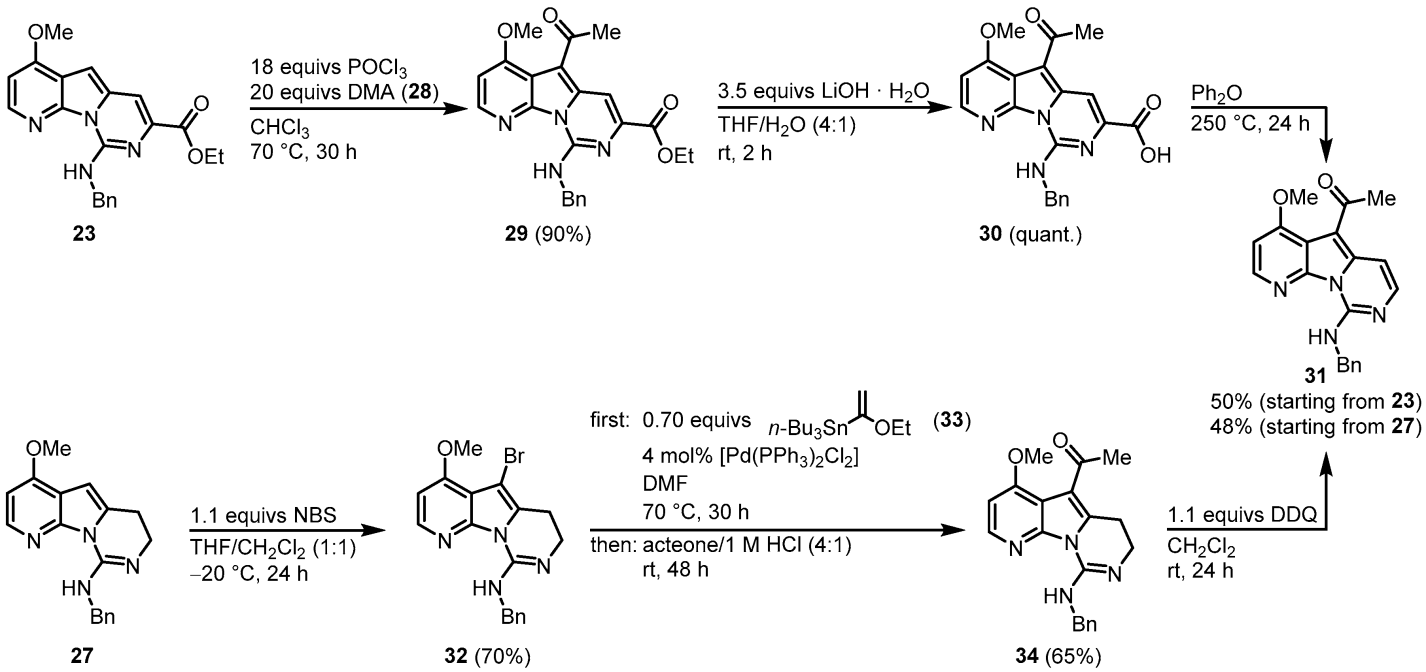


Figure 4. Introduction of an acetyl group at C-5 [3].

The 2-aminopyrimidine substituent was synthesized using a protocol developed by Bredereck (**Figure 5**) [5]. Enaminone **36** was synthesized from **31** with *N*,*N*'-dimethylformamide di-*tert*-butylacetal (**35**) in DMF. Condensation with guanidine hydrochloride (**37**) led to ring closure and formed the desired 2-aminopyrimidine **38**.

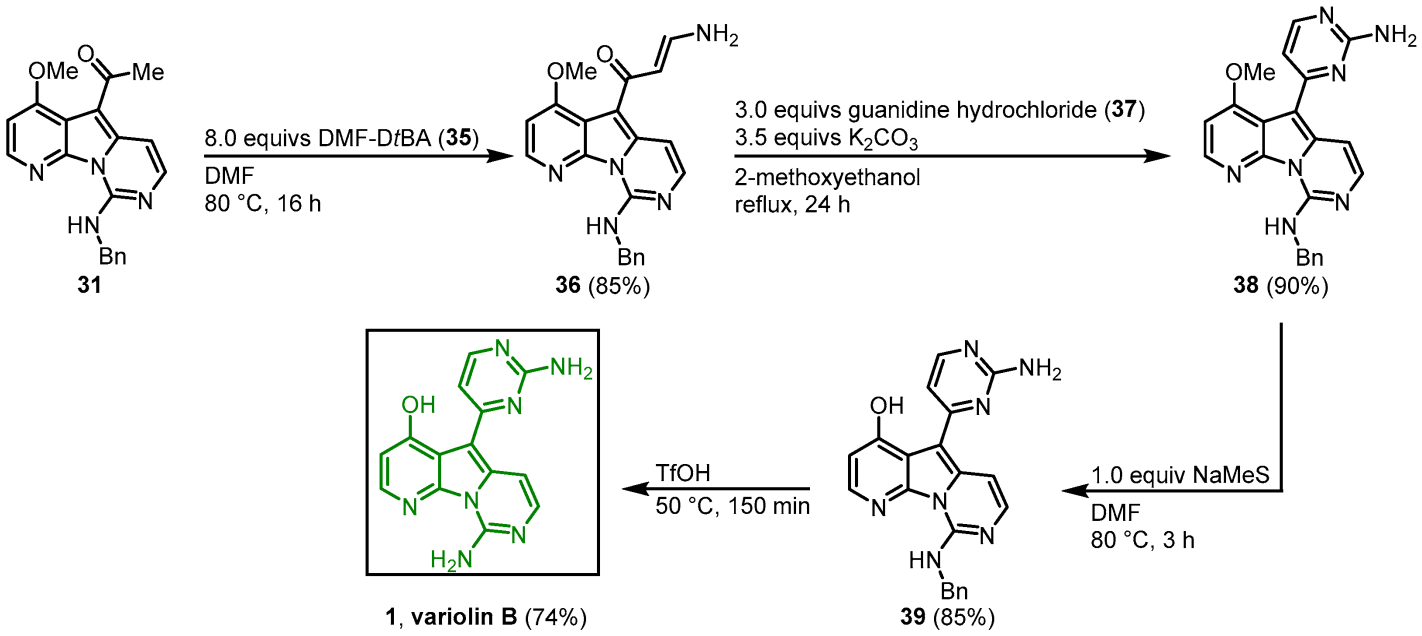


Figure 5. Synthesis of the 2-aminopyrimidine ring to give access to variolin B (**1**) [3].

1.3. Variolin B Approach by Alvarez

In 2003, Alvarez published the synthesis of variolin B (**1**) and the synthetic analog desoxyvariolin B [6][7][8]. Starting from 4-methoxy-7-azaindole (**40**), a lithium carboxylate was used as an *N*-protecting group as well as an *ortho*-directing substituent to form a 2-lithio-7-azaindole with a protocol by Katritzky [9]. Reaction with 2-(1,3-dioxoisindolin-2-yl)acetaldehyde (**41**) gave the alcohol **42** that was protected with dihydropyran. *N*-deprotection of **43** by hydrazinolysis gave the aminoacetal **44**. Ring closure was achieved by the reaction with *N*-tosylcarbonimidic dichloride (**45**) and diisopropylethylamine (DIPEA) giving **46** in a diasteriometric mixture in a ratio of 1:1. Removal of the *O*-tetrahydropyran (THP) protecting group and elimination of the resulting hydroxy group by the formation of its mesylate and treatment with triethylamine afforded the pyridopyrrolopyrimidine scaffold (**48**). Regioselective iodination with *N*-iodosuccinimide (NIS) gave the key intermediate **49** (**Figure 6**).

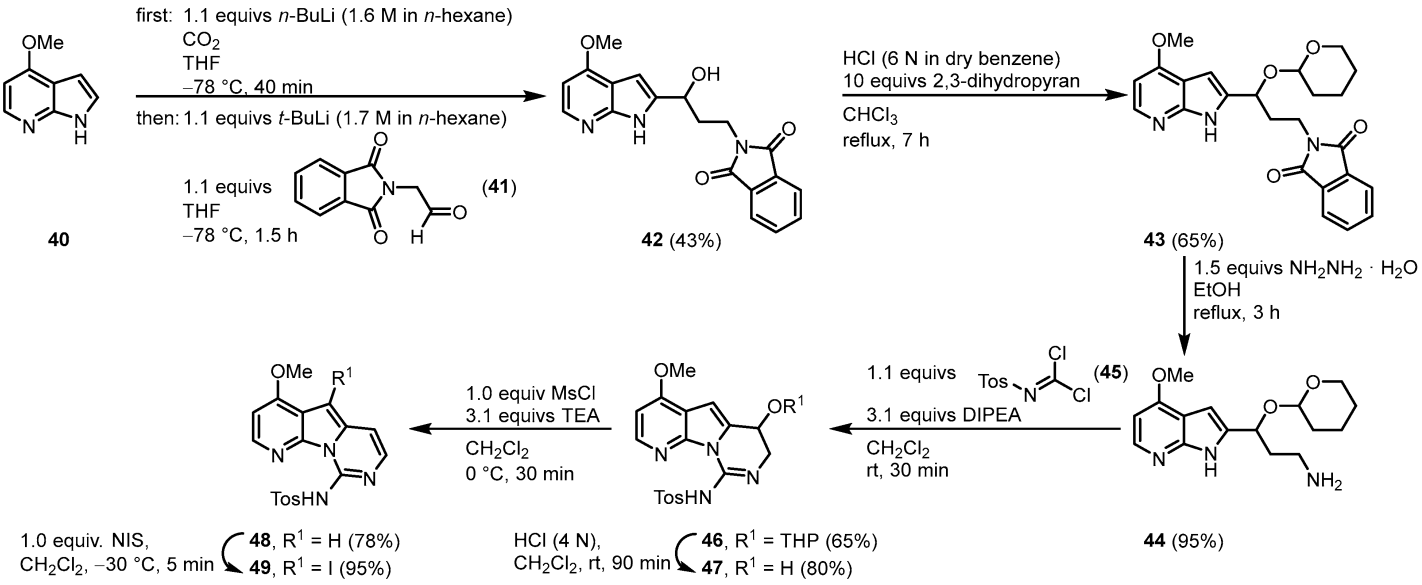


Figure 6. Synthesis of the key intermediate iodide **49** [6].

A Stille reaction of **49** and 2-acetylamino-4-trimethylstannylpyrimidine (**50**) in the presence of tris(dibenzylideneacetone)dipalladium(0) afforded **51**. The *O*-demethylation and *N*-acetyl-deprotection were achieved by the treatment of **51** with hydrobromic acid, and after reductive photolysis with hydrazine as a reducing agent and 1,4-dimethoxybenzene as an electron source, the tosyl group was cleaved to give variolin B (**1**) in a 10-step synthesis with an overall yield of 1% (**Figure 7**).

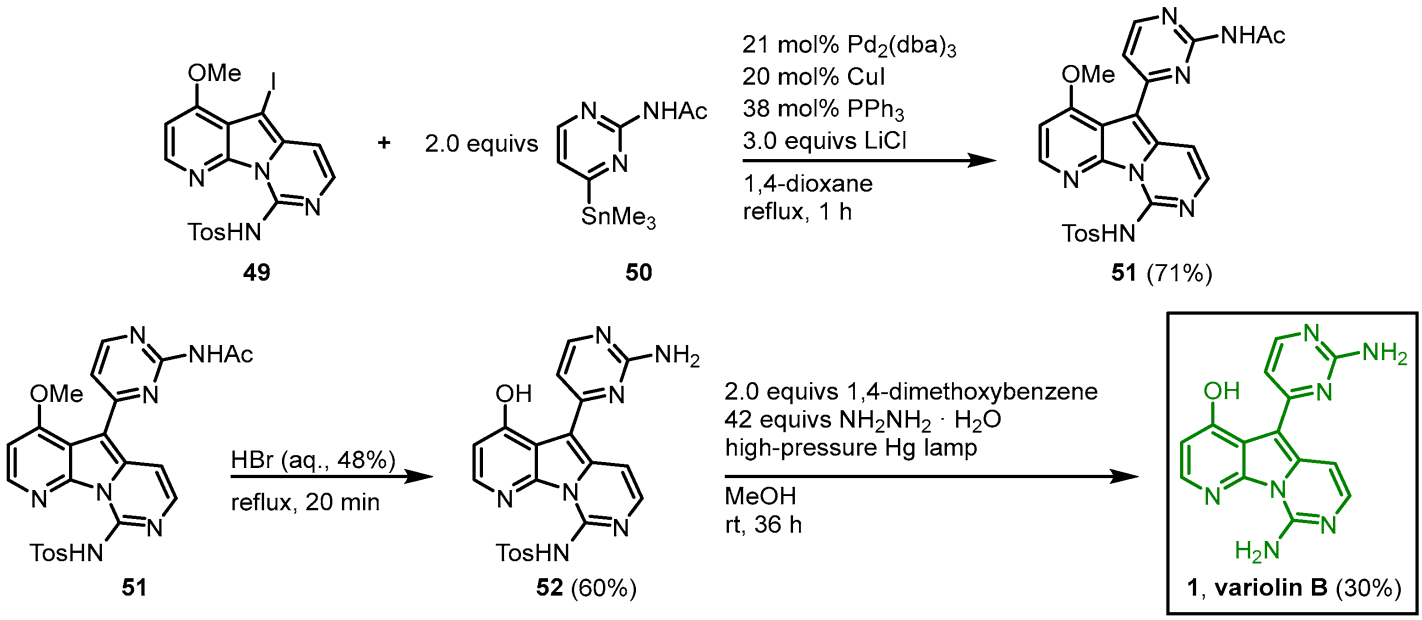


Figure 7. Synthesis of variolin B (**1**) via Stille coupling as a key reaction step [6].

