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The synthesis of biologically active indolocarbazole natural products

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Covering: up to 2020

The indolocarbazoles, in particular indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole derivatives, are an important class of natural products that exhibit a wide range of biological activities. There has been a plethora of synthetic approaches to this family of natural products, leading to advances in chemical methodology, as well as affording access to molecular scaffolds central to protein kinase drug discovery programmes. In this review, we compile and summarise the synthetic approaches to the indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole derivatives, spanning the period from their isolation in 1980 up to 2020. The selected natural products include indolocarbazoles not functionalised at indolic nitrogen, pyranosylated indolocarbazoles, furanosylated indolocarbazoles and disaccharideindolocarbazoles.

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1 Introduction

1.1 The indolocarbazoles

The indolocarbazoles are a family of heterocyclic natural products consisting of a carbazole core fused to an indole system through its nitrogen-containing ring (Fig. 1). There are several indolocarbazole isomers, of which the five most commonly isolated are the 11,12-dihydroindolo[2,3-*a*]-carbazole (**1**), 5,7-dihydroindolo[2,3-*b*]carbazole (**2**), 5,8-dihydroindolo[2,3-*c*]carbazole (**3**), 5,12-dihydroindolo[3,2-*a*]carbazole (**4**) and the 5,11-dihydroindolo[3,2-*b*]carbazole (**5**). The indolocarbazoles have been the subject of several extensive

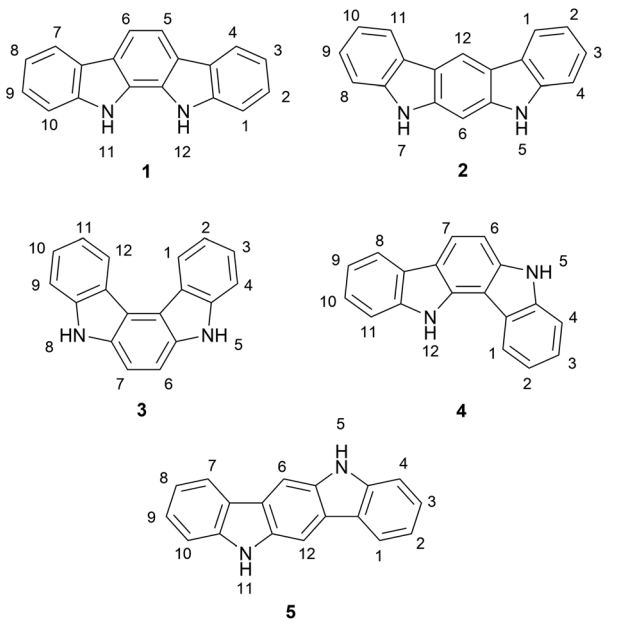

Fig. 1 Indolocarbazole isomers.

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reviews covering their chemistry, properties and biological activity.[1–5]

Of the indolocarbazole isomers described, the most rigorously studied is 11,12-dihydroindolo[2,3-*a*]-carbazole (**1**). In particular, a sub-family known as the indolo[2,3-*a*]pyrrolo[3,4-*c*] carbazole derivatives (**6**) ascended to prominence in the early 90 s after discovery of interesting biological activities associated with these compounds, in particular their nanomolar inhibition of protein kinase C (PKC) (Fig. 2). This broad sub-family of natural products includes compounds both with and without indolic functionalisation, and for convenience throughout this review they will be referred to as indolocarbazole natural products. These natural products have been reviewed previously from a broader perspective,[6–8] as well as on more specific aspects such as their biological activity,[4,5,9] biosynthesis[10] and therapeutic application.[7,11,12] The primary focus of the present review is on synthetic approaches to the indolocarbazole natural products.

George Chambers grew up in south–east England and studied chemistry at the University of Southampton, where he received a first class MChem in 2018. During his studies, he spent 6 months at the University of Sydney working in the group of Associate Prof. Christopher McErlean on the synthesis of trehalose-6-phosphate analogues. He then joined the group of Prof. Richard Brown for his PhD where he is currently working on the total synthesis of indolocarbazole alkaloids.

Emre Sayan was born in Ankara, Turkey, in 1972. He completed his BSc degree in Bogazici University, followed by MSc and PhD degrees (2002) in Bilkent University, department of Molecular Biology and Genetics. He worked in INSERM (Paris), MRC Toxicology Unit (Leicester, UK) and University of Leicester (UK) as postdoctoral and career development fellow between 2002–2010. He was appointed as a Lecturer in University of Southampton, UK (2010). His research group's interests include biomarker discovery and drug development for metastatic cancers. He has a fascination for natural products and he always takes lessons from nature.

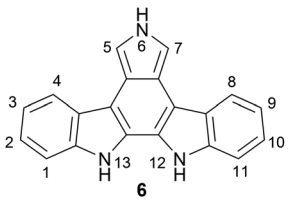

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Fig. 2 An isomer of indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole.

1.2 The indolocarbazole alkaloids and their discovery

In 1977, Omura and co-workers isolated a novel alkaloid they named AM-2282, from the bacterium Streptomyces staurosporeus.[13] Preliminary testing of the alkaloid revealed strong hypotensive activity as well as antimicrobial activity against fungi and yeast.[13] Much effort was devoted to elucidate the alkaloid's structure, which was later confirmed by X-ray crystallography, as an indolocarbazole core bearing two glycosyl linkages at the indolic nitrogens. AM-2282 was subsequently renamed staurosporine (**7**, Fig. 3).[14,15]

In 1985, Clardy and co-workers isolated rebeccamycin (**8**),[16] and later that year Sezaki and co-workers reported the discovery of another important indolocarbazole alkaloid that subsequently became known as (+)-K252a (**9**) when Kase and co-workers isolated several more compounds with the indolocarbazole core including the staurosporine aglycone (**10**).[17–19] An excellent account of the discovery and isolation of members of the indolocarbazole family can be found in Knölker and Reddy's review.[20]

A pivotal development in the indolocarbazole alkaloid story was realisation of their potential as therapeutic agents, or as leads to develop more selective drugs. In particular, their high potency as inhibitors of protein kinase C (PKC) caused great excitement;[18,21,22] K252a (**9**) exhibited nanomolar inhibition of PKC (IC_{50} = 32 nM) whilst staurosporine (**7**) displayed the greatest inhibitory power (IC_{50} = 2.7 nM).[4,18,23] The PKC family

Richard Brown was born in Canterbury, UK, in 1968. Following undergraduate and postgraduate studies at the University of Southampton, UK (PhD 1994, supervisor Prof. Philip J. Kocienski), he took up a NATO postdoctoral fellowship at UC Berkeley (Prof. Clayton H. Heathcock). He returned to the University of Southampton in 1996 as a Royal Society University Research Fellow, and was promoted to Professor in 2010. His group's research includes natural product total synthesis, oxidative cyclisation methodology and electro-organic synthesis using flow reactors. Natural products provide a major inspiration for his research, with current synthetic targets including bioactive alkaloids.

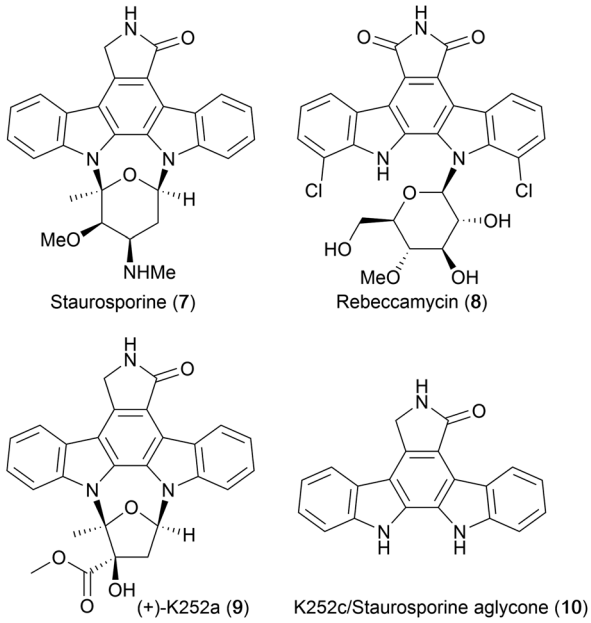


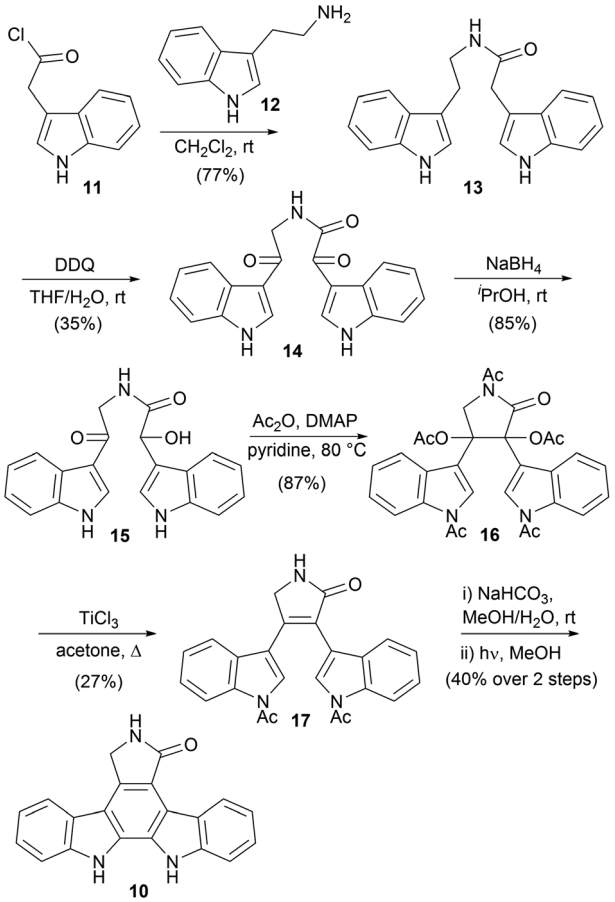
Fig. 3 Structures of indolocarbazole alkaloids.

of enzymes has an important role in regulation of cellular responses, which include gene expression, cell proliferation, and inflammatory response. Consequently, PKC's have been under intense investigation over many decades in order to understand their structure, molecular mechanisms and impact upon cellular function. The discovery that inhibition of PKC can lead to cancer cell apoptosis stimulated huge interest in the search for new classes of anti-cancer drugs.[6,23,24] This exciting biological activity clearly heightened interest in indolocarbazoles, stimulating many synthetic endeavours that extend over four decades.

2 Syntheses of indolocarbazoles not functionalised at indolic nitrogen

2.1 Staurosporine aglycone (staurosporinone, 10)

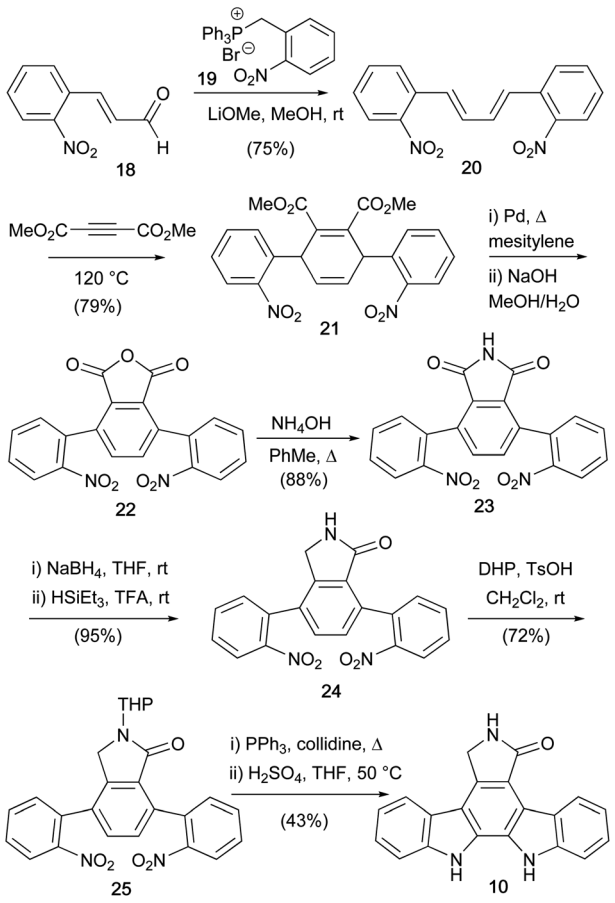
The first indolocarbazoles covered herein are the natural products devoid of functionalisation at indolic nitrogen. One of the most important is the staurosporine aglycone (**10**), also commonly referred to as K252c and staurosporinone. The first synthesis was described in 1983 by Winterfeldt and co-workers (Scheme 1).[25] The synthesis began with acylation of tryptamine (**12**) to give amide **13**. Oxidation of both benzylic positions with DDQ followed by a chemoselective reduction of the α-ketoamide **14** gave hydroxyketone **15**. Acylation was accompanied with cyclisation to the pentaacetate **16**, which only underwent reductive elimination to the desired lactam **17** in appreciable yields when treated with $TiCl_3$.[26] Subsequent deacylation and 6π photochemical cyclisation, with oxidative aromatisation occurring under the reaction conditions, furnished aglycone **10** in moderate yield. Winterfeldt's application of the photocyclisation approach is significant, as it paved the way for many subsequent synthetic endeavours.



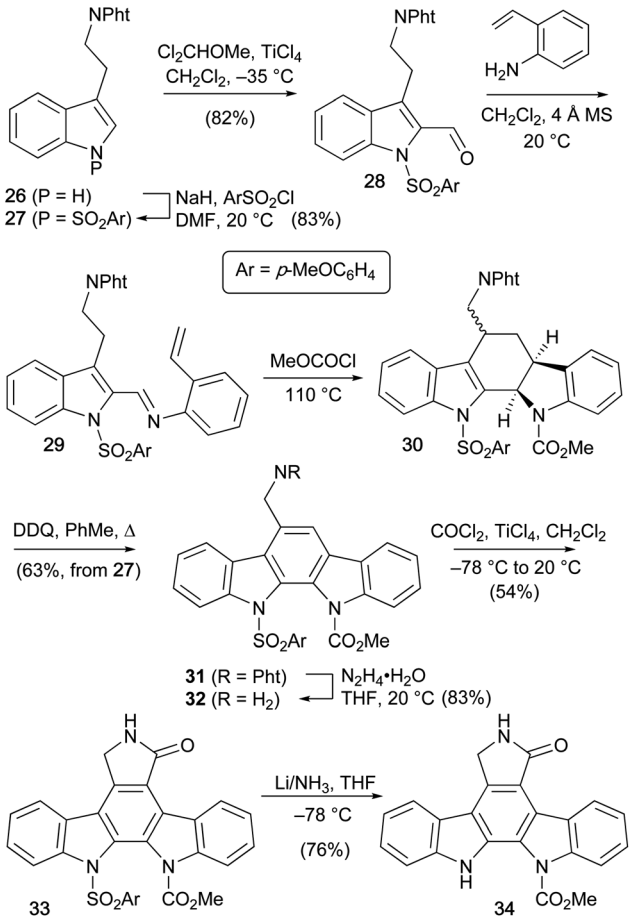
Scheme 1 Winterfeldt and co-workers' synthesis of staurosporine aglycone (**10**).

Discovery of important biological activity exhibited by these natural products sparked a dramatic upsurge in synthetic interest.[6] In 1983, Raphael and co-workers developed a Diels–Alder/nitrene insertion approach to aglycone **10** (Scheme 2). Frustratingly, an initial attempt was thwarted by failure to cleave *N*-benzyl protection from the aglycone.[27] However, a synthesis of the unprotected aglycone **10** was ultimately published in 1990,[28] commencing with a Wittig reaction between 2-nitrocinnamaldehyde (**18**) and phosphonium salt **19** to give butadiene **20**. The ensuing Diels–Alder reaction with dimethyl acetylenedicarboxylate gave 1,4-cyclohexadiene **21**, which was subjected to dehydrogenative aromatisation and annulation to give phthalic anhydride **22**. Aqueous ammonia treatment of **22** afforded maleimide **23**, before two-step reduction to lactam **24**.[29–31] The lactam N–H was then THP protected before application of Cadogan's deoxygenative nitrene insertion, a strategy subsequently exploited in many indolocarbazole syntheses, secured aglycone **10** after acid cleavage of the lactam protection.[32]

Magnus and co-workers reported the synthesis of a selectively mono-protected staurosporine aglycone **34** in 1984, which is of significance as it has the potential to allow regiocontrolled functionalisation (Scheme 3).[33] Phthalimido tryptamine derivative **26** was protected at its indole nitrogen,[34] followed by



Scheme 2 Raphael and co-workers' synthesis of staurosporine aglycone (**10**).



