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Pyrrole protection

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Contents

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1. Introduction

The chemistry of pyrrole and its derivatives is enjoying a relative renaissance of interest due to the growing abundance of pyrrolic components in natural products, pharmaceuticals, and new materials. Pyrrole is the major constituent of naturally occurring tetrapyrroles, such as heme and chlorophyll, the tripyrrolic prodigiosin skeleton, and many alkaloid natural products of varying complexity and biological activity.[1–6] Increasingly, pyrroles are being investigated as potential pharmaceuticals because of their less restricted patent position relative to more common heterocycle skeletons such as indole and imidazole. Moreover, the blockbuster atorvastatin calcium (Lipocor, Lipitor®) is a pentasubstituted pyrrole, and is, the most-prescribed prescription drug for cholesterol lowering.[7] Furthermore, pyrrolic molecules exhibit a wide variety of useful and emerging optical and electronic properties.[1,8–11]

The synthetic chemistry of the pyrrolic unit is dominated by electrophilic aromatic substitution and pyrrole is much more reactive than benzene in this respect, as a result of the lone pair at nitrogen and the consequent stability of σ-complexes (Wheland intermediates, Fig. 1).[10] Polymerization of pyrrole, and substituted pyrroles, is acid-catalyzed and polypyrroles (dark tars) are often the result of the careless management of reactions involving pyrroles. Such reactivity necessitates that a delicate balance[12] be achieved between

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Keywords: Pyrrole; Pyrrolic; Protecting group; Protection; Deprotection; Electron withdrawing; Blocking.

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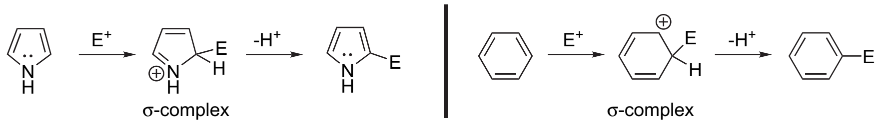


Figure 1. Electrophilic substitution of pyrrole and benzene.

the exploitation of nucleophilicity for required electrophilic aromatic substitution, and the containment of nucleophilicity (through electronic or steric means) to inhibit over-substitution and/or unwanted transformations. Harnessing the reactivity of pyrrole is often achieved by the use of protecting and blocking groups, most usually involving N-substitution (1-substitution) and 2-substitution. Electron-withdrawing groups serve to both lessen nucleophilicity and block certain positions from unwanted substitution. Sterically bulky protecting groups can block the pyrrole to prevent alpha-substitution. Certain groups have been shown to activate the pyrrolic core. As with any useful synthetic protecting group, three criteria must be met: facile introduction; robust reactivity of the protected moiety; and efficient deprotection.

Over the last century, synthetic pyrrole chemistry has played a crucial role in the preparation of porphyrins. The final steps to prepare the porphyrinogenic skeleton typically require large quantities of pyrroles as starting materials, as the reactions can be low yielding and give complex product mixtures. Consequently syntheses and derivatizations of functionalized pyrroles are routinely achieved on multi-molar scales using modest laboratory facilities. Many traditional reactions involving pyrroles incorporate harsh acidic or caustic conditions, as well as high reaction temperatures. With the absolute goal of synthesizing porphyrins, the moderate yields from such reaction conditions were tolerated; however, as other needs for pyrroles have surfaced, more elegant syntheses and manipulations of pyrroles have been required to achieve more effective and selective chemistry. Although protecting groups suitable for pyrroles[13] have been included within comprehensive sources,[14,15] and many authorities of synthetic pyrrole and porphyrin chemistry have necessarily included protected pyrroles in the discussion of synthetic strategies,[10,16–18] a modern and comprehensive survey is desirable. This review embraces the gamut of protecting groups for pyrroles, including the availability, utility, and deprotection of protected pyrroles. Without a doubt this review does not include every report of protected pyrroles, nor does it fully summarize all aspects of the cited references. Instead, examples have been chosen based on their demonstrated and potential usefulness, in the opinion of the authors. The aim of this review is to provide practicing and aspirant pyrrole chemists with a survey and flavor of the types of groups used to protect pyrroles, and insight into why certain groups are advantageous under particular circumstances.

2. Pyrroles protection by N-substitution

2.1. *N*-Sulfonyl protecting groups

The sulfonyl groups are among the more common protecting groups for pyrrole protection at nitrogen because of their strong electron-withdrawing effect. Their ability to reduce the reactivity of pyrrole allows a wider range of reactions and higher yields in regioselective alkenylation[19] and acylation[20] at the alpha and beta positions. Some representative sulfonyl protecting groups that have been used in pyrrole chemistry are presented in Figure 2.

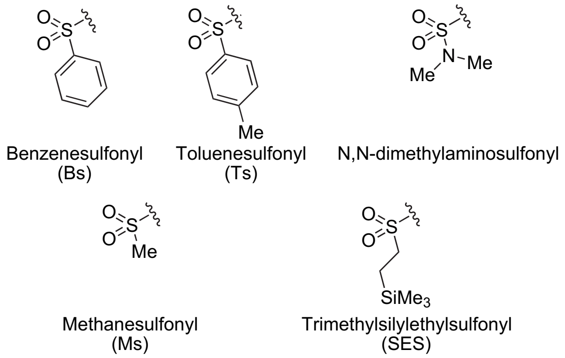


Figure 2. Sulfonyl groups for pyrrole chemistry.

The effect of the sulfonyl group on the electron density distribution in pyrrole has been evaluated by analysis of ^{13}C NMR chemical shift data and X-ray crystal structure analysis.[21] The four major resonance forms **A**–**D** of 3,5-dimethylpyrrole-2-carboxylate are shown in Figure 3. The introduction of an electron-withdrawing group (EWG) on the nitrogen of the pyrrole significantly changes the distribution of the resonance contributors by decreasing the availability of the nitrogen lone pair, favoring **A**. As the strength of the EWG was increased (N–H<*N*-Boc<*N*-Ms<*N*-Tf), the aromatic carbons were proportionally deshielded in the respective pyrrole ^{13}C NMR spectra (Fig. 3).[21]

N-Phenylsulfonylpyrroles react regioselectively under Friedel–Crafts acylation conditions contingent on Lewis acid.[22,23] For example, benzoylation of *N*-phenylsulfonylpyrrole **1** with benzoyl chloride gave only 3-benzoyl-1-phenylsulfonylpyrrole **4b** using $AlCl_3$ as Lewis acid in DCM. Highly regioselective acylation at the 2-position of *N*-phenylsulfonylpyrrole with benzoyl chloride was later

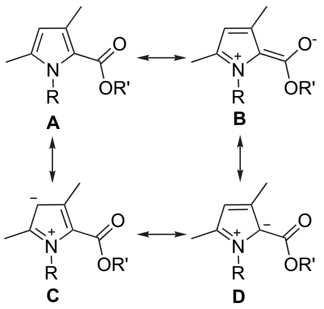


Figure 3. Major resonance forms **A**–**D**.

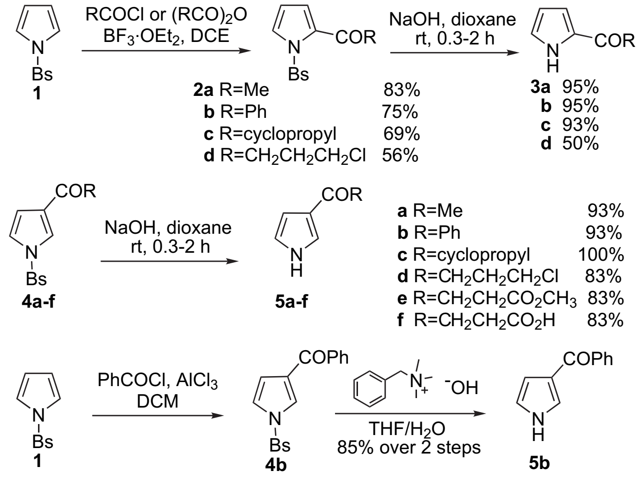


Figure 4. Alkaline hydrolysis of *N*-sulfonylacylpyrroles.

obtained by using $BF_3 \cdot OEt_2$ as Lewis acid in 1,2-dichloroethane to give **2b** (Fig. 4).[20]

The introduction of a sulfonyl group on the nitrogen of pyrrole is generally accomplished by reacting the pyrrolyl anion with the corresponding sulfonyl halide. The counter ion, the solvent, and the electrophile are all important for avoiding electrophilic substitution at the 2-position. Some of the common bases and solvents for *N*-sulfonyl protection include metal hydrides (NaH or KH) in THF, DCM or DMF, as well as trialkylamines in DCM or MeCN. Alternatively, regioselective protection of unsubstituted pyrrole with BsCl or TsCl in ionic liquids [1-butyl-3-methylimidazolium hexafluorophosphate ([Bmim][PF_6]) and 1-butyl-3-methylimidazolium tetrafluoroborate ([Bmim][BF_4])] in the presence of KOH afforded *N*-sulfonylpyrroles in quantitative yields.[24]

The removal of *N*-aryl and *N*-alkylsulfonyl groups has been typically achieved using alkaline hydrolysis with NaOH or KOH (Figs. 4 and 5). For example, sodium hydroxide in dioxane at room temperature effectively deprotected pyrroles **2a–d** and **4a–f**, which possess acyl groups either at the alpha or beta position, to provide pyrroles **3a–d** and **5a–f** in variable yields.[20] Alternatively, benzyltrimethylammonium hydroxide (Triton B) was used to hydrolyze *N*-benzenesulfonyl-3-benzoylpyrrole **4b**, with similar results.[22]

Unsubstituted *N*-sulfonyl protected terpyrroles **6a–b** and bispyrrylthiophenes **7a–b** were deprotected effectively in refluxing MeOH with NaOH.[25] Similarly, the *N*-methanesulfonyl group was cleaved from dipyrrolylmethane **10** using NaOH.[26] The *p*-toluenesulfonyl group was easily removed from **12** and **13** by treatment with KOH in MeOH, giving the corresponding deprotected pyrroles **14** and **15**, respectively.[27] 2-Furanyl-*N*-toluenesulfonylpyrrole **16** has also been deprotected successfully using K_2CO_3 at room temperature to yield pyrrole **17** (Fig. 5).[28]

Other moieties may be affected during deprotection of *N*-sulfonylpyrroles under alkaline hydrolysis. For example, in the preparation of an intermediate for the synthesis of porphyrins, alkaline hydrolysis of *N*-methanesulfonylpyrrole **18** with potassium hydroxide in MeOH caused simultaneous N-demesylation, elimination of methanesulfenic acid, and attack of MeOH to afford 2-(methoxymethyl)pyrrole **19**[29] in quantitative yield in one step. Deprotection of *N*-benzenesulfonylpyrrole **20** with ethanolic sodium hydroxide was accompanied by ester saponification to provide acid **21** (Fig. 6).[30]

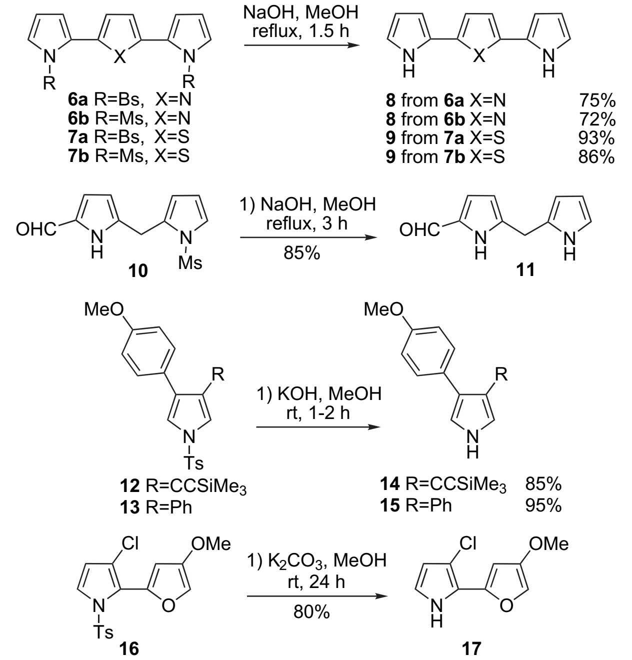


Figure 5. Alkaline hydrolysis of *N*-sulfonylpyrroles.

The relatively harsh conditions of alkaline hydrolysis and lack of selectivity encouraged synthetic chemists to find alternative methods for *N*-sulfonyl deprotection. For example, under relatively mild reaction conditions, *N*-tosyl pyrrole **23** was desulfonylated with magnesium in MeOH to give pyrrole **24**.[31] In comparison, alkaline hydrolysis of **23** with KOH gave a very poor yield of the deprotected pyrrole **24**, together with 60% recovery of the starting material. Ammonium chloride was later shown to be useful for activation of the magnesium surface for the deprotection of *N*-phenylsulfonylpyrrole **25**. Furthermore, improved selectivity for deprotection was observed with pyrroles possessing a variety of functional groups compared to alkaline hydrolysis (i.e., **23**

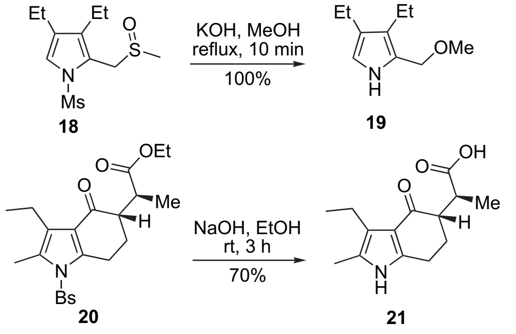


Figure 6. Alkaline hydrolysis of *N*-sulfonylpyrroles.

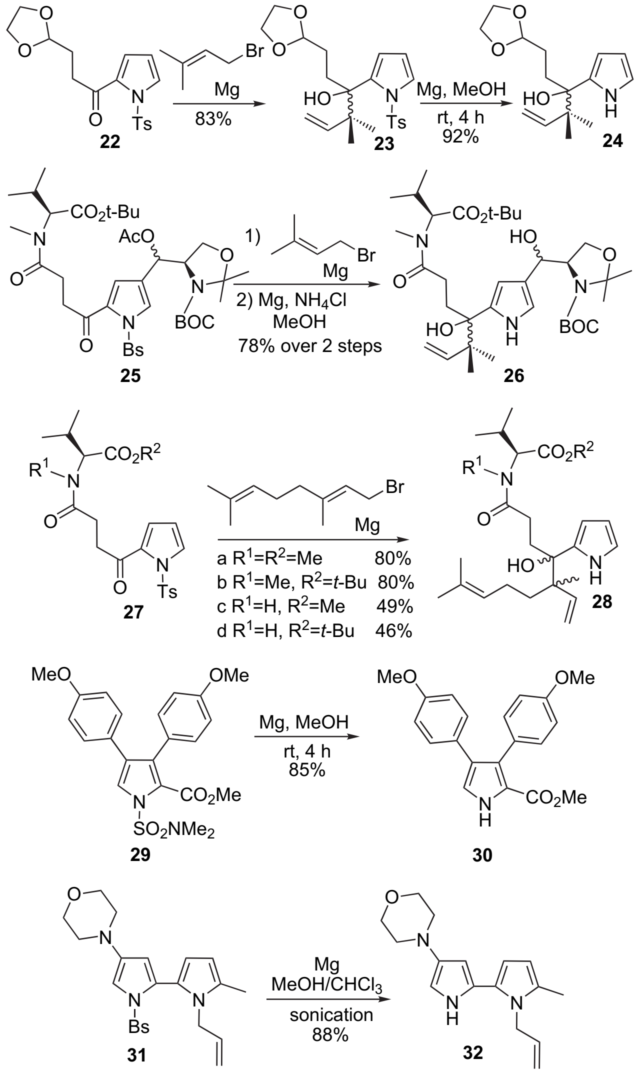


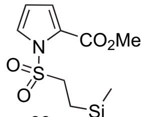
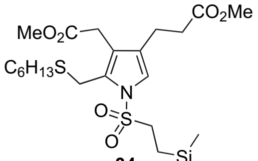
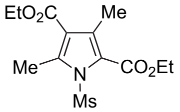
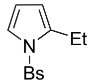
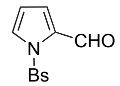
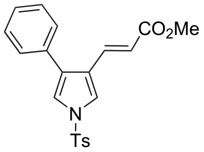
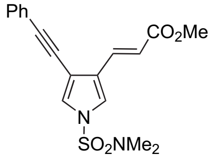
Figure 7. Deprotection of *N*-sulfonylpyrroles with Mg in MeOH.

and **25**).[31,32] Moreover, elimination of the tosyl group of pyrroles **27a–d** occurred concurrently with the Grignard reaction with geranyl bromide and magnesium. The same Grignard reagent was reacted with *N*-tosyl pyrrole **22** without cleaving the protecting group.[33] The magnesium/MeOH conditions have also been used for the deprotection of *N*,*N*-dimethylaminosulfonylpyrrole **29** to provide **30**, an advanced intermediate for the synthesis of the natural product lamellarin O. Deprotection of pyrrole **29** with tetrabutylammonium fluoride (TBAF) gave **30** in moderate yield.[27] 4-Amino-2,2′-bipyrrole **31** failed to react under similar conditions (Mg, NH_4Cl, MeOH) even with heating. However, sonication of bipyrrole **31** and magnesium in MeOH/$CHCl_3$ (99:1) caused complete deprotection in 15 min to give **32** (Fig. 7).[34]

The *N*-trimethylsilylethanesulfonyl (SES) group was developed for pyrrole protection because it can be removed under mild conditions using tetrabutylammonium fluoride (TBAF) in THF at room temperature.[35,36] With additional heating, this methodology was extended to the removal of *N*-methylsulfonyl,[37] *N*-phenylsulfonyl,[37] *N*-*p*-toluenesulfonyl,[38] and *N*,*N*-dimethylaminosulfonyl[38] groups without affecting formyl (i.e., **37**) and carboxylate (i.e., **35**, **38**, and **39**) ring substituents (Table 1).

$$N\text{-sulfonylpyrrole} \xrightarrow[\text{THF}]{\text{TBAF}} \text{pyrrole}$$

Table 1. Desulfonylation of *N*-sulfonylpyrrole with TBAF in THF

N-Sulfonylpyrrole	Time (h)	Temperature (°C)	Yield (%)	Ref.
 **33**	1.5	rt	98	35
 **34**	0.5	rt	89	36
 **35**	0.5	Reflux	96	37
 **36**	24	Reflux	64	37
 **37**	6	Reflux	90	37
 **38**	3	60	96	38
 **39**	2	60	60	38

In addition, deoxygenation by reductive removal of xanthate **40** with triphenyl tinhydride proceeded with cleavage of the tosyl moiety to provide the tricyclic core of the natural product roseophilin **41** (Fig. 8).[39]

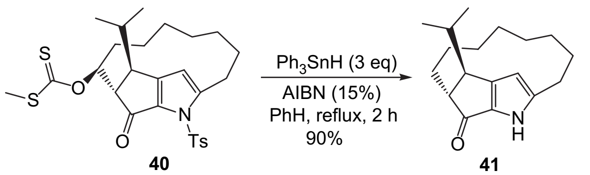


Figure 8. Concomitant xanthate deoxygenation and *N*-toluenesulfonyl group cleavage.

