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Chiral molecules containing the pyrrole framework

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This review summarizes strategies by which chiral pyrroles, both simple and complex, have been prepared: strategies include formation of the pyrrolic ring using starting materials appended with chirality, as well as the attachment of chirality to a pre-formed pyrrolic ring.

Introduction

Pyrroles appear in many complex natural products including chlorophylls, porphyrins (*e.g.*, haem), prodigiosins and marine extracts. Optically active pyrroles vary considerably in their structures and synthesis, with the stereogenic centers appearing at varying distances from the pyrrole core, *i.e.*, directly adjacent to the heterocyclic unit and also remote from the pyrrolic unit. There are numerous reports regarding the synthesis of pyrroles[1–3] and fused pyrroles,[4] as well as their applications in the synthesis of porphyrins,[5] substituted[6] and highly functionalized pyrroles,[7,8] artificial anion receptors[9] and antitumour natural products such as lukianols (**1a**, **1b**), lamellarins (**2a**, **2b**), ningalins (**3**), lycogalic acid (**4**), *etc.* (Fig. 1).[10,11] There are also specialized reports that deal with the utilization of one or more commonly used chemical reactions such as the Michael-type addition reaction.[12]

This review discusses the synthesis of chiral pyrroles and is categorized into five main sections: (i) incorporation of chirality by substitution at the *N*-atom; (ii) integration of chirality *via* reactions that occur at the α-position; (iii) integration of chirality *via* reactions that occur at the β-position; (iv) pyrroles that exhibit axial chirality such as 2,2′-bipyrroles; and (v) other pyrrolic systems such as prodigiosins and polypyrroles. The application of stereoselective reactions to give chiral pyrroles in the synthesis of natural products or drug-like molecules is mentioned under each category. We have made every attempt to include examples of all related work in the above-mentioned categories: we apologize to those whose work we may have failed to recognize in this review.

A potential shortcoming in the synthesis of homochiral pyrrolic compounds is the tendency for pyrroles directly substituted with hydroxy or amino functional groups (Fig. 2) to undergo racemization through an azafulvenium intermediate **6**.[13] Numerous strategies prevent this from

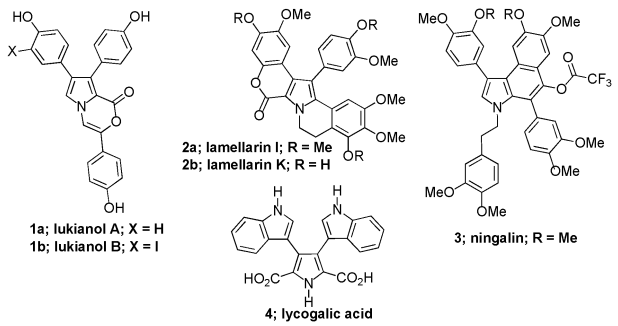

Fig. 1 Antitumour natural products that contain a pyrrolic ring.

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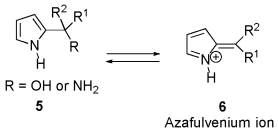

Fig. 2 Racemization through azafulvenium ion.

Fig. 3 Modified Paal–Knorr affords *N*-substituted chiral pyrrole.

occurring, *e.g.*, adding strongly electron-withdrawing substituents to the stereogenic carbon atom,[14] or the *N*-atom of the pyrrole,[15–17] by destabilizing the cationic intermediate and correspondingly stabilizing the chiral center.

Chirality integrated through the *N*-atom

Introduction of chirality at the *N*-position of the pyrrolic ring has been achieved using non-pyrrolic chiral starting materials: the stereochemistry in the starting material is usually faithfully reproduced in the products thus obtained. Alternatively, the nucleophilicity of the pyrrolic *N*-atom has been exploited by reacting pyrroles with chiral and prochiral reagents. The following sections detail efforts carried out in these general areas.

Cyclizations involving chiral non-pyrrolic reagents

Pyrroles are classically synthesized through cyclization reactions such as the Paal–Knorr synthesis[18] and the Hantzsch pyrrole synthesis,[19] both of which employ amines to provide the *N*-atom of the resultant pyrrole. One route to chiral pyrroles involves the integration of chirality into the non-pyrrolic starting materials of these cyclization reactions, although this general approach is limited by the availability and reactivity of the requisite chiral starting materials.[20–22] A modified Paal–Knorr procedure towards *N*-substituted pyrroles utilized primary amines as a source of chirality (Fig. 3).[23] Seven out of the eight reported examples were prepared in good yields (53–90%), and only an extremely sterically hindered triphenyl amino methane substrate failed to produce any Paal–Knorr product. The reaction was explored further, employing diamines such as ethylene diamine and *trans*-1,2- and 1,4-diaminocyclohexane to form bis(pyrrole)s in 30–72% yields.

Another example that utilizes the Paal–Knorr reaction is the synthesis of the blockbuster drug anti-hypertensive atorvastatin (Lipitor, **21**; Fig. 4), as its calcium salt.[24] A number of reports[25–28] described the racemic synthesis of **21**, and enantioselective routes were also developed to afford **21** on a kilogram-scale.[29–32] The synthesis involved the condensation of the β-keto amide **9** with benzaldehyde in the presence of β-alanine and acetic acid to give the enone **10**. Enone **10** was then treated with 4-fluorobenzaldehyde **11** under Stetter reaction conditions using the *N*-ethylthiazolium catalyst **12** to give the highly substituted diketone **13**. The other Paal–Knorr precursor, chiral amine **19**, was prepared from the chiral alcohol **14** as shown in Fig. 4. It was observed that only the route utilizing the 4-chlorobenzenesulfonate **16** was scaleable as the other two analogues, the bromo and the nitro derivatives **17** and **18** respectively, were not stable. The functionalized amine **19** was then reacted with the diketone **13** in a Paal–Knorr reaction to give the pyrrole **20**. Deprotection and formation of the hemi-calcium salt afforded atorvastatin calcium (**21**) in a highly convergent and commercially viable manner.

A pyrrolic thiourea-based organocatalyst, synthesized in five steps (Fig. 5), enables *N*-acyl-Pictet–Spengler-type reactions to give tetrahydro-β-carboline frameworks enantioselectively.[33,34]

Enantiomerically pure *N*-substituted pyrroles were prepared using modified Clausson–Kaas conditions to condense enantiopure α-amino acids, ester hydrochlorides and β-amino alcohols with tetrahydro-2,5-dimethoxyfuran (**30**; Fig. 6a). The acid-catalyzed condensation–cyclization caused partial racemization of the stereogenic center when performed in

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Professor Alison Thompson's research involves pyrroles, dipyrrins and prodigiosins. After her BSc (University of Leicester), she received her PhD from the University of Sheffield for asymmetric aziridination and epoxidation reactions with Professor Varinder Aggarwal. After a year as a Royal Society/NATO postdoctoral fellow in Strasbourg, France she joined Professor David Dolphin's group at the University of British Columbia, Canada. She moved to Dalhousie University in Halifax, Nova Scotia in 2001 and was promoted to full professor in 2009. She received the AstraZeneca Award in Chemistry (Canada) in 2006, and the SPP/JPP Young Investigator Award in 2008.

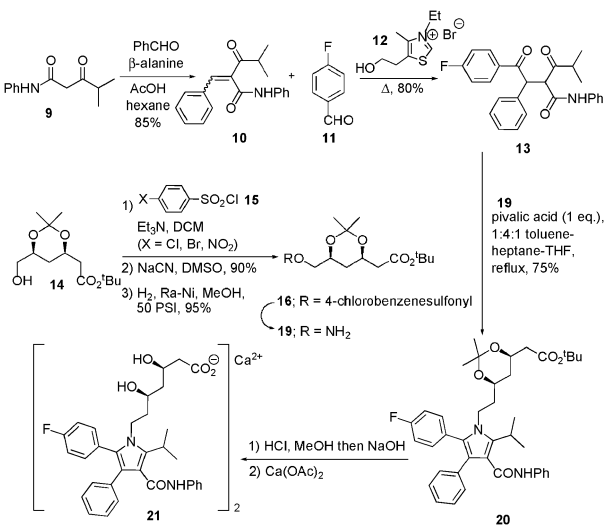

Fig. 4 Enantioselective route to atorvastatin **21**.

