SYNTHETIC STRATEGIES FOR THE SYNTHESIS OF INDOLOQUINOLINE NATURAL PRODUCTS

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Abstract. *Extracts from the plant Cryptolepis sanguinolenta, a climbing vine that grows in West and Central Africa, has been used as treatment for malaria for ages. In addition to anti-malarial activity, extracts from Cryptolepis sanguinolenta also has anti-inflammatory, anti-plasmodial, anti-bacterial, and anti-cancer activity. Modern chemical analysis has shown that the plant is a rich source of indoloquinolines and biological assays has confirmed that the activity is due to these compounds. Due to the medicinal effect of these natural products, in particular cryptolepine, neocryptolepine, and isocryptolepine, the Cryptolepis sanguinolenta derived natural products has become popular targets for synthetic organic chemists and medicinal chemists. This has resulted in the development of a range of synthetic approaches to these natural products. In this chapter, the most recent synthetic strategies for the preparation of quinindoline, neocryptolepine, quindoline, cryptolepine, 11-isopropylcryptolepine, cryptolepinone, quindolinone, and isocryptolepine will be discussed.*

Contents

1. Introduction

Indoloquinolines are plant based natural products containing a fused indole and quinoline ring system. These compounds (Figure 1) are biosynthesized from indole derived precursors.[1] The review by Parvatkar and Parameswaran gives an excellent description of the biosynthetic pathways for the formation of these natural products.[1] *Cryptolepis sanguinolenta*, a climbing vine grooving in West and Central Africa,[2] is a rich source of indoloquinolines (Figure 1). The plant has been found to be the best source of the indoloquinoline natural products,[3] although scattered reports of some of the compounds belonging to this group have been isolated from other plants have been reported. The medicinal properties of aqueous root extracts from *Cryptolepis sanguinolenta* has been used to cure malaria and other disease for ages. Studies conducted over the last 30-40 years has verified the folk medicine reports and shown that the indoloquinolines found in the aqueous extracts possess a range of biological activities such as anti-malarial,[4] anti-inflammatory, anti-plasmodial, anti-bacterial,[5,6] anti-cancer, in addition to moderate antiviral activity.[6]

Cryptolepine **4** is the major alkaloid found amongst the indoloquinolines isolated from *Cryptolepis sanguinolenta*,[7] and compound **4** accounts for most of the activity found in the extracts from the plant. Wright pointed out in a review in 2005 that cryptolepine **4** is an interesting natural product to study further in order to aid the increasing problem of drug-resistance amongst malaria parasites.[8]

The main focus on *Cryptolepis sanguinolenta* has been on root extracts. This is most likely due to the fact that root extracts has been used as remedy for the treatment of disease for decades. However, in 2000 Poulo *et al.*[9] reported the isolation of two new natural products sharing structural motif with cryptolepine **4**,

namely cryptolepinoic acid **9** and cryptolepinoate 1**0**, from the leaves of the plant (Figure 2). In addition to the two new natural products the known compounds cryptolepine **4**, 11-hydroxycryptolepine **7b**, and quindoline **3** were also isolated from the leaves.

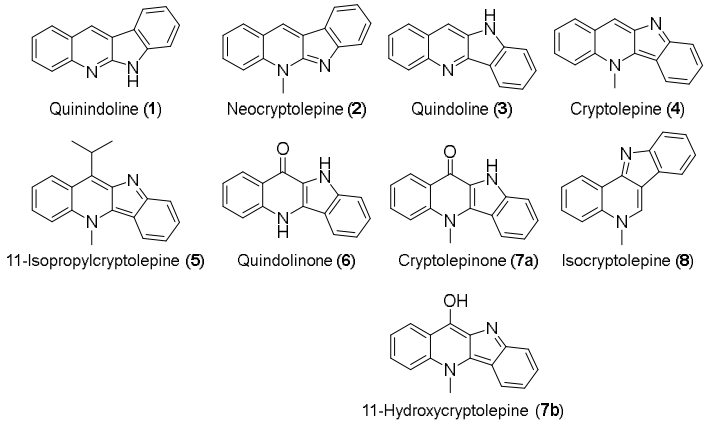


Figure 1. Natural occurring indoloquinolines: quinindoline **1**, neocryptolepine **2**, quindoline **3**, cryptolepine **4**, 11-isopropylcryptolepine **5**, quindolinone **6**, cryptolepinone **7a**/11-hydroxycryptolepine **7b**, and isocryptolepine **8**.

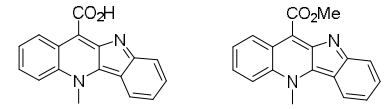


Figure 2. Two new indoloquinolines isolated from the leaves of *Cryptolepis sanguinolenta.*

A related natural product to cryptolepine **4**, viz cryptoheptine **11** (Figure 3), was isolated by Paulo *et al*. in 1995 and assigned the structure depicted for compound **11** in Figure 3.[10]

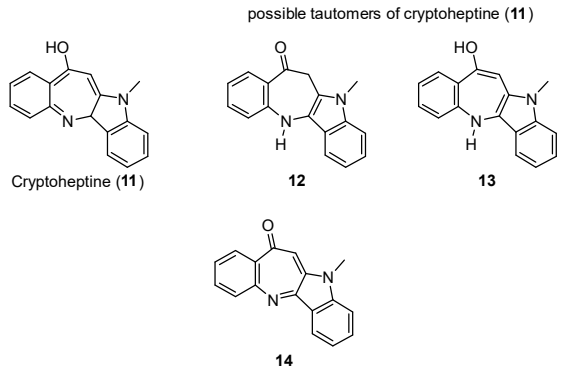


Figure 3. The structure of cryptoheptine **11** and two possible tautomers of the natural product, namely compound **12** and **13**. Compound **14** was the only product obtained by Zhang and Bierer when they attempted to convert compound **12** to the natural product **11**.

The assigned structure of compound **11** was a few years later questioned by Zhang and Bierer.[11] In their attempts to prepare natural product **11** they synthesized compound **12**, one out of two possible

tautomers (compound **12** and **13**) of compound **11**, that they reasoned could be converted to the natural product upon treatment with either base or acid. All their efforts to facilitate the preparation of the reported structure of cryptoheptine **11** only resulted in the formation of product **14**. The difficulties in preparing the natural product **11** from compound **12** warrants further investigations into the structure of cryptoheptine **11**.

Six dimeric indoloquinoline natural products have also been isolated from *Cryptolepis sanguinolenta,* biscryptolepine **15**,[12] cryptoquindoline **16**,[13] quindolinocryptotackieine **17**,[14] cryptomisrine **18**,[15] cryptolepicarboline **19**,[16] and cryptospirolepine **20**[17,18] (Figure 4). The structure of cryptospirolepine **14** was originally wrongly assigned,[17] and the corrected structure was first published more than 20 years later after a substantial NMR campaign lead by Williamson and Martin involving 2D NMR experiments.[18] The dimeric natural products has received much less attention from synthetic chemists then their monomeric counterparts has.

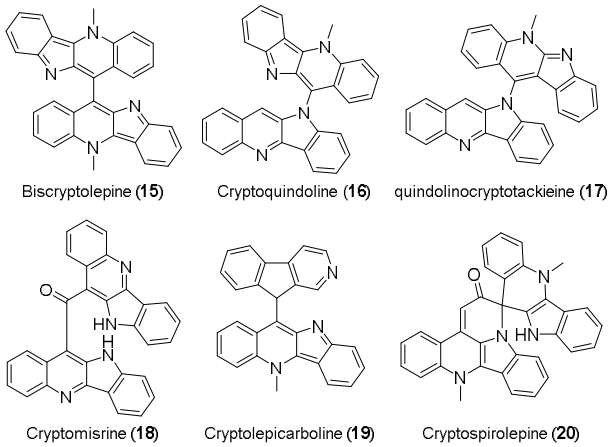


Figure 4. Dimeric indoloquinolines natural products isolated from *Cryptolepis sanguinolenta*.