2.2. *N*-Boc protection

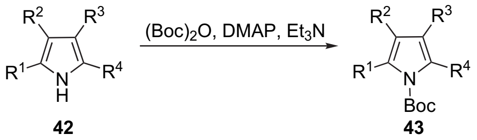
The *tert*-butoxycarbonyl (Boc) moiety has been useful for pyrrole chemistry, because of its electron-withdrawing effect and ease of removal under a variety of conditions. The protection of the pyrrole nitrogen has been performed using different sources of the *tert*-butoxycarbonyl moiety including $(Boc)_2O$, BocOPh, and Boc–ON. For example, pyrroles **42a–j** were protected in the presence of di-*tert*-butyl dicarbonate [$(Boc)_2O$], catalytic 4-(dimethylamino)-pyridine (DMAP), and Et_3N in good yields (Table 2).[40,41]

Employing *tert*-butyl phenyl carbonate (BocOPh) and sodium hydride in THF, pyrrole **42a** and 2,5-dimethylpyrrole **44** were converted to *N*-Boc-protected pyrroles **43a** and **45**, respectively.[43] The N-protection of pyrrole-2-carboxaldehyde **46** using 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile (Boc–ON) and similar conditions gave the Boc analog **47** (Fig. 9).[44]

Although the reactivity of certain pyrroles may limit the use of acidic conditions for Boc group deprotection, success has been achieved with relatively electron-deficient pyrroles. For example, in the pursuit of novel biologically active heteroaromatic thiophenes, thiophenyl pyrrole **49** was obtained by mixing *N*-Boc pyrrole **48** in trifluoroacetic acid (TFA) for 30 min (Fig. 10).[45]

In a study of TFA-induced and thermolytic cleavage of *N*-Boc pyrroles **50a** and **50b**, optimum thermolytic conditions at 180 and 155 °C, respectively, yielded acrylate pyrroles **51a** and **51b**. Pyrrole **51a** could be obtained in similar yield when *N*-Boc pyrrole **50b** was exposed to TFA; however, acrylate **50b** decomposed in the presence of TFA in DCM (Table 3).[41]

Table 2. *N*-Boc protection with $(Boc)_2O$



Entry	R^1	R^2	R^3	R^4	Solvent	Yield (%)	Ref.
a	H	H	H	H	DCM	81	40
b	CO_2Et	H	H	H	DCM	85	40
c	$COCCl_3$	H	H	H	DCM	81	40
d	CO_2Et	H	H	Me	DCM	94	40
e	CO_2Et	Me	H	Me	DCM	94	40
f	CO_2Et	Me	CO_2Et	Me	DCM	81	40
g	CO_2Bz	H	NO_2	H	DCM	87	40
h	CO_2Bz	H	NH(Boc)	H	DCM	80	40
i	CO_2t-Bu	Me	Me	H	MeCN	100	41
j	H	TMS	H	TMS	DCM	100	42

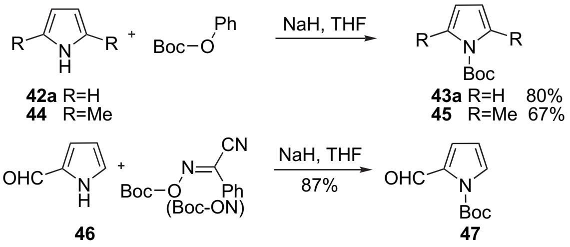


Figure 9. *N*-Boc pyrrole protection.

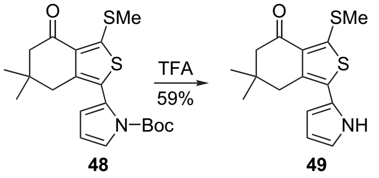


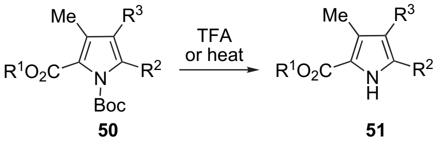
Figure 10. Acidic deprotection of *N*-Boc pyrrole.

Thermolytic removal of the *N*-Boc group from neat pyrrole, at 180 °C for 30 min, was reported to give high yields in the deprotection of a series of pyrrole and bipyrrole analogs, **52**, **54**, and **56**.[46] Similar thermolysis conditions were later used for the selective Boc deprotection of pyrrole amino esters **58a–e** to afford pyrroloprolines **59a–e**.[47] Recently, thermally induced decarboxylation by heating Boc-protected bipyrrole **60** at 230 °C under reduced pressure (10^{-3} Torr) for 30 min produced 1,3-bis(2-pyrrolyl)azulene **61**, a luminescent chemosensor for fluoride ions (Fig. 11).[48]

The Boc group can also be cleaved from the pyrrole nitrogen under basic conditions. For example, *N*-Boc 2-substituted pyrroles **62a–d** were deprotected with sodium methoxide in a mixture of methanol and THF.[49] Furthermore, *N*-Boc deprotection of 3,4-disubstituted pyrrole **64** produced 3,4-bis(trimethylsilyl)pyrrole **65** (Fig. 12).[42]

The utility of the Boc group in natural product synthesis was demonstrated in the synthesis of prodigiosin **75**. Hydroboration and oxidation of olefin **66** furnished ketone **67** as the substrate for the subsequent Wittig olefination. Hydrogenation of olefin **68** and oxidation of the methyl group on

Table 3. Comparison of TFA and thermolysis for *N*-Boc removal



Entry	R^1	R^2	R^3	Method	Yield (%)
a	Et	Me	$CH{=}CHCO_2Me$	TFA/DCM 180 °C, neat	85 86
b	*t*-Bu	$CH{=}CHCO_2Me$	Me	TFA/DCM 155 °C, neat	Decomposition 96

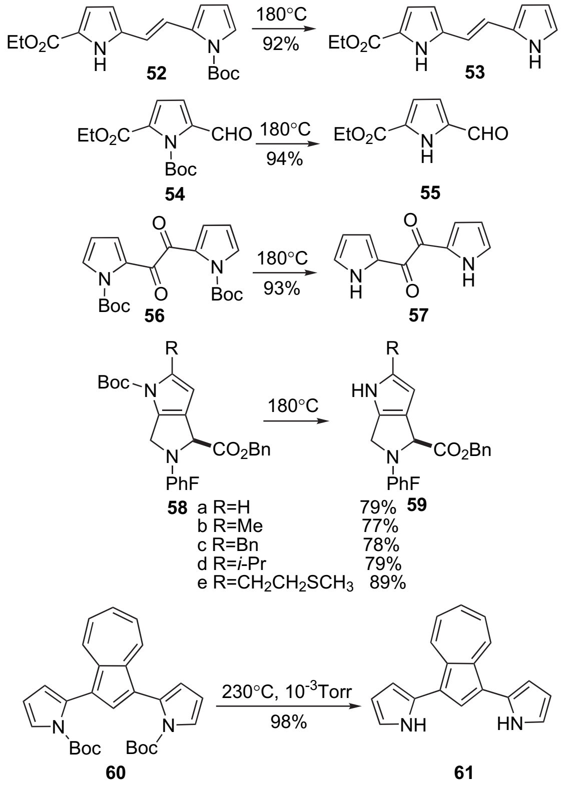


Figure 11. Thermolysis of *N*-Boc pyrroles.

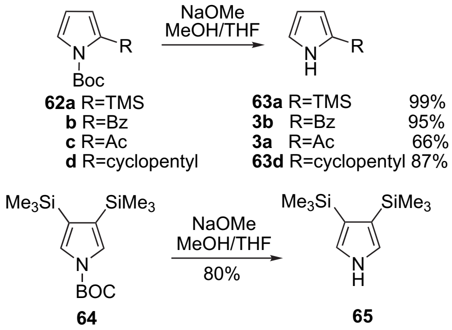


Figure 12. *N*-Boc group removal under alkaline conditions.

pyrrole **69** with cerium ammonium nitrate (CAN) afforded *N*-Boc-protected pyrrole-2-carboxaldehyde **70**. Base-induced condensation of aldehyde **70** with lactam **71** was accompanied with Boc removal such that unprotected dipyrromethene **72** was isolated. Treatment of **72** with Tf_2O produced triflate **73** suitable for the cross-coupling with boronic acid **74** delivering prodigiosin **75** (Fig. 13).[50]

The cleavage of the Boc group has also been observed during Suzuki reactions on bromopyrrole **76**, presumably due to heating under alkaline conditions.[51] Taking advantage of this one-step process, 4-arylpyrroles **77a–d** were prepared from *N*-Boc-4-bromopyrrole **76** and different arylboronic acids at 110 °C (Table 4).[51]

It is noteworthy that a series of *N*-(Boc)-2-arylpyrroles **78a–k** were prepared by Suzuki coupling at 85 °C in 1,2-dimethoxyethane (DME) with retention of the Boc moiety in variable yields (Table 5).[52]

However, palladium-catalyzed cross-coupling reactions of the same pyrrole boronic acid **74** at 130 °C in DMF induced removal of the Boc group, such that 2-arylpyrroles **80a–b** were isolated (Fig. 14).[53]

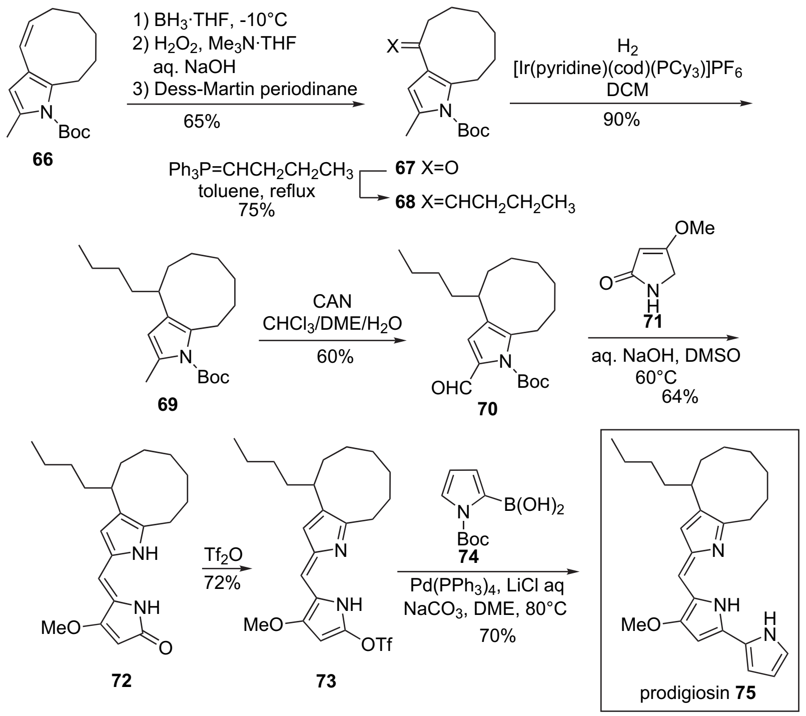
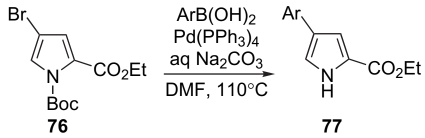


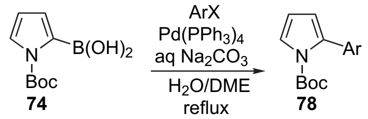
Figure 13. Boc group use in the synthesis of butylcycloheptylprodigiosin **75**.

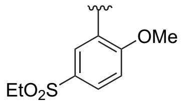
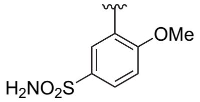
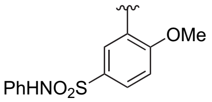
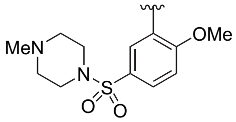
Table 4. *N*-Boc removal during Suzuki coupling



Entry	Ar	Yield (%)
a	3,4-Dimethoxyphenyl	80
b	4-Fluorophenyl	68
c	3-Isopropoxy-4-methoxyphenyl	82
d	2,3,4-Trimethoxyphenyl	84

Table 5. Suzuki coupling with retention of the *N*-Boc moiety



Entry	Ar	X	Yield (%)
a	Ph	I	55
b	Ph	Br	16
c	4-MeC$_6$H$_5$	Br	15
d	4-ClC$_6$H$_5$	Br	34
e	1-Naphthyl	Br	34
f	2-Thienyl	Br	35
g	3-Pyridyl	Br	72
h		Br	98
i		Br	83
j		Br	63
k		Br	70

Alternative methods for Boc deprotection have been developed in recent years. For example, 3-pyrrolylalanine **82** was liberated by simultaneous deprotection of the *N*-(Boc) and *N*-carboxybenzyloxy (Cbz) amino protecting groups using trimethylsilyl iodide (TMSI) and pyridine (Fig. 15).[54] In pursuit of the synthesis of marine alkaloids, *N*-(Boc)pyrrole diester **83** was treated with Br_2, which caused bromination of the 3- and 4-positions, and in situ Boc removal to afford dibromopyrrole **84**[54] (Fig. 15). Moreover, selective deprotection of *N*-Boc pyrrole *tert*-butyl ester **85** was achieved with TBAF in THF at reflux. The proposed mechanism for the deprotection involves nucleophilic attack by fluoride on the carbonyl group to release the pyrrole anion and Boc–F (Fig. 15).[55]

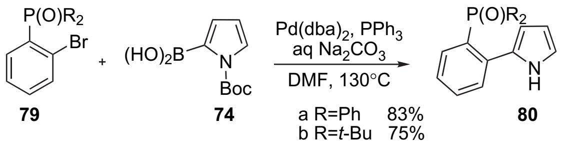


Figure 14. *N*-Boc cleavage under Suzuki reaction conditions.

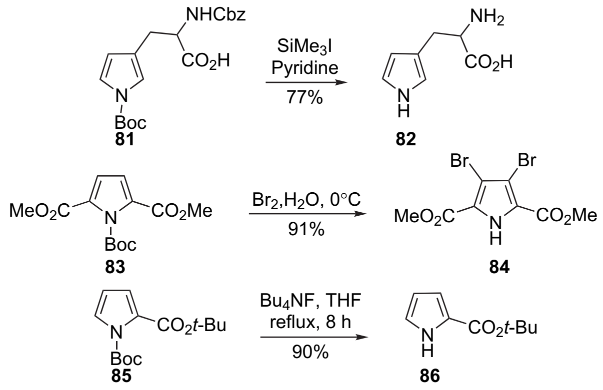


Figure 15. Various conditions for *N*-Boc deprotection.

2.3. *N*-Benzyl, alkyl, and allyl protection

The N-benzylation and alkylation of pyrrole, rather than substitution at the 2-position, is enhanced by the use of soft pyrrolyl anions (e.g., potassium, ammonium, and thallium) and polar aprotic solvents.[56–59] Phase-transfer catalysis has been a useful strategy for the N-benzylation of pyrrole, making use of the soft trialkylammonium cation.[59] This method was shown to be applicable to the N-benzylation of pyrroles with electron-withdrawing groups at the 2-position. Ionic liquids[24] and phase-transfer catalysis conditions with polyethylene glycols[60] have also been reported to be advantageous for the preparation of *N*-benzyl pyrrole. A synthesis of *N*-benzyl pyrroles bearing 2-morpholino substituents has been developed featuring the reaction of an imine **87**, as its enamine, with a diimmonium salt **88** (Fig. 16).[61] In electrophilic substitution reactions, the effects of the *N*-benzyl group on the regioselectivity have been investigated in pyrrole bromination, nitration, and Vilsmeier–Haack formylation. Bromination and nitration gave 3-substituted pyrroles as major products (66 and 60%, respectively). On the contrary, formylation gave the pyrrole-2-carboxaldehyde as the major product, with an increased amount of pyrrole-3-carboxaldehyde (15%) compared to product from Vilsmeier–Haack formylation of *N*-methylpyrrole under the same conditions.[62] Debenzylation of *N*-benzyl pyrroles was originally found to be problematic[63] as catalytic hydrogenation methods resulted in reduction of the phenyl ring to give *N*-cyclohexylmethyl derivatives, and acid-catalyzed deprotection conditions induced migration of the benzyl group to an unsubstituted 2-position. Debenzylation via hydrogenation over Raney nickel was also unsuccessful, with only starting material being recovered.[62] Effective removal of the benzyl group has been achieved by reaction with a reducing metal such as sodium in liquid ammonia (Fig. 16).

En route to indoles, *N*-benzyl pyrroles have been employed in the synthesis of 4-oxo-4,5,6,7-tetrahydroindole derivatives (Fig. 17).[64] The *N*-benzyl group proved stable to conditions for a variety of synthetic steps, including reduction

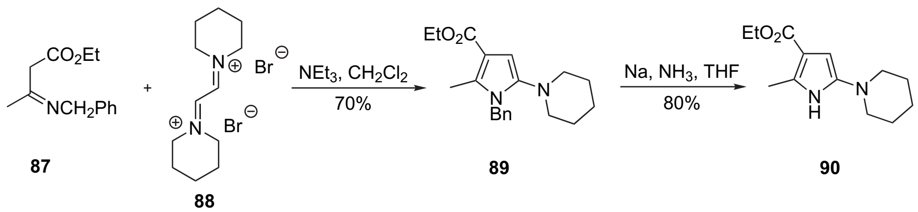


Figure 16. Synthesis and deprotection of **89**.

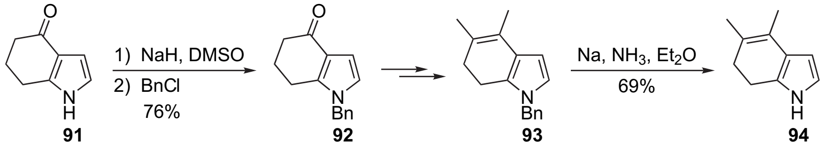


Figure 17. Use of the benzyl group in the synthesis of dihydroindole **94**.

(NaBH$_4$ and Wolff–Kishner), Wittig, aldol and alkylation reactions. Final removal of the benzyl group from dihydroindole **93** was performed using sodium in liquid ammonia.

In the synthesis of indole **100**, *N*-benzyl pyrroles were employed in a sequence featuring a Stille cross-coupling reaction, Grignard addition to aldehyde **97**, alkylation, and electrocyclization (Fig. 18).[65] Removal of the benzyl group from indole **99** was found to be problematic, and best achieved by transalkylation.

In the synthesis of the macrotricyclic segment **41** of the antitumor agent roseophilin, a benzyl group was used to protect the pyrrole nitrogen during the intramolecular acylation, sulfone elimination, and conjugate addition reactions to provide the protected intermediate **103** (Fig. 19).[28] The benzyl group was first introduced by a palladium-catalyzed amination to form pyrrole **102**. Model debenzylation studies with 2-acetyl-1-benzyl pyrrole revealed that deprotection could be achieved by transalkylation (AlCl$_3$, benzene);[66] however, these conditions were not effective for the deprotection of *N*-benzyl pyrrole **103**. Instead, the benzyl group was removed from pyrrole **103** by reductive cleavage using calcium in liquid ammonia, which caused concurrent ketone reduction such that oxidation was necessary to reinstall the carbonyl group.