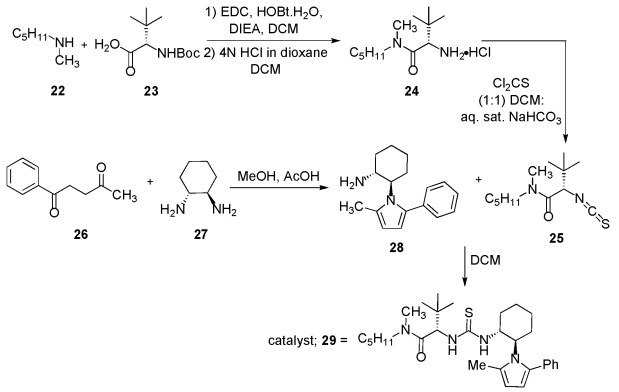

Fig. 5 Thiourea-based organocatalyst **29** for Pictet–Spengler reactions.

solely acetic acid, but the integrity of the stereocenter was maintained using a mixture of acetic acid and dichloroethane.[35] Six examples were synthesized with yields of 59–90% and complete retention of stereochemistry. A similar, and perhaps milder, variation on the Clausson–Kaas strategy first involved the addition of a separate step to hydrolyze **30** to form 2,5-dihydroxyfuran (**33**), and then the modified reaction was performed in a buffered solution (Fig. 6b).[36] Excellent yields were reported for seven examples, four of which contained optically pure chiral centers that experienced complete retention of stereochemistry. The reaction conditions were developed in response to limitations in the previous synthesis.[37]

(2*S*)-2-Pyrrol-1-ylsuccinic acid 4-methyl ester was manipulated to yield bromopyrrolic alkaloids such as (*S*)-(−)-cycloroidin (**38**),[38] longamide B, as both the carboxylic acid (**35**) and the methyl ester (**36**), and hanishin (**37**; Fig. 7a).[39] These pyrrolic alkaloids have been isolated from marine sponges:[40–43] hanishin is cytotoxic toward non-small-lung carcinoma, and longamide B exhibits antibiotic activity

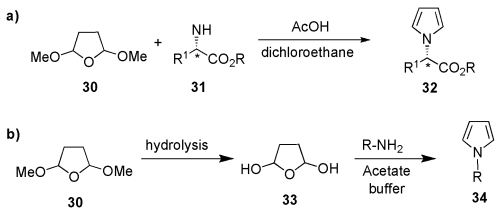

Fig. 6 Modified Clausson–Kaas condensation reaction.

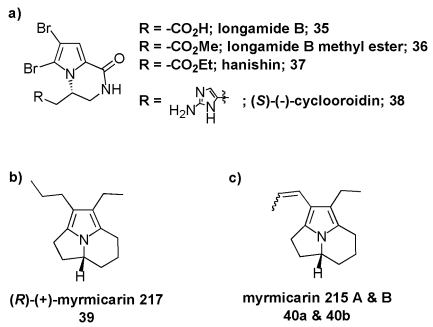

Fig. 7 Structures of bromopyrrole and myrmicarin alkaloids.

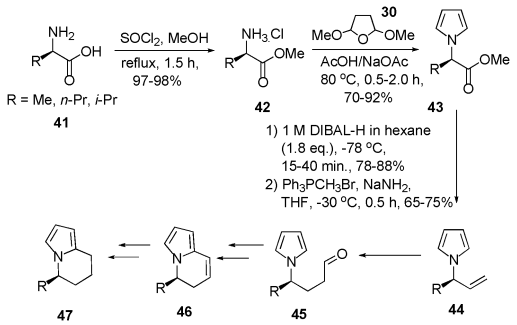

Fig. 8 Synthesis of *N*-allylpyrroles and the structures of indolizines.

against Gram-positive bacteria while its methyl ester shows activity against lymphocytic leukemia cells. Formation and modification of (2*R*)-2-pyrrol-1-ylglutamic acid 1,5-diethyl ester gave (*R*)-(+)-myrmicarin 217[44] (**39**; Fig. 7b) and the myrmicarins 215A and 215B (**40a** and **40b**; Fig. 7c),[45] originally isolated from the poisonous gland secretion of the African ant, *Myrmicaria opaciventris*.[46–48]

In another report, *N*-allylpyrroles were prepared using **30** and α-amino acids.[49] The *N*-allylpyrroles (**44**) were converted into the carbocyclic moiety of the pyrrolic core to give 5,6-dihydro- and 5,6,7,8-tetrahydroindolizines **46** and **47**, respectively, all with retention of stereochemistry (Fig. 8).[50]

Another approach to chiral *N*-substituted pyrroles involved the reaction of chlorenones with chiral amines, α-amino acids and α-amino alcohols using solvent-free conditions on the surface of silica gel (Fig. 9). The reaction was demonstrated to be versatile with 15 substituted pyrroles synthesized in yields of 68–88% with preservation of stereochemistry.[51] The proposed mechanism involved the amine initially reacting with the chloride, and then cyclization and final elimination of water gave the desired pyrrole.

A number of functionalized pyrroles were prepared using cyclopropanes and amines.[52] More nucleophilic amines such as aromatic amines were much more reactive than less nucleophilic amines such as carbamates, which did not react at all. The only example of an optically pure pyrrole derived its chirality from homochiral α-methyl benzylamine (Fig. 10).[52] The reaction was proposed to proceed *via* an initial nucleophilic ring-opening at the 2-position of the doubly-activated cyclopropane by the amine, followed by intramolecular condensation of the ring-opened intermediate to yield the dihydropyrrole, which was then oxidized using DDQ to give the desired pyrrole.

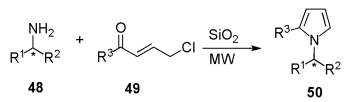

Fig. 9 Microwave-assisted cyclization of chlorenones and amines.

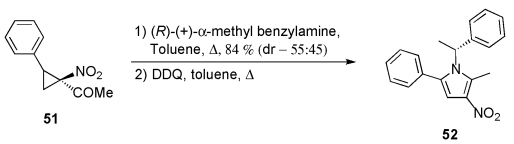

Fig. 10 *N*-Substituted pyrrole from cyclopropane precursors.

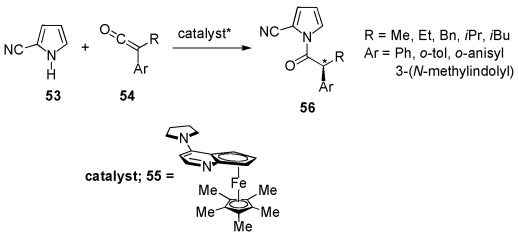

Fig. 11 Catalyzed asymmetric coupling of pyrroles and ketenes.

Asymmetric nucleophilic addition of pyrroles to ketenes

A chiral analogue of DMAP proved useful in the catalytic asymmetric addition of α-cyano pyrroles to ketenes (Fig. 11). Initial investigations involved unsubstituted pyrrole, pyrroles substituted with a nitro group, a cyano group, an acetyl group and an alkyl group, as well as di- and tri-substituted pyrroles. The enantiomeric ratios (er's) of the resultant *N*-acyl pyrrolic products ranged from 50 : 50 to 89 : 11, although when the pyrrole was substituted with a cyano group, an er of 95 : 5 was observed. Further explorations used the α-cyano pyrrole (**53**) while varying the aryl and the alkyl groups on ketene **54**. The reaction was robust to slight variations in the structure of the ketene, and >80% yields with 90 : 10 er were obtained for all ketenes reacted with **53**.[53,54] In the suggested mechanism the catalyst (**55**) was proposed to act as a chiral Bronsted acid, stereoselectively protonating from one face of the prochiral enolate obtained from the initial addition of the pyrrolic nitrogen atom to the carbonyl carbon atom of the ketene.

N-Alkylation of pyrroles

N-Alkylation of pyrrole followed by cyclization onto the α-position of the product **58** gave the bicyclic ring-containing intermediate **59** in racemic form. This strategy was then exploited in the racemic synthesis of the indolizidine alkaloids (±)-monomorine (**60**) and (±)-indolizidine 209D (**61**) (Fig. 12).[55]

In an attempt to synthesize pyrrolic alkaloid natural products, an asymmetric annulation gave pyrrolopiperazinones **65**.[56] The stereoselective alkylation–annulation coupled methyl 5-bromopyrrole-2-carboxylate (**62**) and the vinyl aziridine **63** (Fig. 13) using a palladium-based catalyst to give the product in very high enantioselectivity (72%; 97.5 : 2.5 er). The reaction was proposed to proceed *via* *N*-allylation with the π-allyl-palladium complex of the pyrrolic nitrogen atom in a stereoselective and kinetically controlled manner, followed by

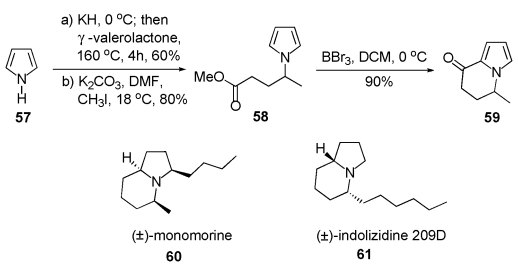

Fig. 12 Reactions towards (±)-monomorine and (±)-indolizidine 209D.

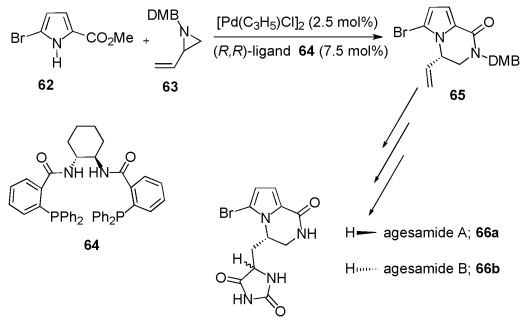

Fig. 13 Pyrrolopiperazinone and agesamide A and B.