Due to the broad biological activity amongst the indoloquinolines **1**-**8** in addition to their structural skeleton being regarded amongst a group of important privileged scaffolds[19] these natural products have been and are popular synthetic targets. In particular neocryptolepine (**2**), cryptolepine (**4**), and isocryptolepine (**8**) has received considerable attention over the years both amongst synthetic chemists developing new strategies for their formation and medicinal chemists interested in biological activity and the use of the scaffolds for the preparation of analogues in order to enhance the biological activity. A recent review by Wang *et al.*[20] and a book chapter by Sydnes[21] discusses this topic in detail. For readers interested in an update concerning the synthesis of analogues of these natural products are referred to the two mentioned references.

Generally speaking, the most commonly reported approaches to the indoloquinoline natural products uses the following key synthetic strategies: aza-Wittig reaction,[22-25] Pictet-Spengler cyclisation,[26,27] photochemical cyclization,[28-30] Fischer indole cyclisation,[31] palladium catalyzed coupling reactions,[32-36] and one-pot strategies.[37,38] The references cited here are for isoquinoline (**8**) synthesis, but has general validity.

This chapter only present the most recent strategies developed for the preparation of the monomeric indoloquinolines isolated from *Cryptolepis sanguinolenta*. Some of the natural products (compounds **1**-**8**) has been the focus of several reviews over the last 10-15 years. References for these reviews are provided herein. This chapter will therefore only cover new synthesis reported after the latest reviews.

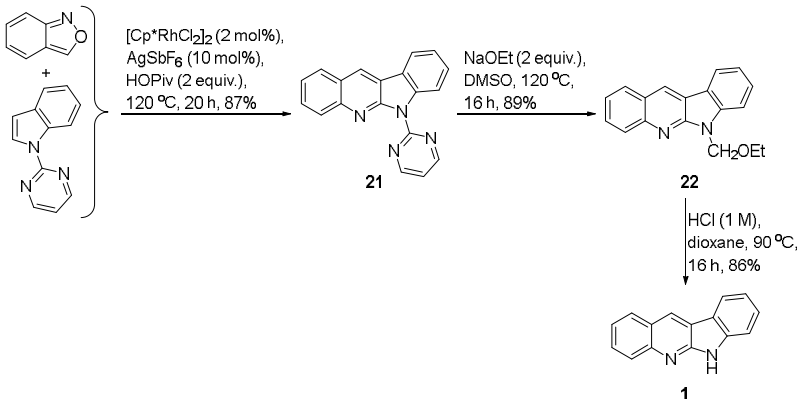
2. Quinindoline

Quinindoline **1**, which occasionally is referred to as norneocryptolepine, was isolation from *Cryptolepis sanguinolenta*.[39] It has also later been isolated from the leaves of *Justica betonica* collected in Balinaidu Kandriga (India).[40] Synthetic efforts directed towards the synthesis of quinindoline **1** has not

previously been reviewed, however, the natural product has been prepared several times in efforts devoted towards the preparation of neocryptolepine and several of the synthesis has therefore been included in reviews although the focus has been on natural product **2**.[1,2,41-44]

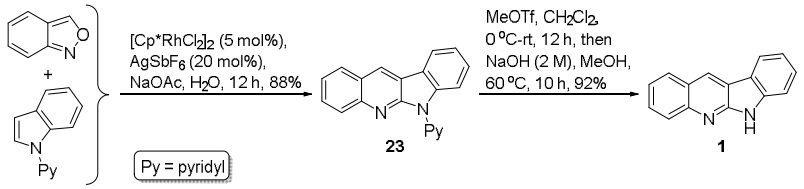
The latest synthesis of natural product **1** was conducted by Yeh *et al.*, and was exactly such an example where quinindoline was use as a precursor for the synthesis of neocryptolepine **2** (Scheme 10).[45] Starting from 2-bromobenzaldehyde and 2-nitrophenylacetonitrile quinindoline **1** could be prepared in three steps in an over all yield of 71% (see Yeh *et al.* synthesis of neocryptolepine for details).

The work of Yu *et al.*[46] was recently reviewed in a book chapter where compound **1** was the precursor for the formation of neocryptolepine **2**.[21] The synthesis is therefore not included herein in section 3, however, in order to discuss the chemistry leading to quinindoline **1** the synthesis are discussed below. Yu *et al.* commenced their synthesis by treating anthranil and *N*-pyrimidinylindole with catalytic amounts of $[Cp^*RhCl_2]_2$ and $AgSbF_6$ (Scheme 1). This resulted in clean conversion to compound **21**, which was converted by a Pummerer rearrangement to substrate **22** in excellent yield (89%). Compound **22** could then be converted to quinindoline **1** upon treatment with HCl in dioxane at 90 °C. After preparing quinindoline the product was methylated using literature conditions[47] to give neocryptolepine **2**.



Scheme 1. Preparation of quinindoline **1** from anthranil and *N*-pyrimidinylindole using a ruthenium catalyzed reaction.

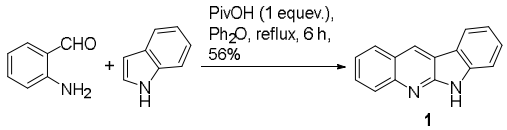
A very similar approach to the one used by Yu *et al.* was published in the same issue of the journal by Shi and Wang.[48] They also commenced their synthesis by starting with anthranil, but utilized 1-(pyridine-2-yl)-1*H*-indole as the indole source (Scheme 2). When subjected to the same catalytic system, viz $[Cp^*RhCl_2]_2$ and $AgSbF_6$, substrate **23** was formed in 88% yield. Removing the pyridine group by treating compound **23** with methyl triflate in dichloromethane gave the desired product **1** in excellent yield (92%).



Scheme 2. Synthesis of quinindoline (**1**) utilizing a $[Cp^*RhCl_2]_2$ and $AgSbF_6$ catalytic reaction as the key step.

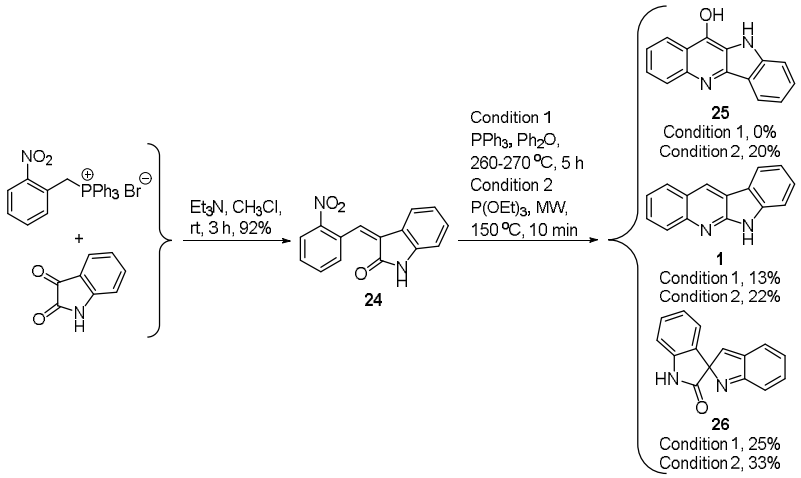
Tilve and co-workers have been active contributors with several synthetic methods reported for the preparation of indoloquinolines. This has amongst the synthesis of several of the indoloquinolines also

resulted in a few synthesis of quinindoline **1**, which will be presented in the following sections. The latest contribution in this series of work from the Tilve group is outlined in Scheme 3 and represents a one-step preparation of the title compound. By treating 2-aminobenzaldehyde and indole with pivalic acid in refluxing diphenyl ether gave the desired product **1** in 56% yield.[49] Although the yield for the reaction is not impressive it does represent a very easy method to prepare the natural product and with only one-step followed by one purification it competes well with many high yielding multistep sequences.