In the synthesis of alkoxyporphyrins (Fig. 20),[67] the benzyl group prevented N-alkylation during the synthesis of dimethoxypyrrole **107**. Benzyl group removal from pentasubstituted **107** was achieved both by hydrogenation and by exposure to acid in the presence of anisole to trap the benzyl carbonium ion. Related debenzylation of *N*-protected 3,4-dialkoxy pyrroles has been achieved using sodium in liquid ammonia.[68]

The 2,4-dimethoxybenzyl (DMB) group has been employed to N-protect pyrrolo[2,3-*d*]pyrimidines, en route to the

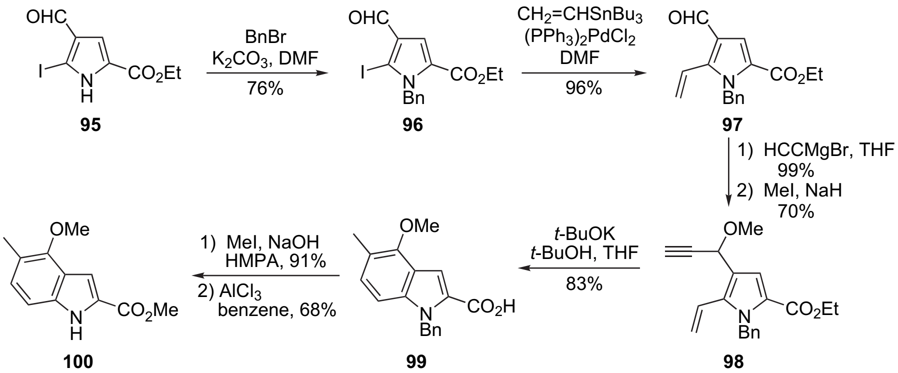


Figure 18. Use of the benzyl group in the synthesis of indole **100**.

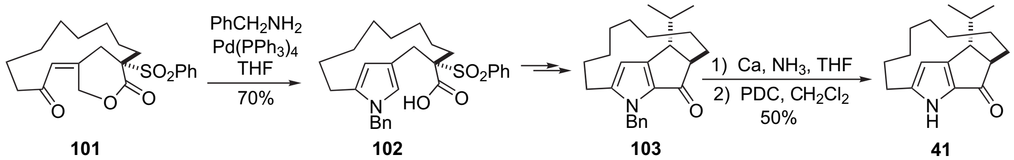


Figure 19. Use of the benzyl group in the synthesis of macrotricyclic segment **41**.

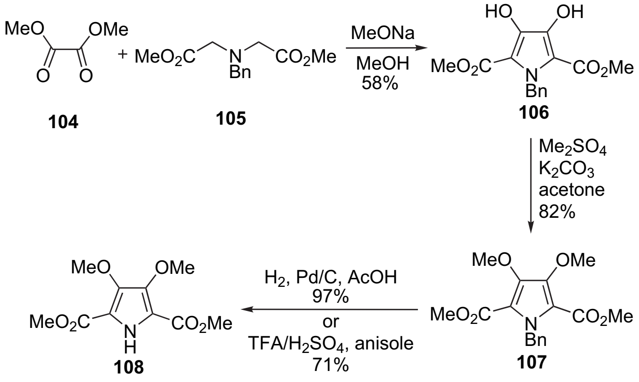


Figure 20. Use of the benzyl group in the synthesis of dimethoxypyrrole **108**.

natural product rigidin (Fig. 21).[69] The pyrrolo[2,3-*d*]pyrimidine **110** was prepared by ring closure of pyrimidinone **109**, via intramolecular acylation. Conversion to the corresponding triflate **111**, Stille cross-coupling and then TFAA-promoted acylation gave a mixture of DMB-protected product **112** (18%) and pyrrolopyrimidine **113** (47%), from loss of the DMB group under the acidic conditions. Complete removal of the DMB group was then achieved by treating **112** with TFA. Deprotection of the DMB group in this way surmounted difficulties encountered with the related *N*-benzyl analog of **112**, which had resisted deprotection by a number of methods, including hydrogenation, BBr_3, HBr/AcOH, TMSI/CH_3CN, and Na/NH_3.[69]

The 3,4-dimethoxybenzyl group was also used in the synthesis of porphobilinogen (Fig. 22).[63] Annulation of vinylogous amide **114** gave *N*-DMB pyrrole **115**, which was deprotected cleanly with acid to afford pyrrole triester **116**. Although *N*-benzyl and *N*-*p*-methoxybenzyl pyrrole derivatives of **115** could be prepared, their deprotection was troublesome since hydrogenative methods led to reduction of the benzyl units and acidic methods led to migration of the *N*-substituent to the free α-position.

In a total synthesis of prodigiosin, alkenyl vicinal tricarbonyl compound **117** served in the construction of dipyrrole **119** (Fig. 23).[70] Protected dipyrrole **118** was constructed by condensation of **117** with 3,4-dimethoxybenzyl amine, and subsequently *O*-methylated and *N*-deprotected to provide dipyrrole **119**, after removal of the *N*-tosyl group.[63]

The *N*-(4-methoxybenzyl) (MPM) group has been incorporated into *N*-substituted-2-vinylpyrroles evaluated as potential anti-HIV agents.[71] *N*-(MPM)pyrroles have also served in the synthesis of indoles by an analogous manner to that

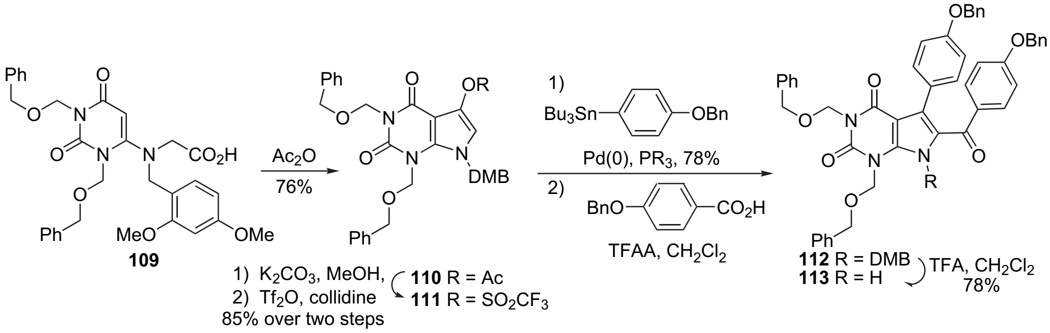


Figure 21. Synthesis of pyrrolo[2,3-*d*]pyrimidine **113**.

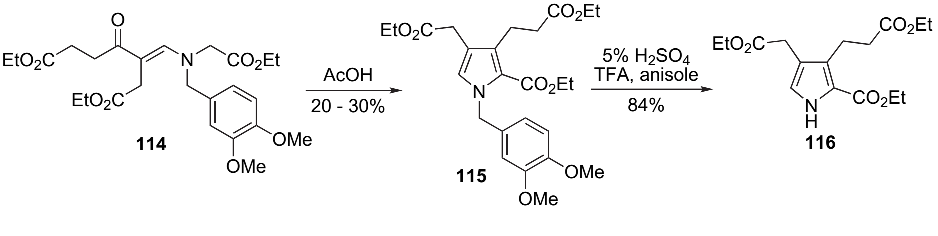


Figure 22. Synthesis of precursor to porphobilinogen.

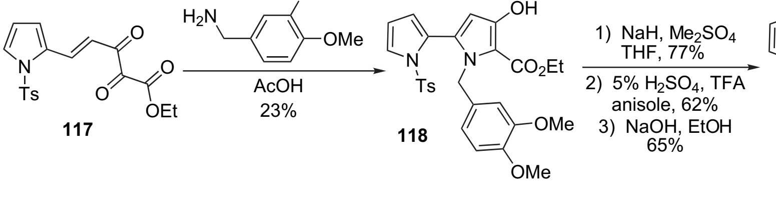


Figure 23. Synthesis of bipyrrole **119**.

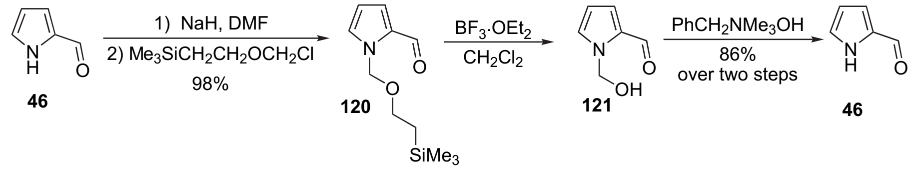


Figure 24. Installation and removal of SEM group.

detailed in Figure 18 for the benzyl group.[65] In a synthesis of porphobilinogen akin to that shown in Figure 22,[63] attempts at hydrogenolytic and acidic deprotection of the corresponding *N*-MPM pyrrole caused reduction of the benzene ring and migration of the protecting group to the free α-position, respectively.

The 2-(trimethylsilyl)ethoxymethyl (SEM) group has been demonstrated to be a useful *N*-protecting group for pyrroles, conferring resistance to reductive, oxidative, acidic, and basic conditions.[72,73] Treatment of the sodium anion of pyrrole-2-carboxaldehyde with SEM-chloride gave *N*-(SEM)-pyrrole **120** in excellent yield (Fig. 24), and pyrroles substituted with formyl, keto, and benzyl groups were also *N*-protected in this manner. Deprotection occurred upon treatment with $BF_3 \cdot OEt_2$, to give the corresponding *N*-(hydroxymethyl)-pyrrole **121**. In situ treatment of **121** with catalytic amounts of Triton B caused loss of formaldehyde. Alternatively, the SEM group has been removed directly using TBAF albeit in lower yields, which are enhanced in the presence of amines; however attempts using $LiBF_4$/MeCN and CsF/HMPA failed to remove the SEM group.[73]

The SEM group has been particularly useful as a directing group for pyrrole metalation. For example, α-lithiation of *N*-(SEM)pyrrole **122** was best accomplished using *n*-BuLi/DME to furnish chelated 2-lithio-SEM-pyrrole **123**.[73] α-Lithiated pyrrole **123** reacted with a series of alkyl halides, acid chlorides, silyl chlorides, aldehydes, and lactones in moderate–good yield.[72,73] In essence the SEM group acts as both an *N*-protecting group and a directing group for substitution. This approach to acylation has been used in the preparation of ketone **126** en route to the ionophore X-14547 A (**127**) (Fig. 25).[74] Halopyrroles have also been protected with the SEM group prior to halogen–lithium exchange and acylation at the β-position.[75,76]

The employment of SEM protection has been critical in two total syntheses of roseophilin.[28,77] N-Protection of pyrrole **41** with the SEM group minimized steric bulk during the addition to the ketone **128**, and provided means for simultaneous removal of the SEM and the triisopropylsilyl (TIPS) groups (Fig. 26). The SEM protection enabled the organocerium addition to ketone **128** to provide protected roseophilin (**130**), which was subsequently deprotected with TBAF. In an alternative synthesis of *ent*-roseophilin[78] employing *N*-(SEM)pyrrole **133**, the SEM group proved robust throughout steps including lactone hydrolysis, reduction, oxidation, Wittig olefination, alkylation (TMS, diazomethane), and ring-closing metathesis (Fig. 27). Organo-cerium addition, followed by removal of the SEM group using TBAF gave *ent*-rosoephilin. A SEM-protected pyrrole was also used in the synthesis of (+)-dragmacidin F.[79]

N-Pivaloyloxymethyl (POM) pyrrole[13] has been prepared in good yield from chloromethylpivalate and the sodium anion of pyrrole. Although removal of the POM group from pyrrole has yet to be reported, deprotection of POM-protected indole with sodium methoxide gave a mixture of indole (50%) and *N*-(hydroxymethyl)indole (30%), and treatment with sodium methoxide followed by KOH gave 95% yield for the deprotection.

The benzylmethyl ether (benzyloxymethyl, BME) group has been introduced to N-protect pyrroles to alleviate problems during functional group manipulations that would occur if the acidic N–H were present.[80] The sodium anion of 3,4-disubstituted pyrrole **134** reacted with benzyl chloromethyl ether to give *N*-(BME)-pyrrole **135** in excellent yield (Fig. 28). Stable to acidic, basic, and acylating conditions, the *N*-BME group has been removed from pyrroles by either hydrogenation or treatment with $AlCl_3$ to give the corresponding 1-(hydroxymethyl)-pyrrole, which as described

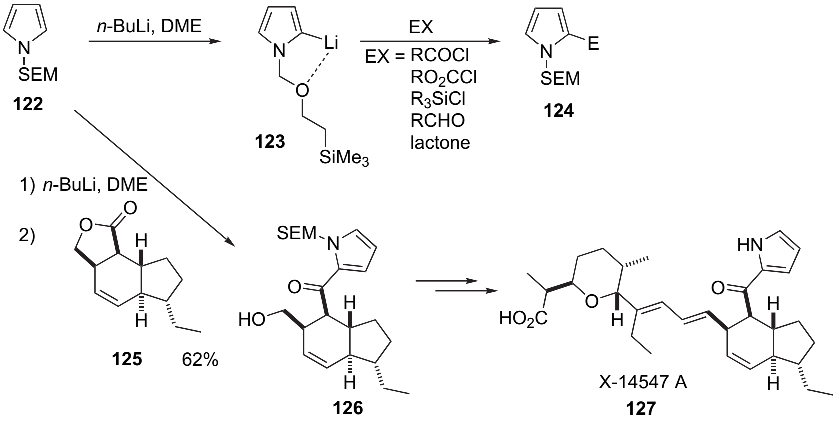


Figure 25. Regioselective acylation of *N*-SEM pyrrole **122**.

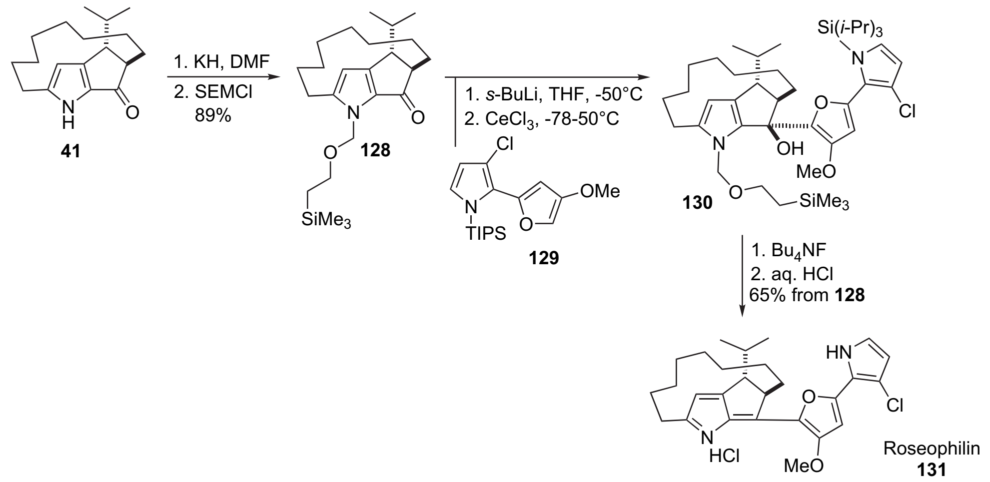


Figure 26. Roseophilin synthesis.

for SEM group removal, can be cleaved with catalytic amounts of Triton B to effect the loss of formaldehyde. In the synthesis of verrucarin E (**139**),[81] the BME group demonstrated utility both for nitrogen protection and for improving the solubility of the pyrrole 3,4-dicarboxylates.

The BME group has been used to N-protect pyrroles involved in mercuration reactions. Difficulties with the deprotection of *N*-benzyl pyrroles and complications with pyrroles bearing electron-withdrawing *N*-protecting groups (benzoyl and tosyl) were surmounted by the electron-donating ability of the BME group, which enhanced nucleophilicity and facilitated β-mercuration of *N*-(BME)-pyrrole **140** (Fig. 29).[41] With the BME group, higher yields of organomercuration were obtained than with the corresponding *N*-methylpyrrole.[41] Subsequent Heck-type coupling of **141** with methyl acrylate gave pentasubstituted pyrrole **142**. N-Deprotection occurred with concurrent reduction of the alkene in the hydrogenation step.[80] In the removal of the BME group, the solvent was key for successful hydrogenation (use of THF was prohibitively slow), and the addition of NEt_3 to the reaction mixture gave the *N*-(ethoxymethyl)-pyrrole. The use of more than catalytic amounts of Triton B for deformylation resulted in partial hydrolysis of the 3-methylpropanoate. α-Mercuration of *N*-BME-2-unsubstituted pyrroles has also been demonstrated.[41]

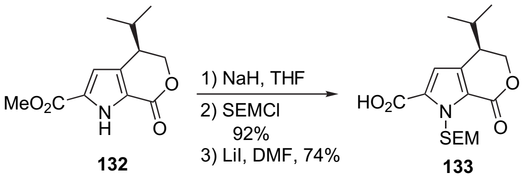


Figure 27. Alternative route toward *ent*-roseophilin using *N*-(SEM) pyrrole **133**.

The trityl group may act as both a nitrogen blocking group and a bulky directing group.[82] Pyrrole N-protection with the triphenylmethyl (trityl, CPh_3) group has been particularly used to favor substitution at the 3-position. *N*-Tritylpyrrole (**145**) was synthesized by condensation of 2,5-dimethoxytetrahydrofuran and triphenylmethylamine (Fig. 30). *N*-Tritylpyrroles have also been prepared by treating the potassium salt of the pyrrolyl anion with trityl chloride, albeit with variable yields due to difficulties in product purification. Formylation of *N*-tritylpyrrole (**145**) proceeded with reasonable selectivity for the 3-position, and the regioselectivity was improved by modification of the formylating agent. Bromine and triphenylphosphine in DMF gave better selectivity than

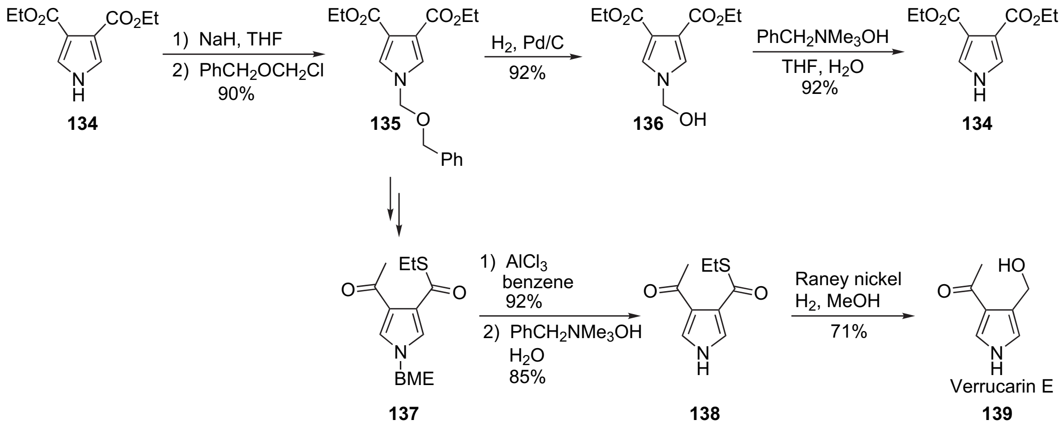


Figure 28. Use of BME protecting group.

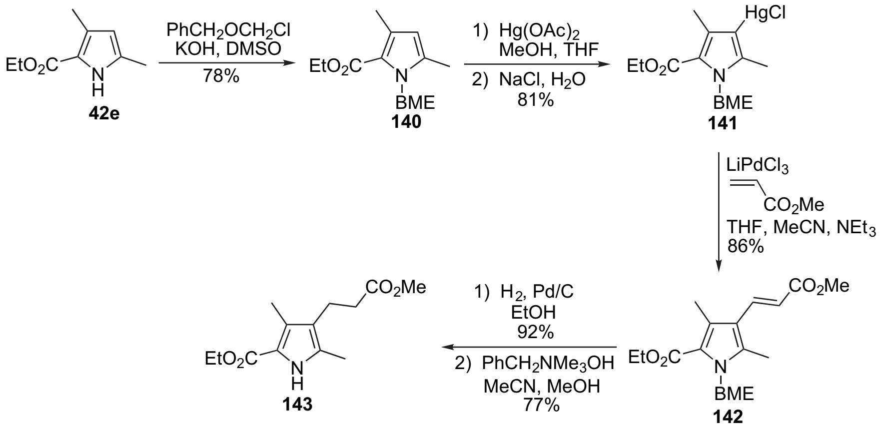


Figure 29. Use of the BME group during mercuration.