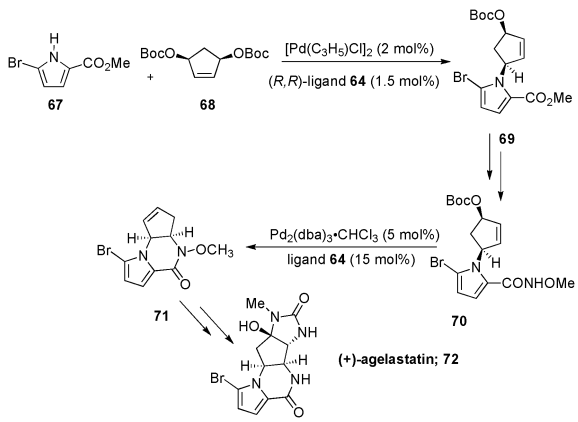

Fig. 14 Formation of a pyrrolopiperazinone towards (+)-agelastatin.

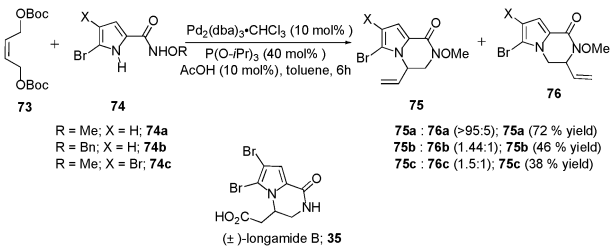

Fig. 15 *N*-Alkylation of an α-amidopyrrole towards *rac*-longamide B.

cyclization of the *N*-allyl pyrrole derivative. The pyrrolopiperazinone thus obtained was modified into natural products such as longamide B, cyclooroidin, hanishin (Fig. 7) as well as agesamides A and B (**66a** and **66b**, respectively; Fig. 13). The same catalytic system was used in the total synthesis of (+)-agelastatin A (**72**; Fig. 14).[57] Several racemic routes for the synthesis of agelastatin A have been reported.[57–60]

In an attempt to synthesize the brominated pyrrolic alkaloid *rac*-longamide B (**35**),[61] following the same strategy used to prepare (+)-agelastatin (**72**),[57] conditions were investigated for *N*-alkylation of the amidopyrrole **74** followed by cyclization under palladium-catalyzed conditions to obtain the bicycle **75** (Fig. 15).

Asymmetric reduction

Although the CBS reagent is of significant use in asymmetric reductions, its utility in the preparation of chiral pyrroles is

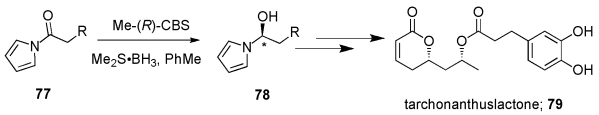

Fig. 16 Asymmetric reduction of *N*-acyl pyrroles.

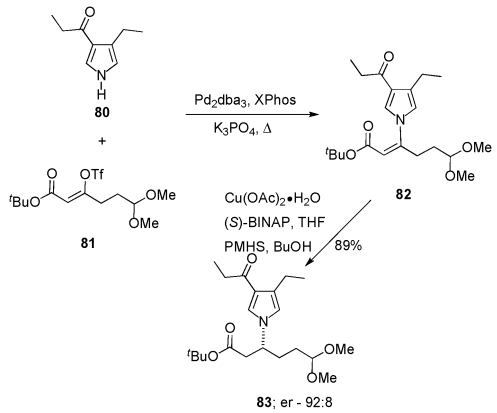

Fig. 17 Asymmetric reduction of an enolate.

relatively unexplored. In one example the *N*-acyl pyrroles **77** were reduced in 79–99% yield and with 92 : 8–99 : 1 er (Fig. 16).[62] The resultant chiral alcohol was then used in subsequent *syn–syn* reductions to direct the formation of several new stereocenters, and the pyrrolic ring was subsequently disassembled to give the non-pyrrolic target tarchonanthuslactone (**79**), a natural product isolated from the *Trichonanthus trilobus* tree.[63]

A total synthesis of the myrmicarin alkaloids (Fig. 7) involved asymmetric reduction of the enolate **82** using a copper–(*S*)-BINAP catalyst and polymethylhydrosiloxane (PMHS) (Fig. 17).[64] The reduction of the vinyl group proceeded with 89% yield and 92 : 8 er.

Catalytic cyanation of *N*-acyl pyrroles

Enantioselective conjugate formal addition of HCN across the vinyl group of an α-substituted unsaturated *N*-acyl pyrrole was developed using a chiral Gd catalyst (Fig. 18).[65] The reaction was performed on a number of substrates with a range of alkyl and aryl substituents giving yields of 80–98% and er's from 91 : 9–95 : 5.[65] The utility of the conversion was demonstrated by modifying the products into useful chiral building blocks such as a chiral 1,4-diester and a hydroxyaryl nitrile derivative.

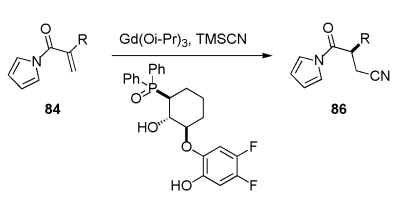

Fig. 18 Chiral *N*-acyl pyrroles *via* catalytic enantioselective cyanation.

Chirality integrated through the α-position

Pyrroles may be alkylated or acylated stereoselectively starting from achiral reactants and asymmetric catalysts, or by using an auxiliary approach. The following sections detail synthetic efforts using strategies directed towards the α-position.

Acylation, alkylation and addition reactions

An enantioselective Friedel–Crafts alkylation of pyrrole with 2,2,2-trifluoroacetophenones utilized a zirconium-based Lewis acid catalyst (Zr-2,2-dibromo-BINOL) to obtain pyrroles bearing a substituent with a quaternary stereogenic center in the α-position in excellent yields and er's.[14] Conditions for the asymmetric alkylation were optimized for 2,2,2-trifluoroacetophenone, and these conditions were applied to fifteen trifluoromethyl ketones (**87**) where R was varied to include a range of substituted aryl groups (Fig. 19).[14] An alkyl example using ethyl trifluoromethyl ketone (R = Et) gave good yield (95%) but poor er (60 : 40).

The racemic synthesis of the antitumour natural product rhazinilam (**98**) initially[66] formed the pyrrole from an iminium salt, in the presence of silver carbonate (Fig. 20).[67] The reaction was proposed to proceed *via* an initial cyclization of the iminium salt, followed by aromatization. One of the challenges in the enantiopure synthesis was the enantioselective C–H bond activation of one of the ethyl groups. The proximity of an amino group to the ethyl groups has been known to provide a favourable environment for C–H bond

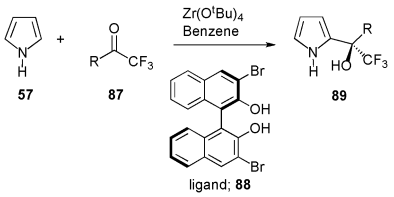

Fig. 19 Catalyzed addition of pyrroles to trifluoromethyl ketones.

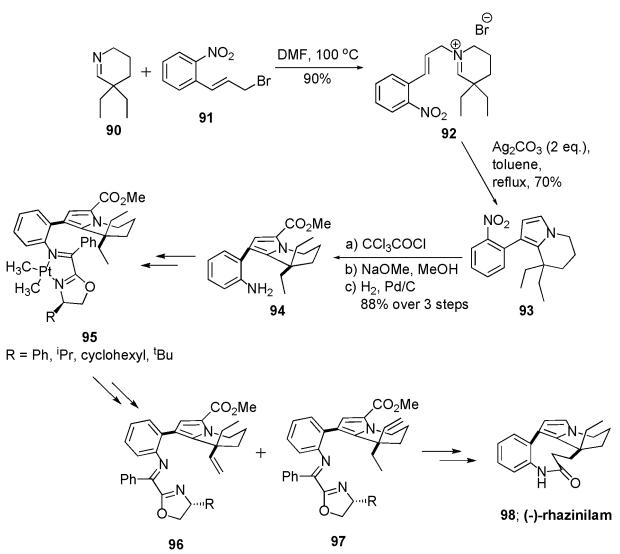

Fig. 20 Cyclization and acylation towards (−)-rhazinilam.

activation.[68–75] A variety of metals and ligands were explored and it was found that a cationic platinum complex facilitated the transformation. Platinum complexes have previously been known[76,77] to activate methane, and sp^2-hybridized nitrogen atoms present favourable ligands for active platinum complexes in a C–H bond activation step.[78,79] Reaction of the platinum complex **95** with triflic acid resulted in the rapid formation, with concomitant loss of methane, of the platinum cation which, when heated in trifluoroethanol, selectively activated the C–H bond of the proximal ethyl group to give the alkenes **96** and **97**. This particular step was investigated using a variety of chiral oxazoline ligands at different temperatures and two major trends were observed: first, higher temperatures improved yields (42% *vs.* 20% at 70 °C *vs.* 60 °C, respectively) at the expense of diastereoselectivity (4.4 : 1 *vs.* 7.5 : 1); second, bulkier ligands (cyclohexyl *vs.* phenyl) afforded better selectivity (7.5 : 1 *vs.* 6 : 1 at 60 °C). The alkene, after removing the platinum metal by treatment with aqueous potassium cyanide and subsequent hydrolysis of the Schiff-base, was transformed to the aldehyde, towards (−)-rhazinilam (Fig. 20).[80] Several groups have elaborated the racemic synthesis of rhazinilam,[81–83] and other enantioselective routes are known.[84,85]

A series of pyrroles alkylated at the pyrrolic nitrogen atom *via* reaction with acrylates and other related functionalities have been reported.[86] These pyrrolic derivatives were obtained from unsubstituted pyrroles and the corresponding electrophiles to give *N*-alkylated pyrrole adducts which were then utilized in intramolecular Michael-type addition reactions to give the corresponding 8-substituted tetrahydroindolizidines and their homologues in an enantio- or diastereoselective manner. For example, pyrrole was first alkylated with 5-bromo-1-pentene to give the *N*-pyrrolyl olefin **100** which was then subjected to olefin metathesis reaction conditions with *N*-acryloyloxazolidinone to give the cyclization precursor **101** (Fig. 21). Subsequent cyclization in an intramolecular Michael-type addition using a copper catalyst[87] gave the indolizine intermediate **102**. In the proposed transition state, the prochiral center lies on the ligand C_2-axis and Michael-type addition occurs from the *Re* face to give the cyclized product in a stereoselective manner (94 : 6 er) and high yields (95%). The stereochemistry of the products was confirmed by further manipulation to give the indolizidines (−)-tashiromine (**103**) and (−)-*epi*-tashiromine (**104**) (Fig. 21).[86]

An enantioselective oxidative coupling reaction was employed[88] to achieve alkylation/cyclization through the α-position of a pyrrole in the synthesis of ketorolac **109**, a bicyclic arylacetic acid anti-inflammatory and analgesic agent.