Scheme 3. Converting 2-aminobenzaldehyde and indole to quinindoline **1** in one-step.

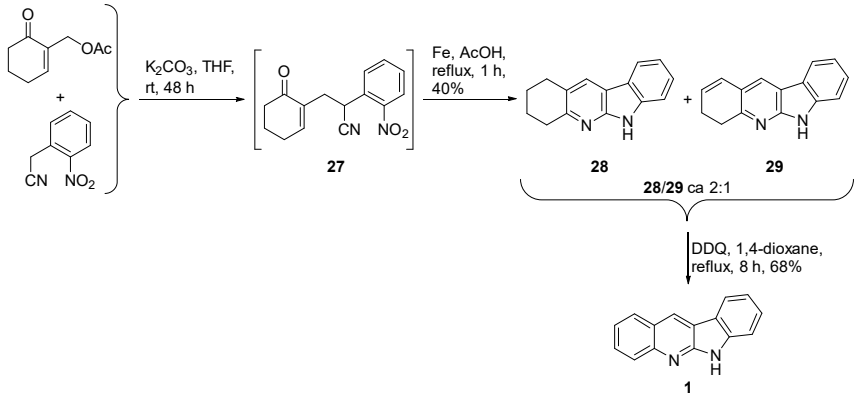
Parvatkar and Majik prepared key intermediate **24** in high yield (92%) by a Wittig reaction between indoline-2,3-dione and (2-nitrobenzyl)triphenylphosphonium bromide at room temperature in chloroform (Scheme 4).[50] Treating substrate **24** in diphenyl ether at high temperature in the presence of triphenylphosphine (condition 1) gave a very low yield of compound **1** (13%) together with spirocycle **26** (25%). Changing the reaction conditions to heating substrate **24** in a microwave oven together with phosphore triethoxide (condition 2) gave quinindoline (**1**) in a slightly better yield (22%) together with substantial amounts of compounds **25** (20%) and **26** (33%).



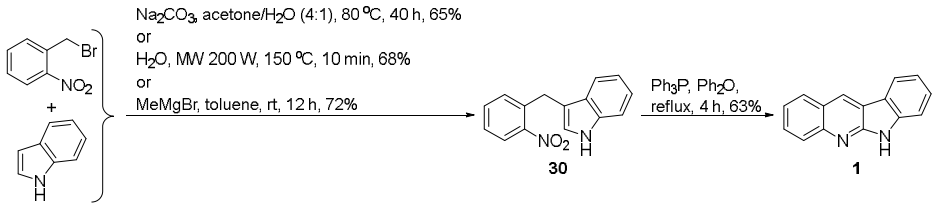
Scheme 4. A high yielding Wittig reaction commenced Parvatkar and Majik's preparation of quinindoline **1**, which suffered from a poor yield an low selectivity in the final cyclization step.

Treating 2-acetoxymethylcyclohex-2-enone and (6-oxocyclohex-1-en-1-yl)methyl acetate with base in THF at room temperature gave intermediate **27**, which was directly cyclized upon treatment with iron powder in acetic acid resulting in a 40% combined yield of **28** and **29** (ca. 2:1) (Scheme 5).[51] Treating the product mixture (**28** and **29**) with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in refluxing 1,4-dioxane converted compounds **28** and **29** to the desired natural product **1** in 68% yield. Basavaiah and Reddy then converted compound **1** to neocryptolepine **2** upon treatment with methyl iodide.

Kadam, Parvatkar, and Tilve reported three different methods to convert 1-(bromomethyl)-2-nitrobenzene and indole to the key intermediate **30** (Scheme 6).[52] The yields for the three methods ranged from 65-72% with the use of methyl magnesium bromide in toluene resulting in the highest yield (72%). With key intermediate **30** in hand the substrate could be converted to compound **1** (63% yield) by a cyclization and oxidation process facilitated by triphenyl phosphine in refluxing diphenyl ether.

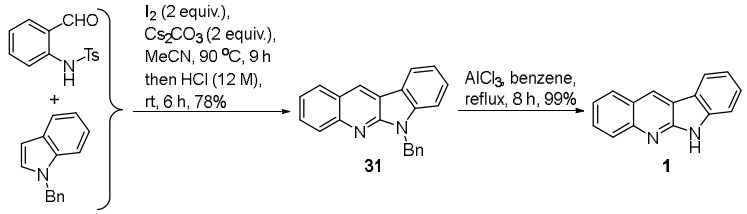


Scheme 5. Formation of quinindoline (**1**) using an iron catalyzed reaction to facilitate the key cyclization process.



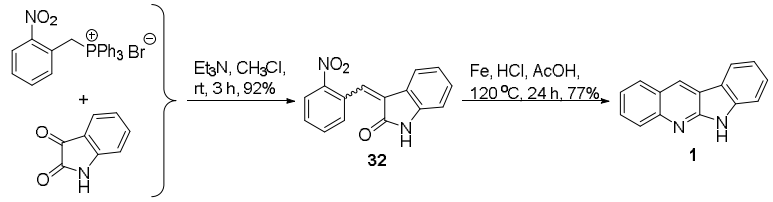
Scheme 6. Three different conditions gave key intermediate **30**, which could be converted to target compound **1** by treatment with triphenyl phosphine in refluxing diphenyl ether.

Ali *et al.* [47] prepared quinindoline **1** as one of their compounds during the development of a one-pot procedure for the formation of indolo[2,3-*b*]quinolines. The benzyl protected natural product **31** could be generated by treating *N*-(2-formylphenyl)-4-methylbenzenesulfonamide and benzyl protected indole with iodine and cesium carbonate in acetonitrile at elevated temperature (Scheme 7). This gave after column chromatography the desired product in 78% yield, which was deprotected upon treatment with aluminium trichloride in refluxing benzene giving natural product **1** in 99% yield.



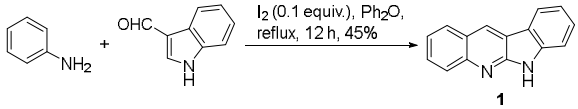
Scheme 7. Iodine and cesium carbonate facilitated formation of the benzyl protected natural product **31**, which was readily converted to the natural product **1**.

Parvatkar and Tilve commenced one of their synthesis of quinindoline (**1**) by a Wittig reaction between isatin and (2-nitrobenzyl)triphenylphosphonium bromide (Scheme 8).[53] With the Wittig product **32** (92% yield) in hand the formation of compound **1** was facilitated by treating compound **32** with iron in acetic acid in the presence of catalytic amounts of HCl. This gave quinindoline **1** in 77% yield. Natural product **1** was then finally converted to neocryptolepine **2** (96% yield) upon treatment with methyl iodide in refluxing THF.



Scheme 8. Iron and HCl promoted cyclization of intermediate **32** to quinindoline **1**.