1.4. Synthesis of Variolin B by Burgos and Vaquero

The 2008 approach by Burgos and Vaquero to synthesize variolin B (**1**) followed the strategy to design the highly functionalized trihalo-substituted pyridopyrrolopyrimidine core **55** and introduce the substituents via palladium-mediated cross-coupling reactions [10][11]. The functionalized 7-azaindole **53** was synthesized from 7-azaindole in six single steps [12]. The **53** was reacted with *N*-tosylmethyl dichloroformimide (**54**) under phase-transfer conditions in the two-phase system LiOH (aq., 30%)/CH_2Cl_2 (1:1) with tetrabutylammonium chloride to give the trihalo-substituted compound **55**. The C-9 amino substituent was introduced by a palladium-mediated C-N bond formation, using lithium bis(trimethylsilyl)amide (LiHMDS) and triphenylsilylamine as an ammonia source. The reaction required the use of the ligand [1,1′-biphenyl]-2-yldi-*tert*-butylphosphane (JohnPhos). After *N*-acetyl-protection, **56** was obtained (**Figure 8**).

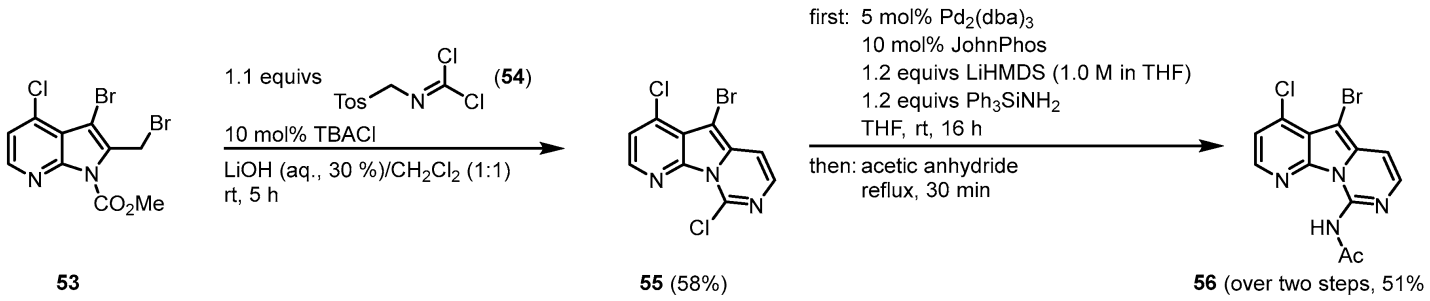


Figure 8. Synthesis of the trihalo core and introduction of the C-9 amino substituent [10].

Next, in a debromination-iodination process, tris(trimethylsilyl)silane (TTMSS) and azobisisobutyronitrile (AIBN) and subsequently NIS were used to exchange the bromo compound **56** to the more reactive iodo derivative **57**. In a palladium-catalyzed cross-coupling reaction with the pyrimidyl stannyl reagent **58,** the C-C bond at C-5 was formed and the deprotection of both amino groups led to **59**. Then, in a palladium-promoted C-O coupling microwave (MW) reaction with sodium *tert*-butoxide, the *tert*-butyl group was introduced at C-4 to give the *tert*-butyl ether **60**, and in a final step, the *tert*-butyl moiety was cleaved to give variolin B (**1**) (**Figure 9**). Starting from **53,** variolin B was synthesized in seven steps with an overall yield of 5% [10][11].

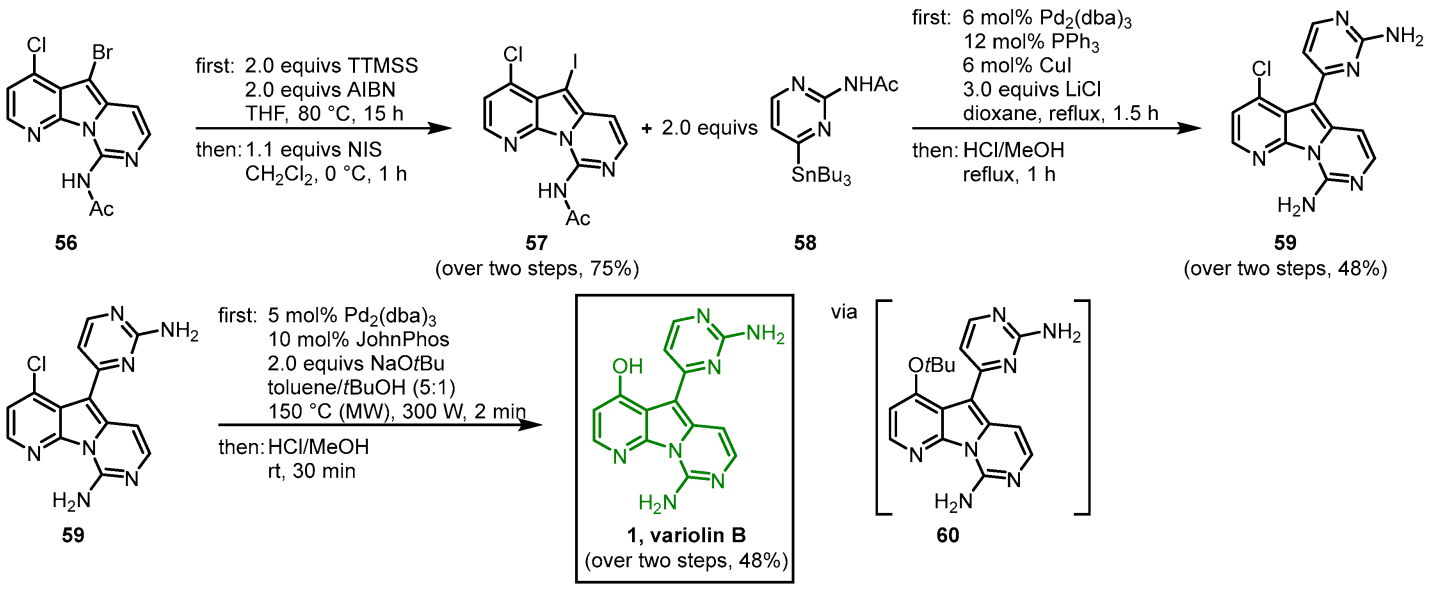


Figure 9. Palladium-mediated synthesis of variolin B (**1**) [10].

2. Syntheses of Meridianins

2.1. First Total Synthesis of Meridianins D and G by Jiang and Yang

In the early 2000s, Jiang and Yang published a straightforward synthesis of meridianins D and G. Starting from the corresponding indolyl boronic acid, **61** with 4-chloropyrimidine **62a** is the key reaction in this meridianin synthesis to furnish protected meridians **63** (**Figure 10**). After *N*-tosyl-deprotection of compounds **63** with sodium hydroxide, meridianin G (**2g**) is obtained in an overall yield of 63%, and meridianin D (**2d**) in an overall yield of 40% in this two-step synthesis [13].

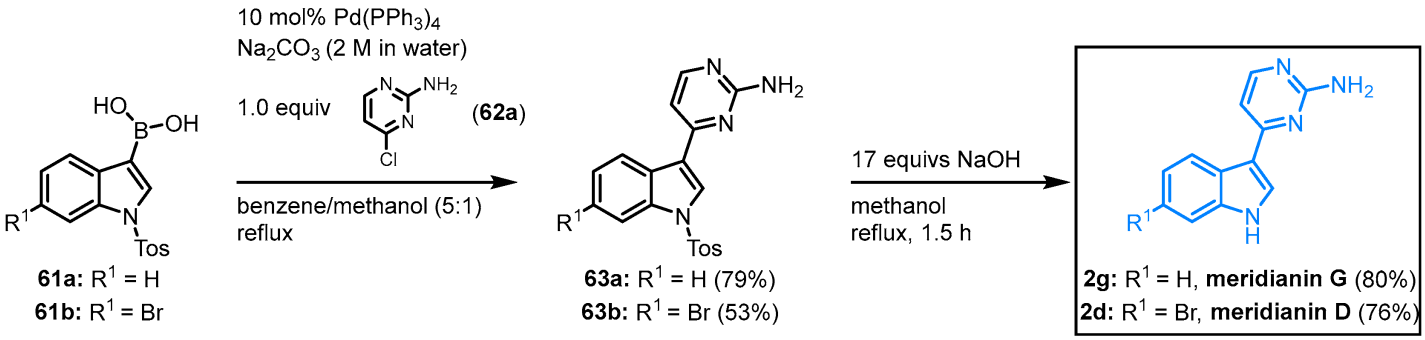


Figure 10. First synthesis of meridianins D and G [13].

2.2. Synthesis of Meridianins by Fresneda and Molina

Shortly after the publication of the first meridianin syntheses, Fresneda and Molina developed a facile two-step synthesis of meridianins, starting from *N*-tosyl-3-acetylindoles **64**. The reaction of **64** with dimethylformamide dimethylacetal (DMF-DMA) gave the enaminone **66**. The key step was the formation of the 2-aminopyrimidine ring by condensation of **66** with guanidine hydrochloride (**37**). Molina and Fresneda described the synthesis of meridianin D (**2d**, 65% overall yield) as well as the first total synthesis of meridianin C (**2c**, 59% overall yield) and *O*-benzyl-protected derivative **2h**. After *O*-deprotection and dehalogenation of **2h** with hydrogen and palladium on carbon, meridianin A was synthesized for the first time (**2a**, 31% overall yield) or respectively by treating **2h** with the milder deprotecting agent; no dehalogenation occurred to give the first total synthesis of meridianin E (**2e**, 24% overall yield) (**Figure 11**) [14][15].

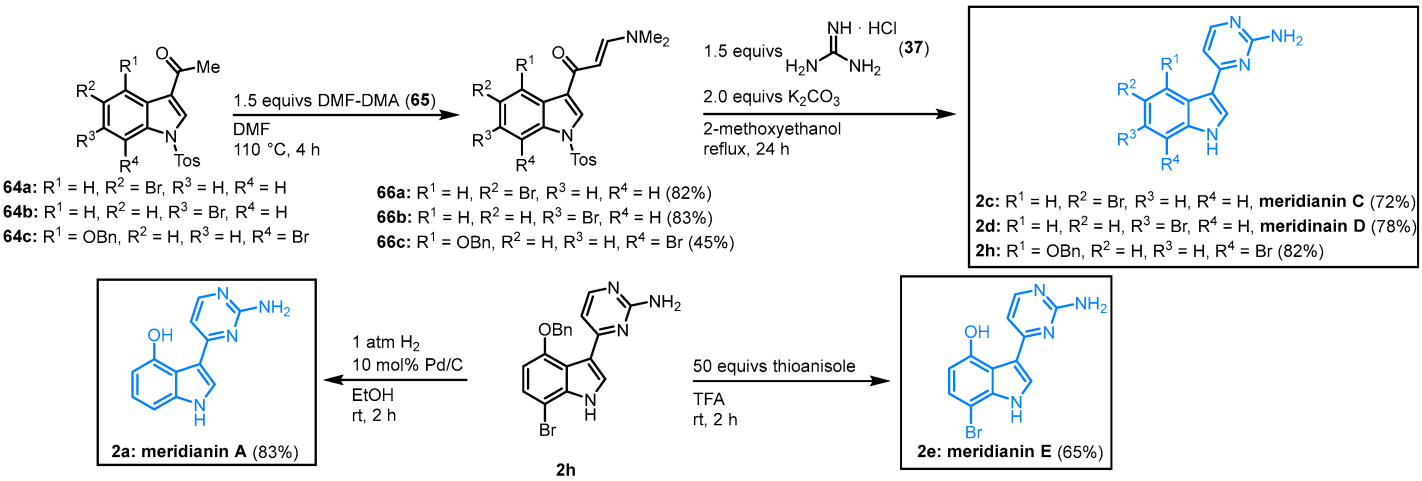


Figure 11. Synthesis of meridianins A, C, D and E by Molina and Fresneda [14].

2.3. Meridianin Synthesis by Müller via Carbonylative Alkynylation

In 2005, Karpov et al. published a concise synthesis of meridianins C, D, and G. *Tert*-butoxycarbonyl(Boc)-protected indoles (**67**) reacted in a palladium-catalyzed three-component carbonylative alkynylation with TMS-protected acetylene (TMSA) (**68**) to the TMS-alkynones **69**. Subsequent cyclocondensation with guanidine (**37**) concluded the meridianin synthesis as both the TMS- and the Boc-group are cleaved under the chosen reaction condition. Meridianin G was obtained with an overall yield of 45%, and meridianin C and D could be isolated with 50% overall yield (**Figure 12**).