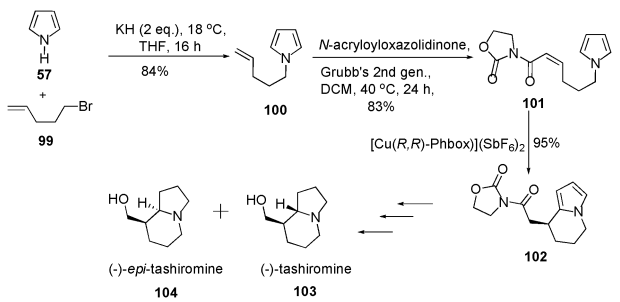

Fig. 21 *N*-Pyrrolyl olefins towards (−)-tashiromine and its epimer.

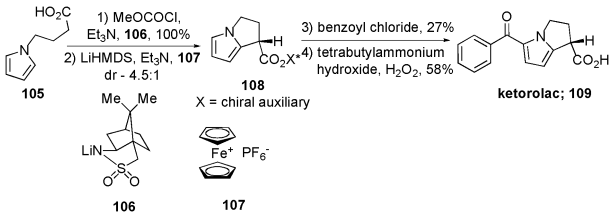

Fig. 22 Enantioselective route to ketorolac **109**.

Efficient linear and convergent racemic syntheses of **109** have been reported[89,90] including a Hantzsch-pyrrole synthesis starting from ethanolamine and dimethyl acetonedicarboxylate, and a Paal–Knorr pyrrole synthesis using ethanolamine and 2,5-dimethoxytetrahydrofuran. Although still marketed as the racemate it is well known[91] that the (*S*)-enantiomer is significantly more active than the (*R*)-enantiomer, and an enantioselective route to **109** has been reported[88] (Fig. 22). The synthesis involved the formation of an Oppolzer sultam as a chiral auxiliary of the acid **105**,[92] but subsequent oxidative coupling was unsuccessful. Ferrocenium hexafluorophosphate (**107**)[93–98] aided enantioselective oxidative coupling to give the desired cyclized product **108**. Immediate benzoylation of **108** followed by removal of the chiral auxiliary by hydrolysis using tetrabutylammonium hydroxide, without epimerization, and treatment with hydrogen peroxide gave ketorolac (**109**) in good yield and enantiopurity.

A thiourea-based organocatalyst **29** (Fig. 5) was developed for *N*-acyl-Pictet–Spengler-type reactions involving the intramolecular addition of indoles onto *in situ*-generated *N*-acyliminium ions to give tetrahydro-β-carboline frameworks in an enantioselective manner.[33,34] Pictet–Spengler-type reactions with catalyst **29** include regioselective cyclizations of pyrroles.[99] Racemic pyrroles gave C2-cyclized products when the pyrrolic nitrogen atom was not protected, and C4-cyclization predominated when the pyrrole nitrogen was protected with a TIPS functionality (Fig. 23). Both these cyclizations proceeded in a highly enantioselective manner.

In similar work, an enantioselective organocatalytic alkylation of pyrroles with α,β-unsaturated aldehydes (Fig. 24) was

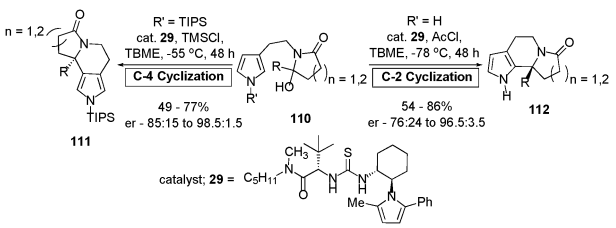

Fig. 23 Regioselective alkylations of pyrroles using a thiourea catalyst.

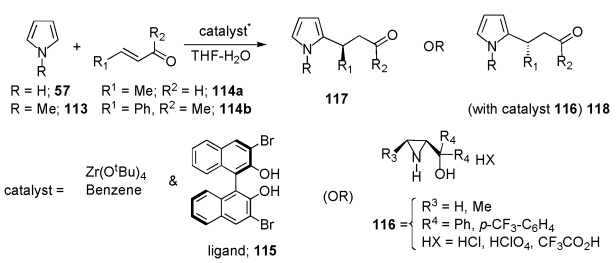

Fig. 24 Catalytic asymmetric alkylation of pyrroles.

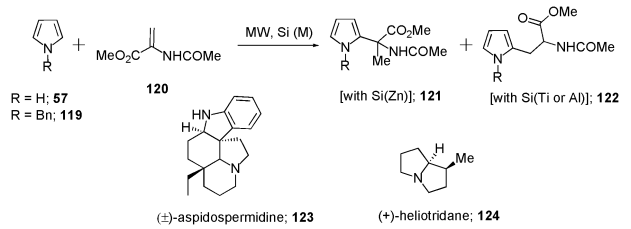

Fig. 25 Michael-type reactions towards natural products.

developed. Using (2*S*,5*S*)-5-benzyl-2-*tert*-butyl-imidazolidinone as a catalyst, the effect of modification of the aldehyde and the nature of the pyrrole, including *N*-unsubstituted variants, were investigated. Pyrroles substituted with alkyl groups in the α- and β-positions were also studied. Overall optimized yields varied from 68–90%, with 93 : 7–98 : 2 er.[15,16] Similar work achieved excellent enantioselectivity with α,β-unsaturated carbonyl compounds and the Zr–BINOL **115** catalyst,[100] whilst another example used aziridine-2-carbinols as organocatalysts but only very modest enantioselectivities were observed.[101]

In an extensive review, the functionalization of indole and pyrrole cores *via* Michael-type addition reactions was discussed.[12] The review covered a variety of Michael-type addition reactions of pyrroles, and also detailed the application of these addition reactions in the synthesis of natural products such as (±)-aspidospermidine (**123**) and (+)-heliotridane (**124**; Fig. 25). One of the most interesting Michael-type addition reactions involves the regioselective addition of methyl α-acetamidoacrylate **120** to pyrrole **57** or **119** under various Lewis acidic catalytic conditions.[102] The catalysts were prepared by treatment of silica with zinc chloride to give [Si(Zn)], with diethylaluminium chloride to give [Si(Al)] and with titanium tetrachloride to give [Si(Ti)]. The reactions catalyzed by [Si(Zn)], under microwave-promoted conditions, yielded the alanine derivatives **121** while those catalyzed by [Si(Al)] or [Si(Ti)] resulted in the α-Michael-type addition product **122** (Fig. 25).

A modified asymmetric alkylation of *N*-substituted pyrroles with imines has been developed.[103] The conditions were optimized using a chiral phosphoric acid catalyst, and by varying the solvent, pyrrolic *N*-substituent and temperature. By applying the optimized conditions to a range of imino substrates it was determined that the nature of the substituents (R) on the aromatic ring (Fig. 26) significantly affected the outcome of the reaction, with more electron-donating substituents affording much better er's than electron-withdrawing substituents (79 : 21–99 : 1). Bulky pyrrolic *N*-substituents (R^1), or substitution on the α- or β-positions of the pyrrole, dramatically decreased

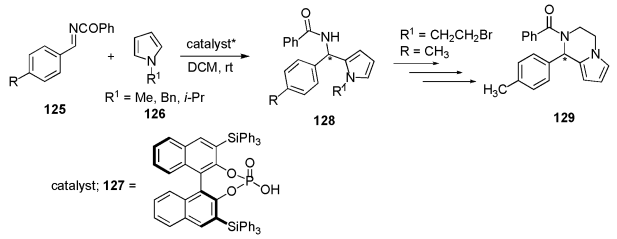

Fig. 26 Friedel–Crafts enantioselective catalytic addition to imines.

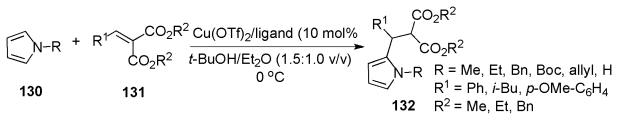

Fig. 27 Friedel–Crafts reactions of pyrroles with alkylidene malonates.

the enantioselectivity of the reaction. Although the precise mechanism is unknown, it has been suggested that 3,3′-bis(triphenylsilyl) groups that are not coplanar with the naphthyl groups would effectively shield the phosphate group thus leading to asymmetric induction.[104] This reaction was applied to the synthesis of a pyrrolo[1,2-*a*]pyrazine **129** in excellent yield (81%; 96 : 4 er).