A simple one step synthesis of quinindoline **1** was facilitated by refluxing aniline and 1*H*-indole-3-carbaldehyde in phenyl ether in the presence of catalytic amounts of iodine (0.1 equiv.). These conditions gave the desired natural product **1** in 45% isolated yield (Scheme 9).[54] Although the yield for the reaction is modest the method developed by Parvatkar, Parameswaran, and Tilve represents a very efficient synthesis. In the same report, they also discussed a second approach for the preparation of quinindoline **1**. Starting with two equiv. of aniline and 1*H*-indole-3-carbaldehyde and treating the reaction with acetic acid at reflux in phenyl ether for three hours gave Schiff base (*E*)-1-(1*H*-indol-3-yl)-*N*-phenylmethanimine, which was directly converted to the natural product upon addition of catalytic amounts of iodine. In addition to compound **1** this method also gave one equivalent of *N*-phenylacetamide. The drawback with this one-pot method was that quinindoline **1** was only formed in maximum 23% yield and the fact that two equiv. or more of aniline had to be used in order to obtain the desired product in very low yield.



Scheme 9. One step synthesis of quinindoline (**1**) from aniline and 1*H*-indole-3-carbaldehyde.

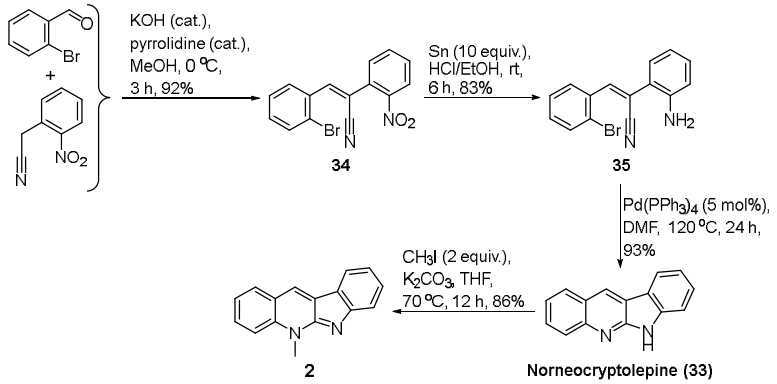
3. Neocryptolepine

Neocryptolepine **2** was reported isolated simultaneously by two different research groups in 1996.[12,55] The compound, which was named cryptotackiene by Sharaf *et al.*[55] and neocryptolepine by Pieters and co-workers,[12] was isolated from the root bark extracts of *Cryptolepis sanguinolenta*. Quickly after the first two reports of its isolation the name was settled as neocryptolepine. Synthetic efforts devoted to the preparation of neocryptolepine **2** has been reviewed several times.[1,2,41-44] Therefore only the most recent synthetic efforts will be discussed herein.

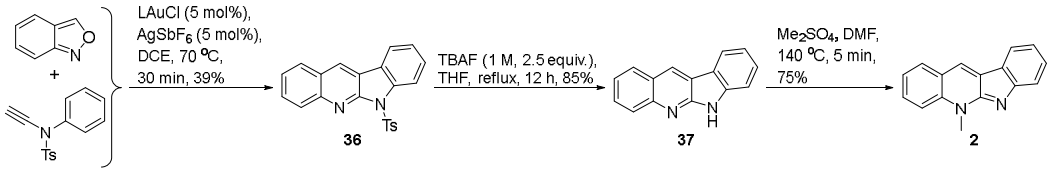
A very recent report by Yeh *et al.* reporting a strategy for the formation of norneocryptolepine **33**, also a natural product isolated from *justicia betonica*, on the rout to neocryptolepine **2** is often used as a precursor for the preparation of neocryptolepine **2**.[45] Treating 2-bromobenzaldehyde and 2-nitrophenylacetonitrile with catalytic amounts of potassium hydroxide and pyrrolidine in methanol at 0 °C gave after three hours compound **34** in 92% yield (Scheme 10). Reduction of the nitro group is then best done upon treatment with tin in acidic (HCl) methanol at room temperature giving the desired product **35** (83%), which is then nicely set up for the catalytic annulation reaction. Treating compound **35** with 5 mol% tetrakis(triphenylphosphine)palladium(0) in DMF at 120 °C gave efficiently after 24 hours norneocryptolepine **33** in 93% yield. Compound **33** could then be alkylated using methyl iodide and a bit of base under standard conditions finalizing the total synthesis of neocryptolepine **2**. The authors then utilized this methodology to prepare a range of norneocryptolepine analogues and related compounds all in fairly good yields.

Gold catalysis has received a lot of interest lately with many groups working on expanding the chemistry of this noble metal.[56-58] Tsai *et al.* used gold catalysis in their key step during the formation of neocryptolepine **2** and a range of related compounds. The annulation of *N*-aryl ynamide and benzisoxazole was catalyzed by LAuCl (L=P(*t*-Bu)$_2$(*o*-biphenyl)) and $AgSbF_6$ in dichloroethane at 70 °C (Scheme 11).[59] This gave after work-up protected 6*H*-indoleo[2,3-*b*]quinoline **36** in rather low yield. Nevertheless, compound **36** could easily be converted to neocryptolepine **2** by first conducting a deprotection upon

treatment with *tetra*-n-butylammonium fluoride (TBAF) forming substrate **37**, which could be converted to neocryptolepine **2** by an alkylation with dimethyl sulfate (Me_2SO_4). This gave the desired natural product in 64% yield over the two steps.

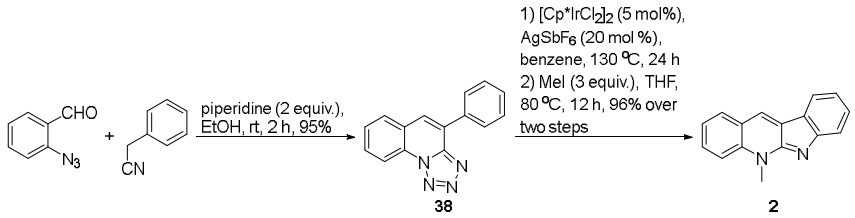


Scheme 10. Synthesis of neocryptolepine **2** using a palladium catalyzed annulation reaction as the key step.



Scheme 11. Gold catalyzed assembly of the neocryptolepine scaffold **36** followed by conversion to the natural product **2**.

Das *et al.* synthesis of neocryptolepine **2** was based on an intramolecular denitrogenative transannulation/C(sp^2)-H amination of 1,2,3,4-tetrazoles bearing a C8 aryl group.[60] Their synthesis commenced by assembling the pivotal starting material 4-phenyltetrazolo[1,5-*a*]quinolone **38**, which was made from 2-azidobenzaldehyde and 2-phenylacetonitrile following a literature procedure (Scheme 12).[61] Quinolone **38** was then treated with pentamethylcyclopentadienyliridium(III) chloride dimer ($[Cp^*IrCl_2]_2$) and silver hexafluoroantimonate in benzene for 24 h to give the desired transannulated product, which was directly methylated using methyl iodide in THF under standard conditions. After column chromatography a 96% yield of neocryptolepine **2** could be obtained. The synthesis by Das *et al.* represents a very efficient preparation of the natural product, which is formed in 91% overall yield.

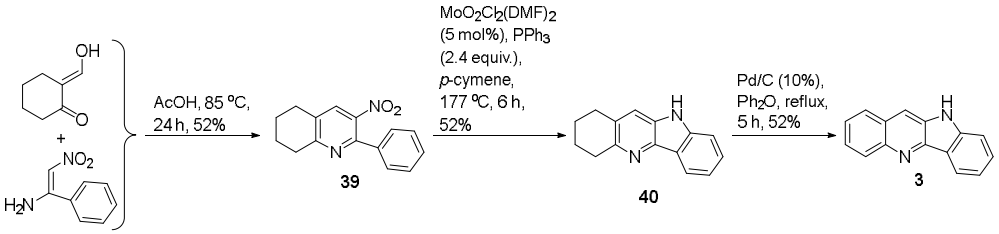


Scheme 12. Synthesis of neocryptolepine **2** by a catalytic intramolecular denitrogenative transannulation/C(sp^2)-H amination.