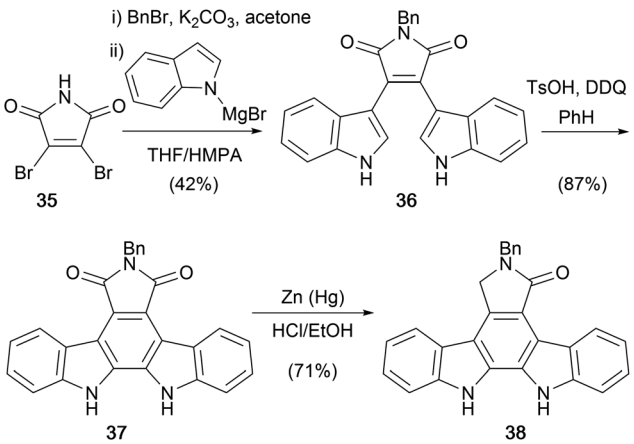
Scheme 3 Magnus and co-workers' synthesis of a protected staurosporine aglycone **34**.

formylation of C2 to afford 2-formyl indole **28.** Condensation with 2-aminostyrene preceded the key intramolecular Diels–Alder cycloaddition, which secured pentacyclic carbamate **30.** Subsequent oxidative aromatisation using DDQ gave indolocarbazole **31.** The phthalimido protecting group was removed using hydrazine hydrate before chloroformylation/cyclisation with phosgene gave protected indolocarbazole **33.** Finally, reductive cleavage of the *p*-methoxyphenylsulfonyl group under Birch conditions delivered a mono-protected staurosporine aglycone **34.**

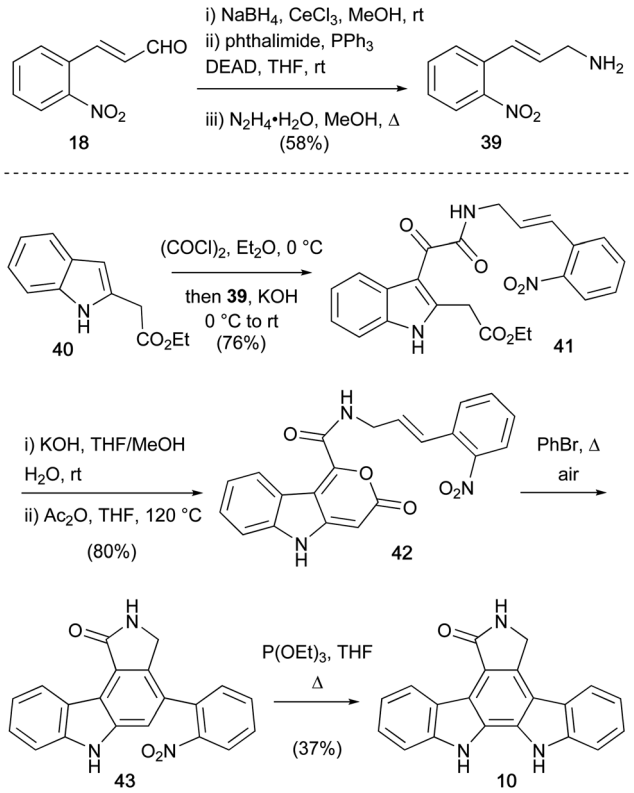
In 1987, as part of investigations towards the aglycone and monosaccharide moieties of staurosporine (**7**), Weinreb and co-workers utilised a modification of methodology developed by Steglich and co-workers to access *N*-benzyl staurosporine aglycone **38** (Scheme 4).[35–37] Dibromomaleimide (**35**) was *N*-benzylated, then treatment with an excess of magnesiated indole gave *N*-benzyl bisindolylmaleimide (**36**). Oxidative cyclisation using TsOH/DDQ and subsequent Clemmensen reduction afforded the targeted *N*-benzyl staurosporine aglycone **38.** The approach to the protected aglycone is notable in its brevity (4 steps from **35**) and efficiency, and provided the basis for further optimisation by others.

The first protecting group free synthesis of the aglycone **10,** was completed by Moody and co-workers in 1990 (Scheme 5).[38,39]

The approach centred on intramolecular Diels–Alder decarboxylation sequence from pyranone **42,** prepared in 6 steps from the commercially available enal **18.**[40,41] Allylic amine fragment **39** was prepared by Luche reduction of **18,** then coupling of the resulting cinnamyl alcohol with phthalimide



Scheme 4 Weinreb and co-workers' synthesis of protected staurosporine aglycone **38**.

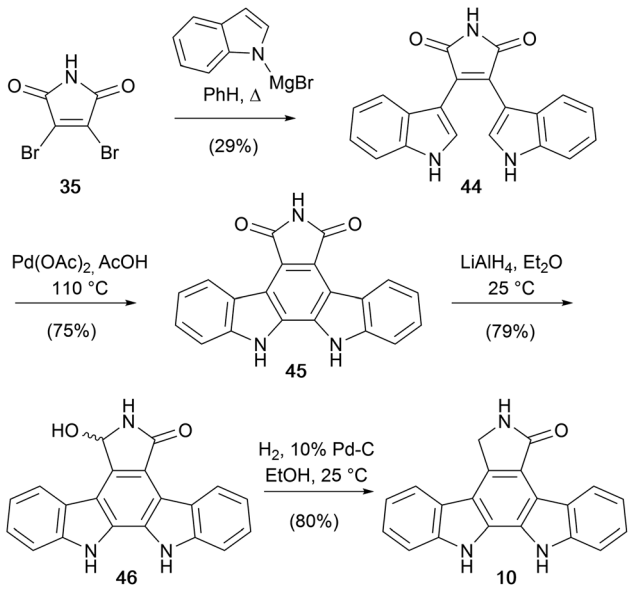


Scheme 5 Moody and co-workers' synthesis of the staurosporine aglycone (**10**).

under Mitsonobu conditions and hydrazinolysis. Friedel–Crafts acylation of indole **40** with oxalyl chloride, and trapping with allylic amine **39**, provided α-ketoamide **41**. Ester hydrolysis and cyclisation using acetic anhydride gave the desired pyranone **42**, which upon refluxing in BnBr open to air, forged the carbazole system in **43**. Adoption of Raphael's deoxygenative nitrene insertion approach completed the staurosporine aglycone (**10**). The approach (8% over 9 steps from enal **18**), presents carbazole **43** as a suitable intermediate for regioselective functionalisation towards staurosporine (**7**). However, some limitations may arise due to the rather forcing thermal conditions of nitrene insertion.

Hill and co-workers from Roche, built upon methodology developed by Steglich and later Weinreb, coupling dibromomaleimide (**35**) with magnesiated indole to obtain bisindolylmaleimide (**44**) (Scheme 6).[42] Cyclisation of **44** using TsOH/DDQ proved challenging, while a novel $Pd(OAc)_2$ mediated oxidative cyclisation gave arcyriaflavin A (**45**). Reduction of the imide to hydroxylactam **46**, and subsequent hydrogenolysis gave staurosporine aglycone (**10**) in only 4 synthetic operations, and without recourse to *N*-protection, constituting the shortest route at the time of publication.

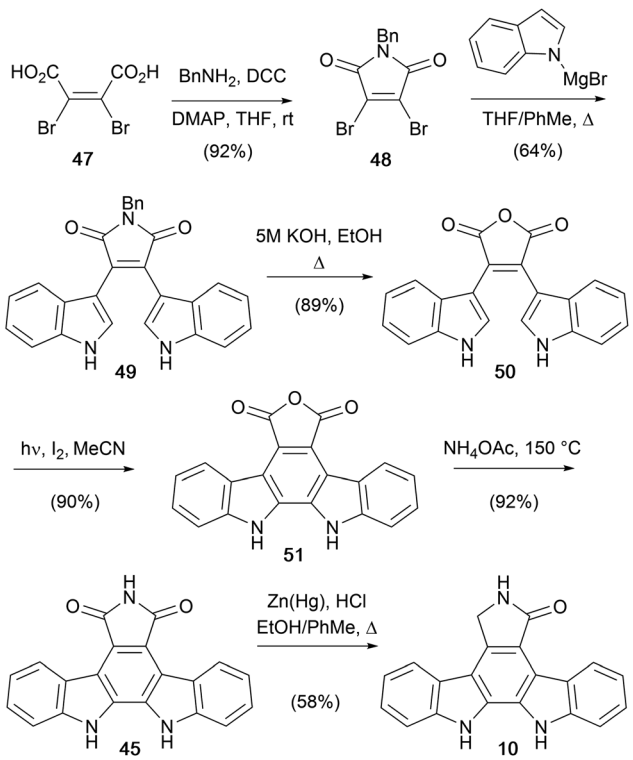
Lown and co-workers went on to disclose a further adaptation of the dibromomaleimide route in 1994, introducing an oxidative photocyclization step to form the pentacycle (Scheme 7).[43] *N*-Benzyl dibromomaleimide (**48**) was obtained from diacid **47**, under peptide coupling conditions. The issue of *N*-debenzylation that thwarted earlier efforts was resolved, albeit



Scheme 6 Hill and co-workers' synthesis of staurosporine aglycone (**10**).

indirectly, by conversion of the maleimide to anhydride **50** prior to oxidative photocyclisation to the indolocarbazole anhydride **51**.[44,45] **51** then delivered arcyriaflavin A (**45**) by aminolysis, and then Clemmensen reduction afforded aglycone **10**.

With a focus directed towards scaling up the synthesis of bisindolylmaleimide (**44**) to meet the need of PKC-β inhibition



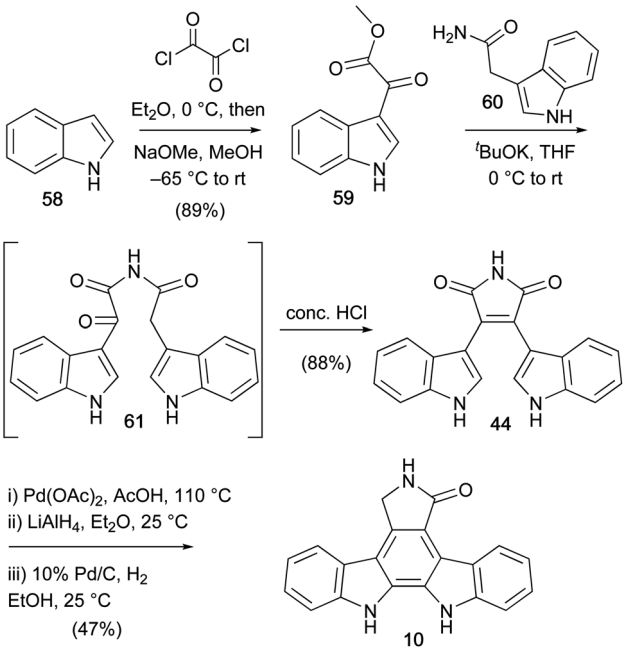
Scheme 7 Lown and co-workers' synthesis of the staurosporine aglycone (**10**).

studies,[46,47] Faul and co-workers reported optimisation of Hills's route substituting **35** with dichloromaleimide.[48] Using this concise and highly efficient 4 step approach, multi-gramme synthesis of staurosporine aglycone (**10**) was realised in 34% overall yield.

In 2000, Burtin and co-workers isolated 6-methylstaurosporinone utilising a similar approach to Faul and co-workers in 1993 (not shown).[49] The route began from dichloro-*N*-methylmaleimide and indolylmagnesium bromide and gave the 6-methylstaurosporinone in 36% yield over 4 steps.

During expansive studies into the indolocarbazole natural product family, in 1995 Wood and co-workers disclosed a novel synthesis of staurosporine aglycone (**10**), which was extended to a series of protected derivatives **38**, **57b–d** (Scheme 8).[50,51] The approach centred upon the addition of diazo-lactams **56a–e** to 2,2′-biindole (**53**), which was prepared by double-Madelung cyclisation of diamide **46**.[52] The diazotetramic acids were prepared using a 4 step protocol from the *N*-substituted glycine esters **54a–e**.[53,54] Amide coupling of the esters with ethyl hydrogen malonate followed by Dieckmann cyclisation gave lactams **55a–e**. The lactams were then subjected to a single pot decarboxylative diazo-transfer reaction to give diazotetramic acids **56a–e**. Finally, a novel diazo-addition of lactams **56a–e** into C3 of 2,2′-biindole (**53**) followed by a cycloaromatisation at elevated temperatures provided the staurosporine aglycone (**10**), and protected derivatives **38**, **57b–d**.

Faul and co-workers described their second approach to the staurosporine aglycone (**10**) in 1998 (Scheme 9).[55] The key step was the coupling to access amide **61** and ensuing Perkin-type condensation to bisindolylmaleimide (**44**). This was then subjected to the oxidative cyclisation, reduction, hydrogenation sequence described by Hill and co-workers to give staurosporine aglycone (**10**). This synthesis represents the highest yielding (36% over 5 steps) synthesis of the aglycone **10** to date, and became a popular approach to obtain bisindolylmaleimide and arcyriaflavin A analogues.



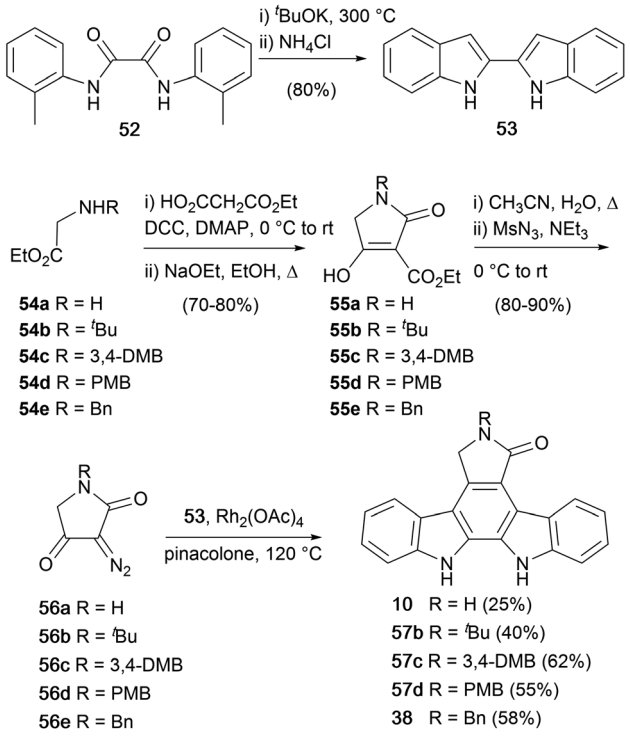
Scheme 9 Faul and co-workers' approach to the staurosporine aglycone (**10**).

In 1998, Beccalli and co-workers disclosed an original synthesis of staurosporine aglycone (**10**) from a readily accessible indole derivative **62** (Scheme 10).[56,57] Treatment with ethyl chloroformate gave the protected indole derivative **63** which was selectively deprotected to give enol **64**. This was converted to the corresponding vinyl triflate **65** and subsequent Stille coupling with stannane **66** secured bisindole **67**.[58–60] Deprotection of both indole moieties was followed by an oxidative photocyclisation to give indolocarbazole **69**. Finally, chemoselective reduction of the cyano group and annulation was achieved with $NaBH_4$–$CoCl_2$ to give the aglycone (**10**).

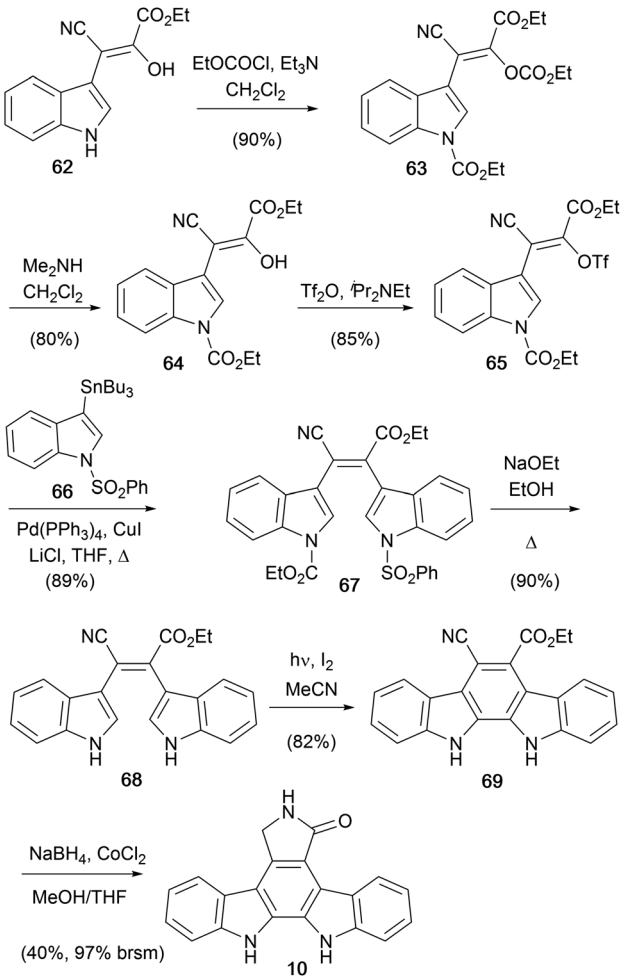
In 1999, Mahboobi and co-workers disclosed a concise approach to the staurosporine aglycone (**10**) utilising a Michael addition to nitro-olefin **70** (Scheme 11).[61–64] This key step provided nitrobutanoate **72** in a modest yield of 10%. Subsequent catalytic hydrogenation/lactamization furnished lactam **73** which was cyclised under oxidative conditions to the staurosporine aglycone (**10**).

Inverse electron-demand Diels–Alder cycloaddition–cycloreversion reactions were at the heart of Snyder and co-workers 2001 synthesis of protected aglycone derivative **82** (Scheme 12).[65] Diels–Alder cycloaddition–reversion of *N*-tosyl indole (**74**) and tetrazine **75** gave the electron deficient indole system **76**.[66–68]

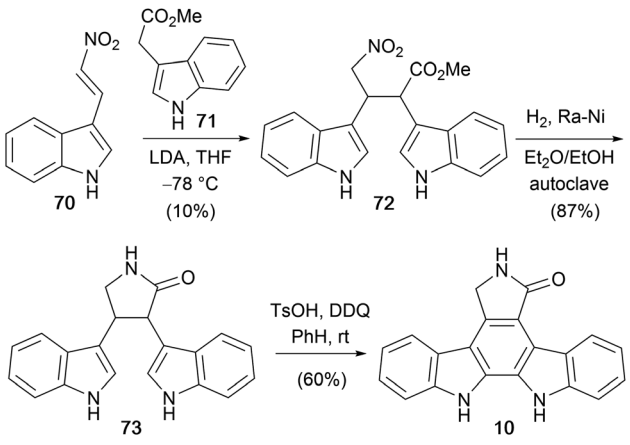
Introduction of the acetylenic dienophile **77** was achieved by regioselective amidation of the less encumbered and more



Scheme 8 Wood and co-workers' synthesis of staurosporine aglycone (**10**) and protected derivatives.