Enantioselective Friedel–Crafts reactions of pyrroles with alkylidene malonates (**131**) using copper triflate/bis- (or tris-) oxazoline catalytic systems have been reported.[105] Several bis- and trisoxazoline ligands were examined and it was observed that the trisoxazolines gave better er's (78.5 : 21.5 to 83 : 17) in a mixed solvent system (*t*-BuOH–Et_2O 1.5 : 1.0 v/v) at 0 °C (Fig. 27).

A two-step sequence employing chiral *C*-acylating reagents under Friedel–Crafts reaction conditions gave enantiomerically pure pyrrolyl ketones **136** in a highly efficient manner.[106] Starting with *N*-protected (either as trifluoroacetyl or fluoroenyl methoxy carbonyl) α-amino acids **133**, which were converted to the benzotriazolyl intermediates **134**, subsequent reactions under Friedel–Crafts conditions gave the desired products in good yields (Fig. 28), with retention of original stereochemistry.

The diastereoselective addition of pyrroles **57** to nitrones **137** bearing chiral auxiliaries (Fig. 29)[107] gave chiral pyrroles in 73–98% yield, but with poor diastereoselectivity (dr = 65 : 35) when the auxiliary was attached through the *N*-atom. Excellent diastereoselectivity was achieved using nitrones with a chiral auxiliary directly attached to the α-carbon atom (R*), but lower selectivity was obtained with remote chiral centres. The relative stereochemistry was determined using X-ray analysis. A chelated Cram model was proposed for the attack of pyrroles onto nitrones that were based on L-serine, while a Felkin–Anh model was proposed for the nitrones that were based on L-proline for the formation of the *anti* isomer as the major product in both cases.

The promising biological activity[108,109] of pyrrolyl-ethanoneamines led to the synthesis of a library of derivatives

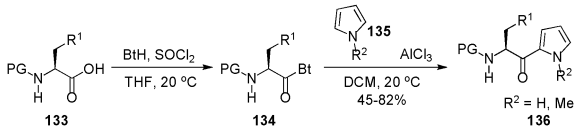

Fig. 28 Preparation of α-amino *N*-pyrrole ketones using Friedel–Crafts.

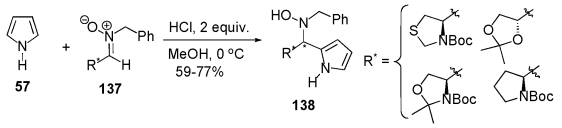

Fig. 29 Diastereoselective addition of pyrroles to chiral nitrones.

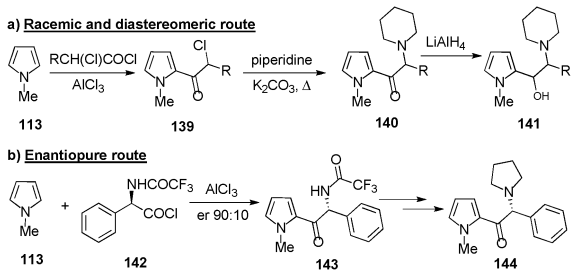

Fig. 30 Approaches to pyrrolylethanonamines.

to test for activity as monoamine oxidase-A (MAO-A) inhibitors. *N*-Methyl pyrrole **113** was acylated to give the α-keto pyrroles **139**, which were then reacted with piperidine to give the aminoketones **140**, which were reduced to give the aminoalcohols **141**. Initially, a mixture of stereoisomers of the aminoalcohols **141** was obtained using a $LiAlH_4$ reduction, and the diastereomers thus obtained were separated using preparative TLC (Fig. 30). The aminoketones **140** were also of interest, and the corresponding enantiomers were separated using HPLC and the biological effects of each enantiomer thus determined. The use of *R*-phenylglycine gave the aminoketones **144** in an optically pure fashion.[110]

Total synthesis of (+)-dragmacidin F (**149**) involved acylation of a pyrrole, starting from its α-lithium salt (**146**) and a chiral Weinreb amide (**145**).[111–113] The acylated derivative **147** thus obtained was then subjected to palladium acetate-catalyzed carbocyclization through the deactivated β-position and gave a pyrrole-fused bicycle (**148**) as a single stereo- and regioisomer in good yield. This synthetic intermediate was then successfully transformed to the target molecule (+)-dragmacidin F (**149**; Fig. 31).

Several reports detail the synthesis of bis(oxazolinyl)- (**152a**, $n = 0$) and bis(oxazolinylmethyl)pyrroles (**152b**, $n = 1$) (Fig. 32). These compounds have a C_2 rotational axis of symmetry and were synthesized *via* the cyclization of amino-alcohols (**151**) with 2,5-bis(cyano)pyrrole (**150a**, $n = 0$) and 2,5-bis(cyanomethyl)pyrrole (**150b**, $n = 1$) in the presence of zinc chloride. Inspired by the catalytic ability of bis(2-pyridyl-imino)isoindole ligands, ligands **152** were designed for use in

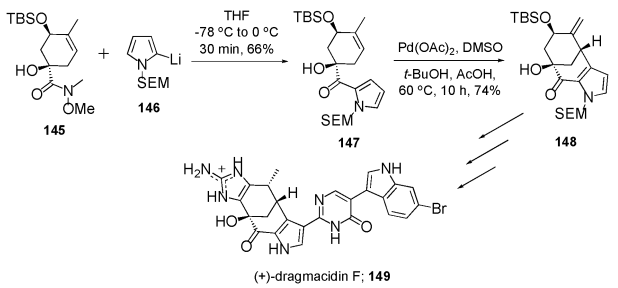

Fig. 31 Acylation and carbocyclization towards (+)-dragmicidin F.

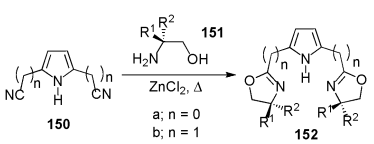

Fig. 32 Synthesis of C_2-symmetric bis(oxazolinyl) pyrroles.

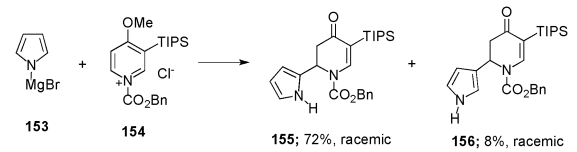

Fig. 33 Pyrrolyl Grignard addition to 1-carbonylpyridinium salt.

asymmetric palladium catalysis.[114,115] However, application of such complexes to the catalytic asymmetric Michael-type addition of ethyl 2-cyanopropionate to produce methyl vinyl ketone gave low yields and er's.

Pyrrolyl Grignard reagents **153** were reacted with the 1-carbonylpyridinium salt **154** to form a racemic mixture of two 1-carbonyl-2-pyrrolyl-2,3-dihydro-4-pyridones, **155** and **156** (Fig. 33). The main focus of this research involved indolyl Grignard reagents, and the attachment of a chiral auxiliary to direct the stereoselective nucleophilic attack, but there was no mention of such work with pyrrolyl Grignards.[116]

Optically pure pyrroles through imino or amido linkages

Chirality can be integrated into pyrroles through the attachment of optically pure amines to pyrroles affixed with carbonyl groups. α-Formyl pyrroles (**157**; Fig. 34) are generally easily synthesized through the Vilsmeier–Hack formylation of a pyrrole,[117] and α-imino pyrroles (**159**) are formed through the condensation of α-formyl pyrroles and primary amines,[118] with retention of stereochemistry in the amines. For example, the condensation between α-formyl pyrrole and an optically active terpene alkaloid generated a homochiral iminopyrrole (Fig. 32).[119] This iminopyrrole was integrated into imino-*N*-pyrrolylphosphines that were studied as ligands with palladium and rhodium.

Chiral iminopyrroles were prepared *via* the condensation of α-formyl pyrroles with chiral primary amines (Fig. 35a).[120] Similar condensation chemistry was used to attach BINOL derivatives to pyrrole to generate chiral compounds that were studied for their use as ligands in lanthanide complexes for asymmetric catalysis (Fig. 35b).[121,122] An amide linkage was utilized to couple pyrrole to a chiral BINAP derivative **162**; Fig. 35c.[123] This compound was designed for use as a simple organic molecule capable of acting as a stereoselective receptor for chiral amino alcohols.

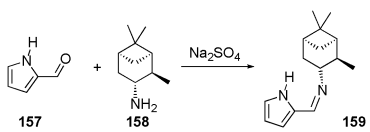

Fig. 34 Pyrrole bearing chiral auxiliary attached through imino group.

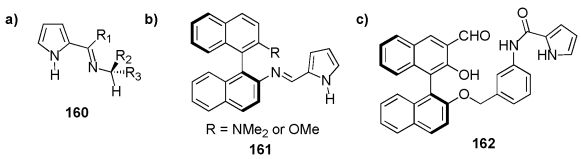

Fig. 35 Pyrroles with chiral auxiliaries *via* imino and amido bonds.