4. Quindoline

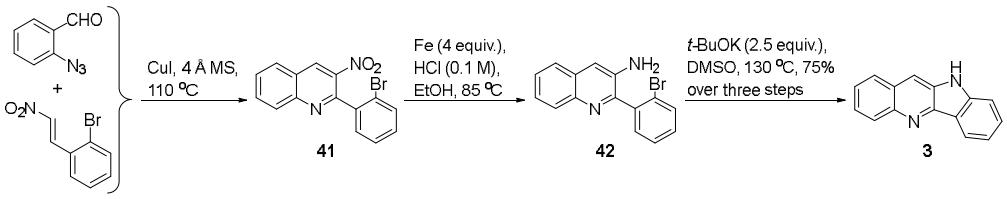
Quindoline **3** was reported isolated 1978 from *Cryptolepis sanguinolenta*.[39] At the stage of isolation it was actually a known compound since its synthesis had been reported 27 years prior to its isolation from the plant.[62] Lately the natural product has also been reported isolated from *Justicia betonica* in India,[40] *Justicia secunda* and *Sida rhombifolia* in America.[63,64] A recent review by Kaufman and co-workers summarizes the synthesis of quindoline conducted until 2018 as well as highlighting the natural products biological activity.[65] Herein only the two latest synthesis will be discussed since they are not included in the mentioned review articles.

Shuvalov *et al.* commenced their synthesis of quindoline **3** by refluxing 2-hydroxymethylenecycloketone and the corresponding nitroenamine in acetic acid for 24 hours. This gave 2-aryl-3-nitro-5,6,7,8-tetrahydroquinoline **39** in 52% yield (Scheme 13).[66] Heating compound **39** in the high boiling solvent *p*-cymene at reflux with $MoO_2Cl_2(DMF)_2$ in the presence of triphenylphosphine gave 2,3,4,10-tetrahydro-1*H*-indolo[3,2-*b*]quinoline **40**, which could be converted to quindoline **3** by treating it with Pd/C (10%) in diphenyl ether at reflux. The conversion from **39** to **40** can also be conducted by treating substrate **39** with 1,2-bis(diphenylphosphino)ethane at 150 °C for 30 min resulting in a similar yield to the one obtained when the conversion was done by $MoO_2Cl_2(DMF)_2$ catalysis.[67]



Scheme 13. Molybdenum catalyzed formation of the quindoline scaffold **40** followed by aromatization.

The key step in Zheng *et al.* synthesis of quindoline **3** was the copper catalyzed cyclisation between *o*-azidobenzaldehyde and (*E*)-1-bromo-2-(2-nitrovinyl)benzene, which was conducted under neat conditions (Scheme 14).[68] This gave intermediate **41**, which was used directly in the next reduction step without purification. The nitro group within compound **41** was then reduced with HCl over iron to give amine **42**, which after an extraction and concentration was subjected to potassium *tert*-butoxide in DMSO at elevated temperature giving natural product **3** in 75% yield over the three steps. The final cyclisation reaction could also be conducted by using 1,2-bis(diphenyl-phosphino)ethane (DPPE) at 150 °C without solvent, however, that only resulted in formation of the target product in 45% yield so those conditions were not further investigated.



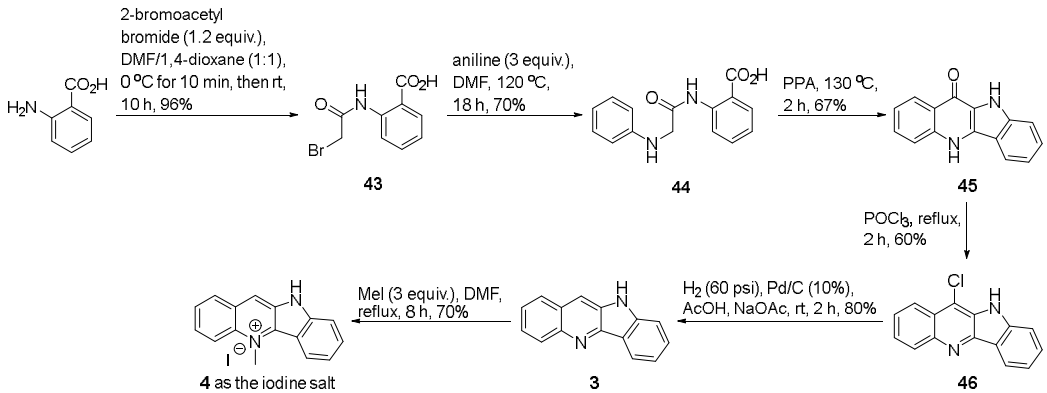
Scheme 14. Formation of quindoline **3** in three consecutive steps without purification of the intermediates.

5. Cryptolepine

Cryptolepine **4**, which is the major constituent isolated from *Cryptolepis sanguinolenta*,[69] was first reported isolated in 1931 by Delaux.[70] However, the structure of cryptolepine **4** was first assigned 60 years later by NMR.[71,72] Cryptolepine **4** has later been isolated from *Sida acuta* collected in Dhaka, Bangladesh,[73] *Microphilis guyanensis* and *Genipa americana* found in the Suriname rainforest,[74] and *Cryptolepsis triangularis* found in West Africa.[75] Synthetic methods for the preparation of cryptolepine **4** has been the

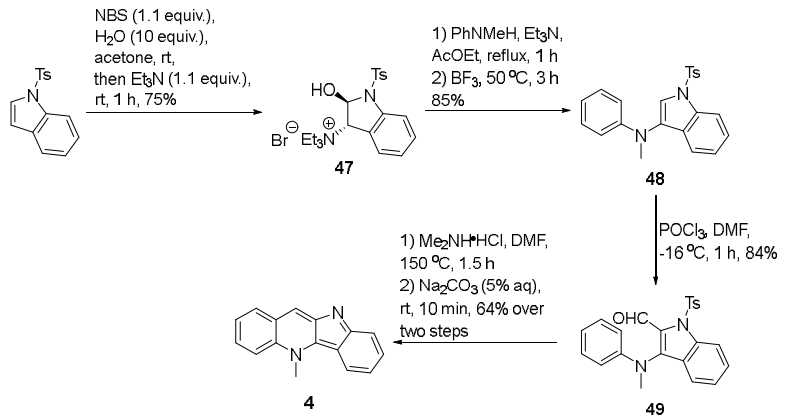
focus of several review articles[1,2,43] and a book chapter.[21] Therefor only the two latest preparations are included herein.

Bharate and co-workers used 2-aminobenzoic acid as starting material in their preparation of the iodide salt of cryptolepine **4**.[76] The acid was treated with 2-bromoacetyl bromide in a mixture of DMF and 1,4-dioxane (1:1) resulting in the formation of acid **43** in excellent yield (Scheme 15). Treating compound **43** with aniline in DMF at elevated temperature gave amide **44**, which could be cyclized to compound **45** upon treatment with poly phosphoric acid at 130 °C. Substrate **45** was then converted to chloride **46** in 60% yield by treating it with phosphoryl chloride at reflux. Hydrogenation of **46** over palladium on charcoal at 60 psi gave quindoline (**3**) in 80% yield. Finally, natural product **3** could be converted to the iodide salt of cryptolepine **4** by reacting it with **3** equivalents of methyl iodide. By adding ethyl acetate to the reaction mixture the desired product precipitated out of solution and could be washed and dried to give 70% yield of the natural product.



Scheme 15. Synthesis of the iodine salt of cryptolepine **4** starting from 2-aminobenzoic acid.