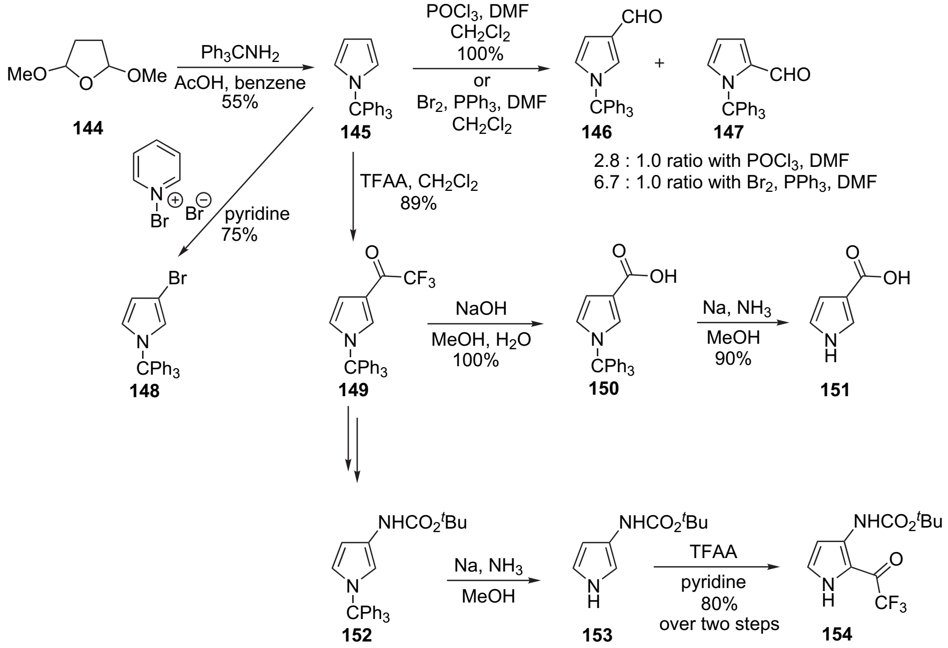


Figure 30. Trityl group as nitrogen blocking group.

$POCl_3$ in DMF (Fig. 30). Trifluoroacetylation of **145** proceeded with high regioselectivity for the 3-position, as did bromination. Pyrrole-3-carboxylic acid (**151**), which was difficult to prepare by other routes, was synthesized from 3-trifluoroacetylpyrrole **149** by a haloform reaction using sodium hydroxide in methanol and deprotection of the trityl group with sodium in liquid ammonia. 3-Trifluoroacetylpyrrole **149** was also used to synthesize 3-amino pyrroles **152–154**, by way of a sequence featuring a Curtius rearrangement. An electrochemical method for the deprotection of the trityl group has also been briefly investigated.[82]

N-Tritylpyrrole (**145**) has been shown to undergo regioselective Friedel–Crafts 3-position acylation with an *N*-protected β-lactam to provide aminoketone **155** (Fig. 31).[83] In comparison, *N*-phenylsulfonylpyrrole underwent acylation solely at the 2-position. The Diels–Alder reaction of *N*-tritylpyrrole (**145**) with acetylenedicarboxylic acid gave the required product in the same yield as for *N*-benzyl pyrrole[84] as part of a study that deduced that steric factors alone do not control the reactivity of *N*-substituted pyrroles.

Allyl (2-propenyl) groups have been used in the N-protection of pyrrole, although with little synthetic application. *N*-Allyl pyrrole (**156**) has been prepared in good yield by alkylation of pyrrole with allyl bromide and potassium hydroxide in DMSO (Fig. 32).[85] Other solvent systems that have been effective for N-allylation include ionic liquids[24] and the application of aqueous/organic mixtures

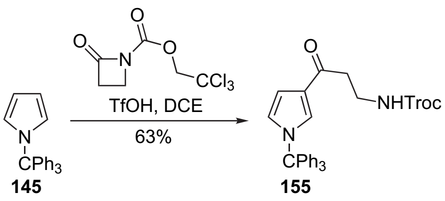


Figure 31. Acylation of *N*-tritylpyrrole.

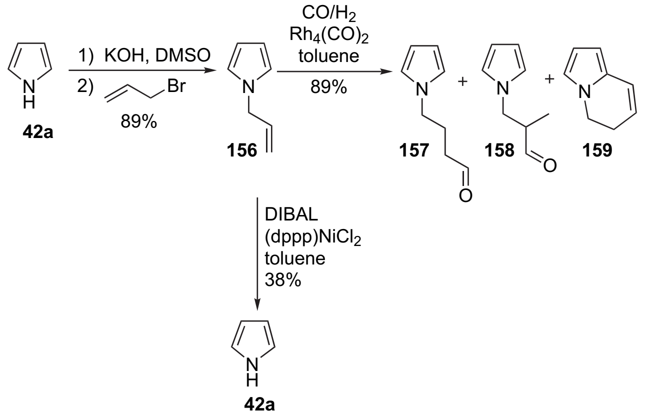


Figure 32. Synthesis, deprotection, and reaction of *N*-allyl pyrrole (**156**).

with polyethylene glycols as phase-transfer catalysts.[60] Subjection of *N*-allyl pyrrole **156** to rhodium-catalyzed hydroformylation gave excellent conversion to furnish a mixture of three products (**157–159**), the ratio of which varied with temperature and reaction time. Removal of the *N*-allyl group from pyrrole has been achieved by treatment with DIBAL in the presence of dichloro[bis(diphenylphosphino)propane]nickel [(dppp)NiCl$_2$], which has been claimed to be vital for success (Fig. 32). This method has not been applied to substituted pyrroles and with *N*-allyl pyrrole (**156**) the low isolated yield after allyl group removal may be due to difficulties in product isolation.[86]

In the synthesis of 3,4-dialkoxy pyrroles for the construction of alkoxy-substituted porphyrins (Fig. 33),[68] *N*-allyl protection was introduced by the condensation of allyl amine with dimethoxy dialdehyde **161**, which was produced in situ from hydrolysis of tetrahydrofuran **160**. The *N*-allyl group was removed by treatment with sodium in liquid ammonia. Deallylation of **162** was also achieved with stoichiometric amounts of methyl Grignard reagent in the presence of a nickel catalyst. With *O*-allyl and *O*-benzyl derivatives of **162**, all of the protecting groups were removed by treatment with either sodium in liquid ammonia or methyl Grignard reagent with nickel catalyst.

2.4. Beta-eliminating protecting groups

N-Ethyl groups possessing a terminal electron-withdrawing group have been used effectively for the protection of the pyrrole nitrogen atom because of their capacity to liberate the negatively charged heterocycle by beta-elimination in a reverse Michael reaction under basic conditions.

The introduction of such beta-eliminating ethyl group protection onto pyrrole has been achieved by alkylation, after nitrogen deprotonation with sodium hydride in DMF.[59] For example, 2-phenylsulfonylethyl chloride reacted with pyrrole-2-carboxaldehyde **46**, 2-methylthio pyrrole (**164**), and 4-oxo-4,5,6,7-tetrahydroindole **91** under these conditions (Fig. 34).[87] Alternatively, pyrrole alkylation has been achieved using phase-transfer conditions with tetrabutylammonium iodide in a benzene/aqueous sodium hydroxide mixture. In this way, 2-phenylsulfinylethyl and 2-phenylsulfonylethyl chlorides reacted with 2-benzoylpyrrole **3b** to provide *N*-alkylpyrroles **176** and **167** (Figs. 34 and 38).[87] Under modified conditions, 1-cyanoethylpyrrole **169** was prepared by alkylation of pyrrole **42a** with 3-chloropropionitrile using tetrabutylammonium bromide in a dichloromethane/aqueous sodium hydroxide mixture (Fig. 35).[59]

Various conditions have also been developed for performing the Michael addition of pyrrole **42a** onto α,β-unsaturated esters, nitriles, ketones, and sulfones in order to protect the heterocycle nitrogen. For example, using KOH in the ionic liquid [Bmim][PF$_6$], pyrrole **42a** reacted respectively with acrylonitrile, methyl acrylate, and methyl vinyl ketone to provide *N*-alkylpyrroles **169–171** (Fig. 36).[24] Reduced reaction times and higher yields were typically obtained in the respective syntheses of *N*-alkylpyrroles **169**, **170**, and **172** by employing ultrasound irradiation in the attack of pyrrole

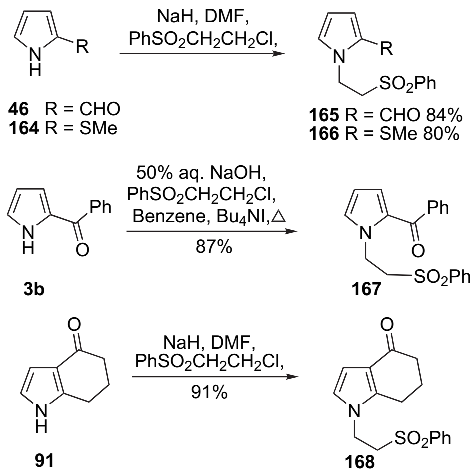


Figure 34. Pyrrole alkylation with 2-phenylsulfonylethyl chloride.

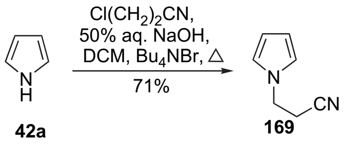


Figure 35. Pyrrole alkylation with 3-chloropropionitrile.

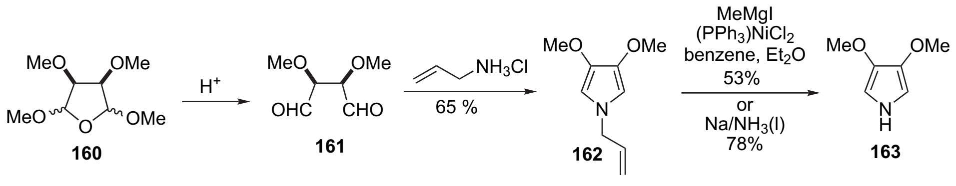
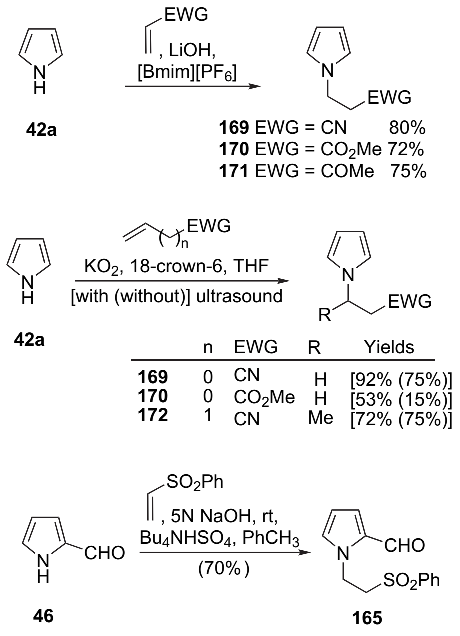


Figure 33. Synthesis of pyrrole **163** from tetrahydrofuran **160**.



	n	EWG	R	Yields
169	0	CN	H	[92% (75%)]
170	0	CO$_2$Me	H	[53% (15%)]
172	1	CN	Me	[72% (75%)]

Figure 36. Pyrrole alkylations by Michael additions.

onto acrylonitrile, methyl acrylate, and allylcyanide using potassium superoxide as base in the presence of catalytic 18-crown-6 in THF (Fig. 36).[88] The alkylation of pyrrole-2-carboxaldehyde **46** with phenylvinylsulfone provided *N*-alkylpyrrole **165** using tetrabutylammonium bisulfate as phase-transfer catalyst in a toluene/aqueous sodium hydroxide mixture for 24 h at room temperature (Fig. 36).[89] At reflux, after 1 h, these same conditions provided a mixture from which *N*-alkylpyrrole **165** was isolated in only 27% yield contaminated with three pyrrolizines **173–175** each of which was isolated in <5% yield (Fig. 37).[89]

Oxidation of phenylthioethyl ether to its corresponding sulfoxide and sulfone has been used to generate the respective phenylsulfinylethyl- and phenylsulfonylethyl-protection for the subsequent alkaline induced beta-elimination. For example, *N*-(2-phenylsulfinylethyl)pyrrole **176** has been synthesized in two steps from *N*-(2-chloroethyl)-2-benzoylpyrrole **177** by nucleophilic displacement of the chloride with sodium thiophenolate in DMF, followed by oxidation with *m*-chloroperbenzoic acid (*m*-CPBA) in dichloromethane (Fig. 38).[87] Treatment of *N*-(2-phenylthioethyl)pyrrole **194** in EtOH with a pH=5 buffered NaOAc/AcOH solution containing oxone oxidized thioether **194** to provide *N*-(2-phenylsulfonylethyl)pyrrole **195** (Fig. 41).[90]

As mentioned, the advantage of *N*-ethyl groups possessing a terminal electron-withdrawing group as pyrrole protection is their effective removal under basic conditions. For example, *N*-(2-phenylsulfinylethyl)pyrrole **176** was deprotected using sodium hydride in DMF at room temperature (Fig. 39).[87] Similar conditions were used to remove the phenylsulfonylethyl group from the tetrahydroindole **185** in the synthesis of aziridinomitosene **187** (Fig. 40).[91] Diazabicyclo-[4.3.0]non-5-ene (DBN) has been employed successfully as a non-nucleophilic base in the presence of diethylamine as a scavenger for the removal of 2-phenylsulfonylethyl groups from pyrroles **165** and **167** at room temperature (Fig. 39). 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) has been similarly employed in DMF to remove 2-*p*-nitrophenylethyl groups from benzoylpyrrole **210** at 100 °C and pyrrolopyrimidines **203** and **205** at 25 °C, respectively (Figs. 42 and 43).[92–94] Furthermore, the phenylsulfonylethyl group has been removed from the tetrahydroindole **195** using potassium *tert*-butoxide in a dichloromethane/THF mixed solvent system (Fig. 41).

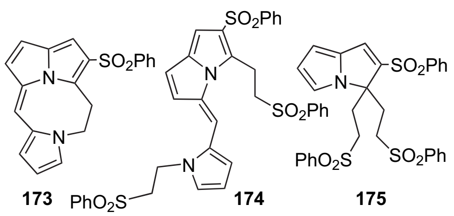


Figure 37. Pyrrolizines **173–175**.

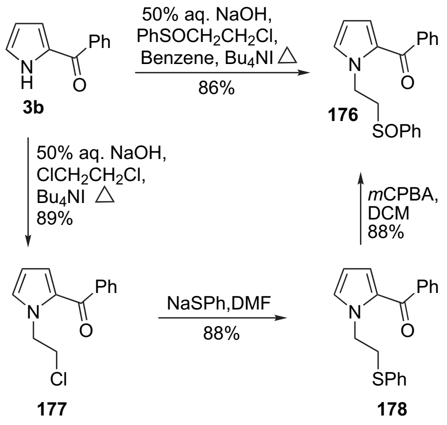


Figure 38. Oxidation of phenylthioethyl pyrrole **178** to sulfoxide **176**.

The 2-phenylsulfonylethyl and 2-*p*-nitrophenylethyl groups have both been employed in the total syntheses of various pyrroles. For example, in the synthesis of aziridinomitosene **187**, alkylation of oxazole **179** with the crystalline triflate **180** (derived from 2-phenylsulfonylethanol and triflic anhydride in pyridine) gave the corresponding oxazolium salt **181** (Fig. 40). Electrocyclic ring opening of the oxazoline on treatment of **181** with cyanide ion provided the azomethine ylide **183**, which reacted in an intramolecular dipolar cycloaddition to furnish tetrahydroindole **185**. Subsequent removal of the 2-phenylsulfonylethyl group with sodium hydride in DMF gave pyrrole **186**, which was converted to the target aziridinomitosene **187**.[91]

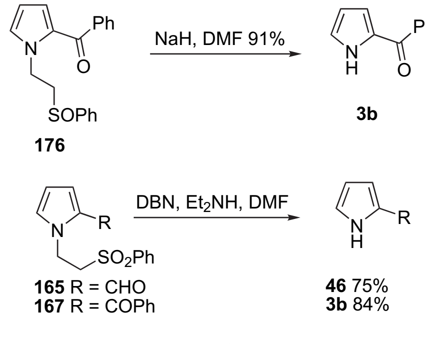


Figure 39. Deprotection by beta-elimination.

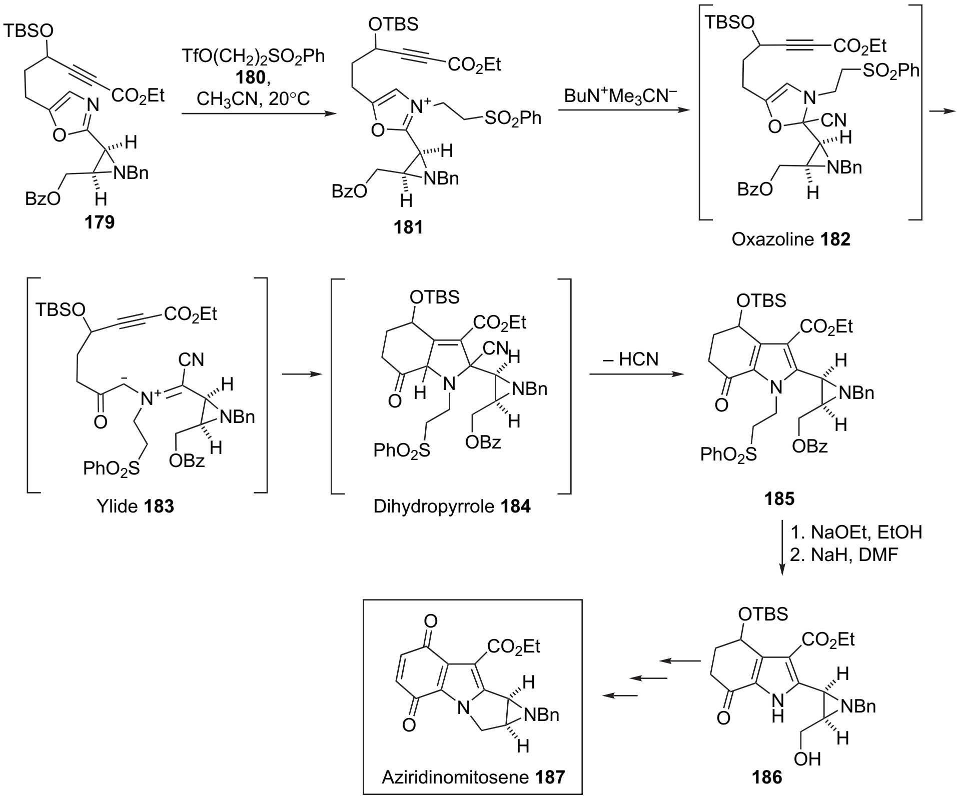


Figure 40. Application of 2-phenylsulfonylethyl group in aziridinomitosene synthesis.