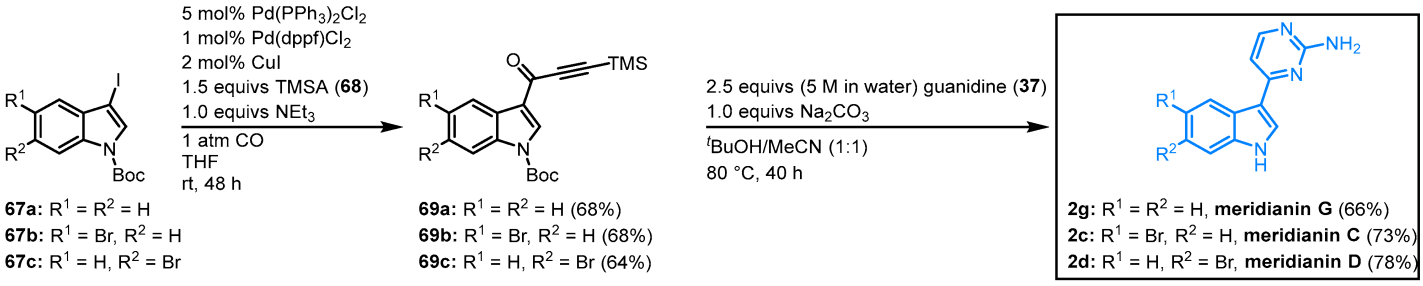


Figure 12. Synthesis of meridianins C, D, and G by Karpov et al. via carbonylative alkynylation [16].

2.4. Meridianin Synthesis by Penoni via Indolozation of Nitrosoarenes

Efficiently, Penoni approached the synthesis of meridianins C and G. In a one-pot process, the corresponding nitrosobenzene **70** was reacted with 2-amino-4-ethynylpyrimidine (**71**) to give the natural products **2c** (28%) and **2g** (41%) (**Figure 13**) [17].

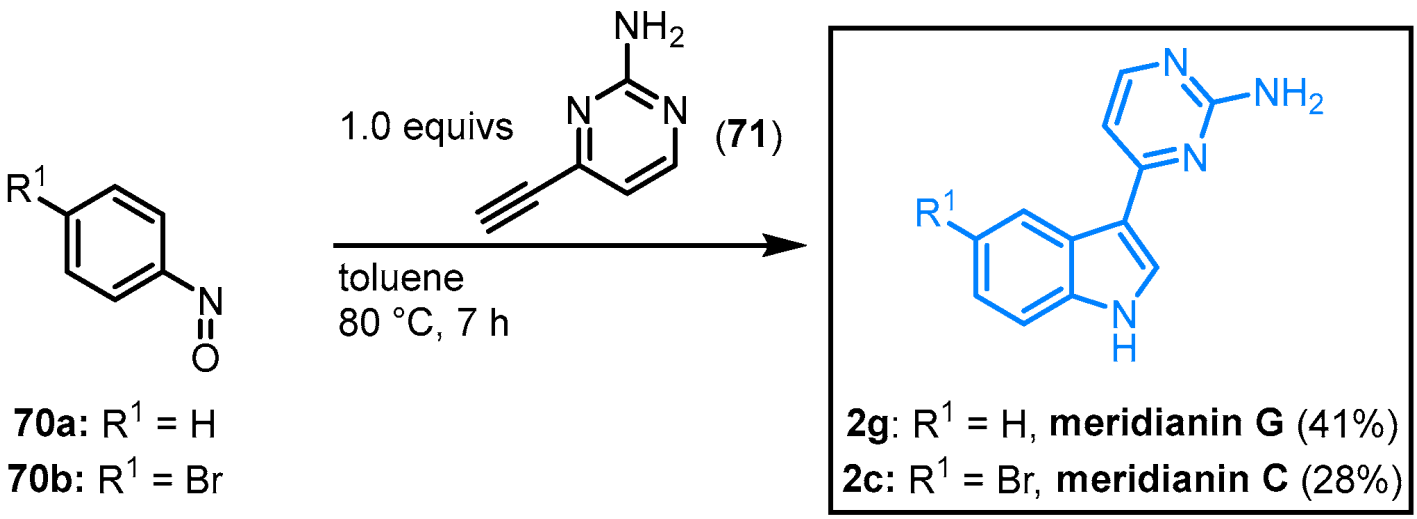


Figure 13. Indolization of nitrosoarenes for the synthesis of meridianins C and G by Penoni [17].

2.5. Synthesis of Meridianins via One-Pot Masuda Borylation-Suzuki Coupling Sequence by Müller

In 2011 and 2022, Müller and coworkers published a different synthetic strategy addressing meridianins. In a palladium-catalyzed Masuda borylation-Suzuki coupling (MBSC), one-pot procedure meridianins C, D, F and G, as well as the meridianin A precursor *O*-methyl meridianin A (**2i**), could be synthesized. 3-Iodo-*N*-protected indoles **67** react with pinacolyl borane (HBpin) (**72**) and without the isolation of the resulting boronic acid ester, the subsequent Suzuki coupling with 2-aminopyridine (**62a**) leads to the formation of *O*-methyl meridianin A (**2i**) and meridianins D (**2d**) and G (**2g**). The Boc-protecting group is cleaved under the Suzuki conditions. In contrast to this, *N*-tosyl-protected indoles **73** require an additional deprotecting step that can be implemented in the one-pot process. Treatment with potassium hydroxide leads to meridianins C (**2c**), F (**2f**), and G (**2g**) (**Figure 14**).

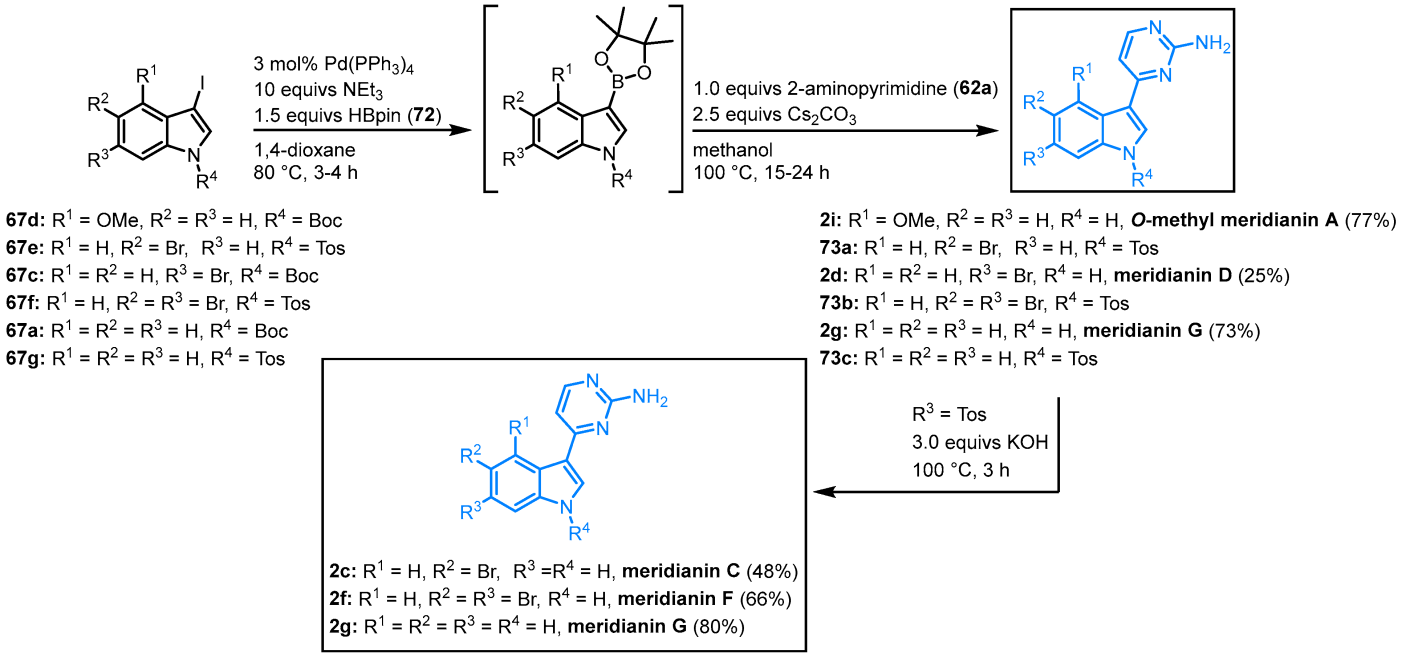


Figure 14. Synthesis of meridianins by Müller via MBSC sequence [18][19].

When *O*-methyl meridianin A (**2i**) was melted with pyridinium hydrochloride, the natural product **2a** could be isolated in 85% (**Figure 15**) [18].

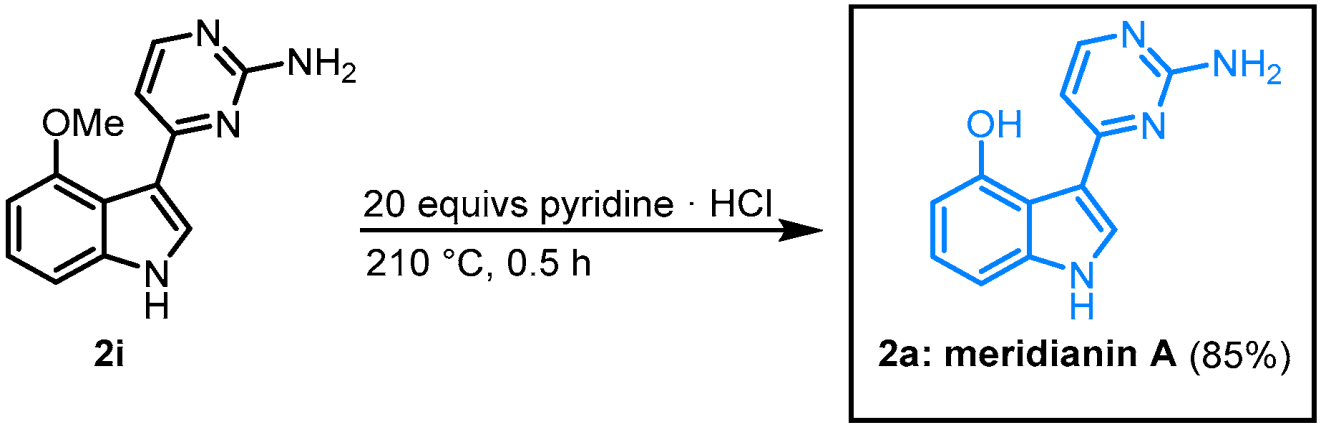


Figure 15. Demethylation of **2i** furnished meridianin A.

2.6. Synthesis of Meridianin F by Grainger

Grainger and coworkers worked on the regioselective dibromination of methyl indole-3-carboxylate and its application in the synthesis of indole building blocks. In this context, the synthesis of meridianin F was performed. Dibrominated indole **74** was reacted with *N*,*O*-dimethylhydroxylamine (**75**) to form the corresponding Weinreb amide **76**. Treatment with lithium(trimethylsilyl)acetylide (**77**) led to the formation of alkynone **78**. In the aftermath, meridianin F (**2f**) was furnished by cyclocondensation with guanidine (**37**) according to the aforementioned protocol by Müller in an overall yield of 37% (**Figure 16**) [16][20].

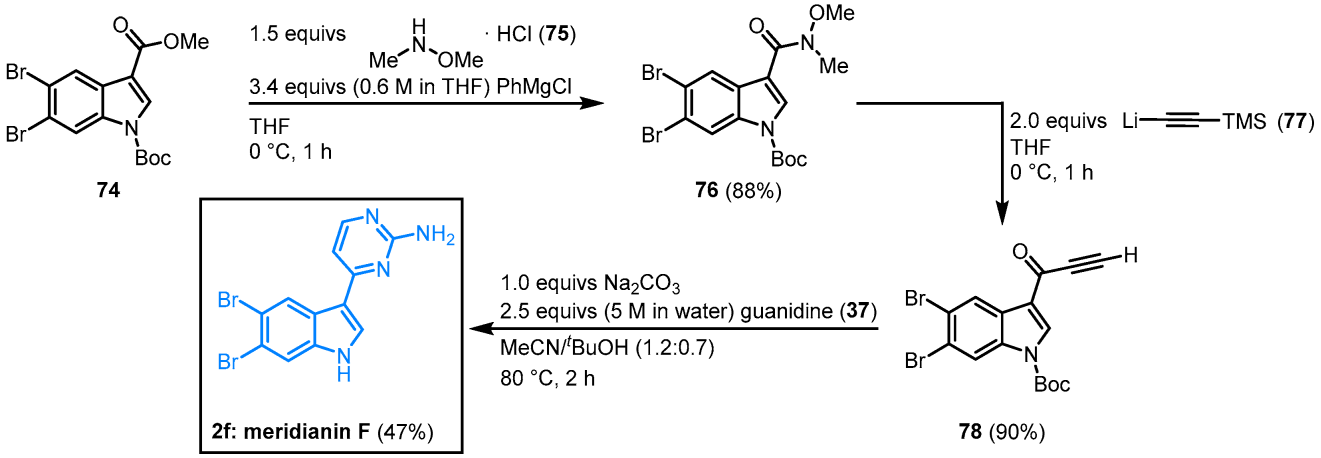


Figure 16. Synthesis of meridianin F by Grainger [20].