Abe *et al.* commenced their preparation of cryptolepine **4** from 1-tosyl-1*H*-indole by treating it with *N*-bromosuccinimide (NBS) and water in acetone followed by treatment with triethyl amine (Scheme 16).[77]



Scheme 16. Conversion of the stable salt *trans*-2-hydroxy-1-tosylindoline-3-ammonium bromide to cryptolepine **4**.

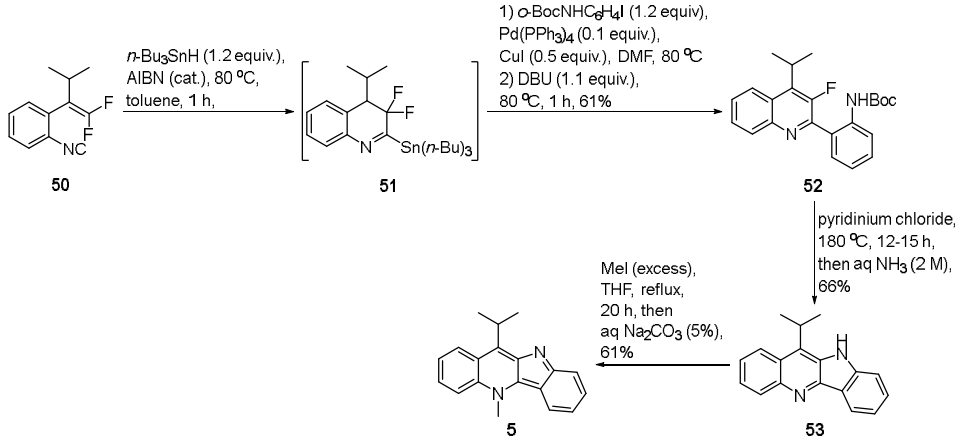
The desired product **47** precipitated out of solution and was collected by filtration in 75% yield. Salt **47**, which is stable for a year under ambient conditions, was then first treated with *N*-methylaniline in

refluxing ethyl acetate with a bit of triethylamine followed by treatment with boron trifluoride resulting in substituted indole **48** in 85% yield. Compound **48** was then converted to aldehyde **49** in 84% yield upon treatment with phosphoryl chloride and DMF at -16 °C. Treating compound **49** first with $Me_2NH^{\bullet}HCl$ in DMF at 150 °C followed by treatment with aqueous base (Na_2CO_3) gave cryptolepine (**4**) in 64% yield over the last two steps.

6. 11-Isopropylcryptolepine

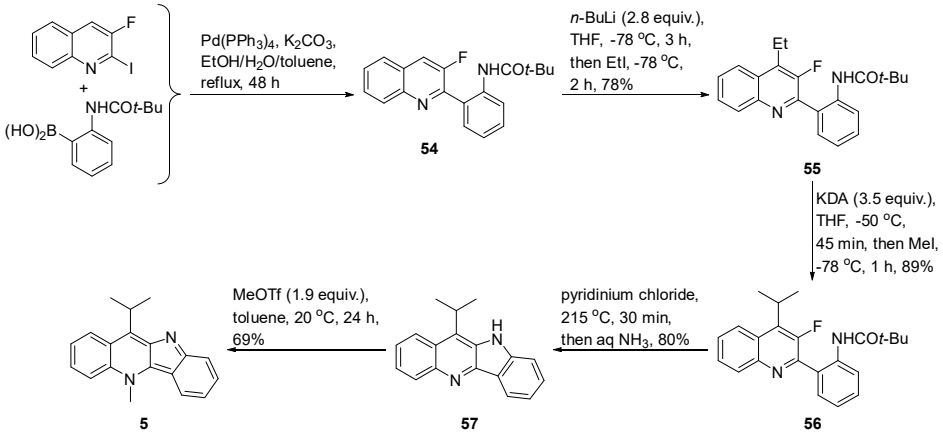
11-Isopropylcryptolepine **5** was reported isolated in 1999 from the roots of *Cryptolepis sanguinolenta*.[78] In the isolation paper there was no report concerning the biological activity of the compound due to small amounts of available natural product. In fact, the structure of the compound was elucidated based on submicro NMR techniques. The compound has only been reported synthesized twice.[79,80] These two synthesis is outlined herein.

The most recent synthesis of 11-isopropylcryptolepine **5** was conducted by Mori and Ichikawa starting from 1-(1,1-difluoro-3-methylbut-1-en-2-yl)-2-isocyanobenzene (Scheme 17).[79] By treating isocyanide **50** with tributyltin hydride together with a catalytic amount of azobisisobutyronitrile (AIBN) at elevated temperature resulted in formation of stannyl **51** as the major product as evident from crude ^{19}F NMR analysis. Treating the crude intermediate **51** with *o*-$BocNHC_6H_4I$ in the presences of catalytic amounts of tetrakis(triphenylphoshine)palladium(0) and copper iodide followed by aromatization upon treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave biaryl **52** in 61% yield. Heating compound **52** in pyridinium chloride at 180 °C facilitated the removal of the protection group followed by the cyclization, thus forming substrate **53**. Compound **53** could then be converted to natural product **5** in 61% yield by treating it with excess methyl iodide and base in refluxing THF.



Scheme 17. Synthesis of 11-isopropylcryptolepine **5** utilizing a free radical reaction as the key step.

The synthesis of 11-isopropylcryptolepine **5** by Arzel *et al.* commenced by preparing biaryl **54** *via* a Suzuki-Miyaura cross-coupling reaction (Scheme 18).[80] Compound **54** was then treated with *n*-BuLi at low temperature (-78 °C) followed by addition of ethyl iodide. By such means it was possible to selectively alkylate quinoline **54** in 4-potion resulting in formation of substrate **55** in 78% yield. Biaryl **55** was then treated with KDA prepared *in situ* by adding *n*-BuLi to a mixture of diisopropylamine and *t*-BuOK mixture in THF at low temperature followed by addition of methyl iodide to install the required isopropyl group in compound **56**. Heating substrate **56** in pyridinium chloride at elevated temperature then gave benzo-δ-carboline **57**, which easily could be converted to 11-isopropylcryptolepine **5** upon treatment with methyl triflate in toluene. The authors also used the method in order to make a range of analogues of the natural product in order to study their cytotoxic, antiplasmodial, and antitrypanosomal activities.

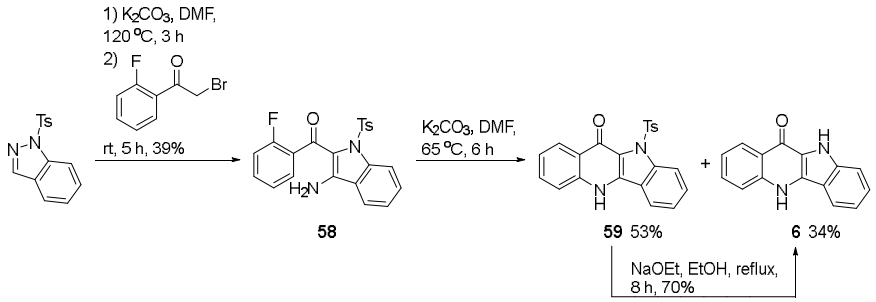


Scheme 18. First synthesis of 11-isopropylcryptolepine **5**.

7. Quindolinone

Quindolinone **6** was originally isolated from the roots of *Cryptolepis sanguinolenta* as a minor component.[1] It has later also been isolated from whole plant extracts of *Sida acuta*.[81] The original structure elucidation was conducted by NMR using micro inverse-detection probes on a 800 μg sample in 140 μL of DMSO-d_6.[82] Out of the indoloquinolines isolated from *Cryptolepis sanguinolenta* quindolinone **6** has resived modest attention from synthetic organic chemists with only scattered reports of its preparation.