In an alternative approach to the aziridinomitosene skeleton, 4-oxo-4,5,6,7-tetrahydroindole **196** was prepared by an oxaza-Claisen rearrangement and subsequent ring closure of the aldehyde intermediate (Fig. 41).[90] The key vinylogous hydroxamate **190** starting material was produced by condensation of 1,3-cyclohexanedione with the hydroxylamine product **189** from reduction of oxime **188** with sodium cyanoborohydride in methanol acidified with 10% HCl. Michael addition, rearrangement, and pyrrole annulation, all were performed in the same pot by treating vinylogous hydroxamate **190** with ethyl propiolate and Hünig's base to provide aminol **193** that eliminated water on exposure to TsOH to give *N*-protected tetrahydroindole **194**. Removal of the *N*-protecting group was then achieved by oxidation of sulfide **194** to sulfone **195** using oxone, and beta-elimination with potassium *tert*-butoxide to give tetrahydroindole **196** in two steps.[90]

The *p*-nitrophenylethyl group has been employed in the synthesis of pyrrolopyrimidines.[93,94] Introduced as the sodium salt of *N*-(*p*-nitrophenylethyl)glycinate (**197**) during the step to form 4-acetoxypyrrole **199**, which featured substitution onto chloride **198** and annulation using acetic anhydride (Fig. 42), the *p*-nitrophenylethyl group was tolerant to subsequent steps involving hydrolysis of the acetate, activation of the resulting 4-hydroxypyrrole **200** as its corresponding triflate, and Pd-catalyzed methoxycarbonylation to provide ester **202**. Both acetoxypyrrole **199** and its corresponding methyl ester **202** could be effectively deprotected with DBU in acetonitrile at 25 °C to provide the pyrrole nitrogen suitable for alkylation with a carbohydrate moiety.[93,94]

In the preparation of the potent activator of L-type calcium channels, FPL 64176 (**211**), the *p*-nitrophenylethyl group played a key role in preventing destruction of the pyrrole

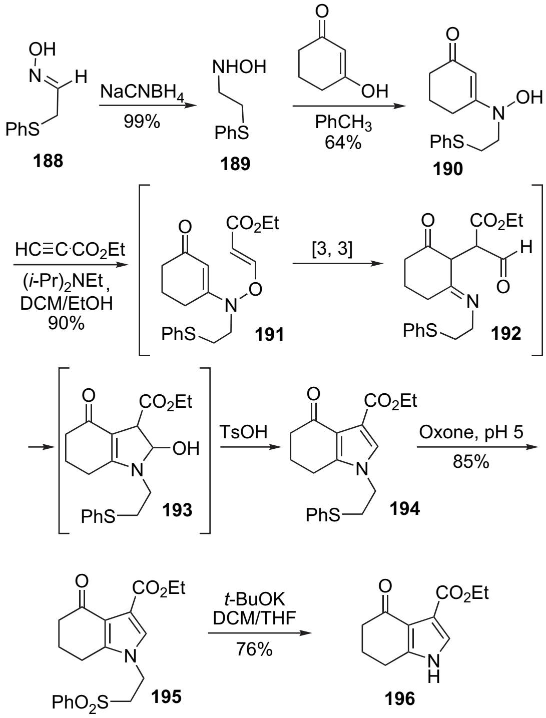


Figure 41. 2-Phenylsulfonylethyl group use in the synthesis of tetrahydroindole **196**.

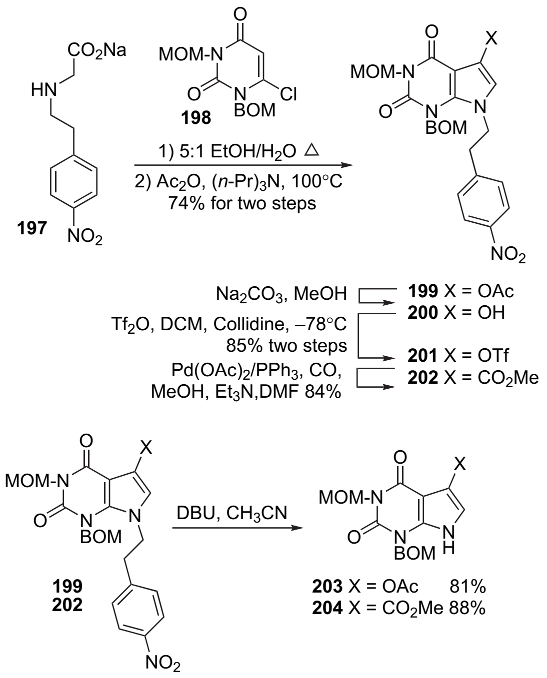


Figure 42. *p*-Nitrophenylethyl group use in the synthesis of pyrrolopyrimidines.

product by Michael attack on dipolarophile **209** during the cycloaddition of azomethine ylide **208** (Fig. 43).[92] Alkylation of *p*-nitrophenylethylamine with ethyl 2-bromopropionate and hydrolysis gave amino acid **207**, which on treatment with acetic anhydride and triethylamine at 70 °C underwent acetylation and dehydration to form oxazolium intermediate **208**. Cycloaddition of the oxazolium onto electron-deficient acetylene **209** yielded the protected pyrrole **210**. Removal of the *p*-nitrophenylethyl group was then accomplished with DBU in DMF at 100 °C giving the desired benzoylpyrrole **211**.[92]

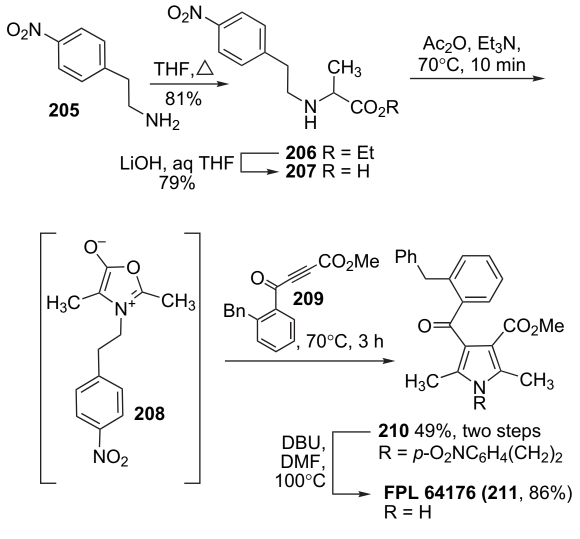


Figure 43. *p*-Nitrophenylethyl group use in the synthesis of FPL 64176.

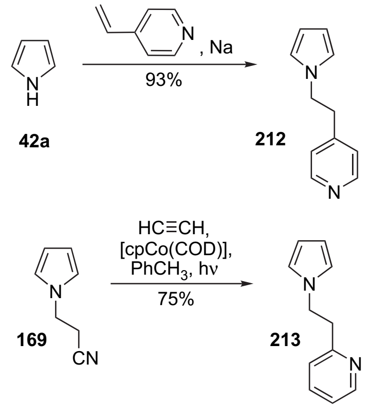


Figure 44. Syntheses of pyridylethylpyrroles **212** and **213**.

The pyridylethyl group has been developed as a safety-catch[95] *N*-protecting group for pyrrole. Alkylation of the pyridine nitrogen of this group generates the corresponding *N*-alkyl pyridinium salt, which on exposure to alkaline conditions undergoes beta-elimination of the *N*-alkyl vinylpyridinium salt to liberate the pyrrole. *N*-(2-Pyrid-4-ylethyl)pyrrole (**212**) has been synthesized by reaction of pyrrole and 4-vinylpyridine in the presence of sodium metal (Fig. 44).[96,97] Isomeric 2-(2-pyrrol-1-yl-ethyl)pyridine (**213**) was made by the photocatalyzed [2+2+2]-cycloaddition of 2-cyanoethylpyrrole **169** with acetylene in the presence of a cobalt catalyst (Fig. 44).[98]

Removal of the pyridylethyl group from *N*-(2-pyrid-4-yl-ethyl)pyrrole (**212**) was performed in two steps.[97] First, alkylation with iodomethane in acetone at 25 °C for 24 h gave a solid, which, after recrystallization, afforded the pyridinium iodide **214** as prisms. Exposure of the pyridinium salt **214** to sodium hydroxide in a 10:1 acetone/water solution released 1-methyl-4-vinylpyridinium iodide (**215**), which precipitated, and delivered pyrrole **42a** (Fig. 45).

N-Vinylpyrroles are relatively stable, but can be hydrated using strong acid to provide the corresponding 1-hydroxyethylpyrroles that can be deprotected with loss of acetaldehyde. The 2-chloroethyl and 2-hydroxyethyl groups have been employed as pyrrole protecting groups because of their ability to be removed by conversion into vinylpyrroles.[87,99]

As mentioned, chloroethylation of pyrrole can be achieved in high yield under phase-transfer conditions with tetrabutylammonium iodide as catalyst in a mixture of 1,2-dichloroethane and 50% aqueous sodium hydroxide (Figs. 38 and 46).[87] Removal of the chloroethyl group involves beta-elimination to the corresponding vinylpyrrole. In the case of 2-chloroethylpyrroles **217a** and **177**, sodium hydride in acetonitrile at 50 °C was employed to generate the

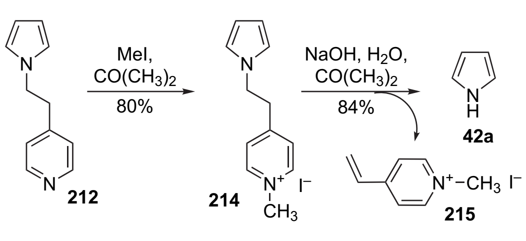


Figure 45. Deprotection of pyridylethylpyrrole **212**.

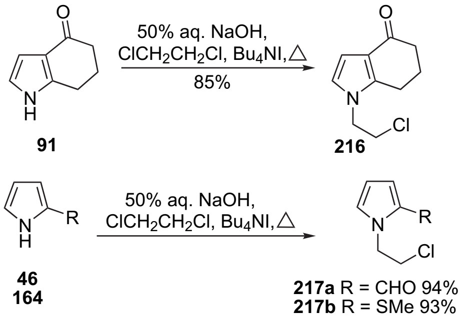


Figure 46. Synthesis of chloroethylpyrroles.

respective vinylpyrroles **218a** and **218b** (Fig. 47).[87] Alternatively, heating 2-chloroethylpyrrole **233** with potassium hydroxide in a methanol/2-propanol solution gave vinylpyrrole **234** (Fig. 50).[100] Moreover, elimination occurred concurrently with the formylation of ketone **216** using sodium methoxide and ethyl formate in methanol to produce vinylpyrrole **220** (Fig. 48).[87]

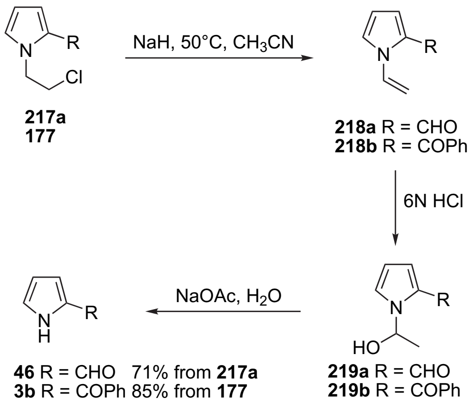


Figure 47. Removal of the 2-chloroethyl group via a vinylpyrrole intermediate.

Vinylpyrroles **218a** and **218b** were subsequently solvolyzed in a two-step process featuring hydration of the enamine with 6 N HCl and hydrolysis of the resulting 1-hydroxyethylpyrroles **219a** and **219b** with aqueous sodium acetate.[87] The three-step deprotections of 2-chloroethylpyrroles **217a** and **177** thus furnished 2-formyl and 2-benzoylpyrroles **46** and **3b**, respectively (Fig. 47). Additionally, vinylpyrrole **234** was hydrated using 12 N HCl and solvolyzed by heating with silver benzoate in wet acetonitrile to provide trisubstituted pyrrole **236** (Fig. 50).[100]

Alternatively, the vinyl group has been used as protection in pyrrole synthesis. For example, vinylpyrrole **220** was employed in the four-step synthesis of benzyl 1,4,5,6-tetrahydrocyclopenta[*b*]pyrrole-4-carboxylate (**223**) featuring rearrangement of alpha-diazoketone **221** to the vinyl protected tetrahydrocyclopenta[*b*]pyrrole-4-carboxylate **222** (Fig. 48).[87] For such pyrroles without electron-withdrawing substituents, the acidic conditions for hydration of vinylpyrroles were claimed to be 'too vigorous to permit survival of the pyrrole moiety'. To liberate the tetrahydrocyclopenta[*b*]pyrrole **223**, vinylpyrrole **222** was, instead, deprotected using mercuric acetate in aqueous acetonitrile. The supposed acetoxy mercury intermediate was reduced in situ with sodium borohydride (Fig. 48).[87] In addition, 1,1′-divinyl-[3,3′]bipyrrole **227** and 1,5-divinyl-4,8-dihydropyrrolo[2,3-*f*]indole **229** were respectively synthesized by treatment of dioximes **224** and **228** with acetylene and potassium hydroxide in DMSO in an autoclave at 100 °C and at 14 atm of initial pressure (Fig. 49).[99]

Installed by using ethanolamine in a Hantzsch synthesis with α-bromoketone **230** and dimethyl acetone dicarboxylate, the 2-hydroxyethyl group has been employed as a precursor to the 2-chloroethyl group in the synthesis of trisubstituted pyrrole **236** (Fig. 50).[100] 2-Chloroethylpyrrole **233** was synthesized by the activation of 2-hydroxyethylpyrrole **231** as the methanesulfonate **232**, using methanesulfonylchloride and trimethylamine in DCM, followed by displacement with lithium chloride in DMF. Removal of the 2-chloroethyl

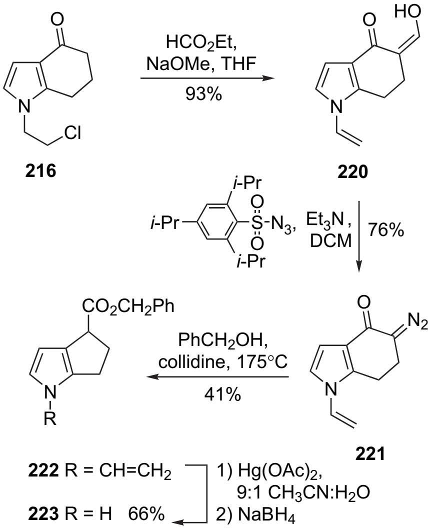


Figure 48. Synthesis of benzyl cyclopenta[*b*]pyrrole-5-carboxylate **223**.

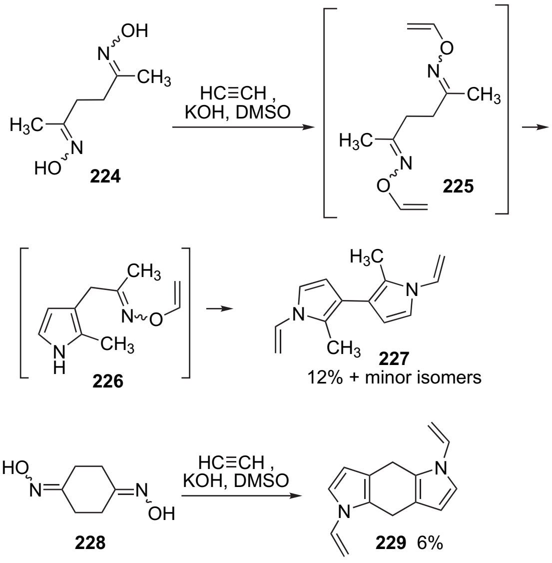


Figure 49. Synthesis of bipyrrole **227** and dihydropyrrolo[2,3-*f*]indole **229**.

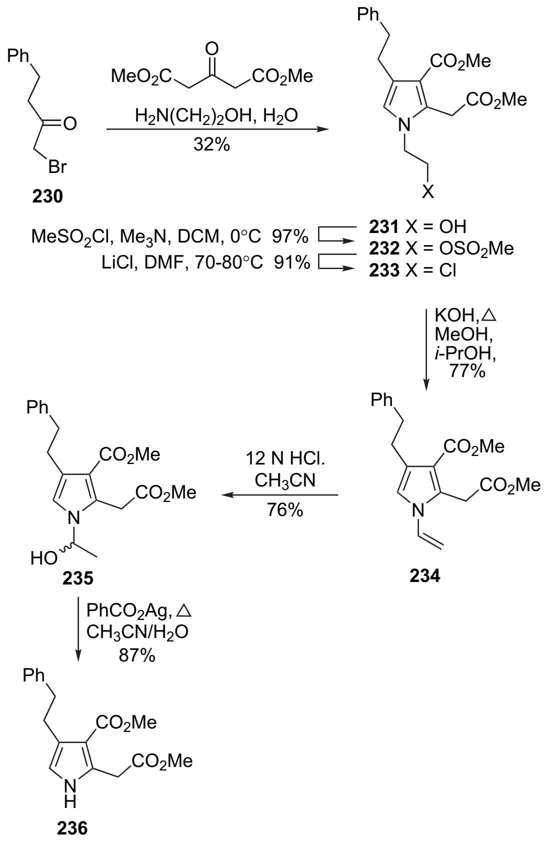


Figure 50. 2-Hydroxyethyl group use in the synthesis of trisubstituted pyrrole **236**.

group was then achieved by way of vinylpyrrole **234** in three steps, as described above.[100]

2.5. *N*-Trialkylsilyl protecting groups

The silyl family of protecting groups has found use in pyrrole chemistry as its members meet the requirements for a relatively stable yet easily removable *N*-substituent. *N*-Trialkylsilylpyrroles are generally prepared from the sodium salt of pyrrole and the corresponding silyl chloride. For example, pyrroles **42a** and **44** were reacted with sodium hydride in THF, and treated with *tert*-butyldimethylsilyl chloride (TBDMSCl) to afford *N*-protected pyrroles **237a–b**.[43] Similarly, 2-(2-phenylsulfinylvinyl)pyrrole **238** was converted to TIPS-protected pyrrole **239** using sodium hydride and triisopropylsilyltrifluoromethane sulfonate (TIPSOTf) in DMF (Fig. 51).[101]

The triisopropylsilyl (TIPS) group was found to be particularly useful for the synthesis of 3-substituted pyrroles. In CPK models of *N*-triisopropylsilylpyrrole **240**, the alpha positions of the pyrrole were sterically hindered. Competitive trifluoroacetylation experiments showed that substitution at the alpha position of TIPS-pyrrole **240** was $>10^4$ times slower than for pyrrole itself. However, reactivity at the beta position was not changed. Reactions of TIPS-pyrrole **240** with different electrophiles have produced predominantly or exclusively products from substitution at the beta position. Desilylation of **241a–d** was performed using TBAF in THF to afford 3-substituted pyrroles **242a–d** (Fig. 52).[102,103]

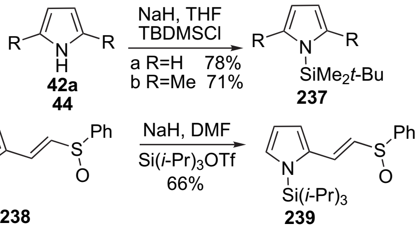


Figure 51. N-Silylation of pyrroles **42a**, **44**, and **238**.

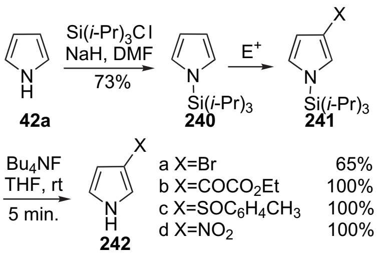


Figure 52. Synthesis of 3-substituted pyrroles based on the use of TIPS protecting group.