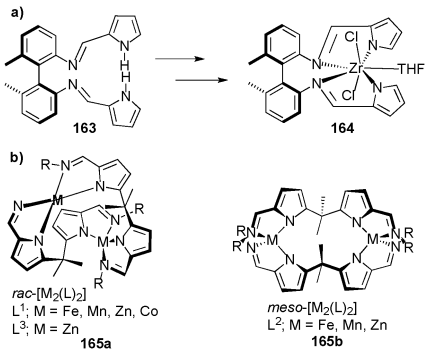

Fig. 36 Chiral bis(iminopyrrole)s.

One example of chiral bis(iminopyrrole) complexes includes two iminopyrrolyl moieties joined by a bianiline (Fig. 36a).[124] This tetradentate bianiline-based ligand was complexed with zirconium to give the complex **164** and the use of this complex in methylaluminoxane (MAO)-activated olefin polymerization of propene was studied. It was observed that the complexes were moderately active in that partly isotactic polypropene was obtained. Another example includes the incorporation of terminal (*R*)-CH(Me)Ph or (*R*)-CH(Me)^{t}Bu groups into a dipyrromethane through an α-imino moiety (Fig. 36b) to give chiral di-iminodipyrromethane ligands such as **165**.[125] These ligands were complexed with dinuclear iron, zinc and manganese and the structures of the resultant complexes in solution and in the solid state revealed that chiral mesocates were formed for L = L^2 while a racemic mixture of helicates was observed for L = L^3 (Fig. 36).

The synthesis of pyrrole-oxazolines **168** (Fig. 37) was reported starting from 2-pyrrole carbonitrile **166a** (R = CN) or methyl 2-pyrrole carboximidate **166b** (R = C(=NH)OMe), and chiral amino alcohols **167**,[126] with retention of stereochemistry. Attempts were made to use the oxazolines as ligands in copper-catalyzed cyclopropanation reactions, and although the cyclopropane derivatives were obtained in reasonable yields the enantioselectivities achieved were rather poor.

The racemic synthesis of (+)-dibromophakellin (**172**) has been reported,[127–129] as have the enantioselective total syntheses of (+)-dibromophakellin (**172**) and (+)-phakellin (**173**) as their hydrochloride salts starting from hydroxyproline.[130,131] The initial steps in one route involved formation of a chiral amide which was cyclized *via* the *N*-atom of the pyrrole ring to give the tricyclic intermediate **171** as a 1 : 1 diastereomeric mixture.[131] The initial intermediate formed from the first step epimerized during the subsequent base-promoted cyclization step. The diastereomeric mixture was oxidized and converted to the alkene **171a**, which was then converted to the acetate **171b** and **171c** (1 : 1 dr, Fig. 36) and modified to give (+)-dibromophakellin (**172**) and (+)-phakellin (**173**), respectively (Fig. 38).

In a related report on the total synthesis of the marine antitumour alkaloid (−)-agelastatin A (**179**; Fig. 39), amidation gave

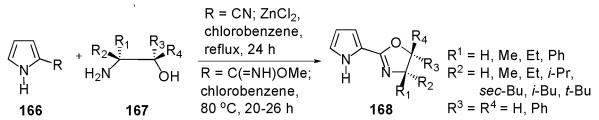

Fig. 37 Preparation of pyrrolyl-oxazolines.

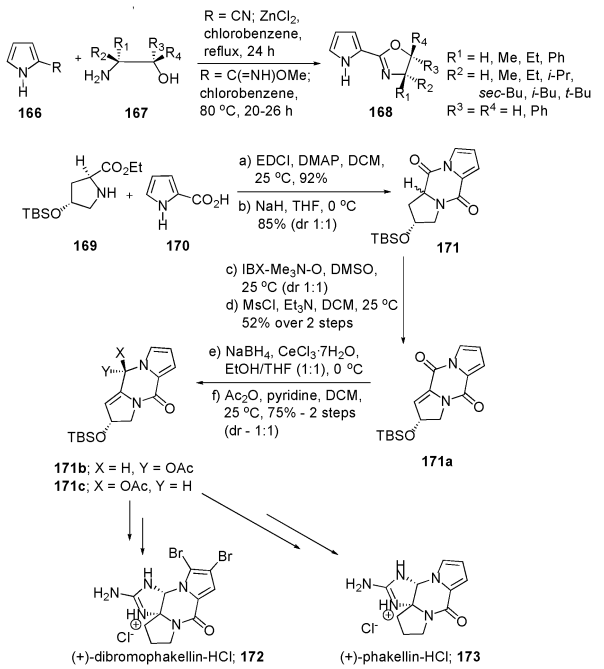

Fig. 38 Towards (+)-phakellin and (+)-dibromophakellin.

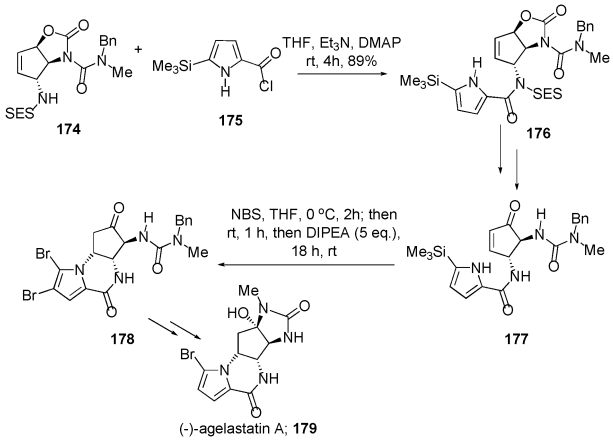

Fig. 39 Towards (−)-agelastatin A.

the chiral amidopyrrole **176** with retention of stereochemistry.[132] This compound was subjected to radical reaction conditions using tributyl tin hydride and AIBN in toluene to remove the SES protecting group and give the parent pyrroloamide, which was then hydrolyzed and subsequently oxidized to give the Michael-type acceptor, a cyclic enone **177**. This derivative was subjected to a Michael-type addition reaction to give tricyclic **178** that was then converted to (−)-agelastatin A **179** (Fig. 39). There are other reported enantioselective routes to (−)-agelastatin A.[133–143]

Pyrroles containing optically pure sulfinyl groups

Chiral sulfinyl groups can be directly attached to a pyrrolic ring without the concern of racemization *via* an azafulvenium ion. A route to pyrroles bearing a homochiral sulfinyl moiety

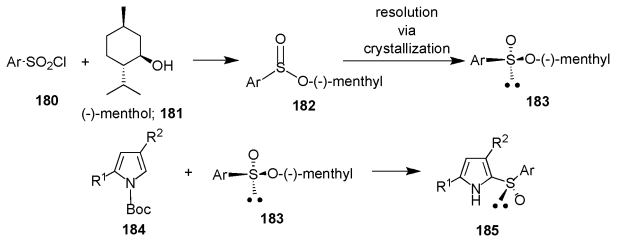

Fig. 40 Pyrrole bearing chiral sulfinyl moiety.

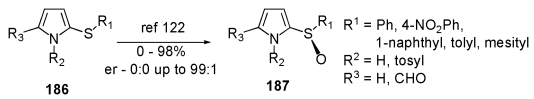

Fig. 41 Chiral sulfinyl pyrroles from 2-(arylsulfenyl)pyrroles.

was developed[144] in which the α-sulfinylation of *N*-*t*-butoxycarbonylpyrroles **184** was achieved using (−)-menthyl-(*S*)-*p*-toluenesulfinate (**183**) and lithium diisopropylamide as a base (Fig. 40). These optically pure pyrroles were elaborated to generate chiral phosphino ligands that were used in asymmetric catalysis. The synthesis is limited by the availability of the chiral sulfinate starting materials that are accessed through a resolution using (−)-menthol (**181**) as a chiral auxiliary (Fig. 40).

In an attempt to prepare chiral 2-(arylsulfinyl)pyrroles (**187**),[145] various prochiral 2-(arylsulfenyl)pyrroles were subjected to the asymmetric oxidation conditions described by Kagan[146] and Modena[147] (Fig. 41). Prochiral sulfides bearing two sterically different substituents were generally observed to be good substrates whereas the sulfides bearing similar groups gave low enantiopurities. It was observed that electron withdrawing groups enhanced the stereoselectivity of oxidation.

Cyclizations involving chiral non-pyrrolic materials

The synthesis of tetrahydroxybutyl pyrroles **190** starting from D-glucosamine (**188**; Fig. 42) has been reported.[148] It was suggested that such pyrrole derivatives could be degraded to simple functionalized pyrroles and cyclized to give C-nucleoside analogues such as the substituted furan derivative **191** (Fig. 42). Although many other heterocycles were reported in the investigation, no other examples of pyrroles were presented.

Asymmetric reduction of ketones

Pyrroles with hydroxymethylene groups at the α-position are susceptible to racemization due to the lability of the hydroxyl group. *N*-Substitution with an electron-withdrawing group on

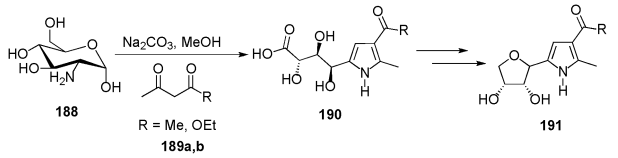

Fig. 42 Pyrrole-generating cyclization of chiral carbohydrate.