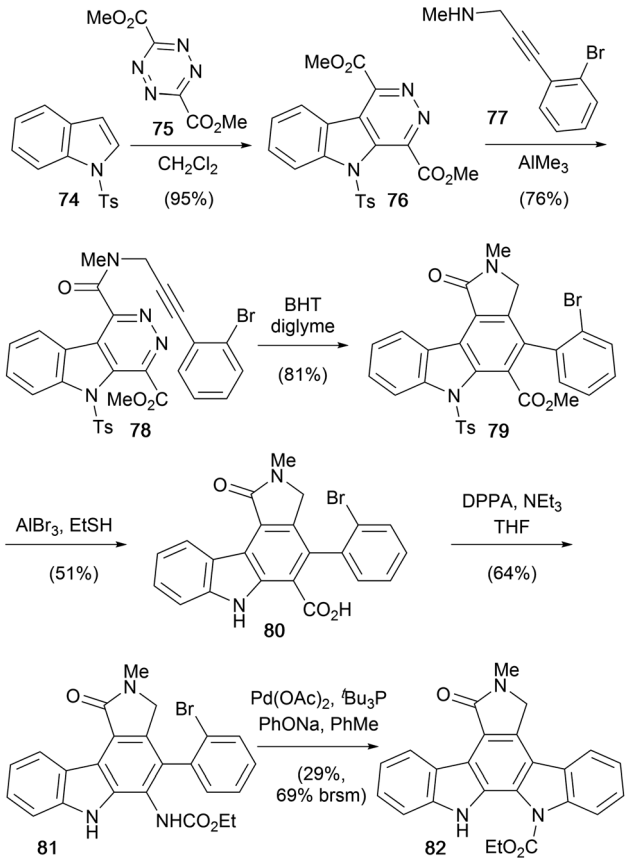


Scheme 10 Beccalli and co-workers' synthesis of the staurosporine aglycone (**10**).



Scheme 11 Mahboobi and co-workers' synthesis of the staurosporine aglycone (**10**).

electrophilic ester, promoted by $AlMe_3$, to give amide **78**.[69] Subsequent intramolecular annulation gave carbazole **79** and ensuing demethylation and carbazole deprotection secured



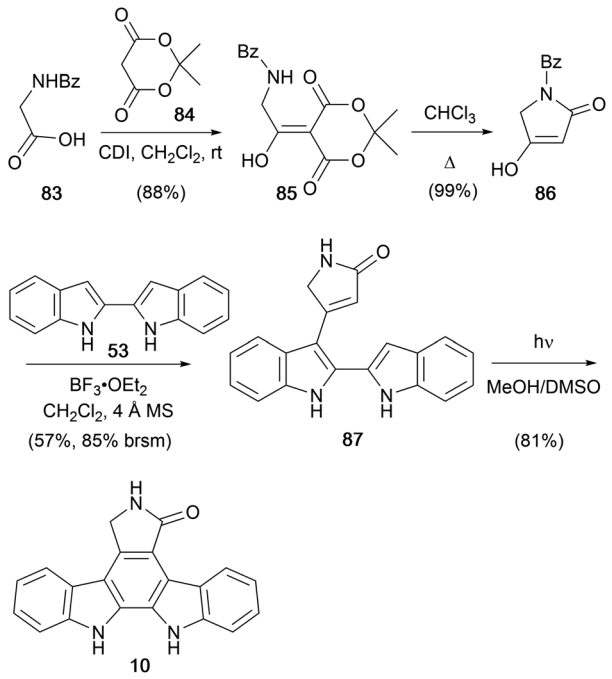
Scheme 12 Snyder and co-workers' synthesis of protected staurosporine aglycone **82**.

carboxylic acid **80**. Finally, Curtius rearrangement of acid **80** and Pd-catalysed amination realised protected aglycone **82**.[70]

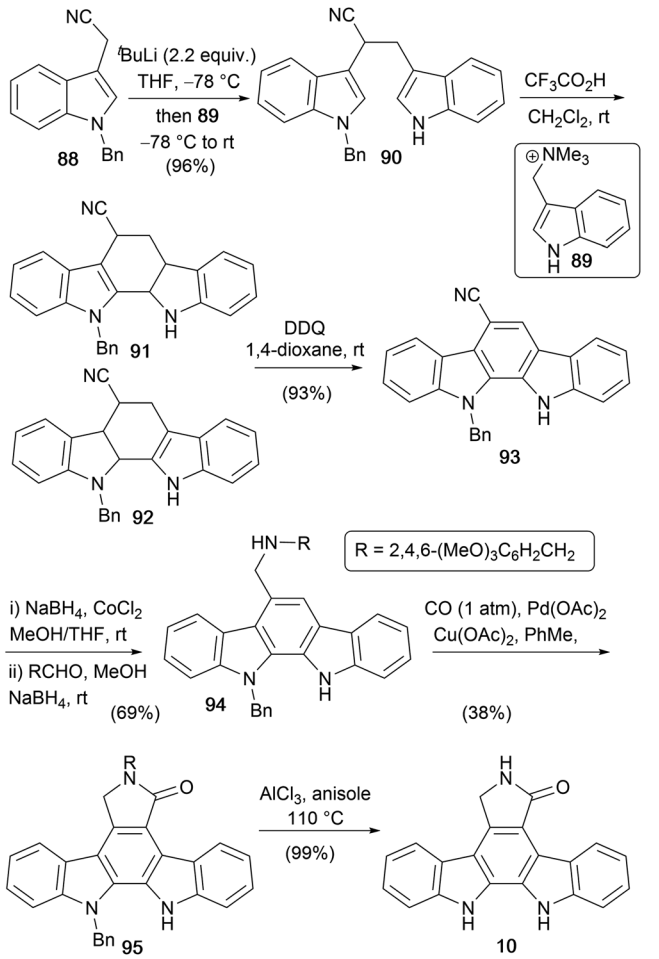
In 2003, Prabhakar and co-workers disclosed a short approach to staurosporine aglycone (**10**, Scheme 13).[71] Tetramic acid **86** was prepared in two-steps from hippuric acid (**83**) and Meldrum's acid (**84**) as described by Sandris.[72] 2,2′-Biindole (**53**) was prepared according to the procedure described by Bergman (see Scheme 8), and the two were coupled to give lactam **87**.[52] Oxidative photocyclisation of this intermediate yielded staurosporine aglycone (**10**). The group subsequently published a modified approach to protected derivatives.[73]

In the same year, Uang and co-workers reported optimisation of the photocyclisation of halogenated and methoxylated bisindolylmaleimide derivatives. Photocyclisation was performed in THF : MeCN (1 : 1) with catalytic I_2, and was applied to the synthesis of aglycone (**10**).[74] Electron-withdrawing groups were found to reduce irradiation times, however on multi-gram scale (5 g), 96 h of irradiation with two 400 W mercury lamps was required for full conversion of bisindolylmaleimide (**44**) to arcyriaflavin A (**45**).

In 2007, Orito and co-workers described a new route to aglycone **10** from 3-(*N*-benzylindolyl)acetonitrile (**88**, Scheme 14).[75] Coupling **88** with the carbocation precursor ammonium salt **89** gave bisindole **90**, which was subjected to acid-mediated cyclisation and subsequent DDQ oxidation to give



Scheme 13 Prabhakar and co-workers' synthesis of the staurosporine aglycone (**10**).



Scheme 14 Orito and co-workers' synthesis of the staurosporine aglycone (**10**).

indolocarbazole **93**.[76–79] The cyano group was reduced before a 2-step reductive alkylation with 2,4,6-trimethoxybenzaldehyde gave amine **94**.[80] This was subjected to Pd-catalysed carbonylation, before $AlCl_3$ deprotection of the two benzyl-type protecting groups gave staurosporine aglycone (**10**).

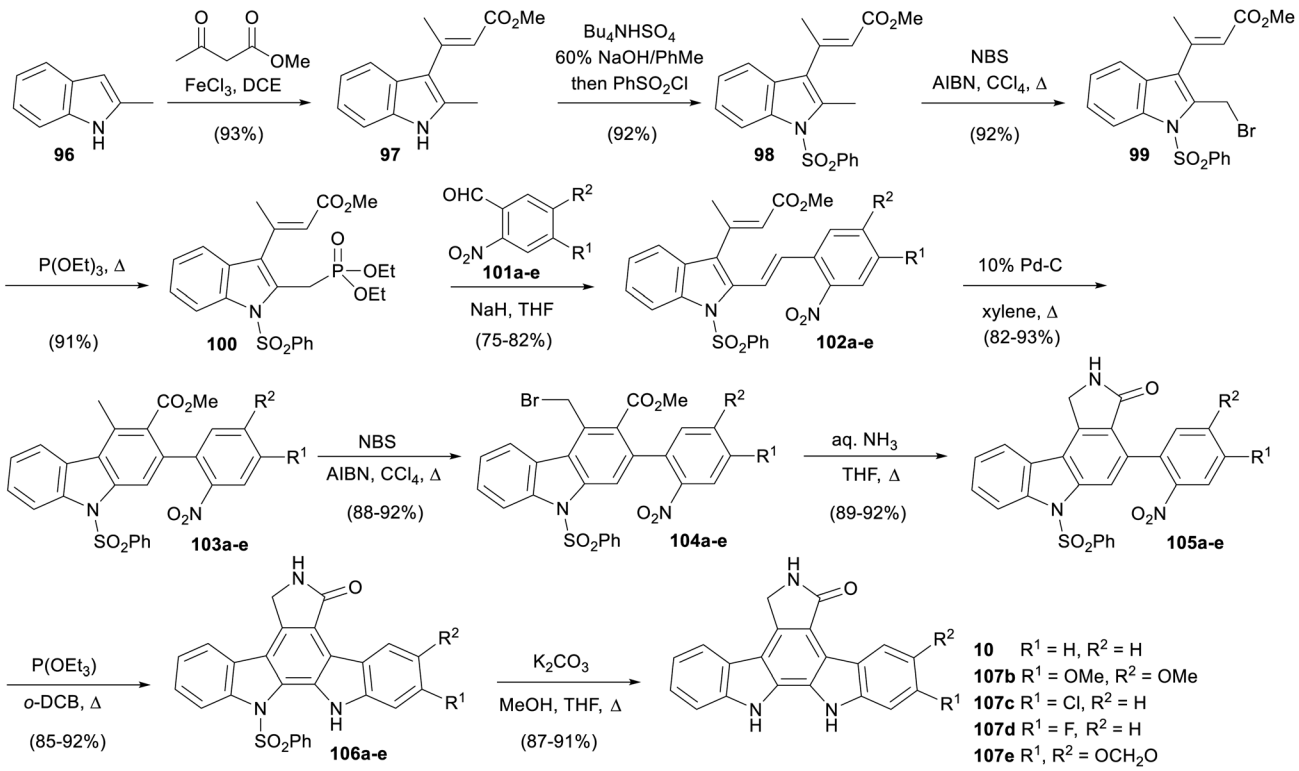
In 2011, Mohanakrishnan and co-workers published a route to various aglycone derivatives starting from 2-methylindole (**96**, Scheme 15).[81] Condensation of indole **96** with methyl acetoacetate gave vinylindole **97** then *N*-sulfonylation afforded protected indole **98**.[82] Benzylic bromination preceded the Michaelis–Arbuzov reaction with $P(OEt)_3$ to give phosphonate ester **100** upon workup. This was subjected to a Wittig–Horner reaction with a variety of 2-nitroarylaldehydes **101a–e** to give divinylindoles **102a–e**, which underwent electrocyclisation/aromatisation with Pd–C to afford carbazoles **103a–e**.[83] Benzylic bromination and subsequent reaction with aqueous ammonia gave lactams **105a–e**. Triethyl phosphite mediated nitrene insertion effected the final ring closure, before deprotection of the phenylsulfonyl group secured staurosporine aglycone (**10**), as well as derivatives **107b–e**. The same group subsequently reported extending the approach to synthesise a variety of aglycone analogues.[84]

An approach centred on strategic C–H functionalisations was published in 2016 by Gaunt and co-workers, which exploited the amine moiety in the central ring to direct four out of the seven key transformations (Scheme 16).[85]

Ortho-arylation of aniline **108** was followed by hydrogenolysis and carbamoylation to switch the directing nature of the group and give anilide **110**.[86,87] A subsequent *meta*-arylation followed by nitration gave the nitro-arene **111**, which underwent an oxidative cyclisation to carbazole **112**.[88] A one-pot radical bis-bromination, formylation and concomitant cleavage of the carbazole *N*-protection secured aldehyde **113**.[89] Reductive amination, and C–H carbonylation protocol gave γ-lactam **114**, which was subjected to Cadogan nitrene insertion then *N*-debenzylation to form staurosporine aglycone (**10**).

A recent synthesis of a staurosporine aglycone derivative was described by Pelkey and co-workers in 2016 (Scheme 17).[90] *N*-Methylindole-3-acetic acid (**115**) was coupled with amine **116** and the resulting amide cyclised to tetramic acid **118**.[71,91] Lewis-acid mediated arylation with *N*-methylindole gave lactam **119** which was cyclised to staurosporine aglycone derivative **120** using Scholl-type oxidative conditions.[92]

In 2018, Maji and co-workers described a route to the indolocarbazole core, leading to the synthesis of both staurosporine aglycone (**10**) and arcyriaflavin A (**45**, Scheme 18).[93] The route was designed around the Brønsted acid catalysed one-pot benzannulation of 2-alkenylindoles.[94–96] The first generation synthesis began by coupling diethyl 2-oxosuccinate (**121**) with alkenylindole **122** in the presence of phosphoric acid diphenyl ester before oxidation and Cadogan cyclisation all in one-pot gave the diester **123**.[32,97] This was hydrolysed before annulation with ammonium acetate gave arcyriaflavin A (**45**). Imide **45**



Scheme 15 Mohanakrishnan and co-workers' synthesis of staurosporine aglycone derivatives.

was reduced *via* a Clemmensen reduction as described previously by Raphael and co-workers (see Scheme 4).[28] In addition to this approach, the same group developed an alternate route from a similarly derived carbazole **124**.[93] Phenylsulfonyl protection of the indole *N*–H gave the intermediate carbazole **125**, which was converted to staurosporine aglycone (**10**) using the benzylic bromination/lactamization/Cadogan cyclisation/hydrolysis process reported by Mohanakrishnan and co-workers.[81]

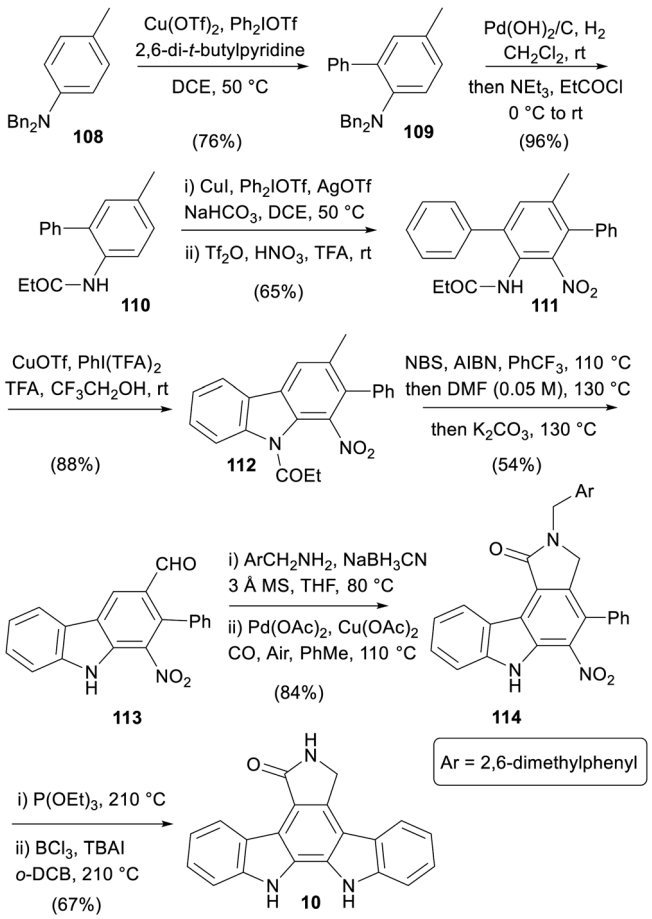
The most recent synthesis of staurosporine aglycone (**9**) was disclosed by Pabbaraja and co-workers in 2019 (Scheme 19).[98] The synthesis began with addition of phenyl acetylene to aldehyde **126** before oxidation to ynone **127**. This then underwent the key cascade upon treatment with ethyl nitroacetate to give carbazole **128**.[99] This was proposed to occur *via* initial Michael-addition and subsequent intramolecular aldol-type addition to a strained cyclobutene intermediate. A retro-nitroaldol followed by generation of an indolic iminium ion led to the final C–C bond formation with concomitant aromatisation to give the key carbazole core **128**. Formation of the triflate was followed by Negishi-coupling to give cyanated nitrocarbazole **129**.[100,101] Cadogan cyclisation was followed by reduction to the protected aglycone **131**, which was debenzylated using $AlCl_3$ to give staurosporine aglycone (**10**).