2.7. Domino Amino-Palladation Reaction for the Synthesis of Meridianins C and G by Morris

Morris and coworkers came up with a modified Cacchi protocol [21] to synthesize meridianins from readily available monocyclic precursors in a catalytic domino amino-palladation reaction [22]. The four-step synthesis starts with a Sonogashira coupling of 2-iodoaniline **79** and TMSA (**68**) to give 2-alkynyl anilines **80** followed by *N*-mesylation to give the activated sulfonamide **82**. The reaction of **82** with the *N*-Boc-protected 4-iodo-2-aminopyrimidine **83** in a Cacchi-type protocol led to the formation of the protected meridianin precursors **84**. The global deprotection was achieved in a one-pot acid/base process and furnished meridianins C (**2c**, 31% overall yield) and G (**2g**, 45% overall yield) in four steps (**Figure 17**).

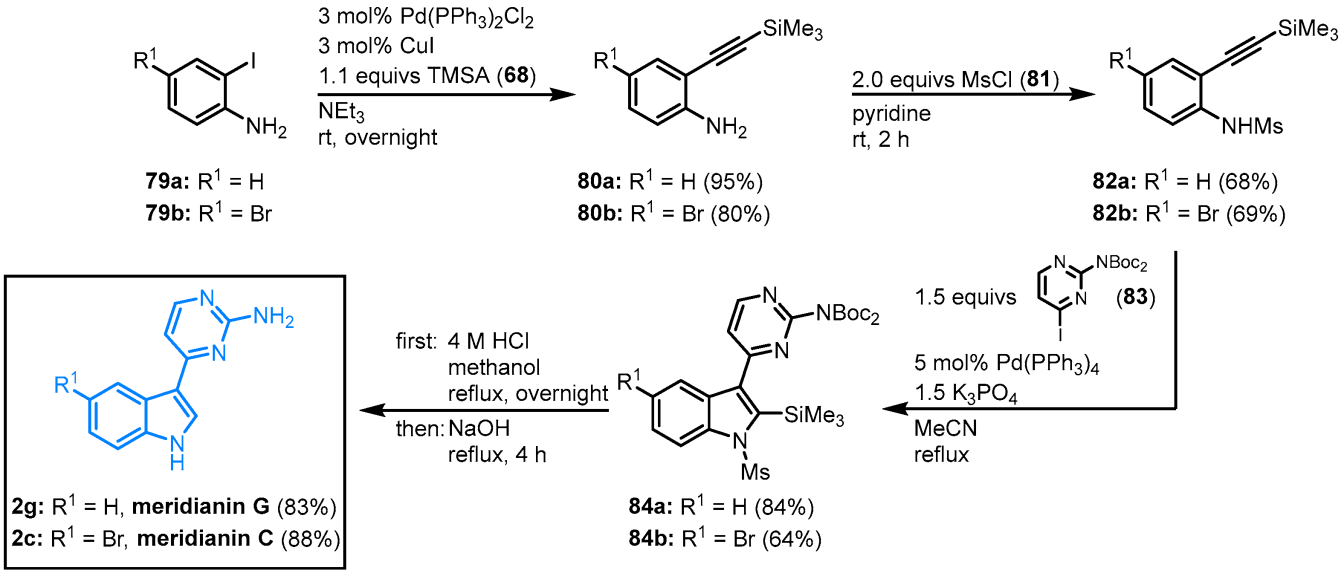


Figure 17. Synthesis of meridianins C and G via palladium-catalyzed domino reaction by Morris [22].

3. Syntheses of Meriolins

3.1. First Synthesis of Meriolin 1 by Molina and Fresneda

With their protocol for the synthesis of meridianins in hand, Molina and Fresneda were able to extend their strategy to 7-azaindoles, leading to the first synthesis of meriolin 1 (**3a**). 7-Azaindole (**85a**) was treated with acetyl chloride (**86**) in the presence of tin (IV) tetrachloride, which afforded 3-acetyl-7-azaindole (**87**). After *N*-tosyl-protection, the enaminone **90** was furnished after the reaction of **89** with DMF-DMA (**65**) similarly to the meridianin synthesis. Cyclocondensation with guanidine (**37**) led to the 2-aminopyrimidine formation and meriolin 1 (**3a**) was obtained in the 16% overall yield (**Figure 18**) [14].

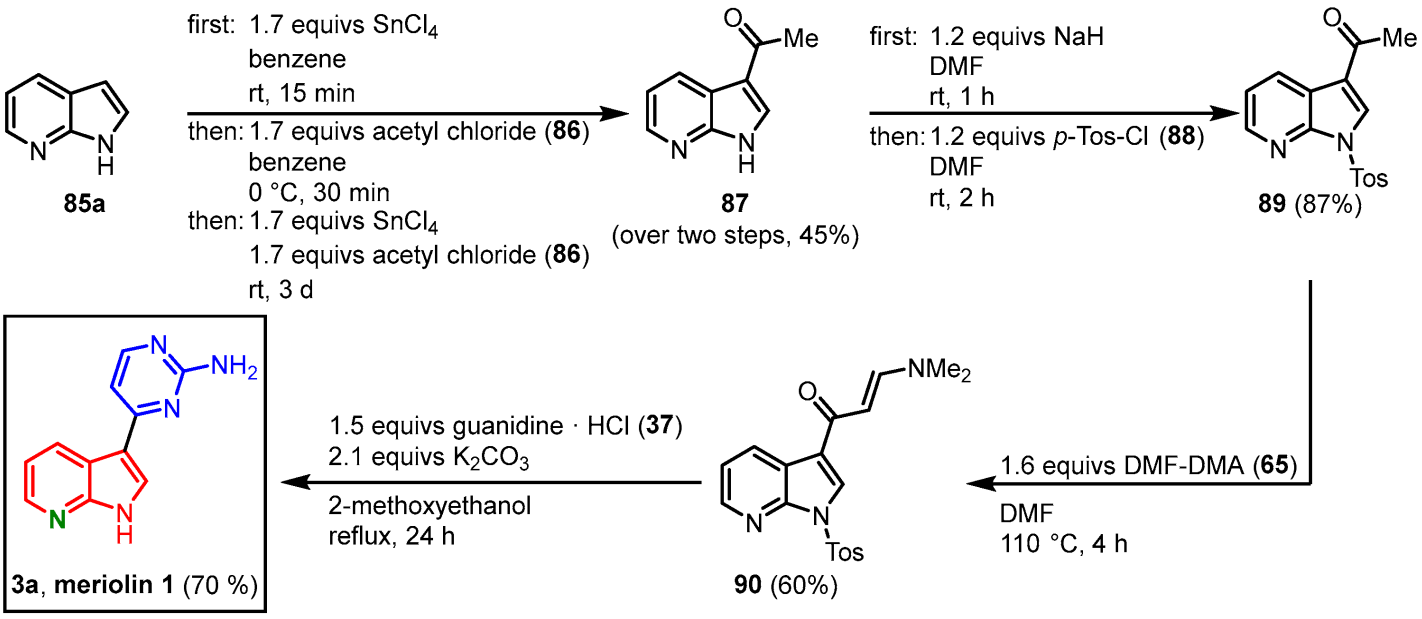
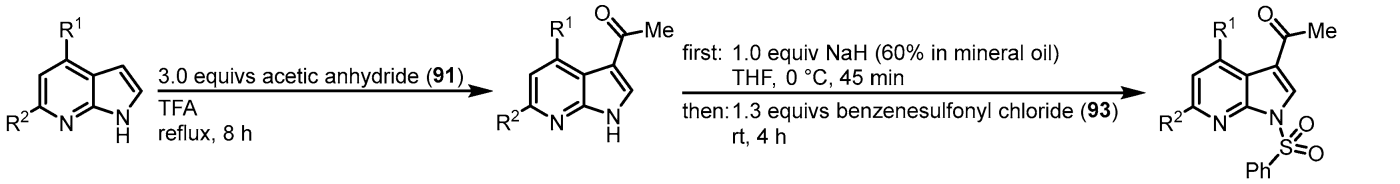


Figure 18. Synthesis of meriolin 1 by Molina and Fresneda [14].

3.2. Synthesis of Meriolin Derivatives by Joseph and Meijer

Joseph, Meijer, and coworkers used the strategy by Molina and Fresneda for the synthesis of meriolin 1 and in addition to that were able to generate a large substance library of novel meriolin derivatives. Starting from substituted 7-azaindoles **85,** acylation in 3-position was achieved by treatment with acetic anhydride (**91**) and trifluoroacetic acid. *N*-protection with benzenesulfonyl chloride (**91**) afforded the derivatives **94** (**Figure 19**) [23][24].



85b: R^1 = Cl, R^2 = H
85c: R^1 = OMe, R^2 = H
85d: R^1 = H, R^2 = Br
85e: R^1 = OEt, R^2 = H
85f: R^1 = OPr, R^2 = H

92a: R^1 = Cl, R^2 = H (85%)
92b: R^1 = OMe, R^2 = H (55%)
92c: R^1 = H, R^2 = Br (99%)
92d: R^1 = OEt, R^2 = H (84%)
92e: R^1 = OPr, R^2 = H (80%)

94a: R^1 = Cl, R^2 = H (93%)
94b: R^1 = OMe, R^2 = H (90%)
94c: R^1 = H, R^2 = Br (88%)
94d: R^1 = OEt, R^2 = H (68%)
94e: R^1 = OPr, R^2 = H (70%)

Figure 19. Preparation of 3-acetyl-*N*-protected intermediates **94** [23].

In the case of **85g**, an alternative pathway was chosen to prevent *O*-demethylation under acidic conditions. After its iodination, the resulting **95** was first treated with benzenesulfonyl chloride (**93**) to give the *N*-protected intermediate **96** that was reacted with **33** in a palladium-mediated Stille cross-coupling reaction to form **94f**. Treatment of the 4-methoxy derivative **92b** with dimethyl sulfate (**97**) gave the *N*-methylated intermediate **94 g** (**Figure 20**).

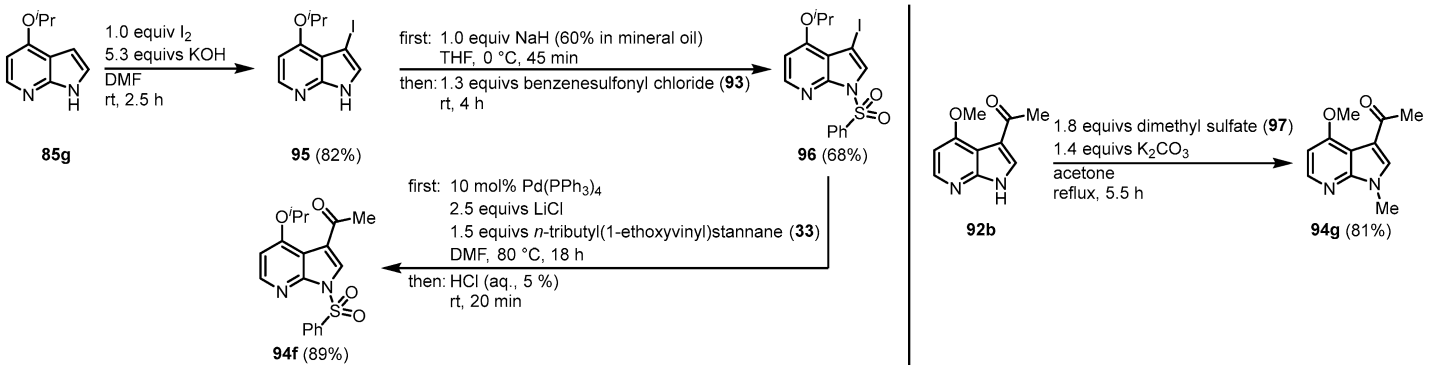


Figure 20. Alternative pathways to access **94f** and **94g** [23].

The functionalized 7-azaindoles **94** were then transformed to the corresponding enaminones **97** according to the Molina and Fresneda protocol, and after cyclocondensation with guanidine (**37**), meriolins 3–7 (**3c**, **3e–g**, **3b'**) and 9–11 (**3h**, **3b**, **3d**) were obtained. Meriolin 7 (**3b'**) was isolated as a side product in the synthesis of meriolin 10 (**3b**), where a nucleophilic substitution of the chlorine substituent took place. Treatment of **97b** with 2-methyl-2-thiopseudourea sulfate (**98**) led to the formation of the 2-methylthiopyrimidine-substituted meriolin 12 (**3i**). The meriolins 3–7 and 9–12 were isolated in overall yields ranging from 12 to 37% starting from the corresponding 7-azaindole **85** (**Figure 21**).