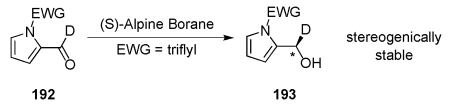

Fig. 43 *N*-Triflyl group suppresses azafulvenium formation.

pyrrole suppresses the formation of the azafulvenium ion that enables racemization.[13,149] The preparation of stereogenically stable deuterated hydroxymethylpyrroles with a high degree of stereopurity using *N*-triflyl-protected pyrroles **192** (Fig. 43) was reported.[13,149] The electron-withdrawing effect of the triflyl group was insufficient to prevent the scrambling of the chiral center when the hydroxyl group was replaced with a chloro or mesyl substituent.

Chirality integrated through the β-position

Chiral pyrroles through amide, ester and imine linkages

Chiral pyrroles were prepared *via* ester and amide linkages where pyrroles functionalized with carboxylic acids were coupled with chiral amines and alcohols (Fig. 44).[150,151] These chiral pyrroles were used in the diastereoselective synthesis of bis(dipyrrinato) zinc complexes with helical geometry.

A peptide coupling strategy was utilized to prepare a key intermediate in an attempt to synthesize palau'mine (**200**; Fig. 45).[152] The reaction conditions were optimized for the coupling reagent so as to give the desired intermediate in very good yields with complete retention of stereochemistry. Although the PyBrOP (bromo-tris-pyrrolidino phosphonium hexafluorophosphate)-coupling agent worked well when R = H or Me (**196**), it failed to give any product when R = CH_2OMe. The use of BOPCl (bis(2-oxo-3-oxazolidinyl)-phosphinic chloride) eliminated this problem and the desired product was obtained in >95% yield. The substituted amide **198** thus obtained was elaborated towards the potential palau'mine precursor **199**.

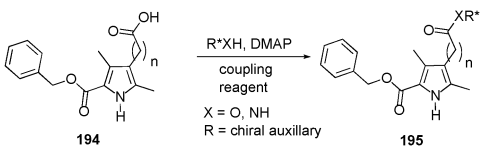

Fig. 44 Chiral auxiliary included through amide or ester linker.

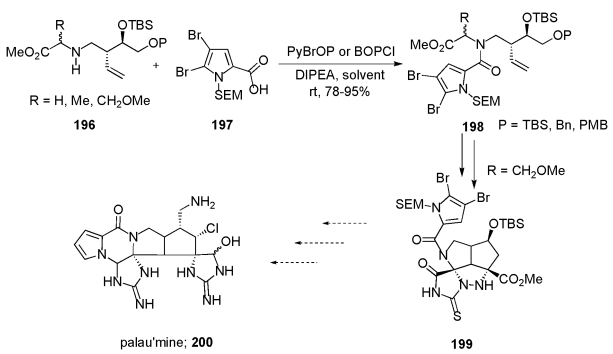

Fig. 45 Chiral pyrrole amides using optimized coupling reagent.

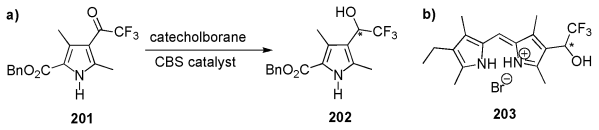

Fig. 46 Asymmetric reduction.

Asymmetric reduction of ketones

This previously discussed route is useful when applied to pyrroles affixed with carbonyl groups on the β-position (Fig. 46). A successful route to β-substituted chiral alcohols such as **202** was developed in a sequence leading to a chiral porphyrin.[153] Stereogenic centers located on a carbon atom directly attached to the pyrrolic ring may undergo racemization if any of the substituents on the chiral center can act as a leaving group (Fig. 2): a hydroxyl group is labile enough to enable such racemization. An electron-withdrawing trifluoromethyl group prohibited racemization by reducing the stability of the azafulvenium intermediate. Reduction of the corresponding ketones using the CBS catalyst and catecholborane as the reductant (Fig. 46a) gave chiral alcohols in greater than 97 : 3 er, with near quantitative yields. Dipyrrin **203**, substituted with a chiral moiety directly attached to the conjugated core, was prepared *via* this route (Fig. 46b).[154]

Cyclizations involving chiral non-pyrrolic reagents

Utilization of chiral non-pyrrolic starting materials in the synthesis of β-substituted pyrroles is useful, just as in the synthesis of *N*-substituted pyrroles discussed earlier. A general synthesis of β-substituted pyrroles **205** from endocyclic, exocyclic and acyclic vinyl sulfone-modified carbohydrates **204** using a modified Barton–Zard reaction (Fig. 47) was developed.[155] This sequence led to highly functionalized chiral pyrroles such as **206** with retention of stereochemical integrity throughout subsequent synthetic manipulations.

Enantioselective alkylation of pyrroles

Another strategy to incorporate chirality into pyrroles involves regioselective alkylation at the β-position using chiral nitrones, similar to the use of this strategy for alkylation at the pyrrolic α-position.[107] It was observed that the alkylation (59–77%) occurred exclusively at the β-position if the nitrogen atom of the pyrrole ring was protected with a triisopropylsilyl functionality as in **207** (Fig. 48a), while the unprotected pyrroles led to alkylation at the α-position. No reaction was observed when the protecting group was a benzenesulfonyl

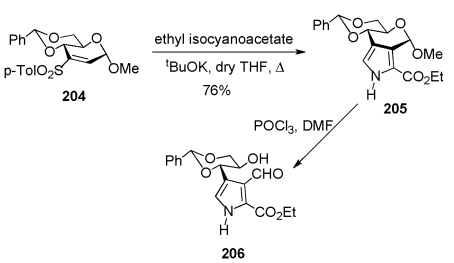

Fig. 47 Pyrroles from vinyl sulfone-modified carbohydrates.

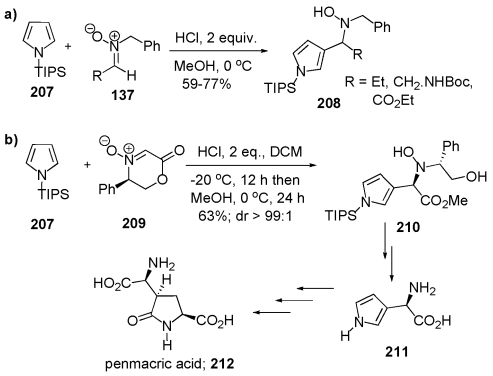

Fig. 48 Synthesis of a novel amino acid towards penmacric acid.

group. The reaction was explored with a chiral cyclic nitrone to give the β-substituted pyrrolic hydroxylamine **210** which was further manipulated to give the novel amino acid **211** (Fig. 46b). This synthetic sequence was further explored to obtain penmacric acid **212** (Fig. 48b).[156] There are other reported routes to penmacric acid.[157,158]

Resolution of pyrrolic racemates

The total synthesis of a bilirubin, with a chiral substituent attached in the β-position of the pyrrole, has been reported.[159] The introduction of the chiral center was addressed in the first step of the synthesis when the pyrrolic moiety was synthesized as a racemic mixture using the Kleinspehn variant of Knorr methodology. The enantiomeric pyrrolic compounds were affixed with a chiral auxiliary, (1*S*)-camphor-2,10-sultam, through an amide linkage and the resulting diastereomers separated using crystallization. The auxiliary was subsequently cleaved to give the enantiopure pyrrole (Fig. 49).[160]

Axially chiral pyrroles

Bipyrroles are found in the prodigiosin natural products,[161] and some exhibit a broad range of activity against bacteria, protozoa and pathogenic fungi, as well as being capable of inducing apoptosis in human cancer cell lines.[162,163] Bipyrroles are also known for their conducting properties. Polypyrroles are extensively studied[164,165] conducting polymers, courtesy of their redox properties, stability and electrical conductivity, and have found applications as supercapacitors, electrochemical sensors, antistatic coatings and drug delivery systems.[166,167] Nonplanar 2,2′-bipyrroles are intrinsically

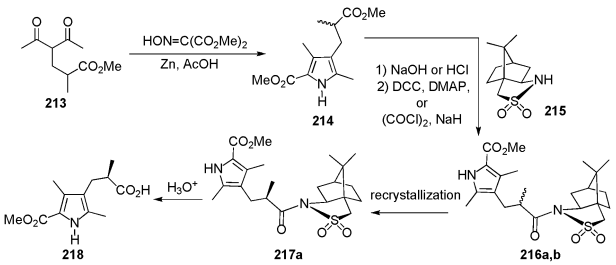

Fig. 49 Kleinspehn–Knorr gives racemate that was classically resolved.

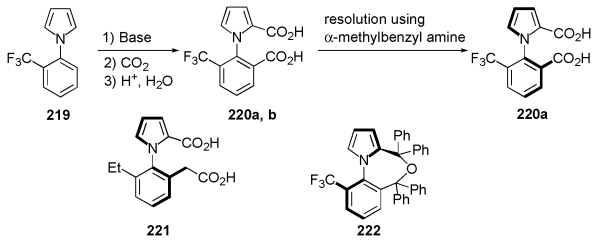

Fig. 50 Atropisomeric 1-arylpyrrole.

chiral, with enantiomeric conformations interconverting by rotation about the C(2)–C(2′) bond.