Furthermore, regioselective alkenylation at the beta position was performed on TIPS-pyrrole **240**. This is in contrast to pyrroles possessing Bn, SEM, Ac, BOC, and Ts N-protection, which afforded only, or predominantly, alpha-substitution products (Fig. 53).[19]

A series of 3-aryl, 3-ethynyl and 3,4-diethynylpyrroles **244a–j** were efficiently desilylated using TBAF (Table 6).[104]

N-Silyl protection of pyrrole has been employed in natural product synthesis. The cross-coupling reaction of organozinc **246** with 3,4-dibromo-*N*-TIPS-pyrrole **247** in the

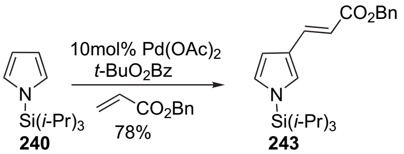
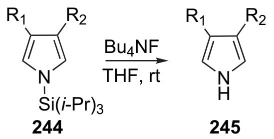


Figure 53. Regioselective alkenylation on *N*-silylpyrrole **240**.

Table 6. Deprotection of *N*-TIPS-pyrroles



Entry	R^1	R^2	Yield (%)
a	H	Ph	92
b	H	4-MePh	90
c	H	4-OmePh	91
d	H	4-ClPh	93
e	H	3-Pyridyl	96
f	H	$C\equiv CH$	62
g	H	$C\equiv CC_5H_{11}$	74
h	H	$C\equiv CPh$	85
i	$C\equiv CH$	$C\equiv CH$	82
j	$C\equiv CPh$	$C\equiv CPh$	85

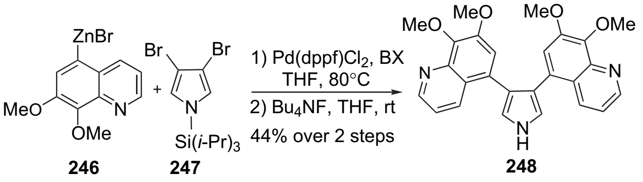


Figure 54. Utilization of TIPS-pyrroles in natural product synthesis.

presence of palladium catalyst gave access to the core of the marine alkaloid halitulin **248** after deprotection with TBAF (Fig. 54).[105] The total synthesis of roseophilin was completed by treating **128** with TBAF in THF to cleave the TIPS group at ambient temperature, whereas the 2-trimethylsilylethoxymethyl (SEM) substituent was removed upon warming to 60 °C. Addition of aqueous HCl caused dehydration and roseophilin hydrochloride **129** was obtained (Fig. 26).[28]

Although tetrabutylammonium fluoride (TBAF) is commonly used as a source of fluoride for silylpyrrole deprotection, sodium fluoride has also been successfully employed in a few cases. For example, *N*-TBDMS-pyrroles **249a–c** were deprotected in 3 h with NaF in a THF/water (1:1) solution at reflux to give 3-acylpyrroles **5a**, **5b**, and **250** (Fig. 55).[106]

It is noteworthy that 1,3,4-tris(trimethylsilyl)pyrrole **251** was selectively *N*-deprotected using methanol to furnish pyrrole **65**. Similarly, desilylation of *N*-TIPS-pyrrole **252** with sodium methoxide in methanol at reflux afforded 3,4-disubstituted pyrrole **253** (Fig. 56).[42]

Finally, it should be mentioned that a rearrangement of the triethylsilyl group (TES) was observed when *N*-triethylsilylpyrrole **254** was exposed to an excess of *t*-BuLi followed by carboxylation and methylation. A mixture of three 2-triethylsilylpyrroles (**255**, **256**, and **257**) was obtained in a ratio of 4:1.5:1, respectively, and each component was isolated and individually treated with TFA to cleave the TES groups (Fig. 57).[107]

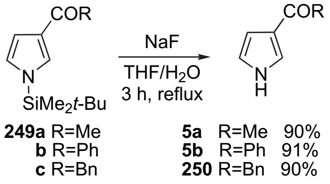


Figure 55. Deprotection of TBDMS-pyrroles with sodium fluoride.

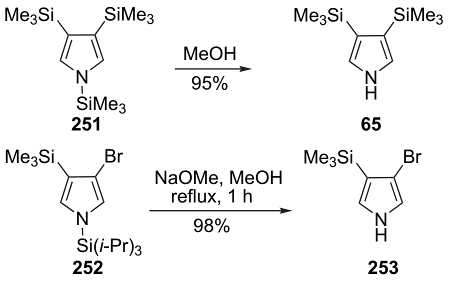


Figure 56. Deprotection of TIPS and TMS-pyrroles using methanol and methoxide.

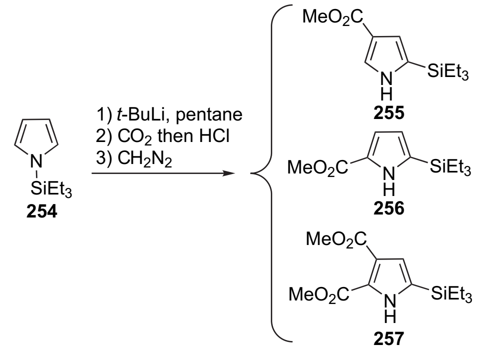


Figure 57. Triethylsilyl group rearrangement.

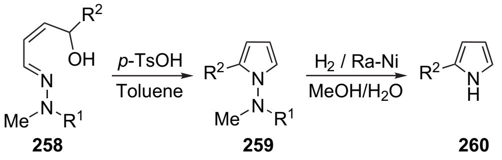
2.6. *N*-Amino protecting groups

N-(Amino)pyrroles are generally formed by intramolecular or intermolecular annulations onto *N*,*N*-disubstituted hydrazines and hydrazones. The most common *N*-aminopyrrole protecting group is *N*,*N*-dimethylamine; however, *N*-methyl-*N*-phenylamine has also been used for pyrrole protection.

N-Aminopyrroles **259** were obtained by intramolecular cyclization with dehydration of hydrazones **258** using *p*-toluenesulfonic acid (*p*-TsOH) in toluene at room temperature. Cleavage of the N–N bond was achieved by hydrogenolysis using Raney nickel in aqueous methanol under hydrogen atmosphere to afford the deprotected pyrroles **260** after 48 h in good yields (Table 7).[108]

2-Substituted *N*,*N*-dimethylaminopyrrole **263** was synthesized by a three-step reaction sequence featuring selective C-alkylation of *N*,*N*-dimethylhydrazone **261** with 2-iodomethyl-1,3-dioxolane, followed by acid-catalyzed dehydration of iminoacetal derivative **262**. Removal of the dimethylamino group by hydrogenation over Raney nickel as catalyst provided pyrrole **264** (Fig. 58).[109]

Table 7. Formation of *N*-aminopyrroles and deprotection of *N*-amino groups



Entry	R^1	R^2	Yield of **259** (%)	Yield of **260** (%)
a	C_6H_5	*p*-$CH_3C_6H_4$	94	89
b	Me	*p*-$CH_3C_6H_4$	87	92
c	Me	*p*-$CH_3OC_6H_4$	n/d	90

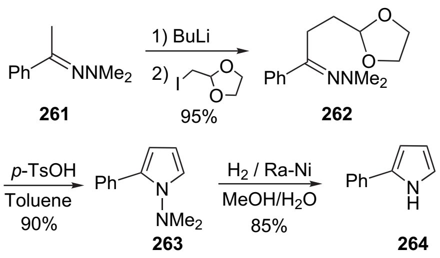


Figure 58. Synthesis of 2-phenylpyrrole **264** from hydrazone **261**.

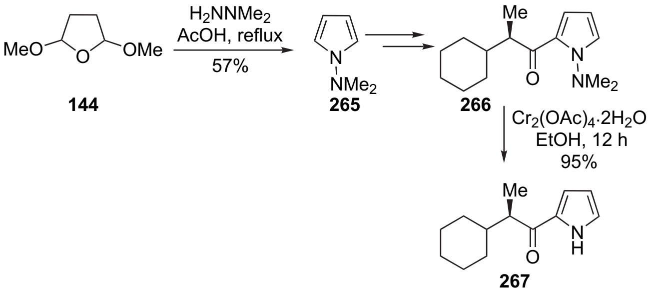


Figure 59. Synthesis of 2-acylpyrrole from 2,5-dimethoxytetrahydrofuran.

N-(*N*,*N*-Dimethylamino)pyrrole **265** was synthesized from 2,5-dimethoxytetrahydrofuran **144** and *N*,*N*-dimethylhydrazine in acetic acid at reflux for 3 h. After C-acylation of the protected pyrrole, reductive cleavage of the N–N bond with chromous acetate gave 2-acylpyrrole **267** (Fig. 59).[110]

Similarly, in the last steps of the synthesis of calcimycin **269**, the *N*,*N*-dimethylamino group was cleaved from 2-acylpyrrole **268** using chromous acetate. Subsequent hydrolysis of the trifluoroacetamide and ester with potassium carbonate in aqueous methanol delivered the targeted pyrrole natural product **269** (Fig. 60).[111]

A one-pot synthesis of 1,2,3-trisubstituted pyrroles (**273**) from hydrazones **270** has been achieved using the carbometalation of vinylstannane, followed by aerobic oxygenation of the *gem*-Zn/Sn dimetallic species **272** (Table 8). In this case, the *N*,*N*-dimethylamino group was removed from **273a** under Birch conditions (Na in liquid NH_3) to afford the corresponding 2,3-disubstituted pyrrole **274** (Fig. 61).[112]

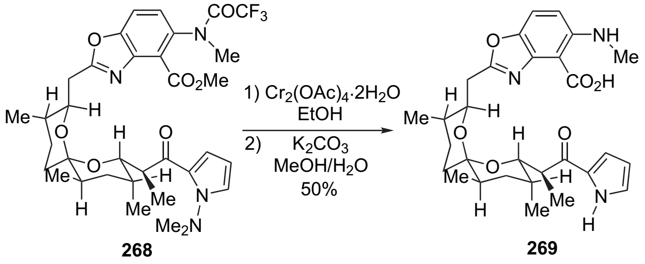


Figure 60. Synthesis of calcimycin **269** by *N*,*N*-dimethylamino group cleavage.

Table 8. Formation of *N*-aminopyrroles **273**

Entry	R^1	R^2	Yields of **273** (%)
a	CH_2Ph	CH_2CH_2Ph	63
b	Pr	*i*-Pr	77
c	CH_2Ph	CH_2Ph	53
d	$–(CH_2)_{10}–$		67
e	$–(CH_2)_6–$		50
f	$–(CH_2)_4–$		29

The reaction of hydrazone **275** with silylenol ether **276** in the presence of titanium tetrachloride for 1–3 days afforded *N*-aminopyrroles **277** (Fig. 62).[113] Alkyl- and aryl-substituted as well as ring-fused pyrroles **278** were obtained after reductive cleavage of the dimethylamino group under Birch conditions (Table 9).[113,114]

2.7. *N*-Amido protecting groups

N-Acylpyrroles exhibit different properties from their respective saturated pyrrolidine amides due to the aromatic ring restricting the ability for the nitrogen lone pair of electrons to conjugate with the carbonyl. For example, lithium aluminum hydride reduction of *N*-acylpyrroles liberates the pyrrole and the respective aldehyde or alcohol, contingent on stoichiometry and order of hydride addition. In contrast, the *N*-alkylheterocycle is typically the major product from reduction of the corresponding *N*-acylpyrrolidines.[115] Moreover, *N*-acylpyrroles are much more labile to alkaline hydrolysis than their pyrrolidine counterparts, by a mechanism that can be first or second order in hydroxide ion, contingent on concentration (Fig. 63).[116] In addition, the acetyl group proved more effective in suppressing azafulvene intermediate (**281**, EWG=Ac) than no protection, yet less

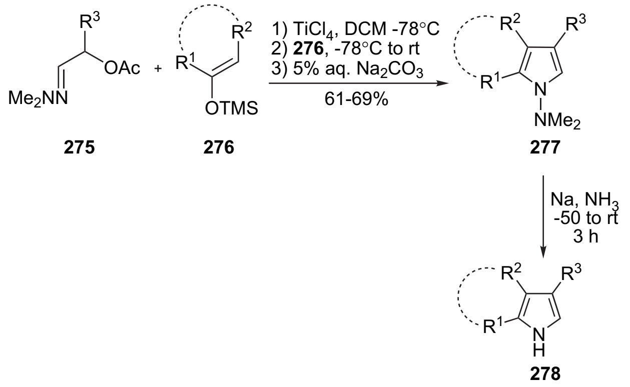


Figure 62. Synthesis of 2,3,4-trisubstituted pyrroles.

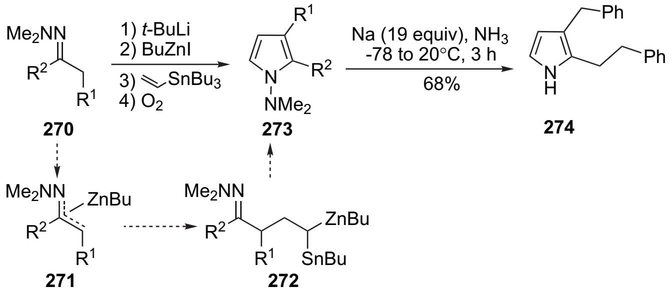
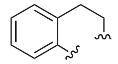


Figure 61. Synthesis of 2,3-disubstituted pyrroles **274**.

Table 9. Synthesis of pyrroles **278** by reductive cleavage of N–N bond

Entry	R^1	R^2	R^3	Yield (%)	Ref.
a	Me	H	Me	32	113
b	*t*-Bu	H	Me	42	114
c	C_6H_5	H	Me	85	113
d	C_6H_5	Me	Me	82	113
e	Et	Me	Me	70	114
f	$-(CH_2)_3-$		Me	90	113
g	$-(CH_2)_4-$		Me	86	114
h	$-(CH_2)_5-$		Me	82	113
i			Me	89	113
j	C_6H_5	H	Et	44	114
k	C_6H_5	Me	Et	51	114
l	C_6H_5	H	*i*-Pr	65	114

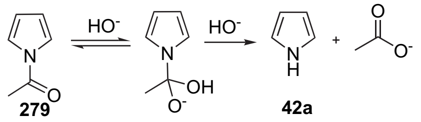


Figure 63. Alkaline hydrolysis of *N*-acetylpyrrole **279**.

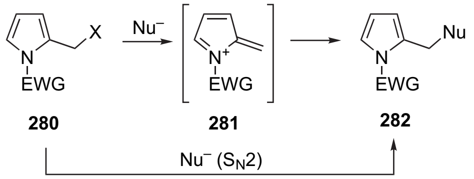


Figure 64. Nucleophilic displacement of 2-hydroxymethylpyrrole **280**.

effective than sulfonyl protection (EWG=mesyl and triflyl), during displacement of 2-hydroxymethylpyrroles **280** (X=OH) with camphanic acid as nucleophile under Mitsunobu reactions (Fig. 64).[44]

Amide protection is usually installed by treating the pyrrolyl anion with the corresponding acyl chloride. For example, pyrrole-2-carboxaldehyde **46** was converted to its acetamide derivative by treating a solution of the pyrrole and sodium hydride in THF with acetyl chloride.[44] Similarly, treatment of a mixture of pyrrole **91** and potassium *tert*-butoxide in benzene with benzoyl chloride at reflux gave benzamide **283** after recrystallization (Fig. 65).[64] Recently, acylation of pyrrole itself (**42a**) with benzoyl chloride has been achieved by heating with KOH in the ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphonate, [Bmim][PF$_6$], at 80 °C.[24] Finally, diamine **287** was converted to diacetate **288** without discernable selectivity for either the pyrrole or enamide nitrogens using acetic anhydride in DMF (Fig. 66).[117]

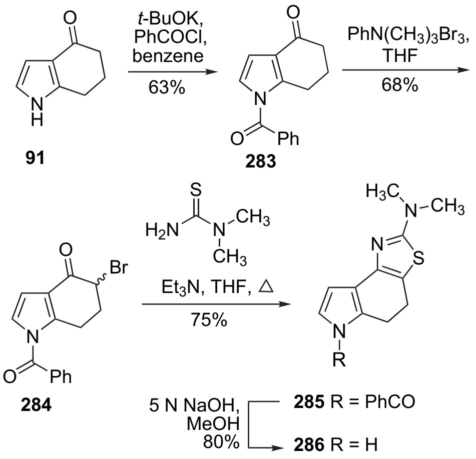


Figure 65. Synthesis of pyrrolo[3,2-*e*]benzothiazole **286**.

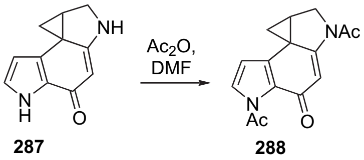


Figure 66. Acetylation of diamine **287**.

Amides have been generally used less often for pyrrole protection than the Boc or sulfonyl groups, because of their greater reactivity to nucleophiles. On the other hand, the application of benzamide protection proved more advantageous than benzenesulfonyl protection in the synthesis of pyrrolo[3,2-*e*]benzothiazole **286**. This is because the former could be removed using sodium hydroxide in methanol, conditions that had no effect on the corresponding sulfonamide derivative, which decomposed under stronger alkaline conditions (Fig. 65).[64] Acetamide protection was abandoned in the synthesis of **286**, after protection of pyrrole **91** with acetic anhydride and sodium acetate, because solvolysis of the acetyl group on attempted recrystallization from methanol returned the starting pyrrole.[64]

3. Pyrrole protection by C-substitution

3.1. Introduction to C-2 protection

As discussed, protection of pyrroles through substitution at nitrogen is well documented and the field benefits directly from advances in amine protection.[15,118] Placing an EWG on the 2-position of the pyrrole ring has proven to be another successful strategy for tempering pyrrole reactivity during the synthesis of substituted porphyrins and other synthetic targets. By utilizing the doubly vinylogous[10] amino-nature of the 2-position, as shown in Figure 67 for carboxylate substitution, a suitable group can serve to diminish pyrrole reactivity. Moreover, by blocking the 2-position such groups can direct catalyzed substitution to the other positions. The natural tendency for pyrrole to undergo 2- (and 5-) substitution is altered by the presence of EWG at the 2-position. In this case, substitution can favor the 4-position. The extent of selectivity is dependent upon the nature of the 2-position substituent and the conditions of the substitution reaction. 2-Position substituents with electron-donating groups can activate the pyrrolic core toward electrophilic aromatic substitution. Careful manipulation and removal of the 2-position substituent has been important for the preparation of a wide range of functionalized pyrroles. The directing effects of various 2-position substituents upon electrophilic substitution of 2-protected pyrroles have been previously reviewed

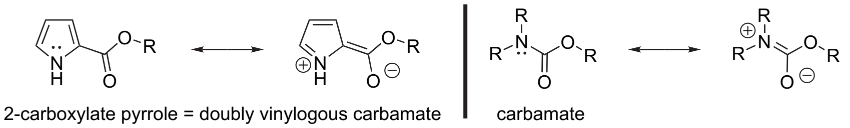


Figure 67. Resonance forms of pyrrole-2-carboxylate and carbamate.

by Anderson.[119] In addition, Trofimov has reviewed the use of 2-vinyl-substituted pyrroles as building blocks within synthesis.[120]

3.2. Pyrrole-2-carboxylates

Pyrrole-2-carboxylates exhibit doubly vinylogous carbamate character[10] (Fig. 67), and the pyrrolic lone pair is stabilized through resonance. Indeed, pyrrole-2-carboxylates are usually air- and moisture-stable crystalline solids, making purification through crystallization or chromatography facile. Furthermore, the 2-carboxylate functionality is stable to oxidation, reduction, and nucleophilic substitution conditions that are often required for the derivatization of other substituents of the pyrrole ring. In these two respects, the carboxylate group at the 2-position of pyrroles represents an ideal protecting group and has widespread application in dipyrromethene[121,122] and porphyrin[17,18] synthesis. Furthermore, the electron-withdrawing ability of the ester[123] and the stability of pyrrole-2-carboxylates render this structural motif useful within pyrrolic targets for the pharmaceutical industry, for example, pyrroles with antiviral,[124] antibacterial,[125] and anticancer[3,126] capabilities.