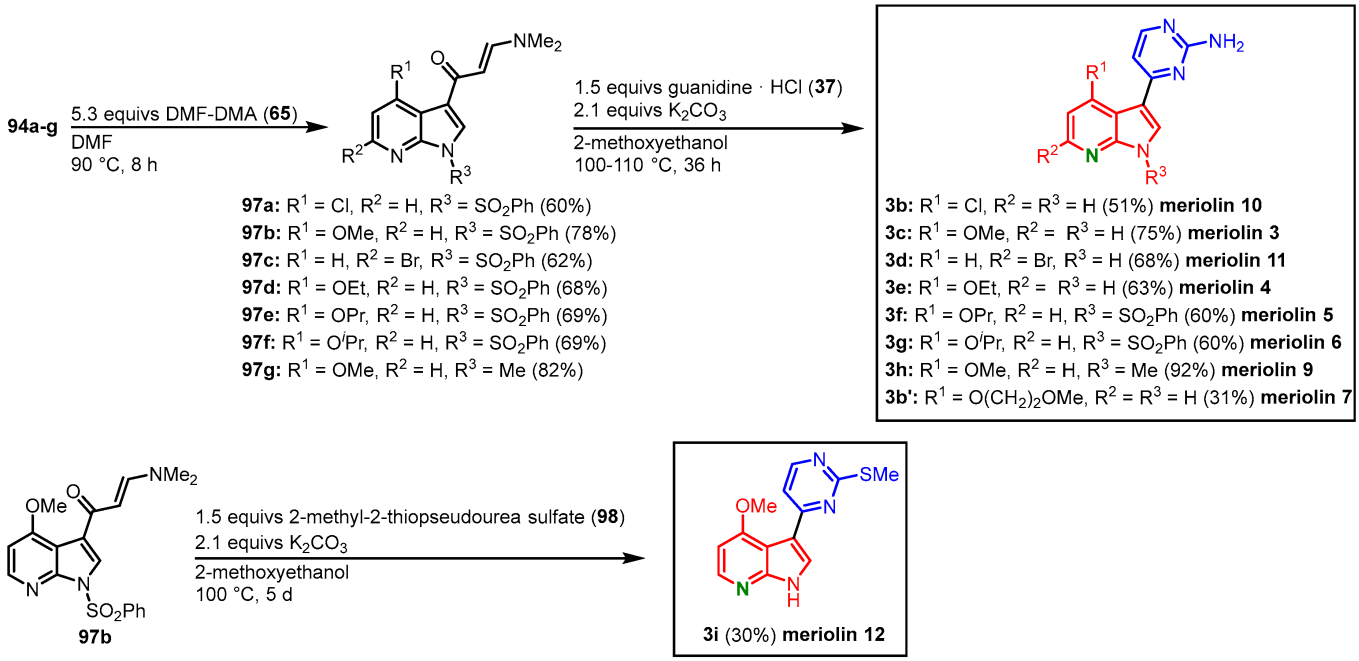


Figure 21. Synthesis of meriolins 3–7 and 9–12 by Joseph and Meijer [23].

The 4-methoxy-substituted meriolins **3c**, **3h**, and **3j** could be transformed to the corresponding 4-hydroxy-substituted meriolins 2 (**3k**, 26% overall yield), 8 (**3l**, 31% overall yield), and 13 (**3m**, 22% overall yield) by *O*-demethylation with hydrobromic acid in acetic acid (**Figure 22**) [23][24].

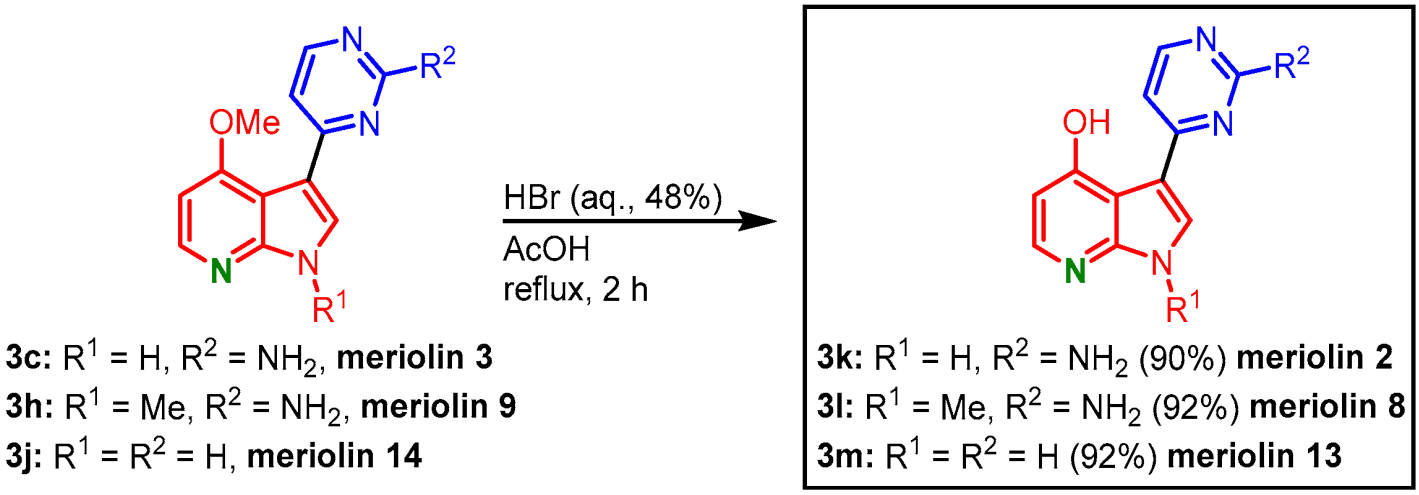


Figure 22. *O*-demethylation of meriolins 3, 9, and 14 gives 4-hydroxy-substituted meriolins 2, 8, and 13 [23].

3.3. Meriolin Syntheses by Müller via Carbonylative Alkynylation

The Müller approach to meridianins via carbonylative alkynylation and subsequent pyrimidine synthesis could be transferred to the synthesis of meriolins. A small library of potential kinase inhibitors has been synthesized for screenings, among them meriolin derivatives **3a** and **3n**. Therefore, 3-iodo-*N*-Boc-7-azaindole (**99a**) was transformed to the alkynones **101** in a Sonogashira coupling with TMSA (**68**) or 1-hexyne (**100**). Alkynones **101** were then cyclized with guanidine (**37**), either in a mixture of *tert*-butanol and acetonitrile or in DMF, to the meriolin derivatives **3a** (37% overall yield) and **3n** (51% overall yield) (**Figure 23**) [16][25].

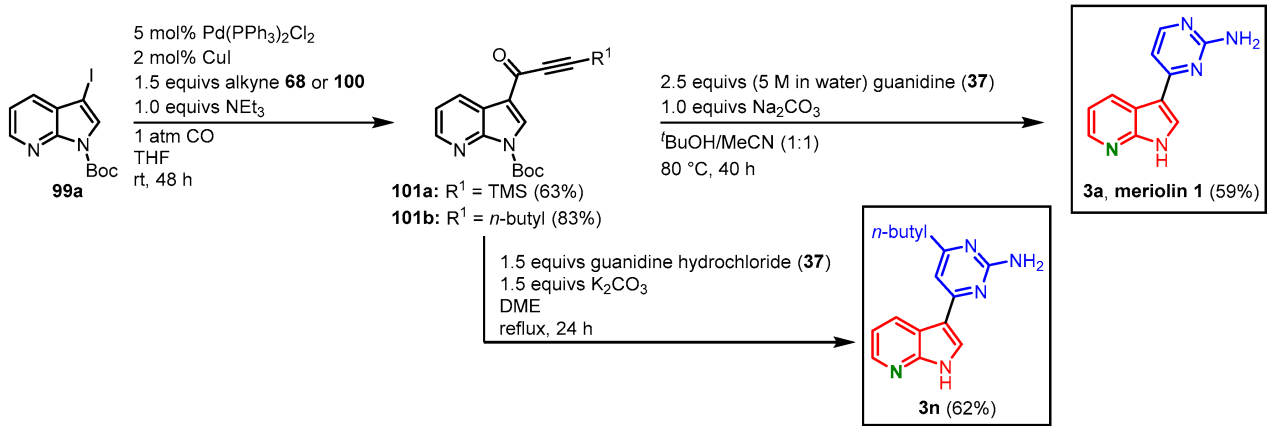


Figure 23. Synthesis of meriolins **3a** and **3n** via carbonylative alkynylation and subsequent pyrimidine synthesis by Müller [16][25].

3.4. Three-Component Glyoxylation Decarbonylative Alkynylation Synthesis of Alkynones by Müller

Another approach by Merkul et al. to address meriolins was performed via a three-component glyoxylation alkynylation reaction, leading to *N*-benzylated and *N*-methylated meriolins **3o** and **3p**. Starting from 7-azaindoles,

85 in the first step reaction with oxalyl chloride (**102**) furnished the indole-3-glyoxyl chlorides. These reactive synthetic equivalents of acid chlorides were directly transformed to alkynones **104** in a decarbonylative Sonogashira coupling with 1-hexyne (**100**) or phenylacetylene (**103**). The cyclocondensation reaction with guanidine (**37**) went similarly as in the previously described strategy, which gave meriolins **3o** and **3p** in 51 and 52% overall yield (**Figure 24**) [26].

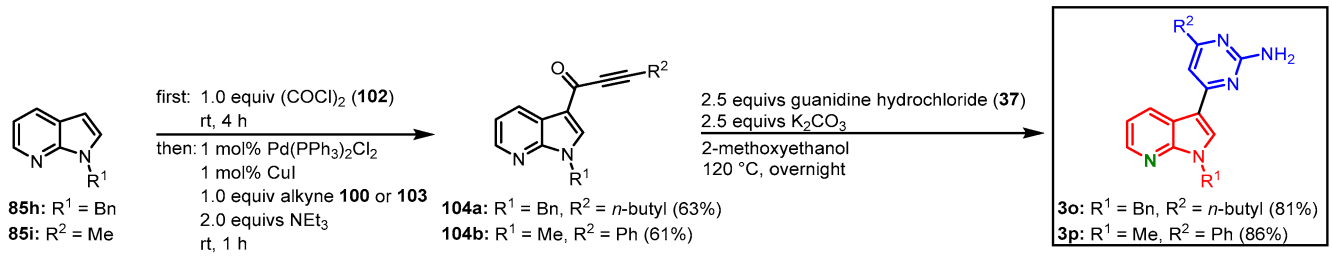


Figure 24. Synthesis of meriolins via three-component glyoxylation decarbonylative alkynylation by Merkul et al. [26].

3.5. Synthesis of Meriolins with a Suzuki Coupling as a Key Reaction by Huang

To investigate their kinase inhibitory effects, Huang and coworkers established a synthetic route to derivatize meriolins via a nucleophilic substitution on the pyrimidine moiety, as well as by functionalizing the N-1 and C-2 position on the azaindole moiety. 7-Azaindole (**85a**) was *N*-protected by treatment with benzenesulfonyl chloride (**93**) before it was selectively brominated in the C-3 position. Brominated and *N*-protected **106** was then transformed to the boronic acid ester **108** in a $Pd(dppf)_2Cl_2$-catalyzed Miyaura borylation with bis(pinacolato)diboron (**107**). Suzuki coupling with 2,4-dichloropyrimidine (**109**) in the presence of $Pd(PPh_3)_4$ gave **110** in superior regioselectivity. The chlorine substituent on the pyrimidine ring could then be substituted by various amines **111** in a nucleophilic aromatic substitution. Two equivalents of amine were used, as one equivalent was consumed by the concurrent cleavage of the benzenesulfonyl group. This furnished 15 meriolin derivatives (**3q-ae**) with overall yields ranging from 48 to 58% (**Figure 25**) [27].

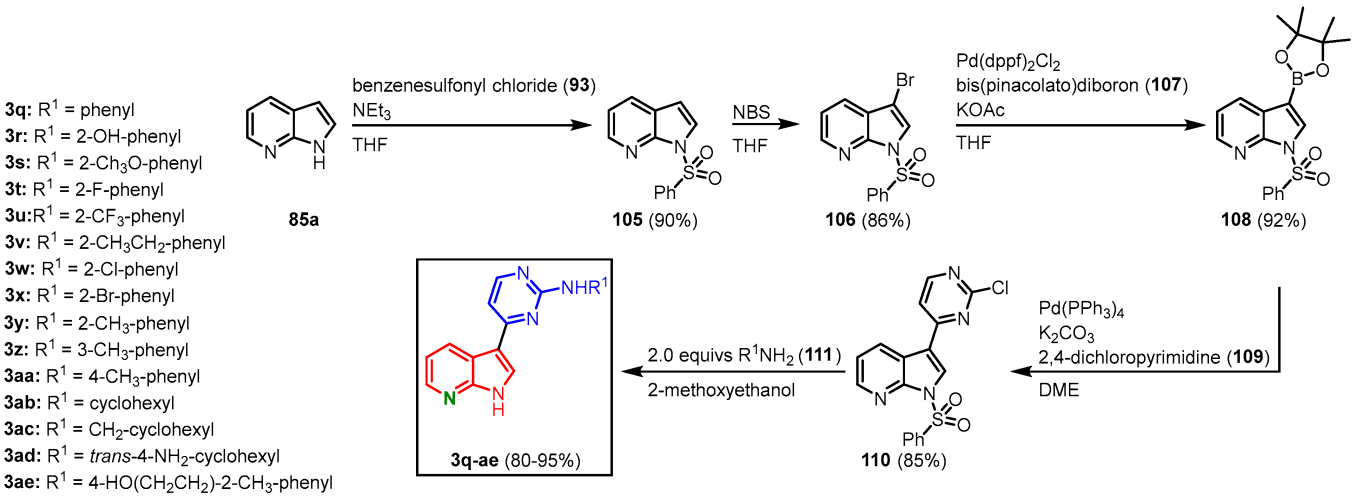


Figure 25. Meriolin synthesis by Huang via nucleophilic substitution on the pyrimidine moiety [27].