2.2 Arcyriaflavin A (45)

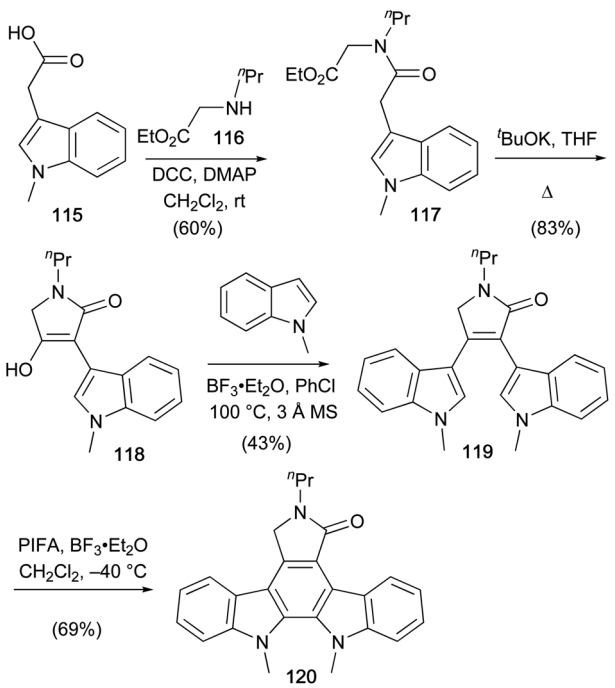
Another sub-family of indolocarbazole natural products that don't bear any indolic nitrogen functionalisation are the arcyriaflavins. Molecularly similar to the staurosporine aglycone (**10**), these feature a distinctive maleimide moiety fused to the indolocarbazole core. The first of these natural products isolated were arcyriaflavin's A–C by Steglich and co-workers from the *Arcyria nutans* and *Arcyria denudata* slime moulds.[35,102–104] Arcyriaflavin D was isolated from a separate slime mould *Dictydiaethalium plumbeum*, whilst arcyriaflavin E was isolated years later from bacterium *Streptomyces cinnamoneus* NBRC 13823 by Abe and co-workers (Fig. 4).[105] Interest in these natural products, as with other indolocarbazoles, stems from their moderate antibiotic and antifungal properties.[35]

Due to the decreased molecular complexity relative to many other indolocarbazole natural products, there has been a plethora of synthetic approaches to this sub-group. In particular, many groups have utilised arcyriaflavin intermediates, particularly arcyriaflavin A (**45**), in the synthesis of more complex indolocarbazoles. These syntheses are covered elsewhere in this review.

The first synthesis of an arcyriaflavin A derivative was reported by Bergman and co-workers in 1987 (Scheme 20).[106] The key step in their approach was oxidative coupling of the methyl indol-3-ylacetate dianon to give diester **136** as a mixture of *dl* and *meso* forms, which were easily separated by crystallisation and chromatography.[107–109] Their initial approach was centred on formation of the indol-3-ylacetate trianion utilising similar chemistry, however it proved more fruitful to proceed *via* the dianion. The diester **136** was then subjected to imidation with benzylamine before an oxidative cyclisation gave *N*-benzyl protected arcyriaflavin A **37**.



Scheme 16 Gaunt and co-workers' synthesis of the staurosporine aglycone (**10**).

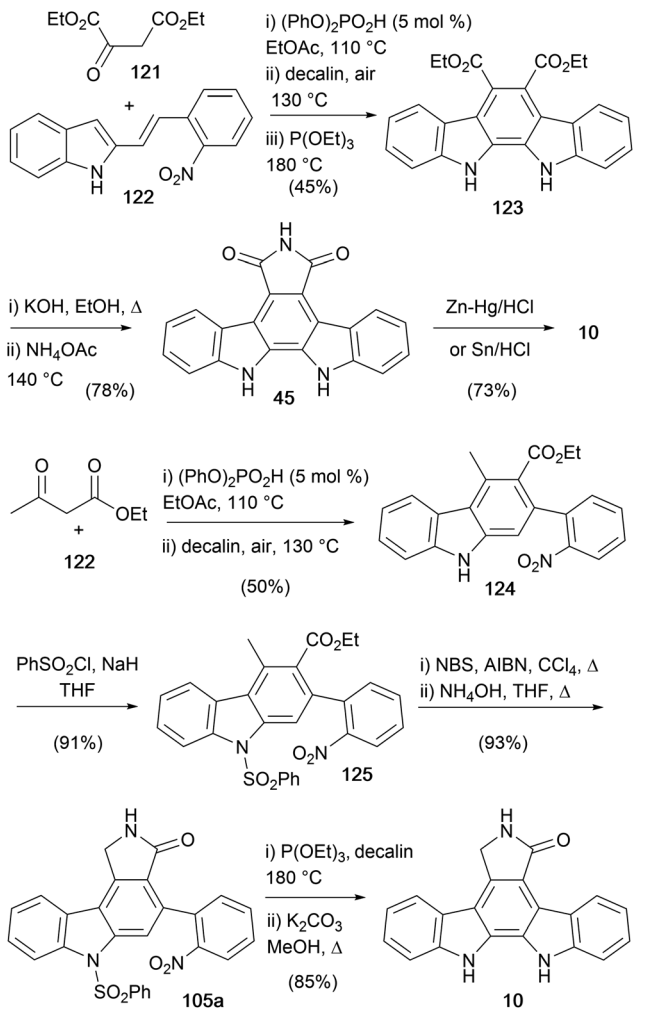


Scheme 17 Pelkey and co-workers' synthesis of the protected aglycone **120**.

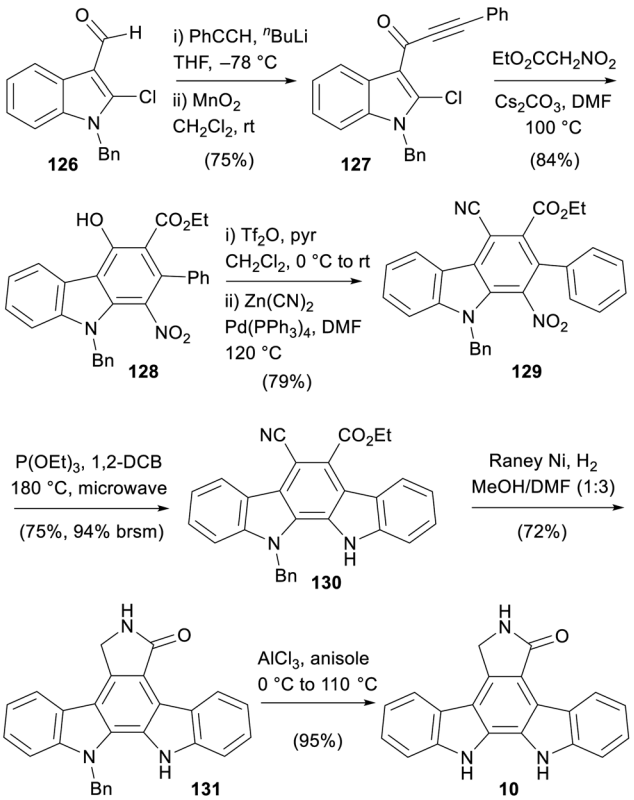
In 1989, the same group developed an alternate route to a variety of arcyriaflavin derivatives, including arcyriaflavin A (**45**, Scheme 21).[110] The approach began with a Diels–Alder cycloaddition between maleimide and butadiene **138** to access olefin **139**. Condensation of the olefin **139** with 3 equiv. of phenylhydrazine gave bis(phenylhydrazone) **140**. This was subjected to the key double Fischer indolisation using polyphosphoric acid trimethylsilyl ester (PPSE)[111,112] before dehydrogenation of the crude mixture gave arcyriaflavin A (**45**).

In 1992, Gribble and co-workers described a related approach to *N*-methylarcyriaflavin A (**147**), again utilising a Diels–Alder cycloaddition between diene **138** and *N*-methylmaleimide (not shown).[113] Oxidation of the derived olefin with *m*-CPBA was followed by condensation with phenylhydrazine and the Fisher indolisation/dehydrogenation protocol as previously described by Bergman to access *N*-methylarcyriaflavin A (**147**).[114]

The same group developed an alternate approach starting from the commercially available cyclohexenes **141** and **142** (Scheme 22).[113] The synthesis began with ozonolysis to give 1,6-dialdehydes **143** and **144**, which were immediately condensed *in*



Scheme 18 Maji and co-workers' syntheses of the staurosporine aglycone (**10**).



Scheme 19 Pabbaraja and co-workers' synthesis of the staurosporine aglycone (**10**).

situ with phenylhydrazine to afford the hydrazones **145** and **146** respectively. Due to instability and decomposition on attempted purification, these hydrazones were treated with PPSE without delay, giving direct access to arcyriaflavin A (**45**) and *N*-methylarcyriaflavin A (**147**).[78] Although yields reported are modest, they represent a 3-step synthesis from commercial compounds without purification of intermediates.

A short synthesis of *N*-phenylarcyriaflavin A (**150**) was published by Somei and co-workers in 1992 (Scheme 23).[115] *Ortho*-

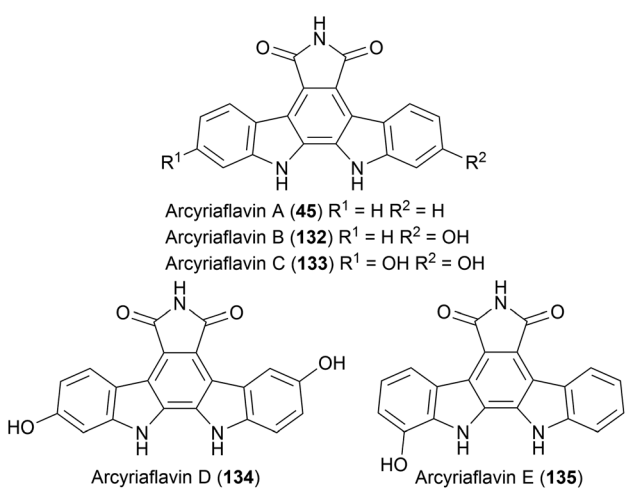
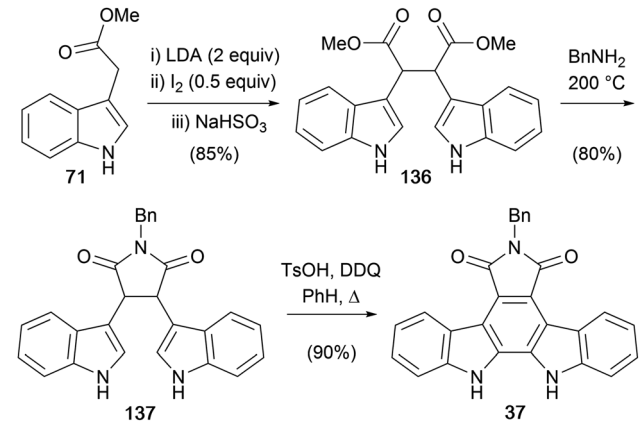
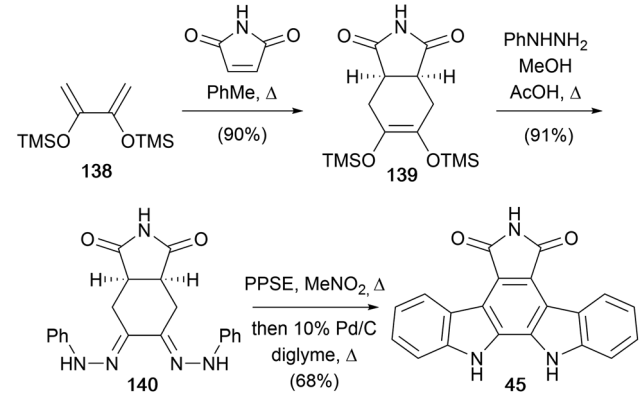


Fig. 4 The structures of arcyriaflavins A–E.

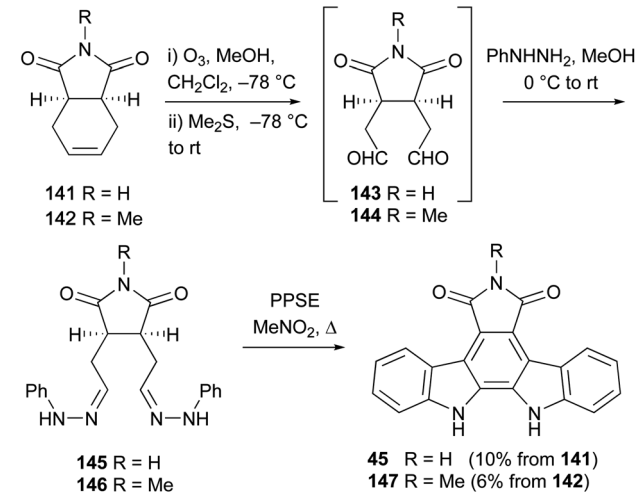


Scheme 20 Bergman and co-workers' synthesis of the arcyriaflavin A derivative **37**.

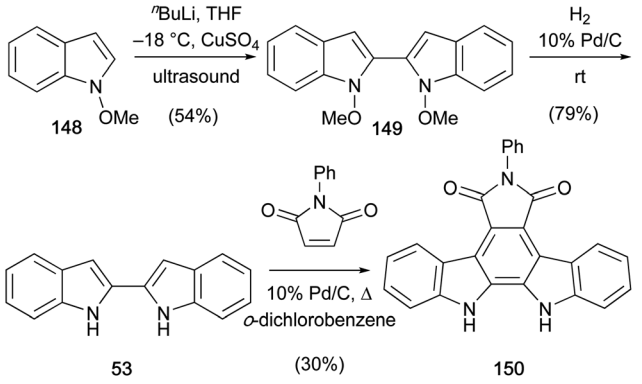


Scheme 21 Bergman and co-workers' synthesis of arcyriaflavin (**45**).

lithiation of *N*-methoxyindole (**148**) followed by copper-mediated oxidative coupling under ultrasonic irradiation gave biindole **149**. Hydrogenolysis of N–O bonds gave 2,2′-biindole (**53**) which underwent the final Diels–Alder cycloaddition–



Scheme 22 Gribble and co-workers' synthesis of arcyriaflavin A (**45**).



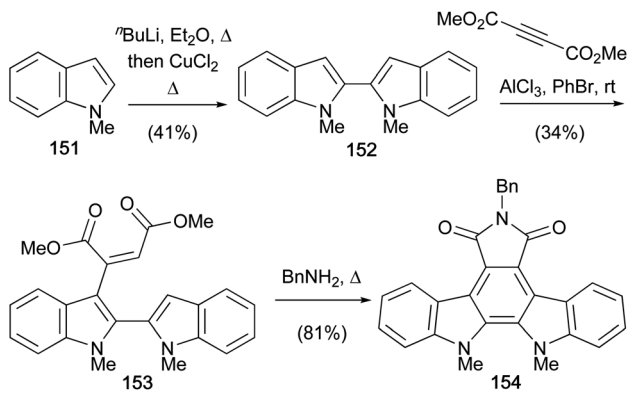
Scheme 23 Somei and co-workers' synthesis of *N*-phenylarcyriaflavin A (**150**).

dehydrogenation with *N*-phenylmaleimide in the presence of a catalytic 10% Pd/C to afford *N*-phenylarcyriaflavin A (**150**).

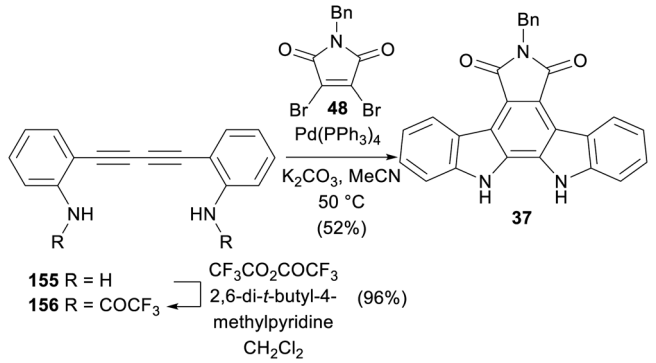
Wallace and co-workers later improved the yield of the cycloaddition step to 58% using diethyl oxalate as solvent (not shown).[116] In addition to this, *N*-methylmaleimide was also coupled with the 2,2′-biindole (**53**) to give *N*-methylarcyriaflavin A (**147**).

Somei and co-workers published alternative routes to protected derivatives of arcyriaflavin A (**45**) and staurosporine aglycone (**10**) later in 1995 and 2002 (not shown).[117,118] The routes again proceed *via* 2,2′-biindole (**53**), with a Diels–Alder cycloaddition reaction with dimethyl acetylenedicarboxylate or *N*-phenylmaleimide and dehydrogenation used to form the central indolocarbazole core.

The oxidative coupling of indolyl anions using copper(II) salts was further explored by Pindur and co-workers, publishing a synthesis of *N*-benzylarcyriaflavin A derivative (**154**) in 1995 (Scheme 24).[119] Lithiation of *N*-methylindole (**151**) followed by oxidative coupling gave the biindole **152**.[120] Interestingly, the 1,4-adduct **153** resulted from Lewis-acid treatment of biindole **152** and dimethyl acetylenedicarboxylate. Thermolysis in $BnNH_2$ effected 6π-annulation, imidation and aromatisation together in one pot, securing arcyriaflavin A derivative **154**.[8]



Scheme 24 Pindur and co-workers' synthesis of arcyriaflavin A derivative **154**.

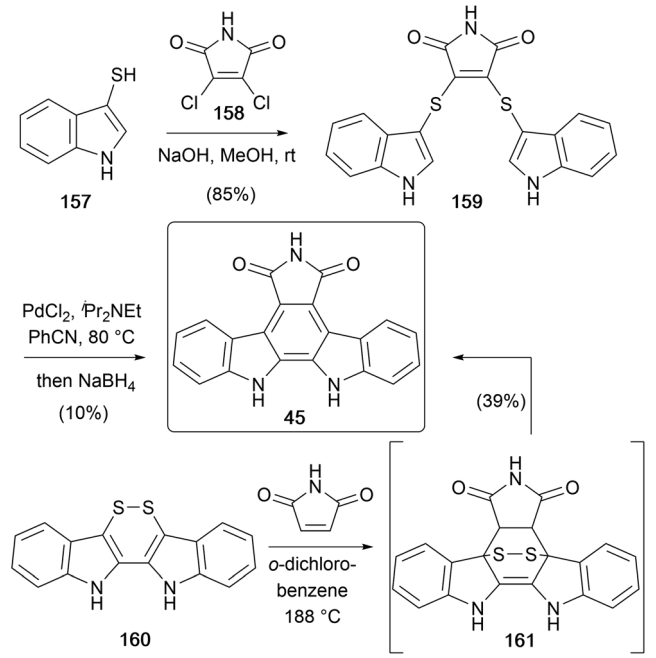


Scheme 25 Saulnier and co-workers' synthesis of *N*-benzylarcyriaflavin A (**37**).