Atropisomeric pyrroles

N-Phenyl pyrroles possessing steric alkyl groups that prevent free rotation about the N–Ph bond are chiral based on their C_2-symmetry and have potential as asymmetric catalysts, chiral shift reagents and resolving reagents.[168] Syntheses were developed for (±)-1-[2-carboxy-6-(trifluoromethyl)phenyl]-pyrrole-2-carboxylic acid (**220**; Fig. 50)[168] and several analogues such as 1-(2-carboxymethyl-6-ethylphenyl)-1*H*-pyrrole-2-carboxylic acid[169] (**221**) and (*R*)-(+)-4,4,6,6-tetraphenyl-10-trifluoromethyl-4*H*,6*H*-pyrrolo[1,1,2-*a*][4]benzoxazepine (**222**).[20] The carboxylates were converted into tetrasubstituted diols and/or pyrrolo[1,2-*a*]benzoxapines either as pure enantiomers or as racemates, depending on the reagents used. The energy of racemization for the dicarboxylic acid **221** (Fig. 50) was estimated to be 30–40 kJ mol^{-1}.

Cyclizations involving chiral non-pyrrolic reagents

Racemic 3,3′-dipyrroles **225** possessing axial chirality were synthesized using a one-step double Michael-type addition using the diaroyl acetylene **223**, a 1,3-dicarbonyl compound **224** and ammonium acetate, with indium trichloride acting as a catalyst (Fig. 51). The activation energy for the racemization of the chiral dipyrroles **225** was estimated to be around 27 kcal mol^{-1}, and the resolution of the racemates was achieved using chiral HPLC.[170]

Other work elaborated the conversion of dioximes **226** with ethylene and base in DMSO, under Trofimov reaction conditions, to give racemic 2,3′-bipyrroles **228** (Fig. 52) in low yields.[171] The two pyrrole rings are non-planar and it was argued that the formation of the second pyrrolic ring from

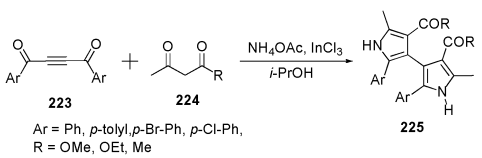

Fig. 51 Atropisomeric dipyrroles.

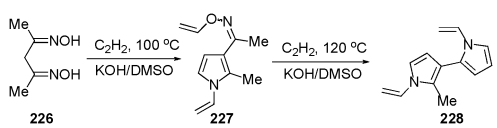

Fig. 52 Preparation of 2,3′-bipyrroles from dioximes.

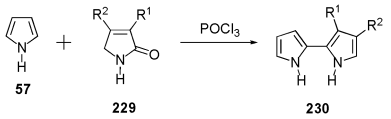

Fig. 53 Synthesis of 2,2′-bipyrroles using $POCl_3$.

O-vinyloxime **227** was hindered due to the increased electron density at the 3-position of the existing pyrrolic ring compared with that at the 2-position. It was suggested that the bipyrrole formation occurs following a [3,3] sigmatropic rearrangement of an enehydroxylamine and that the electron-donating effect of the heterocycle on the *O*-vinyloxime **227** leads to a reduction of the C–H acidity of the neighbouring methyl group, which is unfavourable for tautomeric conversion of the vinyloxime into an enehydroxylamine. When sterically hindered dioximes were used isoxazoles were obtained in moderate yields, instead of the corresponding bipyrroles.

The racemic 2,2′-bipyrroles **230** were prepared in moderate to good yields starting from pyrrole and pyrrolinones **229**, using phosphoryl chloride (Fig. 53).[172–174]

The preparation of 2,2′-bipyrroles starting from 2-formyl pyrroles **231** was reported where a formyl pyrrole was converted into a diketone derivative **232** using α,β-unsaturated ketones in the presence of triethylamine and a 1,3-thiazolium salt.[175] The dicarbonyl intermediate **232** was then reacted with amines to give the racemic 2,2′-bipyrrole derivatives **233** (Fig. 54).

The preparation of a racemic 3,3′-di-*tert*-butyl-2,2′-bipyrrole **239** starting from an achiral pyrrole derivative **236** was reported.[176] Prior to this report, there were only two known optically active bipyrroles: a 1,1′-bipyrrole **234**[177] and a 2,2′-bipyrrole **235** (Fig. 55a).[178] In the 2003 report, the novel bipyrrole was synthesized in four synthetic steps from ethyl 3,5-dimethyl-1*H*-pyrrole-2-carboxylate (**236**) involving an Ullman-type coupling protocol in the bipyrrole forming step. The presence of the *tert*-butyl groups resulted in restricted rotation about the 2,2′-bipyrrole bond, and the CH_2 hydrogen atoms were observed to be diastereotopic, consistent with axial chirality of the bipyrrole **239** (Fig. 55b).

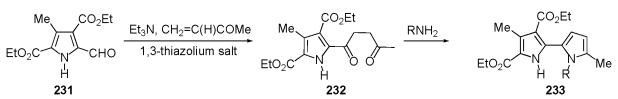

Fig. 54 Synthesis of 2,2′-bipyrroles *via* a dicarbonyl intermediate.

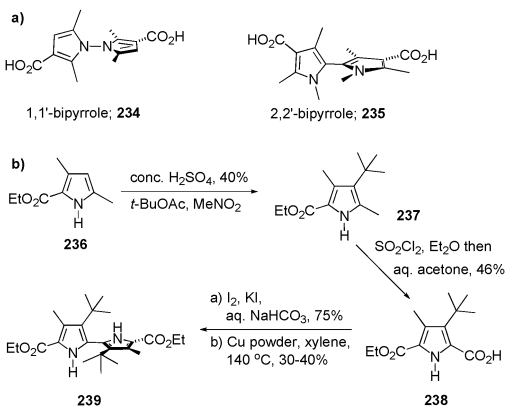

Fig. 55 Ullman-type coupling towards a chiral 2,2′-bipyrrole.

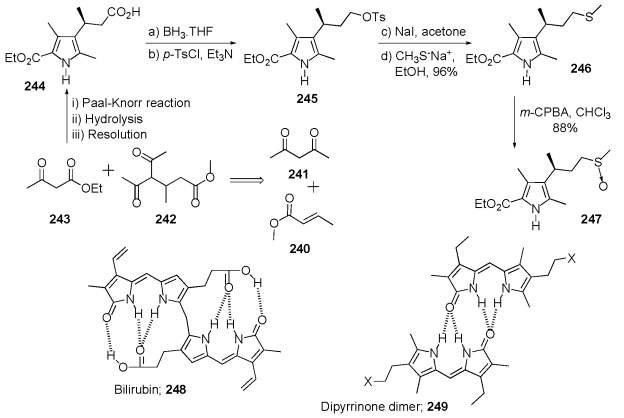

Fig. 56 Synthesis of chiral sulfoxide analogues of bilirubin.

Miscellaneous pyrroles

The hydrogen bonding and π-stacking in dipyrrinone acid dimers, especially in xanthobilirubic acid and chiral analogues, have been studied.[179] Optically active dipyrrinone sulfide and its sulfinyl analogue **247** were prepared as potential precursors to analogues of tetrapyrrolic bilirubin with sulfinyl groups replacing the carboxylic acids.[180,181] The chiral pyrrolic sulfides **246** were obtained starting from a chiral pyrrole-4-propanoic acid (**244**). The pyrrole-4-propanoic acid (**244**) was obtained as a racemate from ethyl acetoacetate **243** and the racemic hexanoate ester **242** using the Kleinspehn variant of Knorr methodology (Fig. 56). Hydrolysis and resolution gave enantiopure **244**.

The chemistry and biology of roseophilin (**252**) and the prodigiosin alkaloids have been reviewed.[182] Prodigiosins **250** and **251** bear tripyrrolic skeletons, and roseophilin **252** is a chiral fused pyrrole derivative containing three rings *viz* two five-membered and a third large, thirteen-membered ring (Fig. 57). Both racemic and enantiopure routes to roseophilin **252** have been reported.[182]

Partial reduction of pyrroles using Birch conditions to give functionalized pyrrolines and the utilization of this elegant chemical manipulation have been exploited for the synthesis of a variety of natural products.[183] Some of these examples include routes towards (+)-lactacystin (**253**), omuralide (**254**), hyacinthacine A_1 (**255**) and 1-epiaustraline (**256**; Fig. 58).

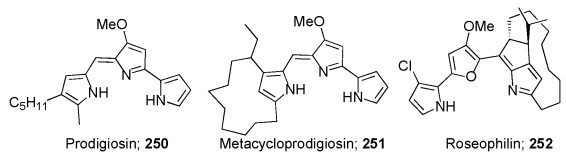

Fig. 57 Prodigiosin, metacycloprodigiosin and roseophilin.

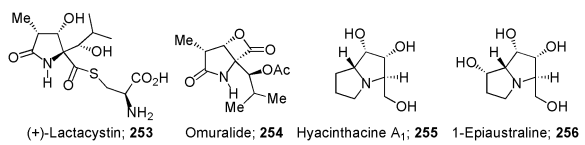

Fig. 58 Natural products synthesized using Birch reduction conditions.

Conclusions

This review has brought together the various approaches that exploit the reactivity and construction of the pyrrole ring for the ultimate goal of synthesizing chiral pyrroles: routes exploiting each of the methods for realizing homochirality have all been reported.

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