For the installment of solubilizing amino side chains, derivative **3ae** was treated with methanesulfonyl chloride (**112**), and the mesylate **3af** was obtained. After treatment with different amines **113,** the meriolin derivatives **3ag**-**ai** have been isolated in overall yields of 76–86% (starting from **3ae**) (**Figure 26**) [27].

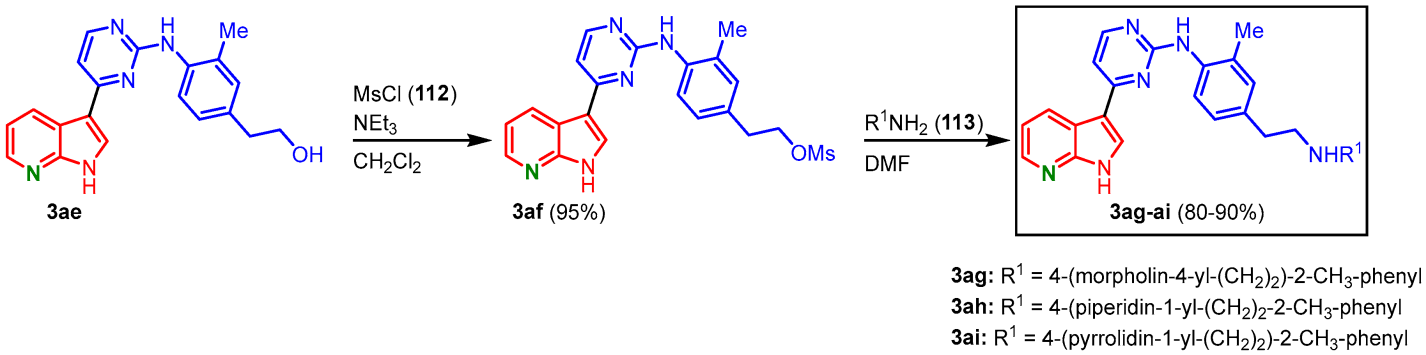


Figure 26. Introduction of solubilizing side chains gave the meriolin derivatives **3ag**-**ai** [27].

To assess the role of the NH group of the 7-azaindole unit in CDK1 binding, *N*-functionalization was anticipated. Compound **3ab** was treated with potassium *tert*-butoxide before it reacted with different electrophiles **114** to give the derivatives **3aj**-**am** (**Figure 27**) [27].

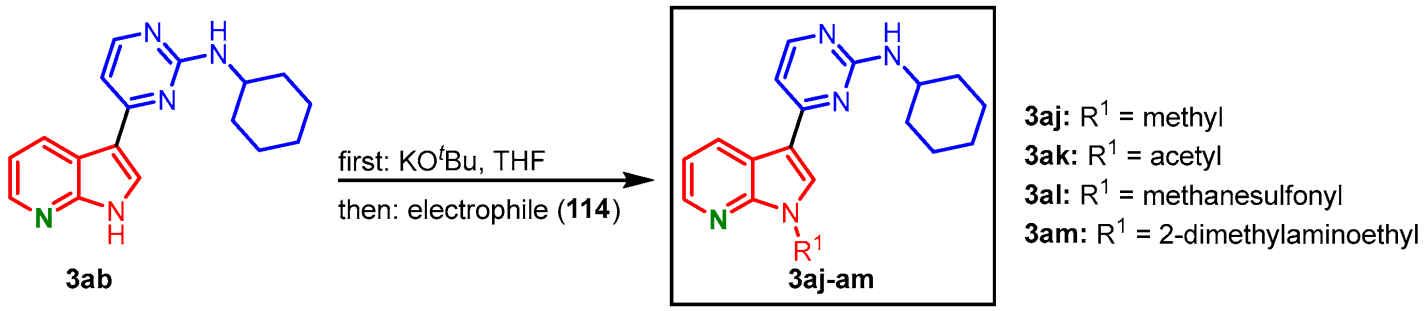


Figure 27. *N*-functionalization of compound **3ab** with different electrophiles gave meriolins **3aj**-**am** [27].

Lastly, compound **110** was treated with lithiumdiisopropylamine (LDA) and methyl iodide (**115**) to introduce a methyl group in the C-2 position. After the reaction with amine **117**, an additional deprotection step was added, since the C-2 methyl group caused the *N*-benzenesulfonyl group to be stable under hot aminolysis conditions. This furnished meriolin **3an** in 6% overall yield starting from **110** (**Figure 28**) [27].

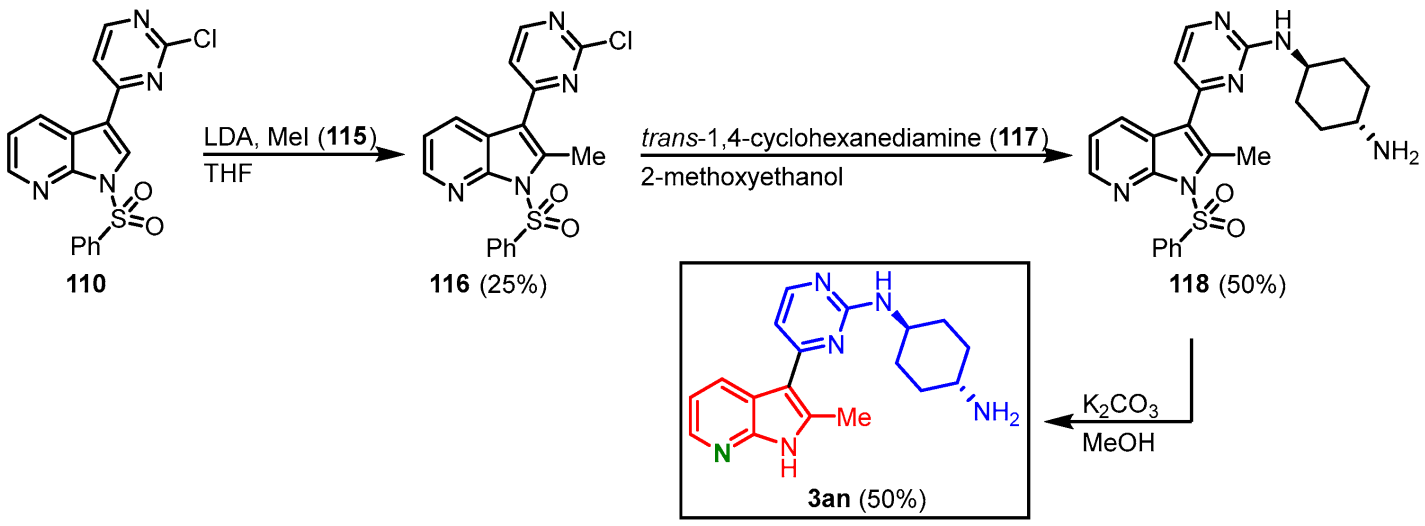


Figure 28. Synthesis of meriolin **3an** [27].

3.6. Meriolin Synthesis via the Masuda borylation-Suzuki Coupling Sequence by Müller

The Müller group could show the versatility of the MBSC sequence by transferring their meridianin protocol to the synthesis of meriolins and other biaryl systems [18][19][28][29]. In a one-pot-process, 7-azaindoles **99** were transformed to the corresponding pinacolyl boronic acid esters in a palladium-mediated Masuda borylation. In the sense of a sequentially catalyzed reaction, a subsequent Suzuki coupling with arylhalide **62** follows (**Figure 29**). Under Suzuki conditions, the Boc group is concomitantly cleaved, leading to meriolin 1 (**3a**), meriolins **3ao-au,** and the *N*-benzylated meriolins **3av** and **3aw,** with yields ranging from 37 to 96% (**Table 1**). If the reaction sequence is started with *N*-tosylated azaindoles **99b** a subsequent deprotection step with a hydroxide base is required. This step can be included in the one-pot process, which led to meriolins **3a** and **3ax-bi** with overall yields ranging from 40 to 91% starting from 7-azaindoles **99b** (**Figure 29**) [18][28].

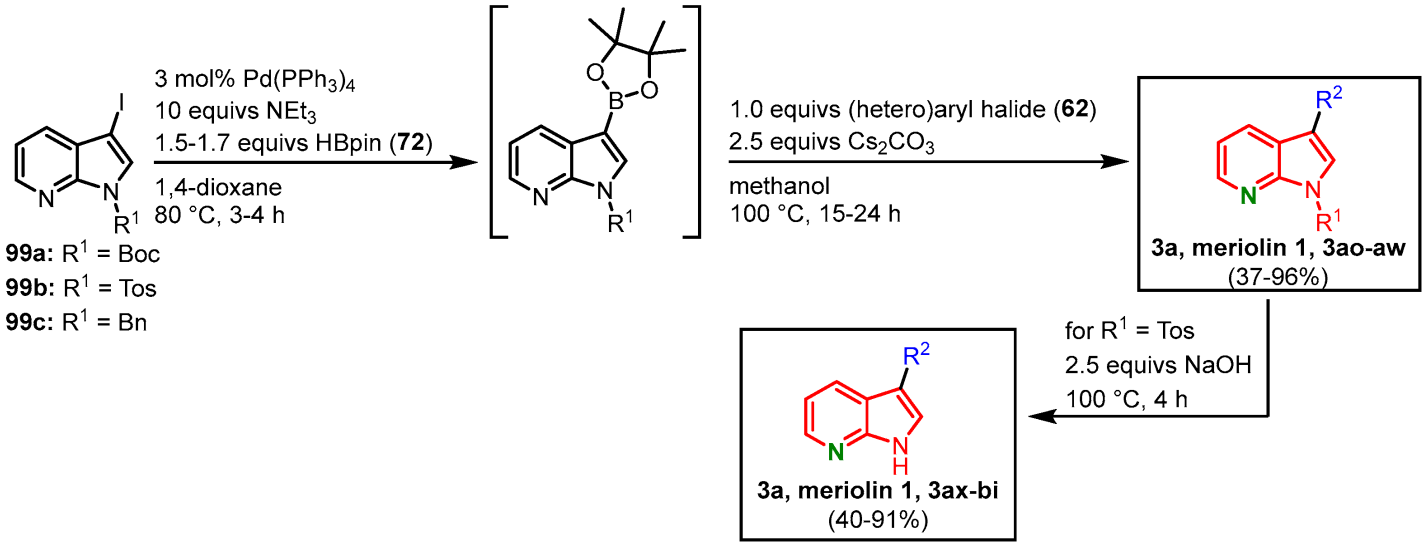


Figure 29. MBSC sequence for the synthesis of meriolins **3a** and **3ao-bi** by Müller [18][28].

Table 1. Introduced heterocycles R^2 **62** and the corresponding yields of the synthesized meriolins **3**

Entry	Azaindole 99	R^1	(hetero)aryl R^2 62	Meriolins 3 (yield)
1	**99a**	H	4-pyrimidin-2-amine (**62b**)	**3a**, **meriolin 1** (63%)
2	**99a**	H	6-pyrazin-2-amine (**62c**)	**3ao** (53%)
3	**99a**	H	5-pyrimidin-2-amine (**62d**)	**3ap** (66%)
4	**99a**	H	2-pyrimidin-4-amine (**62e**)	**3aq** (37%)
5	**99a**	H	6-pyridin-2-amine (**62f**)	**3ar** (81%)
6	**99a**	H	4-pyridin-2-amine (**62g**)	**3as** (64%)
7	**99a**	H	2-aniline (**62h**)	**3at** (74%)
8	**99a**	H	4-phenol (**62i**)	**3au** (57%)
9	**99c**	Bn	4-pyrimidin-2-amine (**62b**)	**3av** (96%)
10	**99c**	Bn	4-pyridin-2-amine (**62g**)	**3aw** (93%)
11	**99b**	H	4-pyrimidin-2-amine (**62b**)	**3a, meriolin 1** (81%)
12	**99b**	H	5-pyridin-2-amine (**62j**)	**3ax** (91%)
13	**99b**	H	4-pyridin-2-amine (**62g**)	**3ay** (75%)
14	**99b**	H	*N*-benzyl-5-pyridin-2-amine (**62k**)	**3az** (77%)

15	**99b**	H	4-(2-methoxypyrimidine) (**62l**)	**3ba** (40%)
16	**99b**	H	4-pyridin-2,6-diamine (**62m**)	**3bb** (67%)
17	**99b**	H	5-pyrimidin-2-amine (**62d**)	**3bc** (47%)
18	**99b**	H	4-(2-methylthiopyrimidine) (**62n**)	**3bd** (83%)
19	**99b**	H	4-(6-methoxypyrimidin-2-amine) (**62o**)	**3be** (62%)
20	**99b**	H	4-pyrimidin-2,6-diamine (**62p**)	**3bf** (53%)
21	**99b**	H	*N*-benzyl-4-pyridin-2-amine (**62q**)	**3bg** (83%)
22	**99b**	H	2-pyrimidin-4-amine (**62e**)	**3bh** (75%)
23 [a]	**99b**	H	5-isoquinolin (**62r**)	**3bi** (82%)

ɔrris

Morris and coworkers tried to adapt their meridianin protocol to the synthesis of meriolins starting from iodinated aminopyridines **119** to give 3-alkynylated 2-amino pyridines **120**. In contrast to anilines (vide supra), it was not possible to prepare the monomesylated aminopyridines directly, which required treatment with trifluoroacetyl anhydride (TFAA) (**121**) first to furnish trifluoroacetamides **122**. Reaction with mesyl chloride (**112**) led to the desired intermediate **123** that could be converted in the optimized domino reaction with *N*-Boc-4-iodopyrimidine-2-amine (**83**) and subsequent acid/base deprotection protocol to give meriolin 1 (**3a**) in 34% overall yield, as well as the 5-bromo meriolin **3bj** in 31% overall yield (**Figure 30**) [22].