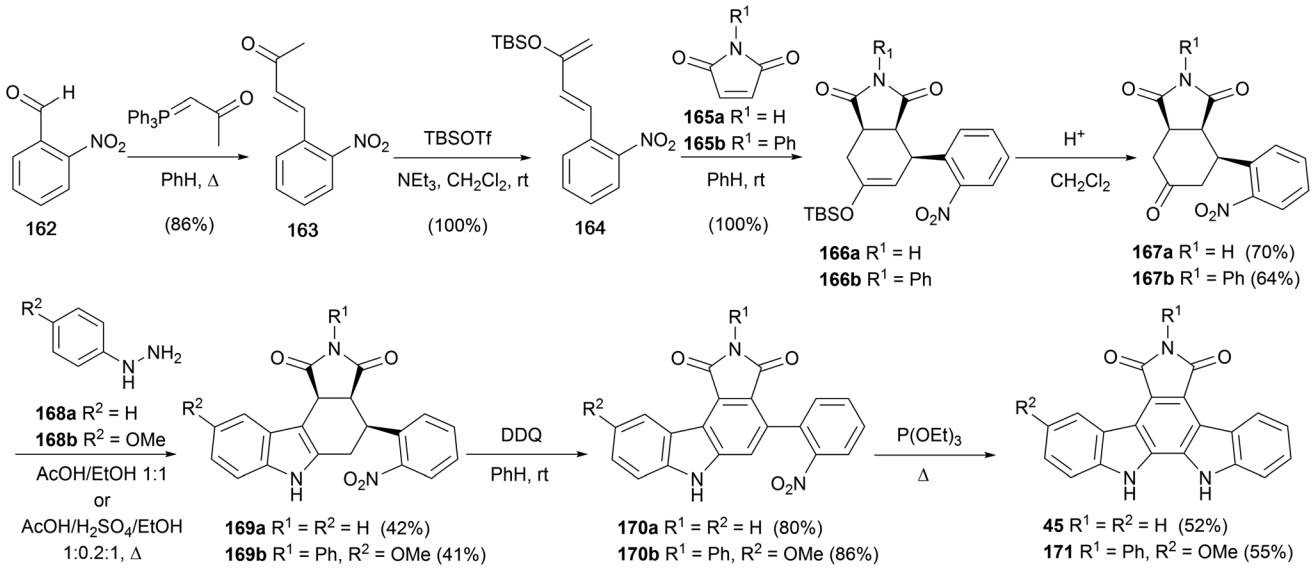
A Pd(0) catalysed reaction of diyne **156** and dibromomaleimide **48** was reported by Saulnier and co-workers in 1995 (Scheme 25),[121] affording *N*-benzylarcyriaflavin A (**37**). After bis-trifluoroacetylation of the known diamine **155**,[122,123] a remarkable polyannulation cascade ensued to realise *N*-benzylarcyriaflavin A (**37**) in 52% yield.

In 1995, Lobo disclosed a novel approach to arcyriaflavin A (**52**) utilising a sulphur-extrusion strategy (Scheme 26).[124] Coupling of readily accessible thiol **157** and dichloromaleimide (**158**) gave bis-sulphide **159**, which when treated with $PdCl_2$ and Hünig's base at elevated temperatures, followed by reductive workup afforded arcyriaflavin A (**45**).[125] The mechanism proposed by the group involved formation of the C_2–$C_{2'}$ bond *via* an organopalladium intermediate, an intramolecular Diels–Alder followed by sulphur extrusion.

The same group developed a modified approach a few years later,[126] this time from disulphide **160**.[127] Diels–Alder



Scheme 26 Lobo and co-workers' syntheses of arcyriaflavin A (**45**).



Scheme 27 Tomé and co-workers' synthesis of arcyriaflavin A (**45**).

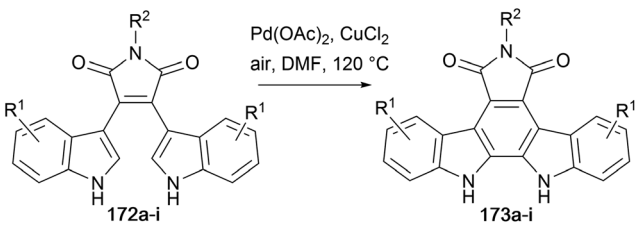
cycloaddition with maleimide gave arcyriaflavin A (**45**) directly in 39% yield (Scheme 26). They propose the reaction proceeds *via* the [4+2] adduct **161**, which then undergoes a retro-Diels–Alder and oxidation, likely from the extruded S_2 or dissolved O_2.[128]

In 2000, Tomé and co-workers reported a hybrid approach to arcyriaflavin A (**45**), wherein classical Fischer synthesis and Cadogan nitrene insertion were applied to indole ring constructions (Scheme 27).[129] From commercial 2-nitrobenzaldehyde (**162**), Wittig olefination gave ketone **163**, which was converted to the diene **164** upon treatment with TBSOTf/NEt_3. Diels–Alder cycloaddition reaction with maleimides **165a** or **165b** gave the *endo*-cycloadducts **166a/b**, which were deprotected to give ketones **167a/b.**[130] These intermediates were subjected to Fischer indole conditions with hydrazines**168a/b** to give indoles **169a/b** in moderate yield. The corresponding carbazoles were obtained by DDQ oxidation before a final Cadogan cyclisation gave arcyriaflavin A (**45**) and analogue **171**.

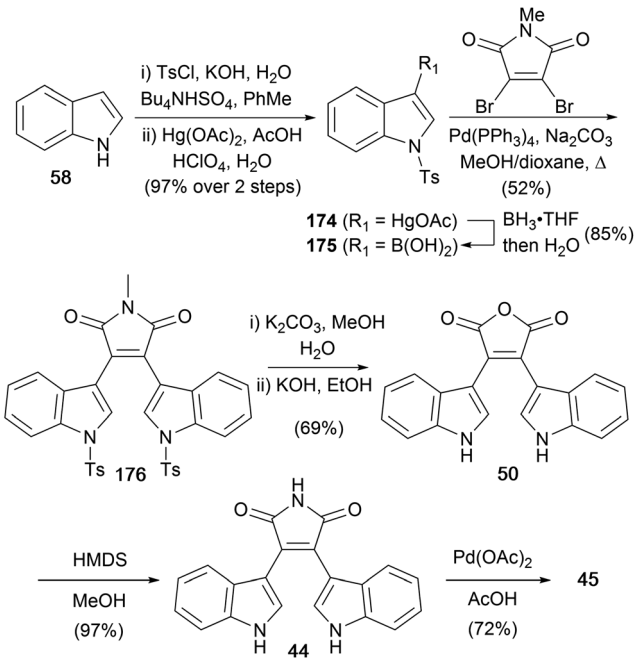
Liu and co-workers adapted the Pd-catalysed oxidative cyclisation approach to produce a range of arcyriaflavin derivatives **173a–i** (Table 1).[131–134] Bisindolylmaleimide derivatives **172a–i** were isolated as previously described from the appropriately substituted indolylmagnesium bromide with *N*-substituted 3,4-dihalomaleimides.[48] This methodology was further developed by Liu and co-workers, using $Pd(TFA)_2$ and $Cu(OAc)_2$, accessing further arcyriaflavin analogues.[135]

The same group developed a synthesis of arcyriaflavin A (**45**) using Suzuki coupling of 3-indolylboronic acid (**175**) with *N*-

Table 1 Liu and co-workers' synthesis of arcyriaflavin derivatives **173a–i** (2001)



Entry	Product	R^1; R^1	R^2	*T* (°C)	Time (h)	Yield (%)
1	**173a**	1-Cl; 11-Cl	*p*-^{t}Bu–Bn	120	12	88
2	**173b**	3-F; 9-F	*p*-^{t}Bu–Bn	120	16	81
3	**173c**	3-Br; 9-Br	*p*-^{t}Bu–Bn	120	10	74
4	**173d**	3-F; 9-F	H	120	8	78
5	**173e**	2-F, 3-F; 9-F, 10-F	*p*-^{t}Bu–Bn	120	16	82
6	**173f**	3-OMe; 9-OMe	*p*-^{t}Bu–Bn	90	4	86
7	**173g**	H; H	*p*-^{t}Bu–Bn	90	8	79
8	**173h**	3-F; 9-F	^{t}Bu	90	6	62
9	**173i**	3-F; 9-F	DMB	90	5	58

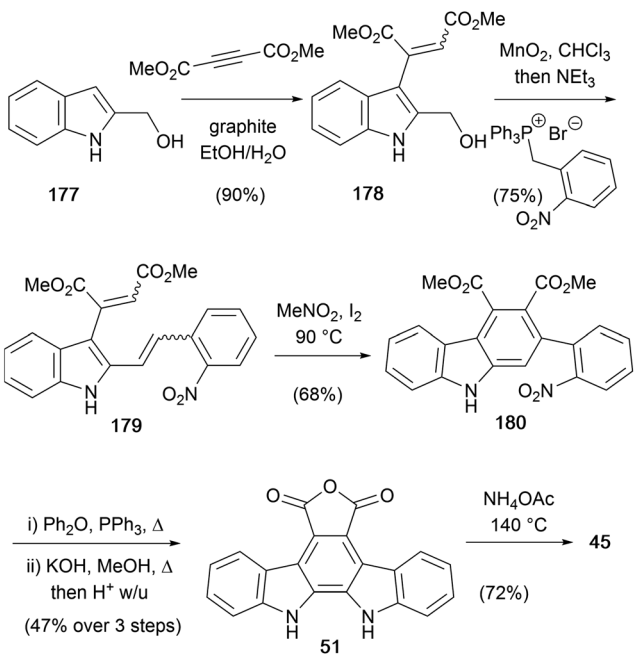


Scheme 28 Liu and co-workers' synthesis of arcyriaflavin A (**45**).

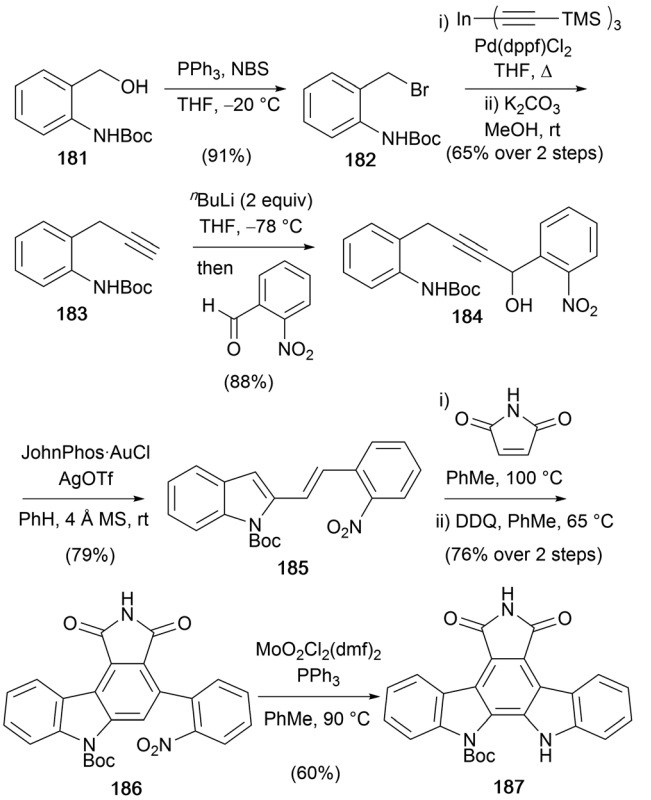
methyldibromomaleimide (Scheme 28),[136] rather than the well-established addition–elimination (*e.g.* see Scheme 4). Synthesis of the boronic acid proceeded *via* an organomercury intermediate **174**, by borylation with $BH_3 \cdot THF$ and aqueous work-up. Suzuki cross-coupling and hydrolysis of the tosyl groups gave bisindolylmaleimide **176**. Formation of the free maleimide required the usual hydrolysis to anhydride **50**,[137] followed by re-imidation with HMDS to obtain bisindolylmaleimide (**44**). Finally, cyclisation in presence of a Pd(II)-catalyst provided arcyriaflavin A (**45**).[42]

Starting from 1*H*-indole-2-methanol (**177**), Tilve and co-workers synthesised arcyriaflavin A (**45**),[138] incorporating a curious graphite-promoted 1,4-addition to dimethyl acetylenedicarboxylate (Scheme 29). The resulting mixture of isomeric alkene adducts **178** (*E* : *Z*, 88 : 12) was subjected to one pot oxidation with MnO_2 followed by a Wittig olefination to afford a mixture of four stereoisomeric trienes **179**. Electrocyclisation of the mixture gave nitro-phenyl substituted carbazole **180**, which was subjected to Cadogan cyclisation followed by hydrolysis to afford anhydride **51**.[32,139] Arcyriaflavin A (**45**) was finally secured in 72% yield through treatment of **51** with NH_4OAc.

A gold-catalysed indolisation was applied by Aponick and co-workers in their synthesis of protected arcyriaflavin A **187** (Scheme 30).[140,141] The key intermediate **184** for the Au-catalysed diene formation was prepared from Boc-protected 2-aminobenzyl alcohol **181** over four steps.[142] Conversion of **181** to the terminal alkyne **183** was achieved *via* bromination, Pd-catalysed cross-coupling with tris(trimethylsilylacetylene)–indium and deprotection of the TMS group.[143] Addition of the dianion prepared from alkyne **183** to 2-nitrobenzaldehyde gave alkyne **184**, which was set-up for the Au-catalysed dehydrative cyclisation reaction to secure 2-vinylindole **185**. Subsequent Diels–Alder cycloaddition with maleimide and oxidation gave carbazole **186**, which was converted to protected arcyriaflavin A (**187**)



Scheme 29 Tilve and co-workers' synthesis of arcyriaflavin A (**45**).



Scheme 30 Aponick and co-workers' synthesis of protected arcyriaflavin A (**187**).

using a Mo-variant of the Cadogan cyclisation, which allowed cyclisation at a lower temperature.[144,145]

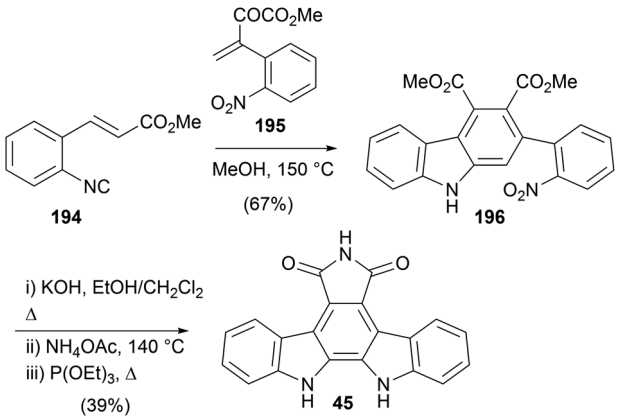
A synthesis of arcyriaflavin A (**45**) was detailed by Cheon and co-workers in 2017 (Scheme 31).[146] The synthesis began by accessing 2,2′-biindole **190** *via* an imino-Stetter approach from 1-benzyl-1*H*-indole-2-carbaldehyde (**188**).[147,148] Protection of the free indolic nitrogen with BnBr gave biindole **191**. Reaction with ethyl glyoxylate followed by oxidation of the resulting alcohol gave diester **192**. Treatment with ^{t}BuOK was immediately followed by hydrolysis and maleimide formation to afford protected arcyriaflavin A derivative **193**. Finally, Lewis-acid cleavage of the benzyl groups delivered arcyriaflavin A (**45**).

The most recently disclosed synthesis of arcyriaflavin A (**45**) was by Tang and co-workers in 2018 (Scheme 32),[149] applying a formal [1+2+3] annulation of alkenyl aryisocyanides and α,β-unsaturated ketones to the synthesis of the carbazole system. 3-(2-Nitrophenol)-2-oxobut-3-enoate (**195**), prepared according to known procedures, underwent formal [1+2+3] annulation reaction with aryisocyanide **194** to give diester **196**. The well-established imide formation and Cadogan cyclisation ultimately secured arcyriaflavin A (**45**).

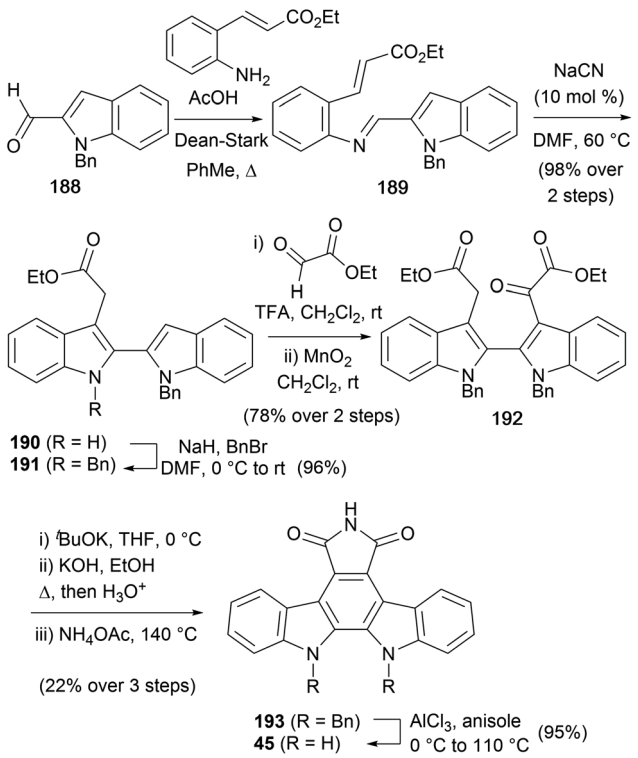
2.3 Arcyriaflavins B–D

As part of their pioneering work on indolocarbazole natural products Raphael and co-workers reported a synthesis of arcyriaflavin B in 1983 (Scheme 33).[27] The synthesis was similar to their approach to the staurosporine aglycone (**10**), and began with Wittig olefination of aldehyde **18** with ylide **197** before iodine-mediated *cis–trans* isomerism gave diene **198**. Diels–Alder cycloaddition with maleimide and DDQ oxidation secured dinitro derivative **199**, which afforded arcyriaflavin B (**132**) after Cadogan cyclisation and demethylation of indolocarbazole **200**.