Courtesy of the Knorr reaction and its modifications (Fig. 68)[18] substituted pyrrole-2-carboxylates are readily available on grand scales from acyclic materials. Typical Zanetti-modified[127] Knorr reaction conditions involve the oxime of an alkylacetoacetate (**289**) and 2,4-pentanedione (acetylacetone). The oxime **290a** is reduced with zinc dust to the corresponding α-aminoketone, which can undergo self-condensation rather than react as desired with the 2,4-pentanedione. Consequently, the modern procedure[18] involves the dropwise addition of the oxime to the acetylacetone with concurrent slow addition of zinc powder, thereby limiting the concentrations of α-aminoketone generated in situ. With practice, the exothermic reaction can be performed on multi-molar scales to obtain moderate–good yields of crystalline pyrroles **291** of very high purity. The ketone functionality can be reduced using diborane[128] and thus the familiar ethyl–methyl substitution pattern of many porphyrin skeletons[129] is created.

The Kleinspehn-modified[130] Knorr reaction replaces alkylacetoacetate with a dialkyl malonate (**292**). Condensation involves an alternative conformation and the resulting pyrrole-2-carboxylate **293** is unsubstituted at the 4-position (R^1=H) if 2,4-pentanedione is used. Alternatively, use of 3-substituted 2,4-pentanediones gives 4-substituted pyrrole-2-carboxylates. The Johnson-modified[131] Knorr reaction also gives 4-substituted pyrrole-2-carboxylates and it uses alkylacetoacetates and 3-substituted 2,4-pentanediones. Although the Kleinspehn modification typically gives higher pyrrole yields than the Johnson modification, the nitrosation of alkylacetoacetates proceeds more readily than the nitrosation of dialkyl malonates.[18] A variety of other Knorr-type reactions, and alternatives, have been reviewed previously.[18] The Barton–Zard route[132] (Fig. 69) to pyrrole-2-carboxylates (**296**) is particularly advantageous in that pyrroles unsubstituted at the 5-position are produced.

Pyrrole-2-carboxylates are the traditional mainstay of synthetic routes to porphyrins and dipyrromethenes. The carboxylate group serves to deactivate the pyrrole ring, thus protecting it from over-reaction and facilitating isolation and purification procedures. The 3-, 4- and 5-positions of pyrroles are typically manipulated with the carboxylate group serving to block the 2-position. Pyrrole-2-carboxylates generated through Knorr-type syntheses are robust under the reaction conditions required for derivatization at the other positions (Fig. 70). By no means comprehensive, Figure 70 serves to show a range of synthetic steps typically encountered in routes to porphyrins and dipyrromethenes. For example, 5-methyl groups of pyrroles protected with 2-carboxylate groups can be mono-oxidized, and the products (**304**) can be either isolated (X=OAc) or self-condensed in situ to give 2,2′-dipyrromethanes (**305**).[133] Trioxidation of the 5-methyl group, followed by decarboxylation gives the 5-unsubstituted pyrrole-2-carboxylate (**307**), the same as the product produced directly via the Barton–Zard procedure. This trioxidation and thermal or iodinative[134]

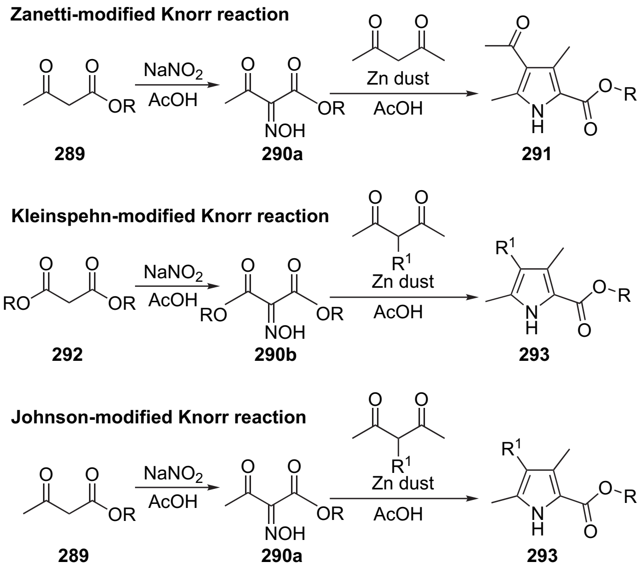


Figure 68. Knorr reactions.

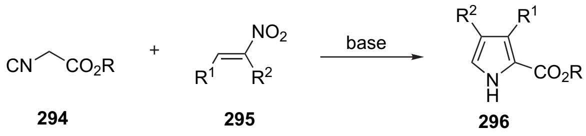


Figure 69. The Barton–Zard reaction.

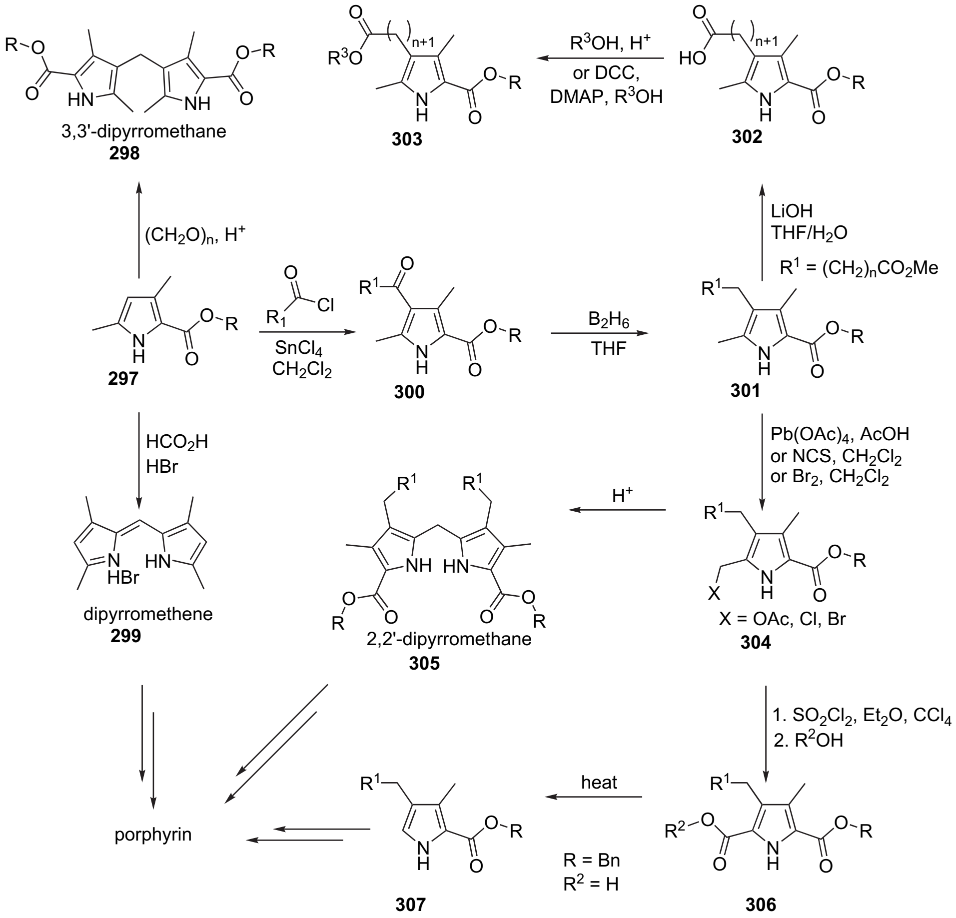


Figure 70. Syntheses involving Knorr pyrroles.

decarboxylation effectively permits a reversal of the orientation of substituents, and is crucial in the synthesis of protoporphyrin IX.[135,136] The 2-carboxylate group is stable under mild hydrolysis conditions giving **302**, and thus alkanoates at other positions can be hydrolyzed and transesterified to give **303**.[137] In many cases, acids are required to catalyze the reaction (e.g., acylation,[138,139] self-condensation[133]) as the electron-withdrawing 2-carboxylate group greatly reduces the nucleophilicity of the pyrrolic core.[21] Without such protection over-reaction and side-reactions leading to dark tars would likely result from exposure of related pyrroles to acidic conditions.

The deprotection and application of the three most popular pyrrole-2-carboxylates (ethyl, benzyl, and *tert*-butyl) will be discussed. Diethylmalonate and ethylacetoacetate are commercially available at very modest cost. Consequently, Knorr-type reactions often utilize these esters. Ethyl pyrrole-2-carboxylates can be saponified by treatment with aqueous KOH, whereby the resulting carboxylic acid undergoes acid-catalyzed decarboxylation to give the corresponding 2-unsubstituted (alpha-free) pyrrole. For example, cryptopyrrole (**310**, Fig. 71) has been used as a common starting material for porphyrin synthesis, despite its relative instability and propensity to give tars under acidic conditions. Cryptopyrrole is best prepared by large-scale saponification of ethyl 4-ethyl-3,5-dimethyl-2-pyrrolecarboxylate (**308**), followed by decarboxylation and steam-distillation (Fig. 71).[138] Exposure to high temperatures has been commonly used for the decarboxylation of pyrrole-2-carboxylic acids,[140,141] and so has treatment with TFA.[142] For example, 3,4-dialkoxypyrroles were made by saponification and decarboxylation of dimethyl-3,4-dialkoxypyrrole-2,5-dicarboxylates.[67] In the presence of formic acid, alpha-free pyrroles were produced by decarboxylation and condensed in situ to give the dipyrromethene hydrobromide salt (**299**, Fig. 70).[143] Such reactions are also applicable to 2,2′- and 3,3′-dipyrromethanes, molecules containing more than one pyrrolic unit.[18,137]

The terpyrrole **312**, protected as its tetra(ethyl carboxylate), was synthesized from **311** by condensation with ammonia.

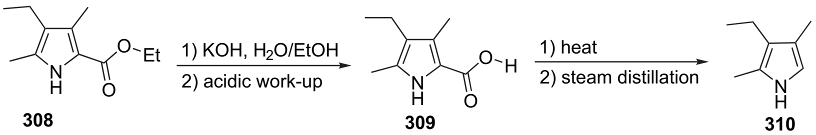


Figure 71. Synthesis of cryptopyrrole.

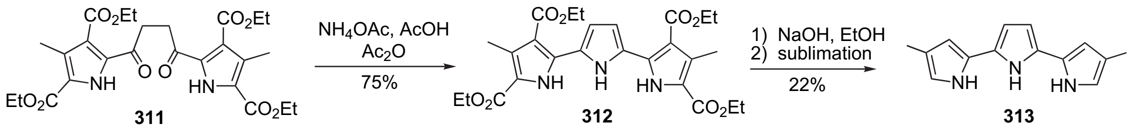


Figure 72. Synthesis of terpyrrole **313**.

Removal of all four ethyl esters, to give **313**, was achieved by hydrolysis followed by decarboxylation under sublimation conditions (Fig. 72).

Following saponification of ethyl esters, acidification is required to give the carboxylic acid. This acidification process must be very carefully controlled, because excess acid can cause side reactions such as polymerization, which may result in the discoloration of the product and formation of dark tars. Trans-esterification of ethyl pyrrole-2-carboxylates such as **308** in benzyl alcohol at reflux with stoichiometric amounts of sodium benzoxide gave benzyl ester **314** (Fig. 73).[144] Trans-esterification can be promoted by microwave energy using catalytic amounts of sodium methoxide in benzyl alcohol.[145] Benzyl pyrrole-2-carboxylates have the advantage that hydrogenolysis catalyzed by Pd/C proceeds very readily and the carboxylic acids prepared in this way are generally less prone to discoloration and polymerization than those prepared by saponification of ethyl pyrrole-2-carboxylates.[18]

tert-Butyl pyrrole-2-carboxylates cannot be prepared by trans-esterification of ethyl or benzyl pyrrole-2-carboxylates. The synthesis of such *tert*-butyl esters has been achieved by Knorr-type reactions employing di-*tert*-butyl malonate and *tert*-butyl acetoacetate.[18,146] *tert*-Butyl pyrrole-2-carboxylates are advantageous in that deprotection can be achieved by treatment of the pyrrole with TFA, although these conditions are not always tolerated by other substituents. Furthermore, *tert*-butyl acetoacetate is less readily available than the ethyl and benzyl analogues.[147] Given the difficulties encountered with the decarboxylation of pyrrole-2-carboxylates, it might appear rather tedious to persevere with their use. However as the Knorr reaction is so adept at providing such pyrroles, and the starting materials for the reaction are inexpensive, the bulk of synthetic chemistry toward porphyrins and dipyrromethenes still uses these pyrroles as building blocks.

The methyl pyrrole-2-carboxylate **316** was prepared in order to temporarily protect the pyrrole **315** (Fig. 74). After a number of steps the methyl ester was hydrolyzed and in situ decarboxylation under acidic conditions gave (−)-rhazinilam **318**.[148]

3.3. Pyrrole-2-carboxaldehydes

Formyl groups are often used to stabilize electron-rich pyrroles within extended synthetic sequences, with the Vilsmeier–Haack reaction[18,147] (e.g., DMF/$POCl_3$[134] or DMF/PhCOCl[149]) and the Clezy formylation reaction ($CH(OMe)_3$/TFA[150,151]) being extremely useful for the preparation of pyrrole-2-carboxaldehydes in situ from pyrrole-2-carboxylates. Although pyrrole-2-carboxaldehydes are key intermediates en route to porphyrins and dipyrromethenes, they are often susceptible to oxidation, reduction, and acid-induced decomposition. This can lead to complex reaction mixtures and unpleasant tars, often making for extremely difficult purification procedures when pyrrole-2-carboxaldehydes are involved. Consequently, the formyl group is often protected as an oxime, hydrazone, acetal or related functionality,[18] among which one of the more useful protecting groups has been the corresponding 2-cyanovinyl pyrroles.[152–154] The cyanovinyl group has acted as an electron-withdrawing protecting group for the pyrrole during mono-oxidation of the 5-methyl group, and isolation of the 5-chloromethyl pyrrole **321** (Fig. 75). 2-Cyanovinyl pyrroles can be readily prepared by treating pyrrole-2-carboxaldehydes with malonitrile or cyanoacetate esters via the Knoevenagel reaction. For example, protection of 3,4,5-trimethylpyrrole-2-carboxaldehyde (**319**), with methyl cyanoacetate gave excellent yields of 2-(2-cyano-2-methoxycarbonylvinyl)-3,4-5-trimethylpyrrole (**320**, Fig. 75).

Coupling of chloromethylpyrrole **321** with 2-cyanovinyl-protected pyrrole **322**[155] under Lewis acid-catalyzed conditions gave the 2,2′-dipyrromethane **323**, which was

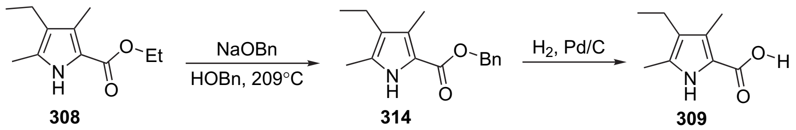


Figure 73. Trans-esterification with benzoxide and hydrogenolytic ester cleavage.

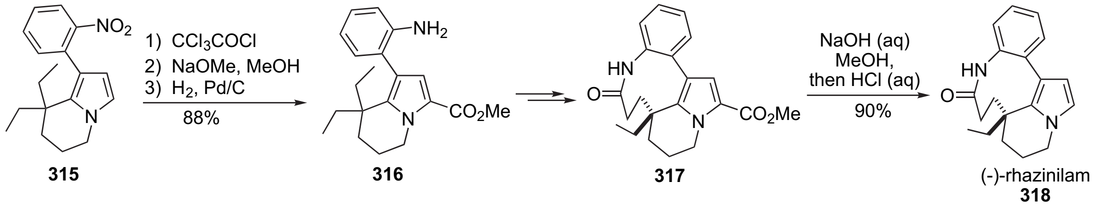


Figure 74. Use of methyl carboxylate in the synthesis of (−)-rhazinilam **318**.

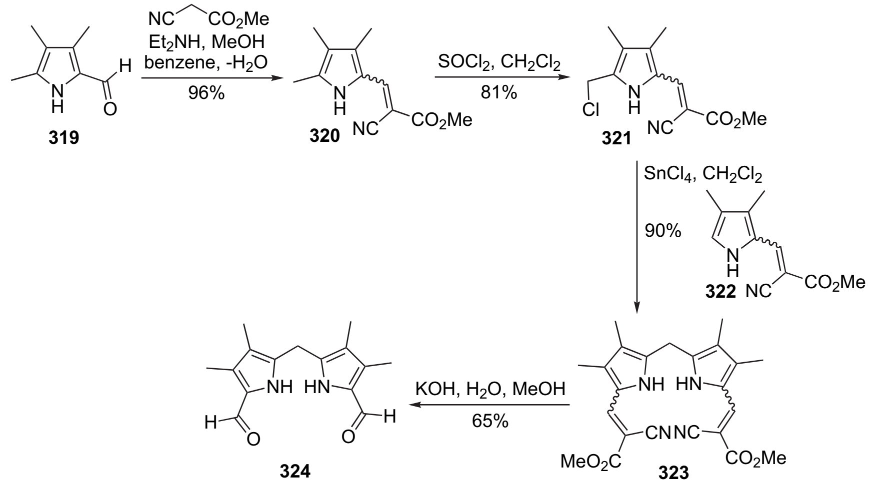


Figure 75. Synthesis of 5,5′-cyanovinyl-protected-2,2′-dipyrromethane (**323**).

hydrolyzed to release the two formyl groups. 2-Cyanovinyl pyrroles are recognizably bright yellow and often crystalline solids. They are quite nonpolar relative to pyrrole-2-carboxaldehydes and simpler to purify using silica-gel chromatography. Due to their easy crystallization and facile chromatographic purification, dicyanovinyl derivatives of pyrrole-2-carboxaldehydes are sometimes made purely for the purposes of facilitating purification. Furthermore, the cyanovinyl group is resistant to oxidation and thus protects pyrrole aldehydes from oxidation to carboxylic acid. This is especially important in the synthesis of strapped porphyrins, etc. whereby both the 2- and 5-positions of the pyrrole must be functionalized. Methyl cyanoacrylates have been reported[155] to be the most useful cyanovinyl group for this purpose, as these are more reactive and more soluble than their 2-dicyanovinyl analogues. However *E*/*Z* isomers, of variable ratio, unnecessarily complicate NMR spectra and so many practitioners favor using 2-dicyanovinyl-protected pyrroles. Disadvantages of cyanovinyl groups include their susceptibility toward hydrogenation, the low reactivity of cyanovinyl-protected pyrroles as a result of the very electron-withdrawing group, and the strongly alkaline conditions required for their hydrolysis (Fig. 75).[155]

5-Substituted pyrrole-2-carboxaldehydes have been efficiently synthesized by protection of pyrrole-2-carboxaldehyde as the dimer **325**. Deprotonation of **325**, followed by treatment with a range of electrophiles and subsequent hydrolysis gave good yields of the required 5-substituted pyrrole-2-carboxaldehydes (**326**, Fig. 76). Protection of the 2-formyl group in this way avoided the mixtures of 4- and 5-substituted products that would likely result from electrophilic aromatic substitution of pyrrole-2-carboxaldehyde, due to the poor regioselectivity induced by the formyl group.[18]

Pyrrole-2-carboxaldehyde has been protected as various iminium salts that have increased selectivity for 4-substitution, compared to pyrrole-2-carboxaldehyde.[156] The electron-withdrawing iminium substituent often limits pyrrole reactivity to only the more reactive electrophilic reactions, for example, bromination and acylation (Fig. 77).[157] After regioselective acylation and subsequent hydrolysis, the formyl group has been removed from disubstituted pyrrole **328** by oxidation to the carboxylic acid and then heat-induced decarboxylation, thus giving ketone **329**.[157]

Acetals have also been used to protect formyl groups. Difficulty was encountered in preparing simple acetal derivatives of pyrrole-2-carboxaldehydes (e.g., with methanol or ethylene glycol) as a result of acid instability and the reduced nucleophilicity of the doubly vinylic amide carbonyl

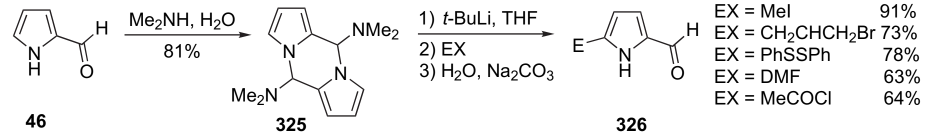


Figure 76. Synthesis and acylation of **325**.