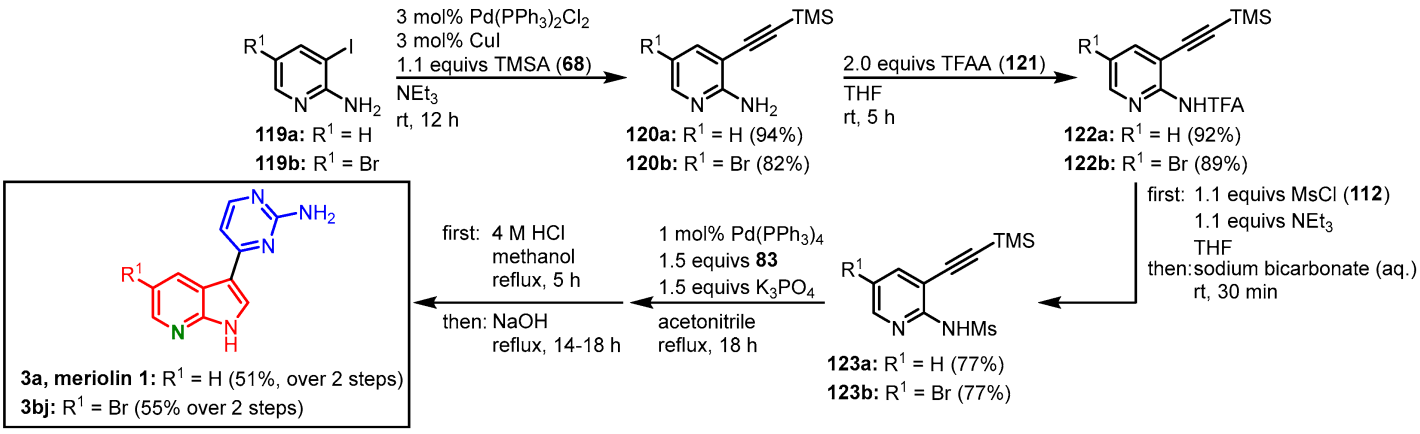


Figure 30. Synthesis of meriolins **3a** and **3bj** via domino amino-palladation reaction by Morris [22].

3.8. Metal-Free CH-Activation of a Pyrimidine and an Indolylboronic Ester by Singh

In 2016, Singh presented a metal-free CH-activation approach toward the synthesis of meriolin 1. The group reported cross-coupling between diazines and related electron-deficient heteroarenes with organoboron species. Treatment of *N*-Boc-protected boronic acid ester **124** with 2-aminopyrimidine (**125**) and potassium persulfate in an acetone-water mixture led to the formation of meriolin 1 in 35% yield (**Figure 31**). The proposed mechanism includes the formation of a sulfate anion radical that activates the boronic acid ester and generates an azaindolyl radical. The radical reacts with the in situ-formed pyrimidinyl salt to form a radical cation. After it undergoes single electron transfer, the protonated form of the desired product is obtained [30].

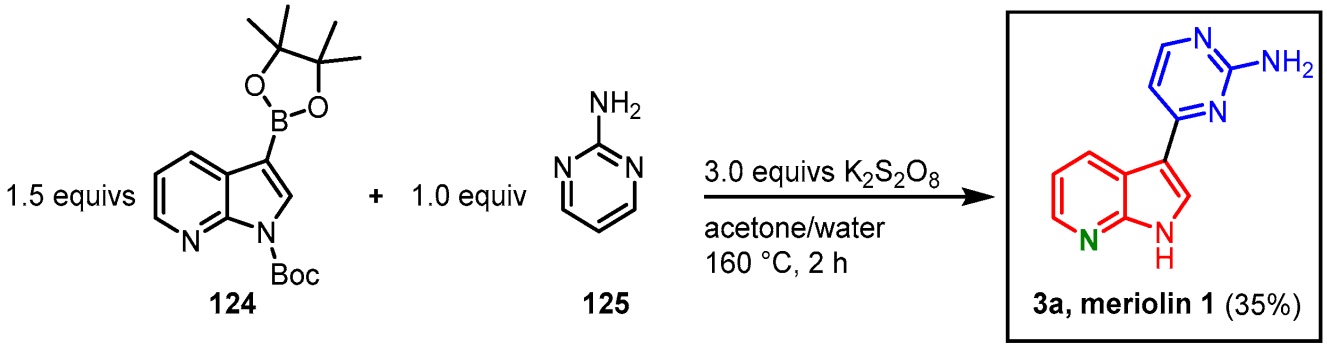


Figure 31. Metal-free synthesis of meriolin 1 via CH-activation by Singh [30].

3.9. Functionalization of Meriolins via Suzuki Coupling or Nucleophilic Substitution Reactions by Singh and Malik

A different approach by Singh in cooperation with Malik was more pragmatic to synthesize a large library of meriolins to establish structure-activity-relationships and determine their potency against CDKs. It was elaborated that functionalization in the C-5 position and N-1 position on the 7-azaindole unit, as well as on the pyrimidine ring, should be accomplished. Starting from 5-bromo-7-azaindole (**85j**) in a Suzuki coupling with several boronic acids, **126** led to functionalized 7-azaindoles **127** (**Figure 32**). After iodination and protection with Boc-anhydride (**128**) to

give 3-iodo-7-azaindoles **129**, a Masuda borylation with pinacolyl borane (**72**) and subsequent Suzuki coupling with 4-chloropyrimidine-2-amine (**62**) gave the meriolin derivatives **3bk-cc** in 25–46% overall yield (**Figure 32**, **Table 2**) [31].

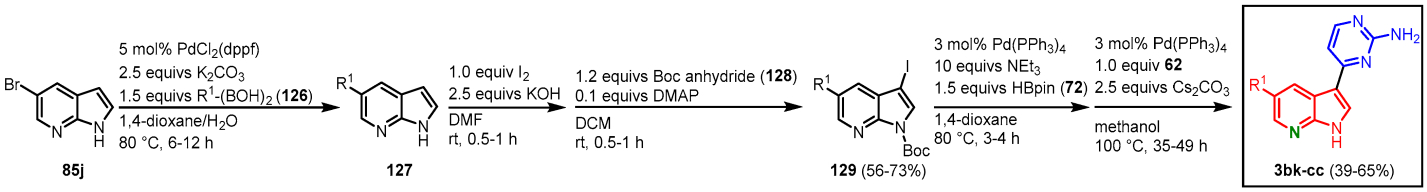


Figure 32. Functionalization of the C-5 position led to meriolins **3bk-cc** [31].

Table 2. Boronic acids **126** used for the functionalization in C-5 position and the corresponding yields of meriolins **3bk-cc**.

Entry	Boronic Acid R^1-$B(OH)_2$ (126)	Meriolins 3 (yield)
1	(4-(trifluoromethyl)phenyl)boronic acid (**126a**)	**3bk** (63%)
2	(4-fluorophenyl)boronic acid (**126b**)	**3bl** (65%)
3	(4-chlorophenyl)boronic acid (**126c**)	**3bm** (62%)
4	(4-(trifluoromethoxy)phenyl)boronic acid (**126d**)	**3bn** (60%)
5	(4-methoxyphenyl)boronic acid (**126e**)	**3bo** (59%)
6	(4-(methylthio)phenyl)boronic acid (**126f**)	**3bp** (54%)
7	(3-fluorophenyl)boronic acid (**126g**)	**3bq** (55%)
8	*m*-tolylboronic acid (**126h**)	**3br** (50%)
9	(3-(trifluoromethyl)phenyl)boronic acid (**126i**)	**3bs** (58%)

10	(2-(methylthio)phenyl)boronic acid (**126j**)	**3bt** (59%)
11	(2-ethylphenyl)boronic acid (**126k**)	**3bu** (48%)
12	naphthalen-1-ylboronic acid (**126l**)	**3bv** (60%)
13	(2-methoxynaphthalen-1-yl)boronic acid (**126m**)	**3bw** (55%)
14	furan-3-ylboronic acid (**126n**)	**3bx** (48%)
15	thiophen-3-ylboronic acid (**126o**)	**3by** (44%)
16	pyridin-3-ylboronic acid (**126p**)	**3bz** (45%)
17	benzo[*b*]thiophen-2-ylboronic acid (**126q**)	**3ca** (40%)
18	benzofuran-2-ylboronic acid (**126r**)	**3cb** (39%)
19	(5-methoxy-1*H*-indol-2-yl)boronic acid (**126s**)	**3cc** (45%)

To derivatize the pyrimidine ring, iodinated and *N*-protected 7-azaindole **124** was transformed to the corresponding pinacolyl boronic ester and reacted with **130** in a Suzuki coupling to give compound **3cd**. The thiomethyl group was oxidized to give the sulfone **3ce** using *m*-CPBA. Nucleophilic substitution by several primary **131** or secondary amines **132** furnished meriolins **3bk**-**cc** in 29–39% overall yield (**Figure 33**, **Table 3**). To vary the substituents in the N-1 position, at first the synthesis of meriolin 1 was approached using a Masuda borylation and subsequent Suzuki coupling. After treatment with sodium hydride, reaction with different sulfonyl chlorides **133** gave meriolins **3cn**-**ct** in 39–47% overall yield (**Figure 33**, **Table 4**).

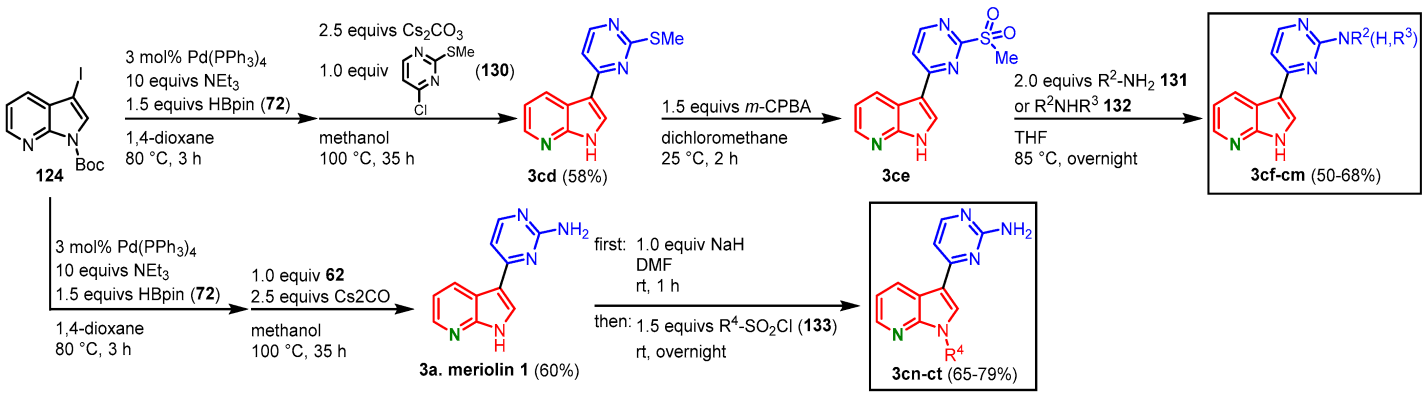


Figure 33. Functionalization of the pyrimidine ring and the N-1 position gave meriolins **3cf**-**ct** [31].

Table 3. Primary **131** and secondary amines **132** used for the functionalization of the pyrimidine ring and the corresponding yields of meriolins **3cf**-**cm**.

Entry	Amine R^2-NH_2 (131) or R^2NHR^3 (132)	Meriolins 3 (yield)
1	2-phenylethan-1-amine (**131a**)	**3cf** (65%)
2	2-(4-methoxyphenyl)ethan-1-amine (**131b**)	**3cg** (60%)
3	2-(3,4-dimethoxyphenyl)ethan-1-amine (**131c**)	**3ch** (68%)
4	2-(1*H*-indol-3-yl)ethan-1-amine (**131d**)	**3ci** (50%)
5	pyrrolidine (**132a**)	**3cj** (52%)
6	piperidine (**132b**)	**3ck** (52%)
7	morpholine (**132c**)	**3cl** (60%)
8	1-methylpiperazine (**132d**)	**3cm** (54%)

Table 4. Sulfonyl chlorides **133** for the functionalization in N-1 position and the corresponding yields of meriolins **3cn**-**ct**.