The latest reported synthesis of quindolinone **6** was reported by Tang *et al.*[83] Starting from 1-tosyl-1*H*-indazoles they could over a two step sequence generate amine **58** in 39% (Scheme 19). Compound **58** could then be cyclized upon treatment with base in DMF at 65 °C resulting in a mixture of compound **59** with the protection group in place and quindolinone **6** in a ca. 10:6 mixture. More of compound **59** could be converted to the natural product by deprotecting tosyl **59** by treating it with sodium ethoxide in ethanol at reflux. The Tang group also demonstrated in the same report that quindolinone **6** could be prepared in one-pot in a total yield of 12%.

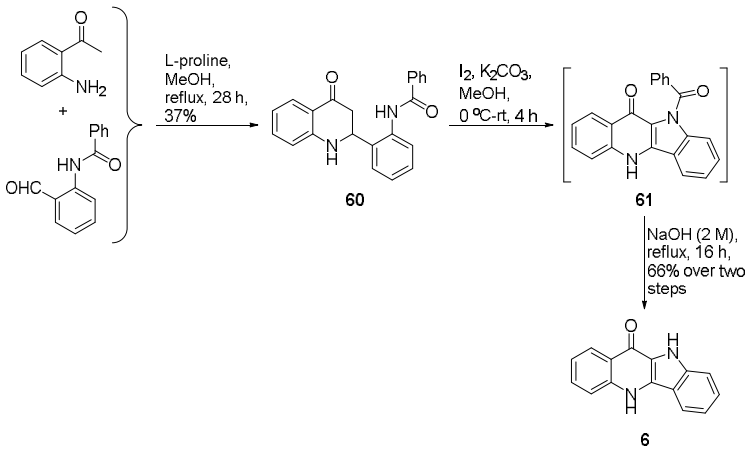


Scheme 19. The latest reported synthesis of quindolinone **6**.

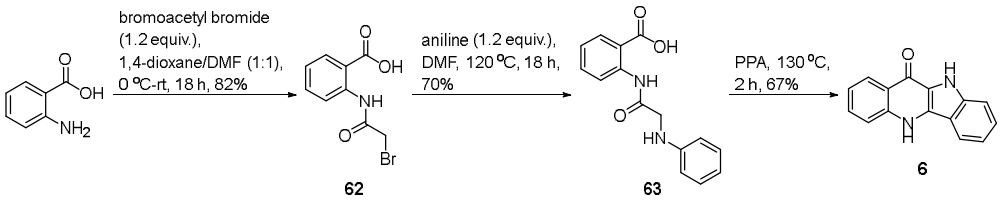
Work conducted by Prabhu and co-workers commenced with the formation of bicycle **60** by treating 1-(2-aminophenyl)ethan-1-one and *N*-(2-formylphenyl)benzamide with L-proline in refluxing methanol (Scheme 20).[84] Treating compound **60** with iodine and base (K_2CO_3) in methanol gave intermediate **61**, which was directly converted to quindolinone **6** by adding 2 M sodium hydroxide and refluxing the reaction mixture for 16 hours. This gave the natural product **6** in 66% yield over the two steps.

The work by Mudududdla *et al.* started by preparing *N*-bromoacetyl anthranilic acid **62** from anthanilic acid and bromoacetyl bromide (Scheme 21).[85] Treating compound **62** with aniline in DMF at 120 °C gave

substrate **63** in 70% yield. Compound **63** was then cyclized to quindolinone **6** upon heating in excess amounts of polyphosphoric acid (PPA). This gave after purification the natural product **6** in 67% yield.



Scheme 20. Synthesis of quindolinone **6** starting from 1-(2-aminophenyl)ethan-1-one and *N*-(2-formylphenyl)benzamide.



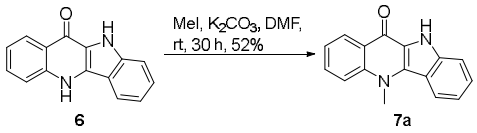
Scheme 21. Synthesis of quindolinone **6** utilizing a polyphosphoric acid promoted cyclization as the final step.

8. Cryptolepinone/11-hydroxycryptolepine

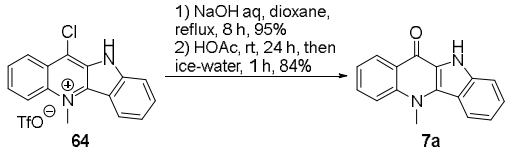
Cryptolepinone **7a**/11-hydroxycryptolepine **7b** was fist isolated from *Cryptolepis sanguinolenta*,[10] and has since then been isolated from *Sida acuta*[86] and *Sida rhombifolia*.[87] The true structure of indoloquinoline **7** has been a mystery with cryptolepinone (keto form, **7a**)/11-hydroxycryptolepine (enol form, **7b**) both being reported isolated from *Cryptolepis sanguinolenta*.[88-93] Which form of the compound that is present in solution depends on pH of the solution and the solvent used. Mixture of the two forms may also occur. This explains why two tautomeric structures for the natural product, viz. the keto and the enol form, has been reported in the literature. A theoretical study conducted by Kataoka and Sato in 2009 showed that cryptolepinone **7a** exists in pyridine, acetone, methanol, acetonitrile, and dimethyl sulfoxide (DMSO), however, experimental work has previously reported that both cryptolepinone **7a** and 11-hydroxycryptolepine **7b** are present in methanol and acetonitrile.[88] Synthetic strategies towards this natural product has not previously been included in a review so the three synthetic reports of this compound in discussed below.

With the synthesis of quindolinone **6** sorted out it was a simple alkylation for Tang *et al.*[83] to prepare cryptolepinone **7a** (Scheme 22). This was executed by treating compound **6** with methyl iodide in DMF in the presence of potassium carbonate resulting in formation of cryptolepinone **7a** in 52% yield.

The synthesis of cryptolepinone **7a** by Fort *et al.*[92] commenced with the preparation of 11-chloroquindolinium hydrotriflate **64** using literature methods.[94] The triflate **64** was then converted to compound **7a** by first treating it with sodium hydroxide in refluxing dioxane followed by treatment with acidic acid (Scheme 23). This gave the desired product **7a** in 80% yield over the two steps.

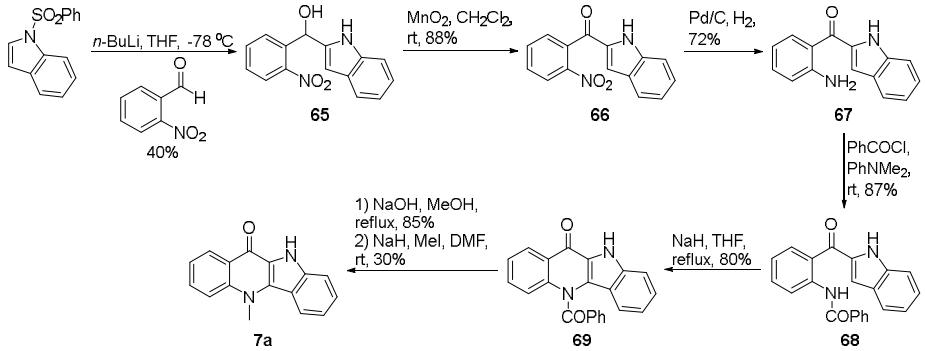


Scheme 22. Methylation of quindolinone **6** to give cryptolepinone **7a**.



Scheme 23. Conversion of 11-chloroquindolinium hydrotriflate **64** to cryptolepinone **7a**.