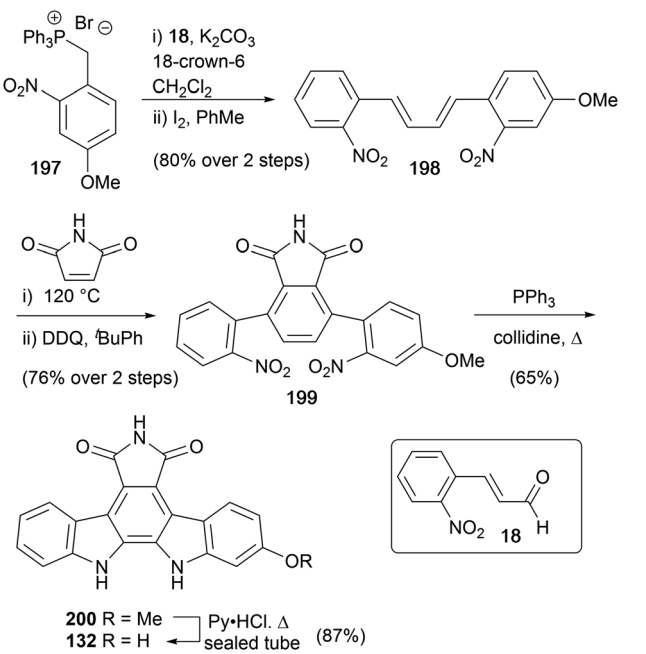
Ohkubo and co-workers described a synthetic approach to arcyriaflavins B (**132**), C (**133**) and D (**134**) that exploited sequential substitutions of 2,3-dibromo-*N*-methylmaleimide (**201**) with indolyl nucleophiles (Scheme 34).[150] Substituted indoles **58**, **202** and **205**, prepared from the corresponding nitrophenols,[151] were lithiated and selectively coupled following a modification of Steglich and co-workers procedure yielding unsymmetrically substituted bisindolylmaleimides **206a–c**.[35] Cleavage of the Boc group preceded cyclisation and oxidation to indolocarbazoles **208a–c**, which were converted to arcyriaflavins B (**132**), C (**133**) and D (**134**) utilising the protocol described by Lown and co-workers.[43]



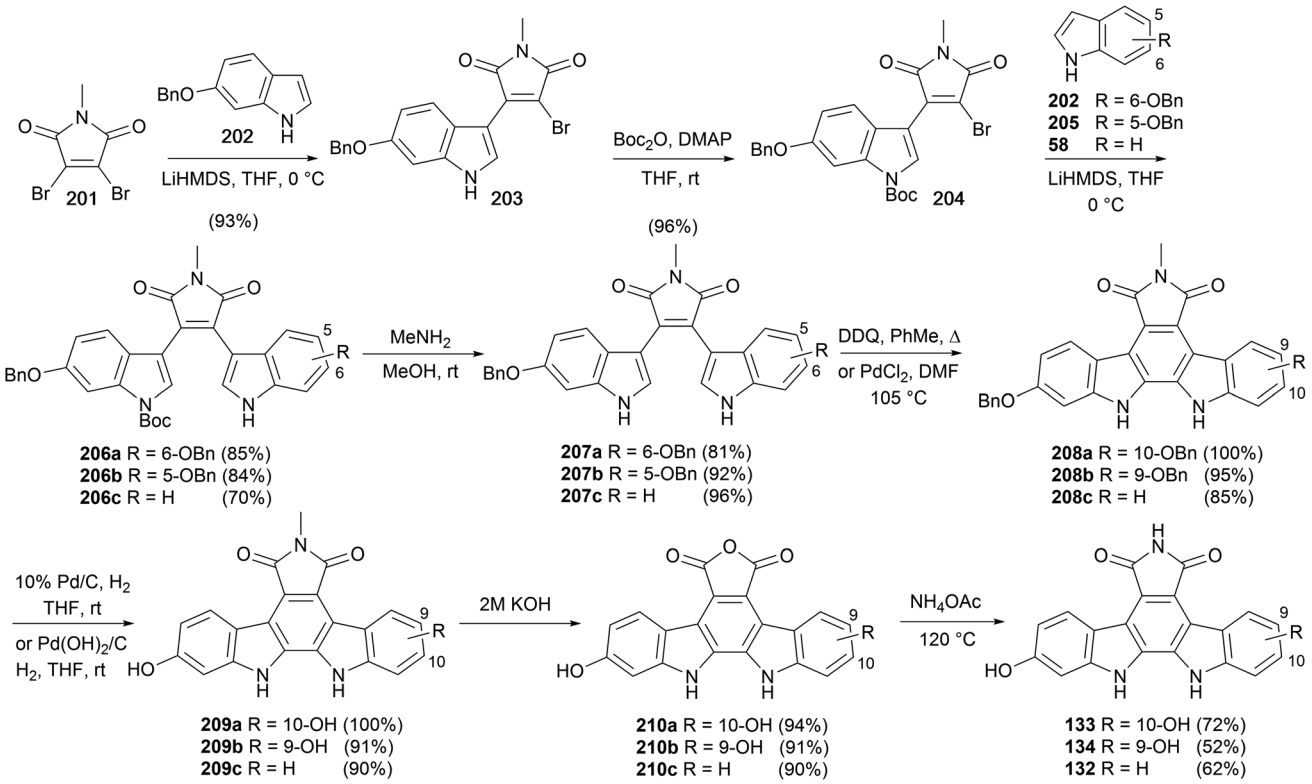
Scheme 32 Tang and co-workers' synthesis of arcyriaflavin A (**45**).



Scheme 31 Cheon and co-workers' synthesis of arcyriaflavin A (**45**).



Scheme 33 Raphael and co-workers' synthesis of arcyriaflavin B (**132**).



Scheme 34 Ohkubo and co-workers' synthesis of arcyriaflavin B (**132**), C (**133**) and D (**134**).

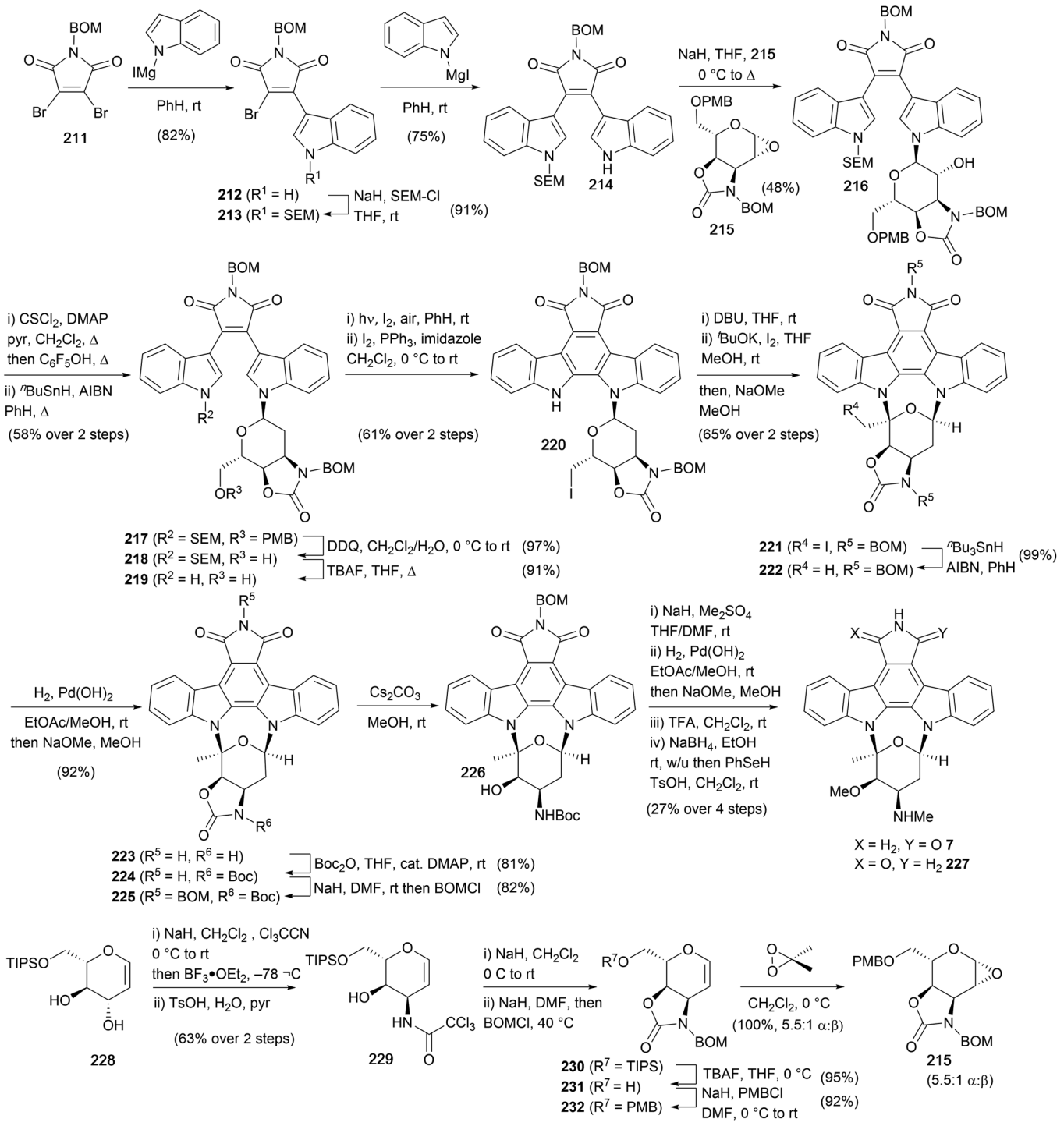
3 Pyranosylated indolocarbazoles

3.1 Staurosporine (7)

Due to its position as one of the most potent PKC inhibitors to date, staurosporine has been an important lead compound in the discovery of viable pharmaceutical derivatives. One such example is midostaurin, which was approved in 2017 by the FDA for the treatment of acute myeloid leukaemia.[152] However, despite impressive biological activity, there have only been two total syntheses of staurosporine (7) to date.

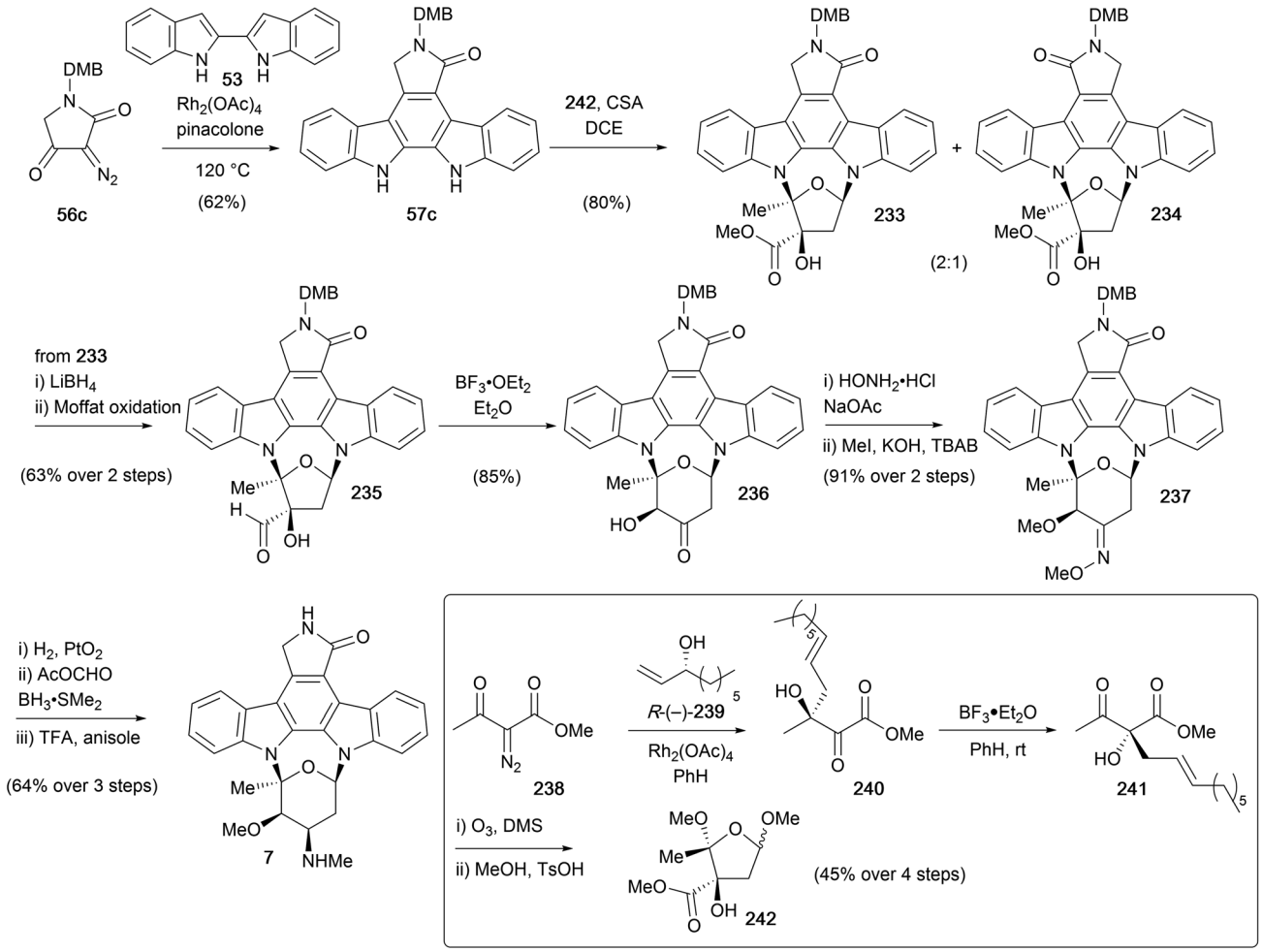
Danishefsky and co-workers completed the first total synthesis of 7 starting from BOM-protected maleimide **211** (Scheme 35).[153–157] Sequential addition of the magnesiated indoles provided access to bisindolylmaleimide **214** with orthogonal protection of nitrogens. The pyranose fragment **215** was prepared in 7 steps from L-glucal derivative **228**, first forming the corresponding bis-(trichloroacetimidate) followed by *N*-cyclisation onto the allylic trichloroacetimidate and hydrolysis of the obtained oxazoline gave trichloroacetamide **229**. Oxazolidinone annulation and protecting group manipulations, before final epoxidation with DMDO gave a 5.5 : 1 mixture of α and β epoxides (major **215**), setting the stage for indole glycosylation. The mixture of epoxides was treated with the sodiated indole **214**, providing alcohol **216**, which was deoxygenated under Barton conditions to give bisindolylmaleimide **217**. Removal of PMB and SEM protecting groups afforded primary alcohol **219**, which underwent an oxidative photocyclisation and conversion of the primary alcohol to the iodide with molecular iodine secured arcyriaflavin A derivative **220**. The staurosporine framework was established in **221** by elimination of HI from **220** and iodocyclisation of the resulting exocyclic enol ether. From **221** radical deiodination, hydrogenolysis of both BOM groups, selective oxazolidinone protection (Boc), reinstallation of the maleimide BOM protection, and final treatment with Cs_2CO_3 in MeOH returned alcohol **226**. Methylation of the amino and hydroxyl residues was followed by BOM deprotection and maleimide reduction without regiocontrol, realising a 1 : 1 mixture of staurosporine (7) and isostaurosporine (**227**).

A subsequent synthesis of staurosporine (7), was reported in 1996 by Wood and co-workers (Scheme 36).[50,51,158] Their approach encompassed syntheses of several indolocarbazole natural products, with initial focus on coupling a furanose fragment to access K252a (**9**, see Section 4.1), with ring expansion giving access to staurosporine. The protected aglycone **57c** was prepared from biindole **53** using a Rh-catalysed coupling–rearrangement–elimination sequence. The furanose fragment **242** was obtained in short order from diazoester **238**, commencing with Rh-catalysed O–H insertion into secondary alcohol *R*-(−)-**239** and ensuing [3,3]-sigmatropic rearrangement providing alcohol **240**. Exposure of the α-ketol **240** to $BF_3 \cdot Et_2O$ resulted in diastereoselective [1,2]-migration to afford β-ketoester **241**. Ozonolysis of the alkene and acid-mediated cyclisation delivered furanose **242**, which underwent an acid-catalysed double-glycosidation of DMB-protected staurosporine aglycone **57c** in the presence of CSA to give a 2 : 1



Scheme 35 Danishefsky and co-workers' synthesis of staurosporine (7) (1993).

mixture of regioisomers **233** and **234**. Interestingly, a mixture containing two regioisomeric pairs of open chain monoamino acetal diastereoisomers was initially observed, which upon prolonged heating induced cycloglycosylation, converging on two of the four possible isomers, **233** and **234**. After separation of the desired major isomer **233**, ester reduction and reoxidation gave aldehyde **235**. Which upon treatment with $BF_3 \cdot Et_2O$, underwent another α-ketol rearrangement/ring-expansion to afford the ketone **236**, elegantly accessing both the pyranosylated (see later section) and furanosylated natural products from a common intermediate. In addition, a copper mediated ring-contraction of ketone **236** to ester **233** was also achieved, highlighting the potential for a biomimetic link. To complete the synthesis, oximation of ketone **236** followed by bis-methylation yielded methyl oxime **237**, before



Scheme 36 Wood and co-workers' synthesis of staurosporine (7).

a stereoselective reduction, reductive methylation and DMB-deprotection sequence delivered (+)-staurosporine (7).