Entry	Sulfonyl Chloride R^4-SO_2Cl (133)	Meriolins 3 (yield)
1	4-fluorobenzenesulfonyl chloride (**133a**)	**3cn** (70%)
2	4-bromobenzenesulfonyl chloride (**133b**)	**3co** (70%)

3	4-(trifluoromethyl)benzenesulfonyl chloride (**133c**)	**3cp** (77%)
4	4-(trifluoromethoxy)benzenesulfonyl chloride (**133d**)	**3cq** (80%)
5	4-acetamidobenzenesulfonyl chloride (**133e**)	**3cr** (71%)
6	2,3-dihydrobenzo[*b*][1,4]dioxine-6-sulfonyl chloride (**133f**)	**3cs** (79%)
7	1-methyl-1*H*-imidazole-5-sulfonyl chloride (**133g**)	**3ct** (65%)

3.10. Meriolin Synthesis via Friedel Crafts Acylation by Grädler

Grädler and coauthors started their approach on meriolins from 5-bromo-7-azaindole (**85j**) with a Friedel Crafts acylation using aluminium chloride and acid chloride **134**. The intermediate **135** was reacted in a cyclocondensation with guanidine carbonate (**136**), which furnished meriolin **3cu** in 40% overall yield. The bromine atom in C-5 position was then employed for further derivatization. Suzuki coupling with Boc-protected pinacolyl boronic acid ester **137** and subsequent Boc-deprotection with hydrochloric acid gave meriolin **3cv** in 41% yield (**Figure 34**). The overall yield after three steps is 17% [25]. Using this method, as well as the carbonylative alkynylation by Müller [16], several derivatives have been synthesized and tested for their PDK1 inhibitory properties [25].

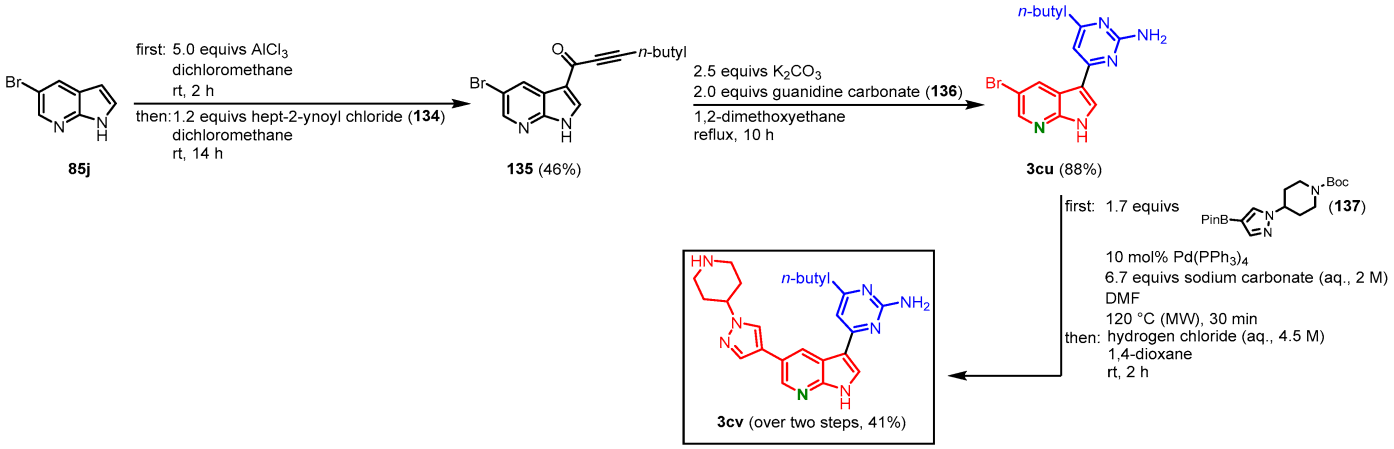


Figure 34. Preparation of meriolin **3cv** via Friedel Crafts acylation by Grädler [25].

References

1. Anderson, R.J.; Morris, J. Total synthesis of variolin B. Tetrahedron Lett. 2001, 42, 8697–8699.

2. Anderson, R.J.; Hill, J.; Morris, J. Concise Total Syntheses of Variolin B and Deoxyvariolin B. J. Org. Chem. 2005, 70, 6204–6212.
3. Molina, P.; Fresneda, P.; Delgado, S.; Bleda, J. Synthesis of the potent antitumoral marine alkaloid variolin B. Tetrahedron Lett. 2002, 43, 1005–1007.
4. Molina, P.; Fresneda, P.; Delgado, S. Carbodiimide-Mediated Preparation of the Tricyclic Pyridopyrrolopyrimidine Ring System and Its Application to the Synthesis of the Potent Antitumoral Marine Alkaloid Variolin B and Analog. J. Org. Chem. 2003, 68, 489–499.
5. Bredereck, H.; Effenberger, F.; Botsch, H.; Rehn, H. Synthesen in der heterocyclischen Reihe, V: Umsetzungen von vinylogen Carbonsäureamiden zu Heterocyclen. Chem. Ber. 1965, 98, 1081–1086.
6. Ahaidar, A.; Fernández, D.; Pérez, O.; Danelón, G.; Cuevas, C.; Manzanares, I.; Albericio, F.; Joule, J.; Álvarez, M. Synthesis of variolin B. Tetrahedron Lett. 2003, 44, 6191–6194.
7. Ahaidar, A.; Fernández, D.; Danelón, G.; Cuevas, C.; Manzanares, I.; Albericio, F.; Joule, J.; Álvarez, M. Total Syntheses of Variolin B and Deoxyvariolin B1. J. Org. Chem. 2003, 68, 10020–10029.
8. Fernández, D.; Ahaidar, A.; Danelón, G.; Cironi, P.; Marfil, M.; Pérez, O.; Cuevas, C.; Albericio, F.; Joule, J.; Álvarez, M. Synthesis of Polyheterocyclic Nitrogen-Containing Marine Natural Products. Monatsh. Chem. 2004, 135, 615–627.
9. Katritzky, A.R.; Akutagawa, K. Carbon dioxide: A reagent for simultaneous protection of nucleophilic centers and the activation of alternative locations to electrophilic attack. V. Activation of the 2-alkyl group of a 2-alkylindole toward proton loss and subsequent electrophilic substitution. J. Am. Chem. Soc. 1986, 108, 6808–6809.
10. Baeza, A.; Mendiola, J.; Burgos, C.; Alvarez-Builla, J.; Vaquero, J. Palladium-mediated C–N, C–C, and C–O functionalization of azolopyrimidines: A new total synthesis of variolin B. Tetrahedron Lett. 2008, 49, 4073–4077.
11. Baeza, A.; Mendiola, J.; Burgos, C.; Alvarez-Builla, J.; Vaquero, J. Application of Selective Palladium-Mediated Functionalization of the Pyridopyrrolopyrimidine Heterocyclic System for the Total Synthesis of Variolin B and Deoxyvariolin B. Eur. J. Org. Chem. 2010, 2010, 5607–5618.
12. Mendiola, J.; Baeza, A.; Alvarez-Builla, J.; Vaquero, J. Reaction of Bromomethylazoles and Tosylmethyl Isocyanide. A Novel Heterocyclization Method for the Synthesis of the Core of Marine Alkaloids Variolins and Related Azolopyrimidines. J. Org. Chem. 2004, 69, 4974–4983.
13. Jiang, B.; Yang, C.-G. Synthesis of Indolylpyrimidiness via Cross-Coupling of Indolylboronic Acid with Choropyrimidines: Facile Synthesis of Meridianin D. Heterocycles 2000, 53, 1489–1498.

14. Fresneda, P.M.; Molina, P.; Bleda, J. Synthesis of the indole alkaloids meridianins from the tunicate Aplidium meridianum. Tetrahedron 2001, 57, 2355–2363.
15. Fresneda, P.M.; Molina, P.; Delgado, S.; Bleda, J. Synthetic studies towards the 2-aminopyrimidine alkaloids variolins and meridianins from marine origin. Tetrahedron Lett. 2000, 41, 4777–4780.
16. Karpov, A.S.; Merkul, E.; Rominger, F.; Müller, T. Concise Syntheses of Meridianins by Carbonylative Alkynylation and a Four-Component Pyrimidine Synthesis. Angew. Chem. Int. Ed. 2005, 44, 6951–6956.
17. Tibiletti, F.; Simonetti, M.; Nicholas, K.; Palmisano, G.; Parravicini, M.; Imbesi, F.; Tollari, S.; Penoni, A. One-pot synthesis of meridianins and meridianin analogues via indolization of nitrosoarenes. Tetrahedron 2010, 66, 1280–1288.
18. Merkul, E.; Schäfer, E.; Müller, T. Rapid synthesis of bis(hetero)aryls by one-pot Masuda borylation-Suzuki coupling sequence and its application to concise total syntheses of meridianins A and G. Org. Biomol. Chem. 2011, 9, 3139–3141.
19. Kruppa, M.; Sommer, G.; Müller, T. Concise Syntheses of Marine (Bis)indole Alkaloids Meridianin C, D, F, and G and Scalaridine A via One-Pot Masuda Borylation-Suzuki Coupling Sequence. Molecules 2022, 27, 2233.
20. Parsons, T.B.; Ghellamallah, C.; Male, L.; Spencer, N.; Grainger, R. Regioselective dibromination of methyl indole-3-carboxylate and application in the synthesis of 5,6-dibromoindoles. Org. Biomol. Chem. 2011, 9, 5021–5023.
21. Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L.; Pace, P. 3-Aryl-2-Unsubstituted Indoles through the Palladium-Catalysed Reaction of o-Ethynyltrifluoroacetanilide with Aryl Iodides. Synlett 1997, 12, 1363–1366.
22. Walker, S.R.; Czyz, M.; Morris, J. Concise Syntheses of Meridianins and Meriolins Using a Catalytic Domino Amino-Palladation Reaction. Org. Lett. 2014, 16, 708–711.
23. Bettayeb, K.; Tirado, O.; Marionneau-Lambot, S.V.; Ferandin, Y.; Lozach, O.; Morris, J.; Mateo-Lozano, S.; Drueckes, P.; Schächtele, C.; Kubbutat, M.; et al. Meriolins, a New Class of Cell Death–Inducing Kinase Inhibitors with Enhanced Selectivity for Cyclin-Dependent Kinases. Cancer Res. 2007, 67, 8325–8334.
24. Echalier, A.; Bettayeb, K.; Ferandin, Y.; Lozach, O.; Clément, M.; Valette, A.; Liger, F.; Marquet, B.; Morris, J.; Endicott, J.; et al. Meriolins (3-(Pyrimidin-4-yl)-7-azaindoles): Synthesis, Kinase Inhibitory Activity, Cellular Effects, and Structure of a CDK2/Cyclin A/Meriolin Complex. J. Med. Chem. 2008, 51, 737–751.
25. Wucherer-Plietker, M.; Merkul, E.; Müller, T.; Esdar, C.; Knöchel, T.; Heinrich, T.; Buchstaller, H.-P.; Greiner, H.; Dorsch, D.; Finsinger, D.; et al. Discovery of novel 7-azaindoles as PDK1 inhibitors.

Bioorg. Med. Chem. Lett. 2016, 26, 3073–3080.

26. Merkul, E.; Oeser, T.; Müller, T. Consecutive Three-Component Synthesis of Ynones by Decarbonylative Sonogashira Coupling. Eur. J. Chem. 2009, 15, 5006–5011.
27. Huang, S.; Li, R.; Connolly, P.; Emanuel, S.; Middleton, S. Synthesis of 2-amino-4-(7-azaindol-3-yl)pyrimidines as cyclin dependent kinase 1 (CDK1) inhibitors. Bioorg. Med. Chem. Lett. 2006, 16, 4818–4821.
28. Drießen, D.; Stuhldreier, F.; Frank, A.; Stark, H.; Wesselborg, S.; Stork, B.; Müller, T. Novel meriolin derivatives as rapid apoptosis inducers. Bioorg. Med. Chem. 2019, 27, 3463–3468.
29. Rehberg, N.; Sommer, G.; Drießen, D.; Kruppa, M.; Adeniyi, E.; Chen, S.; Wang, L.; Wolf, K.; Tasch, B.; Ioerger, T.; et al. Nature-Inspired (di)Azine-Bridged Bisindole Alkaloids with Potent Antibacterial In Vitro and In Vivo Efficacy against Methicillin-Resistant Staphylococcus aureus. J. Med. Chem. 2020, 63, 12623–12641.
30. Thatikonda, T.; Singh, U.; Ambala, S.; Vishwakarma, R.; Singh, P. Metal free C-H functionalization of diazines and related heteroarenes with organoboron species and its application in the synthesis of a CDK inhibitor, meriolin 1. Org. Biomol. Chem. 2016, 14, 4312–4320.
31. Singh, U.; Chashoo, G.; Khan, S.; Mahajan, P.; Nargotra, A.; Mahajan, G.; Singh, A.; Sharma, A.; Mintoo, M.; Guru, S.; et al. Design of Novel 3-Pyrimidinylazaindole CDK2/9 Inhibitors with Potent In Vitro and In Vivo Antitumor Efficacy in a Triple-Negative Breast Cancer Model. J. Med. Chem. 2017, 60, 9470–9489.