Joule and co-workers treated 1-(phenylsulfonyl)-1*H*-indole with *n*-BuLi in THF at -78 °C followed by addition 2-nitrobenzaldehyde to give compound **65** (Scheme 24).[95] Oxidation of the secondary alcohol within compound **65** with MnO_2 gave substrate **66** in excellent yield. The nitro group was then reduced to the primary amine under standard conditions giving amine **67** in 72% yield. Compound **67** was then converted to protected amine **68** in 87% yield. Treatment of compound **68** with sodium hydride in THF at reflux gave protected cryptolepinone **69**. The protection group within **69** could easily be removed followed by a rather low yielding (30%) methylation with methyl iodide giving natural product cryptolepinone **7a**.



Scheme 24. Synthesis of cryptolepinone **7a** using a base promoted cyclization to form the tetracyclic ring system.

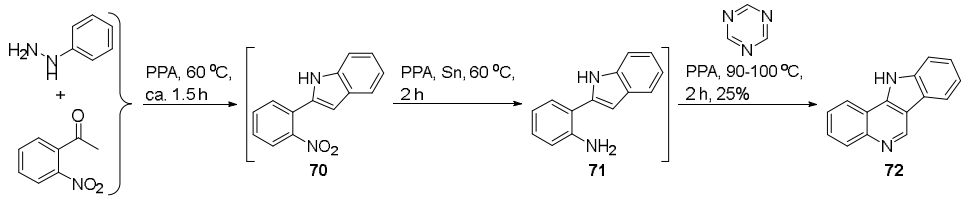
9. Isocryptolepine

Isocryptolepine **8** (also sometimes referred to with the name cryptosanginolentine) was isolated from the West African plant *Cryptolepis sanguinolentain*.[15,96] Isocryptolepine **8** has been and still is a popular target for synthetic chemists. The synthesis of isocryptolepine conducted up to 2016 has been nicely summarized by Parvatkar and co-workers in several review articles.[1,2,41] In addition synthesis conducted between 2016 and 2018 was recently summarized in a book chapter by Sydnes,[21] and two one-pot strategies for the formation of isocryptolepine **8** were reviewed recently.[97] The following section will therefor only report on the very latest updates on the synthesis of isocryptolepine **8** opening up for the preparation opening up the possibility to make a more divers library of analogues.

Following up from their very efficient one-pot strategy for the formation of isocryptolepine **8** reported in 2017,[37] Aksenov *et al.* reported their second generation one-pot strategy towards isocryptolepine analogues.[98] Shortly after their report of the second generation method and the use of that strategy to make analogues of the natural product[38] Aksenov *et al.* recently reported a one-pot strategy where they have replaced 2-aminoacetophenones with 2-nitroacetophenones.[99] The main argument for changing from

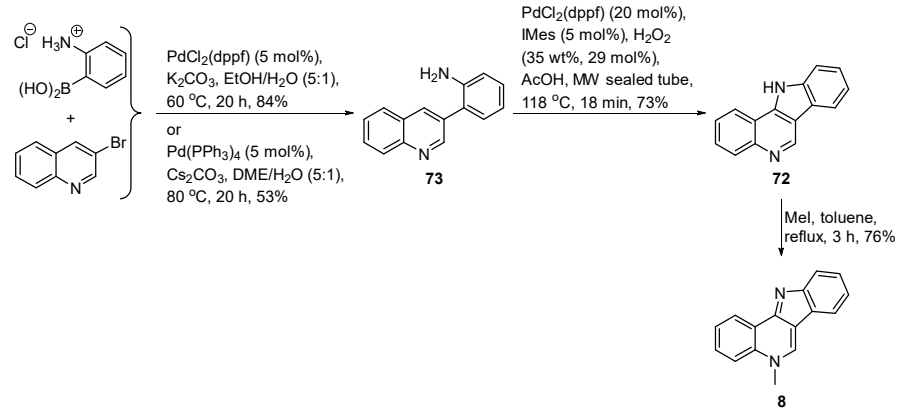
2-aminoacetophenones to 2-nitroacetophenones was that the latter starting material has a broader range of analogues available that can be utilized in the reaction, thus opening up for the formation of a broader range of analogues.

The one-pot procedure commenced by heating phenylhydrazine and 2-nitroacetophenone in polyphosphoric acid (PPA) at 60 °C resulted in formation of intermediate **70** (Scheme 25).[99] Addition of tin to the reaction mixture resulted in reduction of the nitro functionality to the corresponding amine **71**. 1,3,5-Triazine was then added to the reaction mixture and the temperature was elevated to 100 °C. After 2 hours the desired quinoline **72** could be isolated after column chromatography in 25% yield. The main reason for the low yield, which is much lower than what was obtained when using 2-aminoacetophenones (yields ranging from 70-85%), is the thermal decomposition of indole **70**. The authors commented that a shorter reaction time for the reduction resulted in a greater yield of the final product.



Scheme 25. A new one-pot strategy reported by Aksenov and co-workers for the preparation of the quinoline **72** precursor of isocryptolepine **8**.

The Sydnes group used a Suzuki-Miyaura cross-coupling followed by a tandem C-H activation and C-N bond formation in their approach towards isocryptolepine **8**.[100,101] By subjection 3-bromoquinoline and 2-aminophenylboronic acid hydrochloride to $PdCl_2$(dppf) in ethanol/water (5:1) the cross-coupling gave 2-(quinolin-3-yl)aniline **73** in 84% yield (Scheme 26).[101]



Scheme 26. Synthesis of isocryptolepine **8** by a Suzuki-Miyaura cross-coupling and tandem C-H activation and C-N bond formation strategy.

The Suzuki-Miyaura cross-coupling reaction could also be conducted by using $Pd(PPh_3)_4$ as catalyst, but the yield then dropped to 53%. However, when using the same cross-coupling in reactions with other bromoquinolines (2-, 4-, 5-, 6-, 7- and 8-bromoquinoline) tetrakis(triphenylphosphine) palladium(0) was the catalyst of choice.[101] With compound **73** in hand the required C-H activation and C-N bond formation could be conducted upon treatment with $PdCl_2$(dppf), 1,3-bis(2,4,6-trimethylphenyl)-imidazolium (IMes), and hydrogen peroxide in acetic acid under microwave conditions resulting in formation of quinoline **72** in 73% yield. Treating quinoline **72** with methyl iodide in toluene under reflux resulted in smooth conversion to the

natural product **8** (76% yield). This strategy is now being used in order to generate a variety of analogues of isocryptolepine with the aim to enhance the anti-cancer and anti-malarial activity of the natural product. A method that is worth mentioning, which was recently reported by Fan and co-workers,[102] provides a very efficient method for the preparation of isocryptolepine analogues by a Rh(III) catalyzed dimerization of 2-alkynylanilines. However, the reaction failed to give 11*H*-indolo[3,2-*c*]quinoline **72**, the direct precursor for the formation of isocryptolepine **8**, but it is a highly valuable method for the preparation of analogues of the natural product for biological evaluation.

10. Conclusion

As can be seen from the overview of strategies utilized to prepare the indoloquinoline natural products a broad range of starting materials and chemistries has been used. In an overview like the one herein and in the previous reviews that have been written on the subject and referred to herein there will obviously be some methods that stand out as more superior than others. Particular methods that requires few purification steps are attractive. The work by Zheng *et al*.[68] is a good example of that. They prepared quindoline **3** in three consecutive steps with only the need to purify the final product. The one-pot procedures reported on several occasions by Aksenov and co-workers are also very attractive methods to prepare these natural products efficiantly.[37,38,98,99] Several of the synthetic strategies presented in this chapter are now being used in order to prepare analogues with the aim to make more potent compounds than the natural products.

Acknowledgment

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