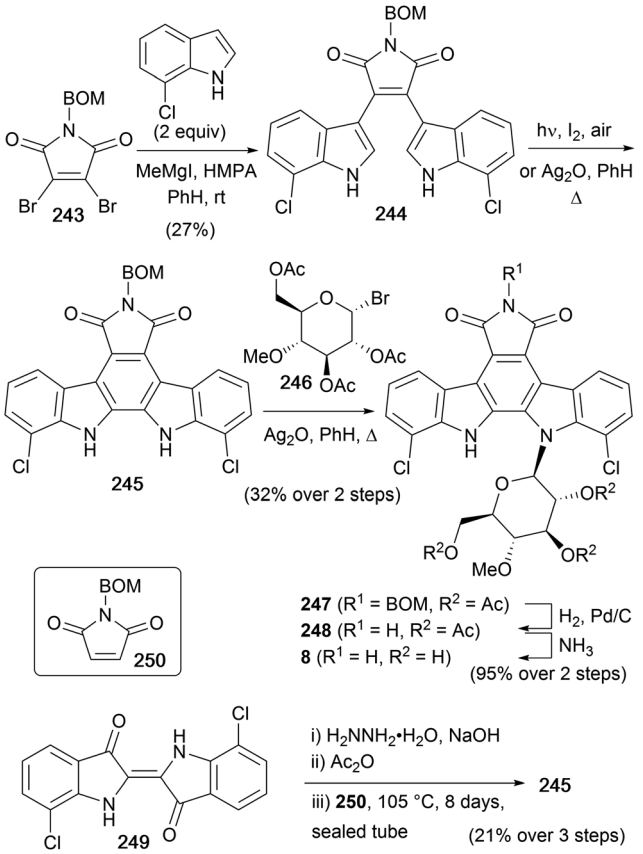
3.2 Rebeccamycin (8)

As the most potent indolocarbazole antitumor agent, rebeccamycin (**8**) has been the focus of both total synthesis and synthetic analogues studies.[159–161] In contrast to the staurosporine class of indolocarbazole glycosides, rebeccamycin only has a single glycosidic linkage. However, many of this subfamily of indolocarbazole natural products exhibit extraordinary activity as poisons of DNA topoisomerase I. This is shown to lead to cell apoptosis, and rebeccamycin derivatives reached phase II clinical trials for the treatment of neoplasias including renal cell carcinoma and stage IIIB or IV breast cancer.[159,162,163]

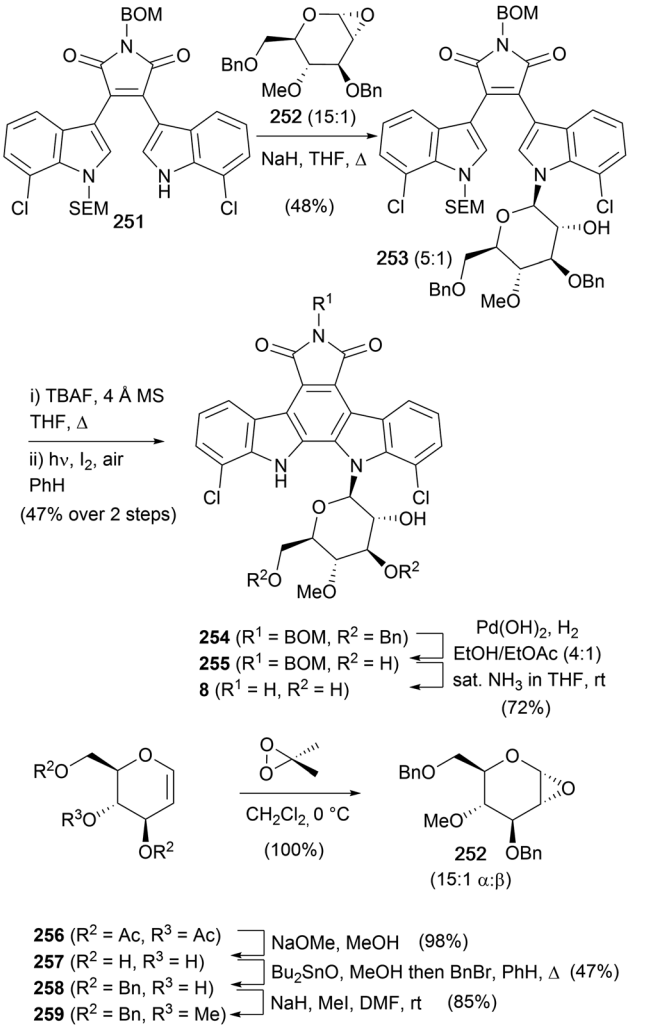
First isolated by Clardy and co-workers in 1985 from the actinomycete strain *Nocardia aerocoligenes*,[16] the rebeccamycin structure was elucidated during synthetic approaches carried out by the same group in 1985.[164] The synthesis began from 7-chloroindole, which was prepared according to the procedure described by Sugasawa and co-workers (Scheme 37).[165] This could then be coupled with *N*-benzyloxymethyl-2,3-dibromomaleimide (**243**) using Steglich's magnesiated indole coupling methodology to give bisindolylmaleimide **244**.[35] Cyclisation of **244** could be achieved photochemically, however a one-pot cyclisation–oxidation and Koenigs–Knorr glycosidation with pyranosyl bromide **246** was developed to give indolocarbazole **247**. Pyranosyl donor **246** was prepared according to the method of Bouveng.[166] Finally hydrogenolysis of the BOM group followed by ammonolysis of the acetyl groups gave rebeccamycin (**8**).

The same group also demonstrated an alternative method to access rebeccamycin aglycone **245** (Scheme 37).[164] Wolff–Kishner reduction of 7,7′-dichloroindigo (**249**) followed by acetylation gave a 2,2′-biindole derivative.[167,168] Finally, Diels–Alder cycloaddition with *N*-benzyloxymethyl maleimide (**250**) gave *N*-benzyloxymethyl aglycone **245**.

In 1993, Danishefsky and co-workers also completed a synthesis of rebeccamycin (**8**, Scheme 38).[156] The synthesis began in similar vein to their synthesis of staurosporine (**7**) using sequential additions of indole magnesium reagents to give the asymmetric, mono-protected bisindolylmaleimide **251**. The required sugar **252** was prepared from the commercially available tri-*O*-acetyl-D-glucan (**256**). Removal of the acetate protecting groups was followed by selective 3,6-*O*-dibenzylation



Scheme 37 Clardy and co-workers' syntheses of rebeccamycin (**8**).



Scheme 38 Danishefsky and co-workers' synthesis of rebeccamycin (**8**).

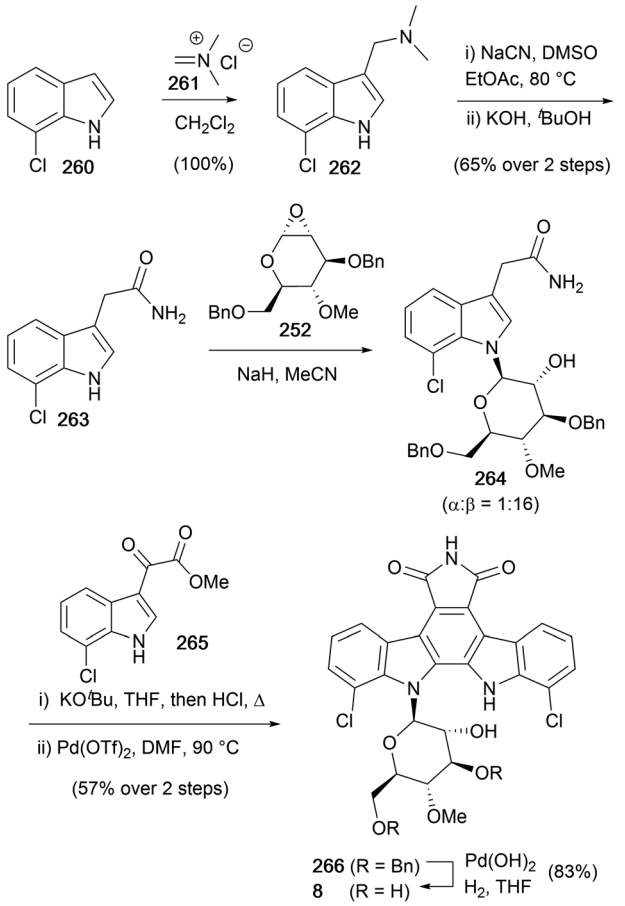
using stannylene chemistry, methylation of the 4-hydroxyl and dioxirane promoted epoxidation gave glucan **252** as a 15 : 1 mixture of anomers.[169] The anomeric mixture was then subjected to the pivotal glycosidation with bisindolylmaleimide **251** to deliver a major β-maleimide **253** in 48% and the α-anomer in 8% yield. The 5 : 1 ratio of **253** *versus* the 15 : 1 ratio in **252** is attributed to the greater reactivity of the minor β epoxide. SEM deprotection, followed by photocyclisation gave indolocarbazole **254**, and finally, hydrogenolytic benzyl cleavage and ammonolysis secured rebeccamycin (**8**).

The most recent synthesis of rebeccamycin (**7**), to date, was disclosed by Faul and co-workers in 1999 (Scheme 39).[170] The synthesis began aminomethylation of 7-chloroindole (**260**), then homologation using cyanation and hydrolysis of the obtained nitrile gave amide **263**. Glycosylation of **263** with epoxide **252**, prepared according to the method of Danishefsky (see Scheme 38),[156] secured glycosylated indole **264**, which was treated with KO^{t}Bu and acetate **265** before addition of acid and heating promoted an intramolecular Perkin-type condensation to give the corresponding bisindolylmaleimide. The synthesis was completed with oxidative-cyclisation using $Pd(OTf)_2$ followed by debenzylation with Pearlman's catalyst to conclude a concise synthesis of rebeccamycin (**8**) in 12 steps and 12% overall yield.

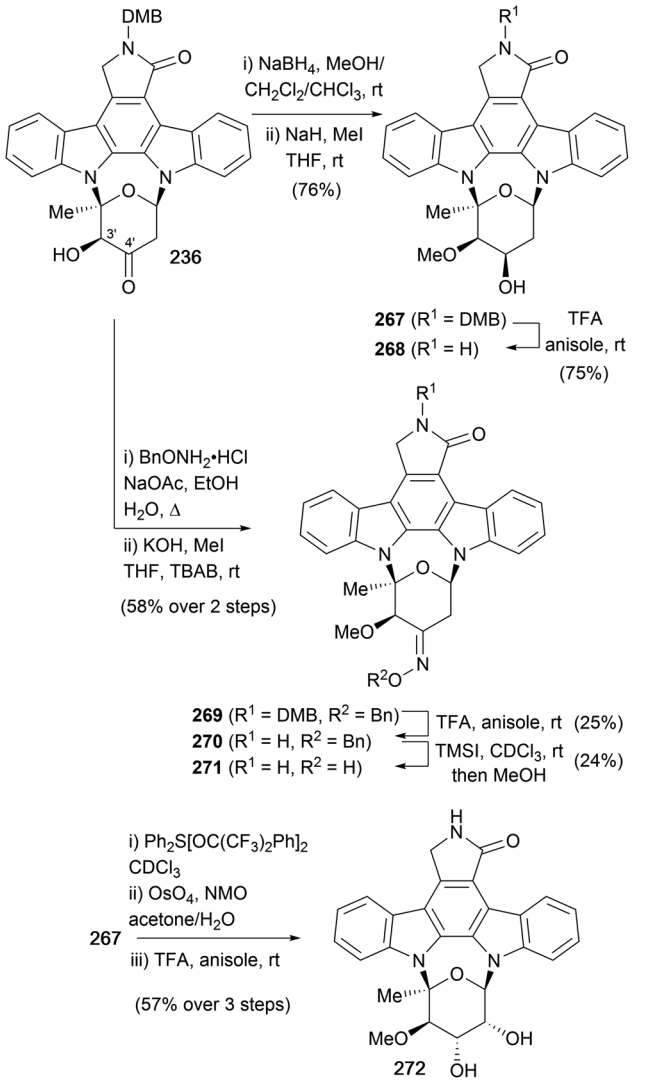
Despite having only been the focus of three synthetic approaches, there has been a great deal of interest in isolating synthetic analogues of rebeccamycin (**8**) as potential therapeutics. For lead references to the preparation of analogues, see recent reviews published by Kirsanov and co-workers[171] and Panov and co-workers.[172]

3.3 Syntheses of (+)-RK-286c (268), (−)-TAN-1030a (271) and (+)-MLR-52 (272)

To date, the only syntheses of (+)-RK-286c (**268**), (−)-TAN-1030a (**271**) and (+)-MLR-52 (**272**) have emerged from the Wood group (Scheme 40, see also Schemes 8 and 36).[51,158] These syntheses share a common ketone intermediate **236**, also employed during their synthesis of staurosporine (**7**, Scheme 36). To access (+)-RK-286c (**268**), ketone **236** was reduced stereoselectively and then regioselective mono-methylation of the resulting vicinal diol gave methyl ether **267** in excellent yield. The highly selective methylation was attributed to the aglycone providing considerably different steric environments for the equatorial [C(3′)] and axial [C(4′)] hydroxyls. Finally, deprotection of the DMB group gave (+)-RK-286c (**268**). To complete



Scheme 39 Faul and co-workers' synthesis of rebeccamycin (**8**).



Scheme 40 Wood and co-workers' syntheses of (+)-RK-286c (**268**), (−)-TAN-1030a (**271**) and (+)-MLR-52 (**272**).

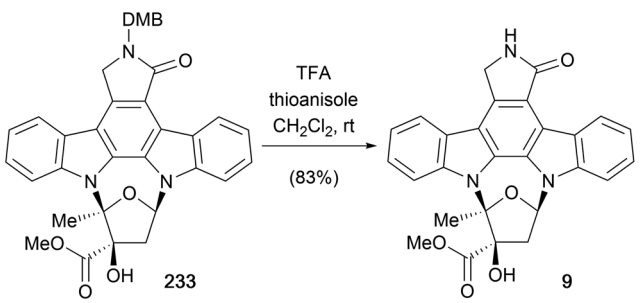
the synthesis of (−)-TAN-1030a (**271**), ketone **236** was subjected to oximation with $BnONH_2 \cdot HCl$, followed by methylation under phase-transfer conditions to give ether **269**. Finally, removal of the DMB and Bn protecting groups furnished (−)-TAN-1030a (**271**). The third natural product obtained using this methodology was (+)-MLR-52 (**272**). Alcohol **267** was dehydrated with Martin's sulfurane, in preparation for stereoselective dihydroxylation of the resulting olefin and deprotection of the DMB group to secure (+)-MLR-52 (**272**).

4 Furanosylated indolocarbazoles

4.1 K252a (9)

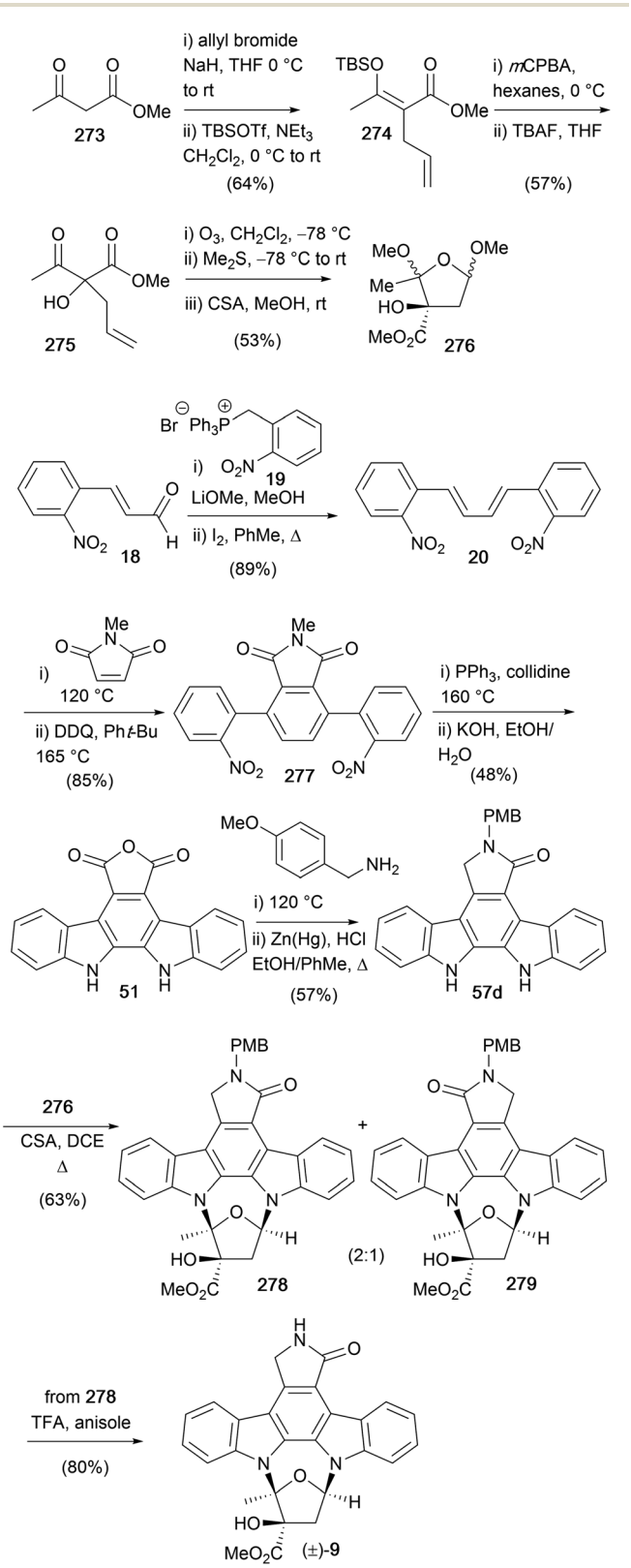
Another group of indolocarbazole natural products are those bearing furanose substitution on the indolic nitrogens, specifically K252a (**9**) is discussed here. The first synthesis of K252a was completed by Wood and co-workers in 1995 as part of their broader work discussed in this review (Scheme 41, see also Schemes 8, 36 and 40).[50] After coupling *N*-DMB staurosporine aglycone (**57c**) and furanose **242** to give a 2 : 1 mixture of regioisomeric indolocarbazoles **233** and **234** respectively (see Scheme 36), separation of the mixture and deprotection of the DMB group provided K252a (**9**).[50]

Later the same year, Lowinger and co-workers also detailed a synthesis of (±)-K252a (**9**, Scheme 42).[173] The synthesis of the carbohydrate moiety of K252a began with allylation of methyl acetoacetate (**273**) and formation of the silyl-enol ether followed by chemoselective epoxidation and desilylation to access olefin **275**. Ozonolysis and quenching with Me_2S gave the intermediate aldehyde which cyclised to glycoside **276** using CSA. The



Scheme 41 Wood and co-workers' synthesis of (+)-K252a (**9**).