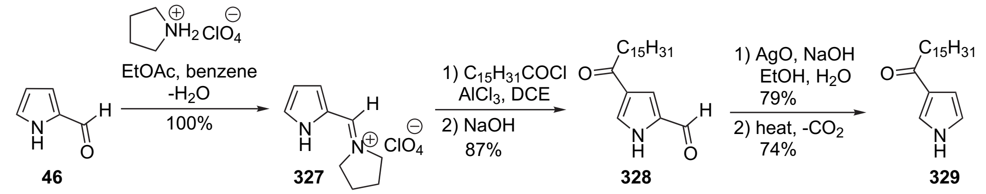


Figure 77. Protection of the formyl group using an iminium salt.

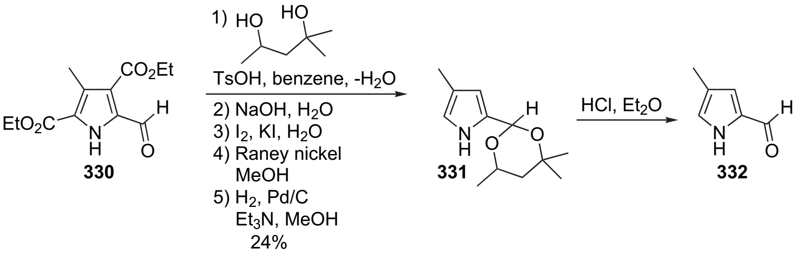


Figure 78. Use of a formyl group protected as an acetal.

group.[140] Acetals of 2-methylpentane-2,4-diol were, however, isolable in cases when the pyrrole bore an EWG in addition to the formyl group. For example, acetylation of pyrrole-2-carboxaldehyde **330** (bearing three EWGs), hydrolysis and decarboxylation yielded acetalpyrrole **331** (Fig. 78).

Thioacetals have also proven to be useful protecting groups for the carbonyl group of pyrrole-2-carboxaldehydes (Fig. 79),[140] with successful condensation again being reliant upon the presence of a second electron-withdrawing substituent (in addition to the formyl group). Reaction of ethanedithiol with the appropriate 2-(dichloromethyl)-pyrrole has also provided the thioacetal directly from the dichloride precursor to the aldehyde. Such thioacetals (**334**) do not introduce chiral centers and have been used effectively in the synthesis of dipyrromethanes (e.g., **337**), preventing self-condensation of 5-unsubstituted pyrrole-2-carboxaldehyde. Removal of the thioacetal has been achieved by treatment with red mercuric oxide and $BF_3 \cdot Et_2O$.

3.4. Blocking and activating groups at the 2-position

Introduction of an electron-rich blocking group at the 2-position of pyrrole group is an alternative and useful strategy for promoting the pyrrole reactivity. For example, the electron-donating[158] thio substituent in 2-sulfenyl pyrroles[159,160] has been used to block the 2-position and activate the other positions toward electrophilic substitution reactions. The 2-methylthio substituent in pyrrole **164** promoted regioselective Vilsmeier–Haack acylation at the 5-position (Fig. 80),[161] exclusively giving ketone **340**. For the synthesis of pyrrolizine **343**, the sulfide was oxidized to the corresponding sulfone (**341**). *N*-Alkylpyrrole **342** was then synthesized by reaction with spiro-activated cyclopropane **344**. Hydrolysis to the dimethyl malonate, deprotonation with sodium hydride, and intramolecular addition with elimination of the sulfinate gave pyrrolizine **343**, an intermediate en route to a potent anti-inflammatory and analgesic agent. In this synthetic sequence, the methylthio substituent served to block the 2-position of the pyrrole toward electrophilic attack, and activated the 5-position toward acylation. On oxidation to the sulfone, a leaving group was generated for intramolecular displacement in the annulation step. The procedure for the preparation of methylthio pyrrole **164** was somewhat general and extended to the syntheses of 2-(alkylthio)- and 2-(arylthio)-pyrroles. Furthermore, the addition–elimination of sulfinate in the annulation was only successful with pyrroles bearing electron-withdrawing ring substituents, and other leaving groups (e.g., Br) also underwent displacement in related cyclizations.

The use of alkylthio groups as masking and activating groups for pyrroles has been extended by the preparation of methylthio, ethylthio, *n*-decylthio, and phenylthio substituents.[160] 2-(Methylthio)-pyrrole (**164**) was prepared by the reaction of pyrrole with dimethyldisulfide under acidic conditions;[160] however this procedure could not be extended to give good yields of the other sulfides (Fig. 81). Instead, the treatment of 2-thiocyanatopyrrole with Grignard reagents gave 2-(ethylthio)-, 2-(decylthio)-, and 2-(phenylthio)pyrrole (**347**, **348**, and **346**, respectively).[162] Deuterium exchange studies showed that the three alkylthio substituents all activated the 3- and 5-positions toward substitution (relative to pyrrole itself), and that these 2-(alkylthio)-pyrroles were intermediate in reactivity between pyrrole and 2-methylpyrrole.

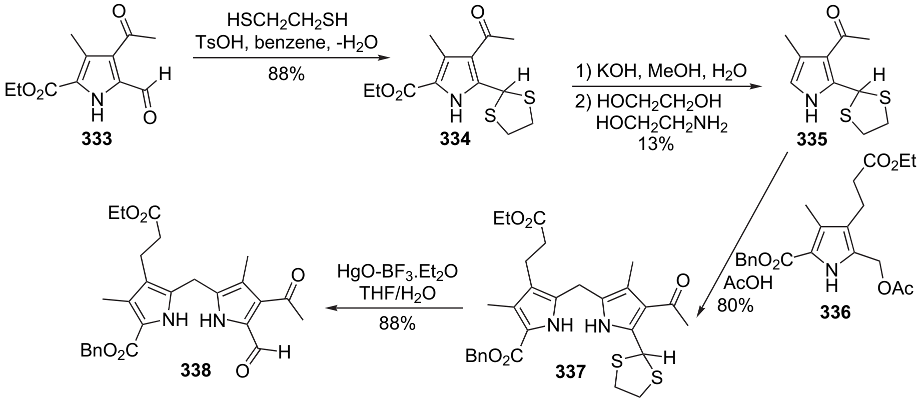


Figure 79. Thioacetal employment in the synthesis of dipyrromethane **338**.

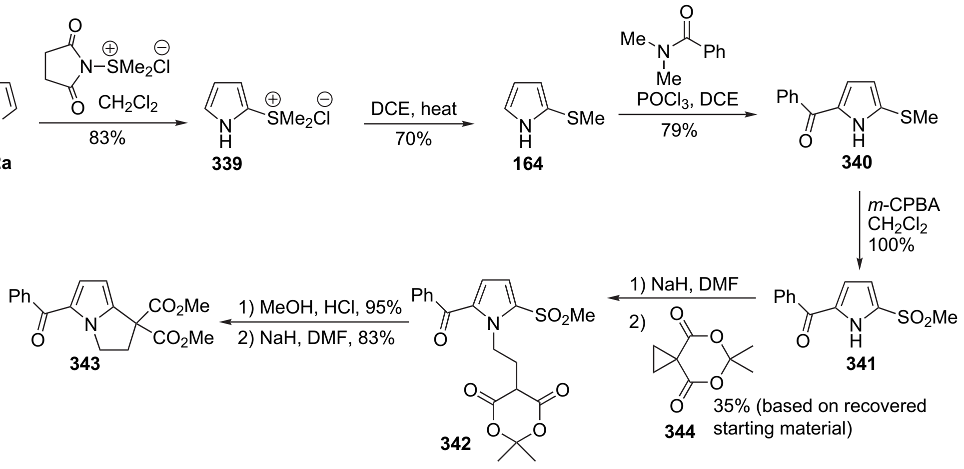


Figure 80. Synthesis of **343** using 2-sulfonium pyrrole **339**.

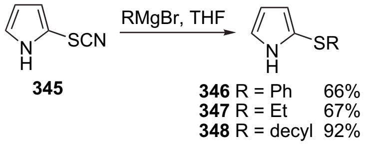


Figure 81. Synthesis of 2-thio-pyrroles.

Significantly, the electron-donating alkylthio substituent deactivated the 4-position (relative to pyrrole itself). In contrast, 2-(phenylthio)-pyrrole was found to deactivate all positions of the pyrrolic ring toward deuterium exchange.

Reaction of 2-(methylthio)-pyrrole (**164**) with pseudo-stoichiometric amounts of benzaldehyde under acid-catalyzed conditions gave the corresponding *meso*-substituted dipyrromethane **349** in moderate yield (Fig. 82), with $InCl_3$ proving to be the best Lewis acid for effecting good regioselectivity between the desired dipyrromethane and its *N*-confused alternative (not shown). This procedure was applied to the ethyl, decyl, and phenyl analogues and represented a significant improvement over existing routes to *meso*-substituted dipyrromethenes, which had typically required the use of a large excess of the pyrrole.[163] Desulfurization of thioether **349** proceeded smoothly with Raney nickel to give dipyrromethane **351**; similar results were obtained for the decyl analog. For the phenyl analog, incomplete reaction and several products resulted from the use of Raney nickel, and nickel boride did not improve the desulfurization process. Oxidation of dipyrromethane **349** with DDQ gave the required dipyrromethene (**350**), and treatment of the decyl and phenyl analogues with *m*-CPBA gave the corresponding sulfones, which proved difficult to purify. A potential route to unsymmetrical dipyrromethanes was also demonstrated, whereby the acylated 2-(methylthio)-pyrrole **340** was reduced and the resulting alcohol was reacted with **164**, as shown in Figure 82.

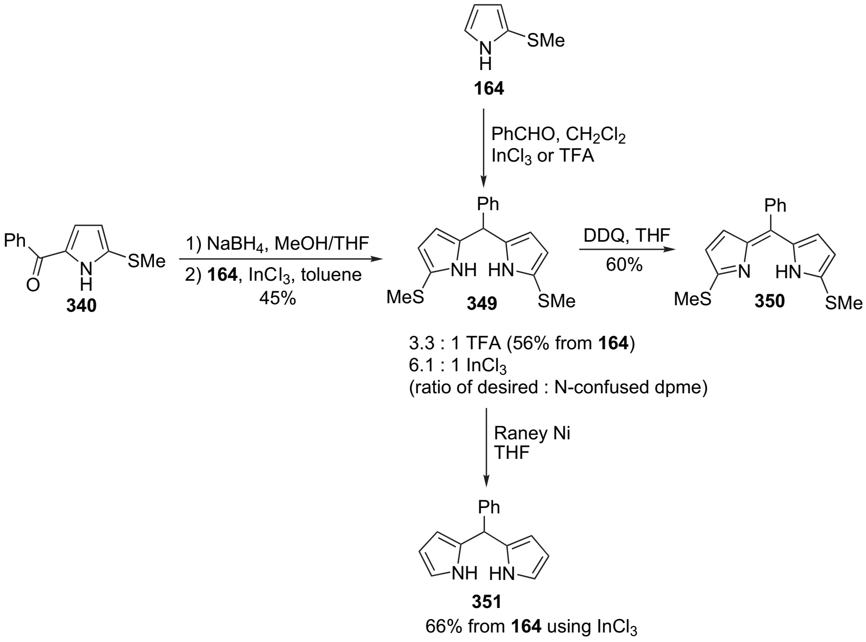


Figure 82. 2-Methylthio-pyrrole in the synthesis of dipyrromethanes and dipyrromethenes.

3.5. 2-Sulfinyl and 2-sulfonyl protecting groups

Sulfonium, sulfinyl, and sulfonyl groups at the 2-position, all stabilize the electron-excessive[119] pyrrolic ring as demonstrated by ^{13}C NMR spectroscopic and X-ray crystallographic studies.[12] Some 2-(arylsulfinyl)-pyrroles rearrange under acidic conditions to give the 3-substituted isomer.[164] 2-(Alkylsulfinyl)-pyrroles also rearrange at slower rates. Although desulfonylation reactions occur usually via treatment with Raney nickel, 2-(arylsulfonyl)-pyrroles undergo radical-induced reductive desulfonylation on treatment with Bu_3SnH/AIBN (Fig. 83).[161] This procedure was used to effect annulation by intramolecular trapping of the radical intermediate with aryl and alkyl bromides to form pyrrolizine and indolizine analogs **355** and **357**, respectively (Fig. 83). The related 3-(arylsulfonyl)-pyrroles were reported to be inert under such conditions.

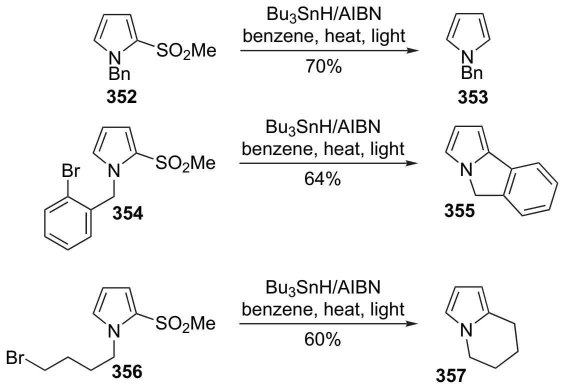


Figure 83. Radical-induced desulfonylation and annulation of 2-sulfonyl pyrroles.

2,4-Dinitrobenzenesulfinyl and sulfonyl groups are effective stabilizing groups for pyrrole. In analogous fashion to the liberation of amines from protection as nitrobenzenesulfonylamides,[165] 2,4-dinitrobenzenesulfinyl and sulfonyl groups can be removed by treatment of the pyrrole with thiol, which produces the thioether **359** as byproduct (Fig. 84).[12]

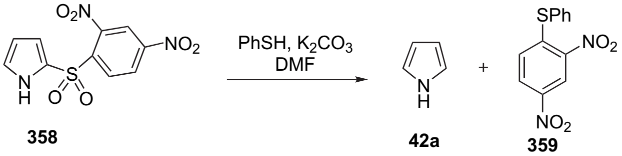


Figure 84. Cleavage of 2,4-dinitrobenzenesulfonyl group from pyrrole.

4. Concluding remarks

Pyrrole chemistry presents particular challenges for mediating the reactivity of this archetypal pi-excessive heterocycle.[166] Innovative strategies have been developed for controlling reactivity and selectivity by modulation of the electron density and steric environment through use of different protecting groups at the pyrrole nitrogen and its 2-position carbon. Growing interest in pyrrolic products for applications in medicine and materials science evokes the need for more selective chemistry and improved methods to effectively introduce, apply, and remove protection for the functionalization of pyrrole. By presenting a survey of these different protection strategies and their application in the synthesis of pyrrolic targets, we hope that this review will facilitate the application of existing methods and inspire creativity for the development of new approaches for performing practical, effective, and selective pyrrole chemistry.

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Biographical sketch

Benoit Jolicoeur was born in Montreal, Canada in 1980. He received his B.Sc. degree in 2003 from the Université de Montréal. He performed undergraduate research under the guidance of Professor William D. Lubell on the synthesis of indolizidin-9-one amino acids as peptide mimics. Presently he is pursuing graduate study in the laboratory of Professor Lubell at the Université de Montréal on the synthesis of prodigiosin analogs.

Erin Chapman received her Bachelor of Science degree with honors in chemistry from Mount Allison University in 2005. While at Mount Allison, Erin conducted her Honors Research Project with Dr. Richard Langler in the area of organosulfur chemistry. She also completed a special topics research project with Dr. Stephen Westcott exploring new rhodium catalysts for hydroboration reactions. Erin is currently a graduate student at Dalhousie University in Halifax, Nova Scotia under the supervision of Dr. Alison Thompson. Dr. Thompson's research group focuses on pyrrole chemistry and Erin's research projects at Dalhousie have included various aspects of dipyrromethene reactivity and synthesis.

Dr. Alison Thompson's research interests include the synthesis and applications of helical dipyrromethene complexes, the development of new methodology for the efficient synthesis of functionalized pyrroles, and the design and synthesis of prodigiosins for evaluation as anti-cancer treatments. Born in Nottingham, England, Dr. Thompson obtained her B.Sc. (Hons. Class I) from the University of Leicester in 1993. In 1996 she gained her Ph.D. from the University of Sheffield for research on the development of catalytic asymmetric aziridination and epoxidation reactions with Professor Varinder Aggarwal. She then moved to Strasbourg, France and worked with Professeur Arlette Solladié Cavallo for a year as a postdoctoral fellow with a Royal Society/NATO award. In 1997 Dr. Thompson joined the University of British Columbia, Canada to work with Professor David Dolphin. In 2001 she moved to Halifax, Nova Scotia to take up a faculty position at Dalhousie University with an NSERC University Faculty Award. In 2006 she was awarded the AstraZeneca Award in Chemistry.

Professor William D. Lubell received his B.A. degree in Chemistry in 1984 from Columbia College and his Ph.D. in 1989 from the University of California in Berkeley under the supervision of Professor Henry Rapoport. As a fellow of the Japan Society for the Promotion of Science, he studied enantioselective hydrogenation with Professor Ryoji Noyori at Nagoya University in Nagoya, Japan. In September of 1991, he joined the faculty at l'Universite de Montreal in Quebec, Canada where he is now Full Professor.

Studying the synthesis of heterocycles, amino acids, and peptide mimics, Lubell's interests lie in making these novel structures for drug discovery and in their use to explore protein folding and molecular recognition. His laboratory has developed effective protocols for creating conformationally biased peptide surrogates, and solid-phase processes for making and introducing these scaffolds into peptide mimic libraries in order to study a spectrum of biologically relevant targets.

Co-author of more than 100 scientific publications, his honors include the Bio-Méga/Boehringer Ingelheim Young Investigator Award (1994), the DuPont Canada Educational Aid Grant (1997), the Danish National Bank Award (1999) and the Merck Frosst Centre for Therapeutic Research Award (2002). Associate Editor of *Organic Letters*, he is a Member of the Editorial Boards of *Biopolymers*, *Peptide Science* and *Chemical Biology and Drug Design*. Council Member of the American Peptide Society, he will co-chair the 20th American Peptide Symposium to be held in Montreal, Canada from June 26–30, 2007.