PMB-protected aglycone **57d** was prepared according to a modification of Raphael's route from aldehyde **18**.[28] The final stages of the synthesis mirrored Wood's approach, coupling the aglycone **57d** and glycoside **276** to give a 2 : 1 regioisomeric mixture of **278** and **279**, respectively, isomer separation, and PMB deprotection delivered (±)-K252a (**9**).[173]



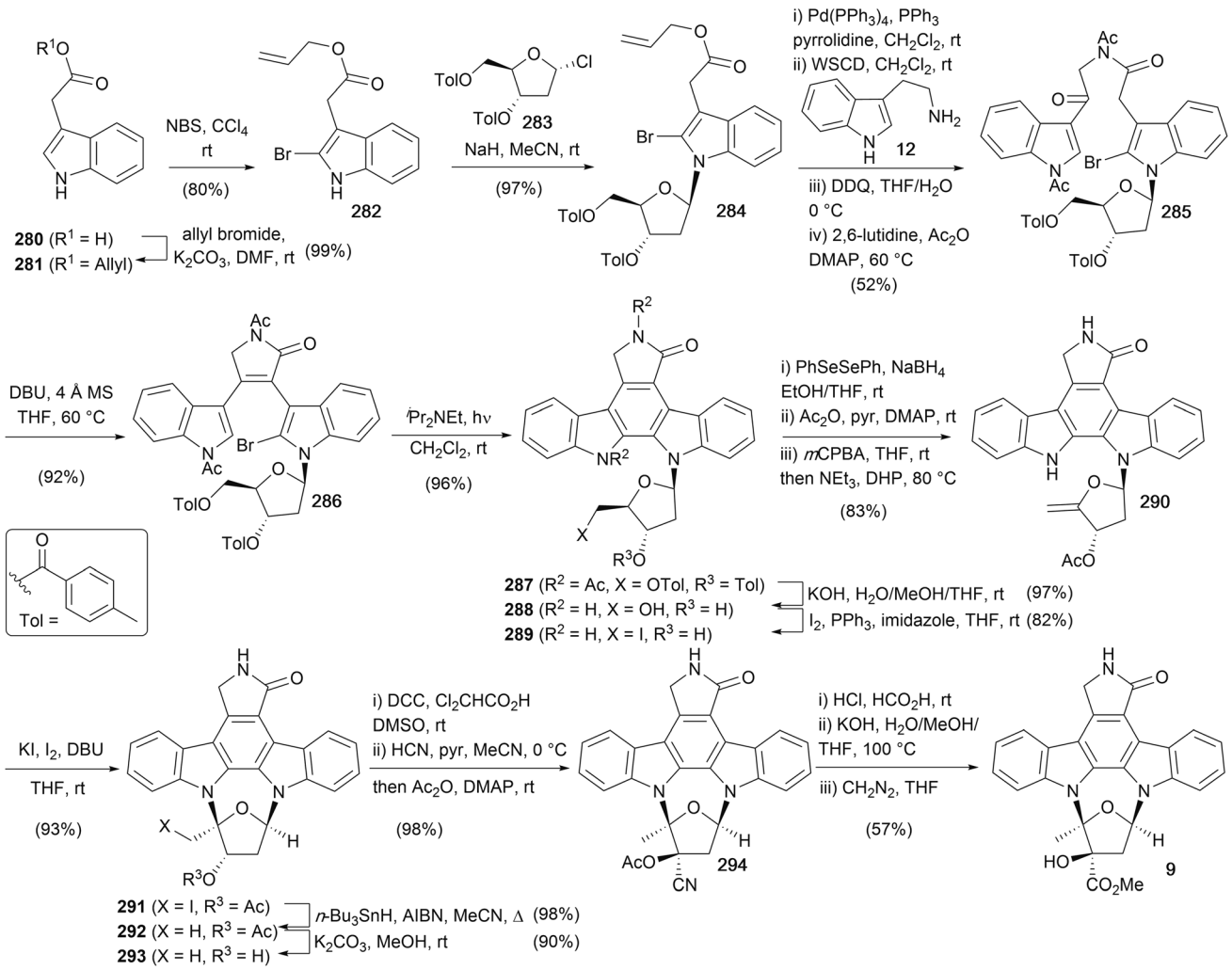
Scheme 42 Lowinger and co-workers' synthesis of (±)-K252a ((±)-**9**).

The most recent synthesis of (+)-K252a (**9**) was completed by Fukuyama and co-workers in 1999 (Scheme 43),[174] focusing on solving regiochemical issues associated with previous furanose annulations reported by Wood and Lowinger. Starting with the commercially available indole acetic acid (**280**), protection as the allyl ester and regioselective bromination gave indole **282**. *N*-Glycosidation was carried out with NaH and the readily available furanosyl chloride **283** to afford indole **284**.[175] Deprotection of the allyl ester and amide coupling with tryptamine (**12**) was followed by benzylic oxidation using DDQ and acetylation of the indole and amide nitrogens to give bisindole **285**. Intramolecular condensation using DBU gave unsaturated lactam **286** as a 1 : 1 mixture of atropisomers before nonoxidative photocyclisation, hydrolysis of the acyl and toluoyl groups and selective Appel reaction of the primary alcohol gave iodide **289**. Conversion of **289** to the exocyclic olefin **290** proved not to be trivial, requiring a three-step sequence involving selenation, followed by protection of the secondary alcohol, oxidation to the selenoxide with elimination providing the desired olefin **290**. NEt_3 and DHP present in the selenoxide elimination prevented oxidative addition of phenylselenous acid to the enol ether formed. Iodoglycosidation of the enol ether using I_2/KI under basic conditions afforded cycloglycoside **291**, which underwent radical deiodination, methanolysis of the acetyl group and oxidation of the secondary alcohol **293** to the corresponding ketone in excellent overall yield.[153] Hydrocyanation secured the kinetic cyanohydrin which was subsequently acetylated to cyanohydrin acetate **294**. Treatment with HCl in HCO_2H gave the primary amide, which was converted to (+)-K252a (**9**) *via* hydrolysis and esterification with diazomethane. The overall sequence provided (+)-K252a (**9**) in 10% overall yield and in 23 synthetic operations.

5 Disaccharide indolocarbazoles

An intriguing family of indolocarbazoles contain a disaccharide unit bonded to the indolocarbazole unit. Isolated in 1989 by Matson and co-workers, these natural products fit into a similar sub-family to the rebeccamycin class of indolocarbazole glycosides, containing a single *N*-glycosidic linkage.[176,177] They have demonstrated activity in the poisoning of DNA topoisomerase I and ultimately in cancer cell apoptosis. In addition to this, they are structurally impressive, particularly in the case of AT2433-A1 (**295**) and AT2433-A2 (**296**), which contain an asymmetric aglycon coupled to the disaccharide unit. This again presents interesting regioselectivity challenges for coupling of the sugar and aglycone fragments (Fig. 5).

The first, and only synthesis of the AT2433 natural products to date, was carried out by Van Vranken and co-workers in 2000,[159] utilising Mannich cyclisations to indolylindolines (Scheme 44).[79,178,179] Their synthesis began with the preparation of asymmetric succinimide **299** *via* Faul and co-workers adaption of Steglich's methodology with sequential addition of magnesiated indole and 7-chloroindole.[48] Hydrogenolysis of the



Scheme 43 Fukuyama and co-workers' synthesis of (+)-K252a (**9**).

obtained maleimide gave succinimide **299**, which was subjected to the key intramolecular Mannich cyclisation delivering indolene **300**. Of particular note is the excellent control achieved in the Mannich cyclisation for either isomeric indolene through careful choice of acid used. Refluxing in neat TFA realised the thermodynamic indolene, where the indolene is formed in the more electron rich indole ring, whilst MsOH provided the desired kinetic isomer **300**. Rationalisation based on the Curtin–Hammett principle, proposed that the electron-withdrawing effect of the chloro group during C–C bond formation destabilises the intermediate indolenium ion, leading to faster, irreversible cyclisation. In contrast, refluxing TFA led to the more stable indolenium ion, likely reversibly, however the group quote a diminished yield due to partial decomposition. The required disaccharide **301** was isolated *via* an 8-step sequence from homoallyl alcohol **304**. Homoallyl alcohol **304** was prepared by Roush and Hunt's procedure from (*R*)-Garners's aldehyde as an 88 : 12 mixture of diastereoisomers.[180] Benzylation of homoallyl alcohol **304** was followed by unveiling the masked aldehyde *via* OsO_4 mediated dihydroxylation and periodate cleavage of the diol. Removal of the acetonide and concurrent cyclisation provided glycol **307**. Formation of the glycosyl fluoride **308** was achieved with DAST, before coupling with primary alcohol **303** was effected under

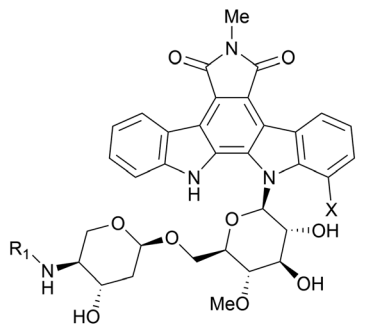
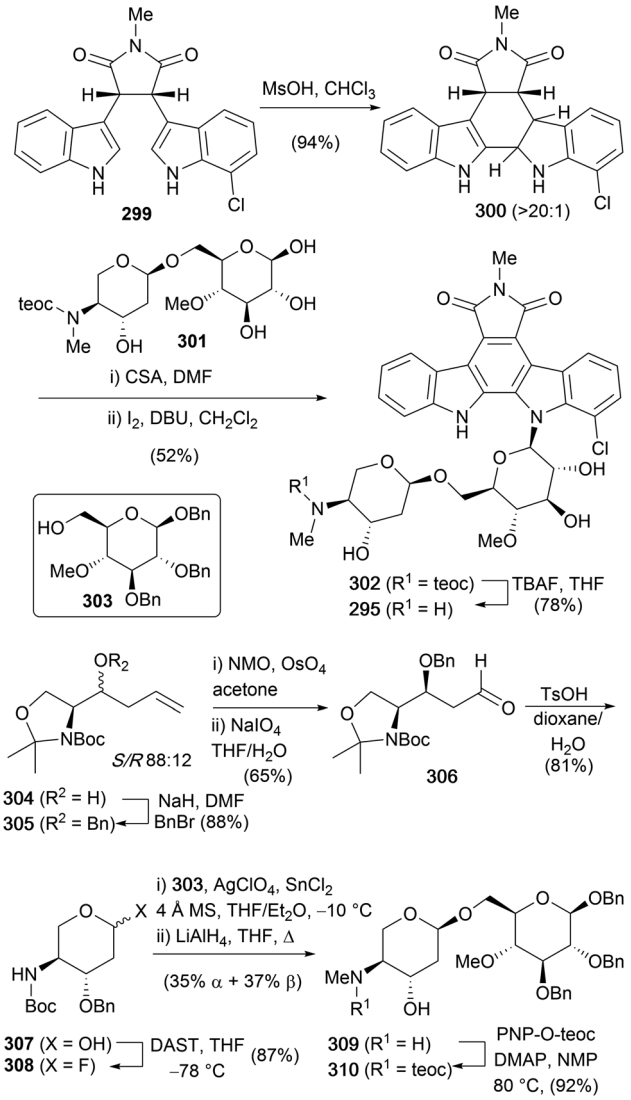


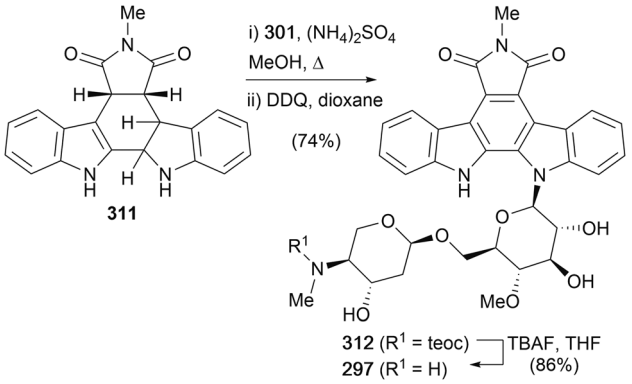
Fig. 5 Structures of AT2433 A1 (**295**), A2 (**296**), B1 (**297**) and B2 (**298**).



Scheme 44 Van Vranken and co-workers' synthesis of AT2433 A1 (**295**).

Mukaiyama–Nicolaou conditions and reductive cleavage of the Boc group provided disaccharide **309** as a mixture of α : β anomers (~1 : 1). Protection of the methylamine moiety as the 2-(trimethylsilyl)ethyl carbamate **310** preceded debenzylation to give disaccharide **301**. Indolene **300**, was then glycosylated chemoselectively with disaccharide **301** in the presence of catalytic amounts of CSA before oxidation of the 1 : 1 mixture of diastereoisomers gave indolocarbazole **302**. Finally, removal of the teoc group with TBAF concluded the first synthesis of AT2433-A1 (**295**).

In addition, the same group also completed the first total synthesis of AT2433-B1 (**297**) (Scheme 45).[159] Indolene **311** was prepared in an analogous fashion to chloroindolene **300**, before coupling with disaccharide **301** and DDQ oxidation of the mixture of diastereoisomers provided indolocarbazole **312** in excellent yield. Removal of the teoc group was achieved with TBAF to complete the first synthesis of AT2433-B1 (**297**).



Scheme 45 Van Vranken and co-workers' synthesis of AT2433 B1 (**297**).

6 Conclusions

Total synthesis continues to be one of the most exciting areas of research, with papers published in the field regarded as some of the most-read manuscripts in chemistry focussed journals.[181] In addition to providing a proving ground for the generality and utility of synthetic methodology, it offers access to bioactive compounds, key to advancing biological and medical science. The indolocarbazoles are prime examples, displaying extraordinary bioactivity and molecular complexity. As evident in this review, this has led to a plethora of synthetic endeavours towards indolocarbazoles. Realisation of the important bioactivities exhibited by many of these compounds spurred a greater emphasis on isolating large quantities of these materials, particularly the staurosporine aglycone (**10**) and arcyriaflavin A (**45**). The synthesis of the aglycone developed by process department at Eli Lily is a great example;[55] concise, efficient and scalable, whilst also allowing access bisindolylmaleimide (**44**) and arcyriaflavin A (**45**), and their derivatives.

Indolocarbazole natural products bearing glycosidic linkages present a different synthetic challenge, where regioselectivity is hampered by the remote nature of the asymmetry in the aglycone and sugar fragments. Wood and co-workers diazo-insertion approach and Danishefsky and co-workers epoxide-glycosylation have enabled the only syntheses of staurosporine (**7**) to date, however regioselectivity issues were not fully addressed during these remarkable approaches. Subsequent synthetic endevours, namely by Fukuyama and co-workers on K252a (**9**) and Van Vranken and co-workers on AT2433-A1 (**295**) have worked to resolve regioselectivity issues. Yet to date, a synthesis of staurosporine, that would enable isolation of large quantities of both the natural compound as well as interesting pharmaceutically relevant derivatives remains elusive. As the cost of the natural product is high, its utility as starting point for SAR studies and optimisation is restricted, and thus, total synthesis remains an attractive option.

The FDA approval of Midostaurin in 2017 for the treatment of acute myeloid leukemia (AML), highlights the remarkable bioactivity of indolocarbazoles and enduring and evolving

interest. The current understanding of cancer therapy dictates a targeted strategy where a key cellular pathway is identified, signalling cascade biologically dissected and one target enzyme is selectively inhibited. This allows patient stratification according to a biomarker and applying a relatively specific drug to treat a condition. In fact, the use of Midostaurin in AML has been approved due to its inhibitory activity on FLT3 kinase, not PKC. However, in the relevant clinical trials, Midostaurin showed clinical efficacy in FLT3 wild type (non-mutated) and mutant subgroups suggesting its clinical benefit extends beyond the aimed association with a biomarker but still allowed clinical translation.[182] Similar observations were made with other staurosporine derivatives such as 7-hydroxystaurosporine (UCN-01) during early phase clinical trials in which unstratified patient groups were used.[183] Therefore the anti-cancer activity of Midostaurin and UCN-01 PKC inhibitors are not in question but their association with a biological condition is missing at the moment.

In recent years characterisation of cancer stem cells have paved the way for specific drugs to inhibit cancer metastasis. PKC inhibitors were identified to specifically inhibit cancer stem cell formation both *in vitro* and *in vivo*.[184,185] Indolocarbazole derivatives may have an important role in these studies, and may even lead to future therapies. Synthetic approaches to these natural products and derivatives will be paramount to advancements, and this review is intended as a useful tool to aid access to these exciting scaffolds. In conclusion, indolocarbazole natural products have an enduring potential as leads for development of new medicines, and inspiration for new synthetic methodologies and approaches. From a biological perspective, interest indolocarbazoles is likely to be maintained well into the future as more biological pathways and patient treatment regimens are revealed.

7 Author contributions

All authors were involved in conceptualisation and writing (review & editing) of the manuscript. GEC was additionally responsible for writing the original draft.

8 Conflicts of interest

There are no conflicts to declare.

9 Acknowledgements

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