

A General Approach to Indoles: Practical Applications for the Synthesis of Highly Functionalized Pharmacophores

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Abstract: The development of a long-term manufacturing route to a potent and selective KDR kinase inhibitor has led to the discovery of several novel methodologies for the general synthesis of indoles. The key transformations involved addition of a trimethylsilylnitro benzene to an aromatic aldehyde which afforded the key nitroalcohol intermediate. Oxidation of the nitroalcohol intermediate led to a nitroketone; whereas, elimination afforded exclusively a *trans*-nitrostyrene. Reductive cyclization gave the target compounds in excellent overall yield from readily available bulk chemicals. Application of this methodology has led to the synthesis of highly functionalized pharmacophores including other KDR kinase inhibitors, biindoles and tjiapanazole natural products, indolo[2,3-*a*]pyrrolo [3,4-*c*]carbazoles, indole-4-carboxylic amides, N-hydroxyindoles, and 2,3-dihydrobenzofurans.

Keywords: Dihydrobenzofuran · Indole · Nitrostyrene · Reductive cyclization

1. Introduction

The indole nucleus is arguably the most widely distributed heterocyclic ring system found in nature. Owing to the vast array of structurally diverse and biologically active indoles, it is not surprising that the indole nucleus is an important component in many pharmaceutical agents [1]. Substituted indoles have been referred to as ‘privileged structures’ since they are capable of binding to multiple receptors with a high degree of affinity [2]. The synthesis and functionalization of indoles continues to be a major area of focus for academic as well as industrial researchers, and numerous methods for their preparation have been developed [3][4]. Starting material availability and functional group compatibility often dictate which particular indole synthesis will be suitable. When particular substitution patterns remain difficult to obtain by standard indole-forming reactions, new methodologies emerge.

Tyrosine kinases are a class of enzymes believed to play a critical role in the signal

transduction of a number of cellular functions and have been implicated in a wide range of diseases and conditions [5]. Angiogenesis is characterized by excessive activity of vascular endothelial growth factor (VEGF) leading to formation of blood vessels necessary for the support of tumor growth. The kinase insert domain receptor (KDR) is a tyrosine kinase that has a high affinity for VEGF. KDR is believed to be a primary mediator of tumor-induced angiogenesis; therefore, inhibition, modulation, or regulation of the KDR receptor may be useful in the prevention and treatment of tumor-induced angiogenesis and various other diseases including cancer, psoriasis, and hyper-immune responses. Merck has identified a number of potent and selective KDR inhibitors for the potential use in a range of cancer indications [6][7]. As part of a program to discover and develop inhibitors of KDR kinase activity, compound **1** was selected for preclinical and clinical development (Fig. 1). The key structural feature of **1** is the indol-2-yl-1*H*-quinolin-2-one ring system bearing a mesylpiperazine moiety where the indolyl quinolinone ring system is the central pharmacophore. The development of a practical, long-term manufacturing route to **1** will be described as well as the evolution of a research program aimed at the application of novel methodologies for the preparation of other highly functionalized indoles and dihydrobenzofurans.

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2. The Problem and Approach

Conventional approaches to 2-aryl indoles have typically relied upon either the classical Fischer indole synthesis [3][4] or cross coupling of 2-indolyl halides, boronic acids, stannanes, and silanes [8]. Although effective methods are now available for the preparation of 2-indolyl boronic acids and silanes [9], the major limitation with most of these approaches are the additional steps required for the preparation of the coupling partners to enter the palladium-catalyzed reactions. The first generation synthesis of **1** relied on a highly efficient Suzuki-Miyaura cross-coupling between indolyl boronic acid **5** and 3-bromo-1*H*-quinolin-2-one **6** (Scheme 1) [10]. This approach provided **1** in seven linear steps and in 55% overall yield, and the route suffered from costly starting materials (*i.e.* **5** and **6**), required protection of the indole and piperazine moieties, and utilized an excess (1.5 equiv.) of **5** in the cross cou-

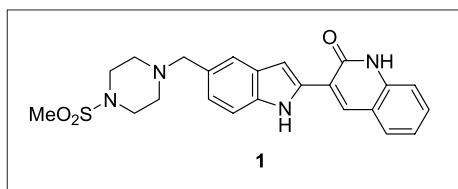
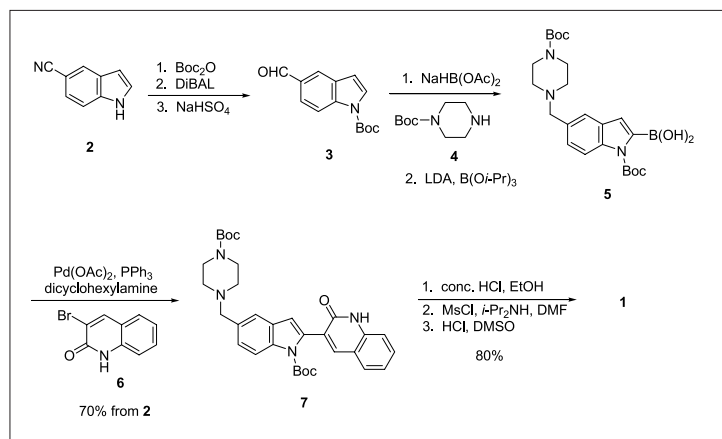
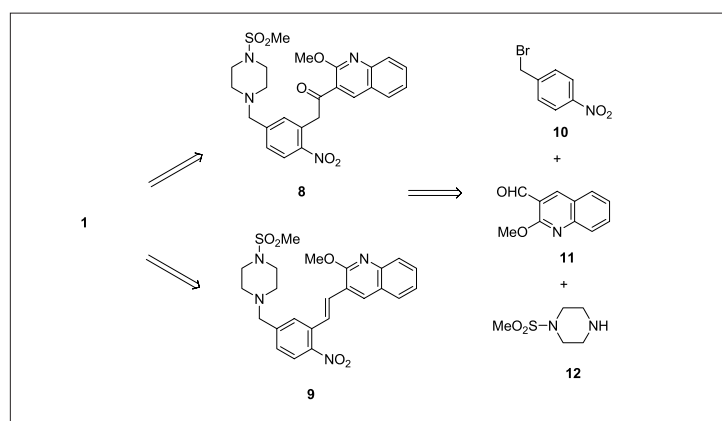


Fig. 1.

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Scheme 1.



Scheme 2.

pling step. In addition, the poor solubility of the quinolin-2-one moiety of **7** and downstream intermediates made processing extremely difficult and necessitated the use of large reaction volumes. Therefore, an improved long-term, cost effective manufacturing route was required.

Retrosynthetic analysis of **1** revealed there may be a number of intriguing methods of constructing the indol-2-yl-quinolin-2-one ring system. Approaches which centered on formation of the indole ring as the key step for the preparation of **1** were particularly attractive. Reactions leading to increasing molecular complexity are important synthetic tools, and it was envisioned that construction of the indole ring as the key synthetic step would allow for the preparation of intermediates from readily available starting materials. Of the many routes investigated [11], the reductive cyclization of nitro ketone **8** or nitro styrene **9** offered the possibility of improved synthetic efficiency and would provide the indol-2-yl-quinolin-2-one ring system of **1** in fewer synthetic steps with better atom economy (Scheme 2). Due to the poor solubility properties associated with the 1*H*-quinolin-2-one ring system of **1** and all related intermediates, the readily available and easily hydrolyzed methoxy-protected quinoline **11** was utilized. This masked quinolinone protecting group became a key design feature and imparted a

significant degree of solubility to synthetic intermediates.

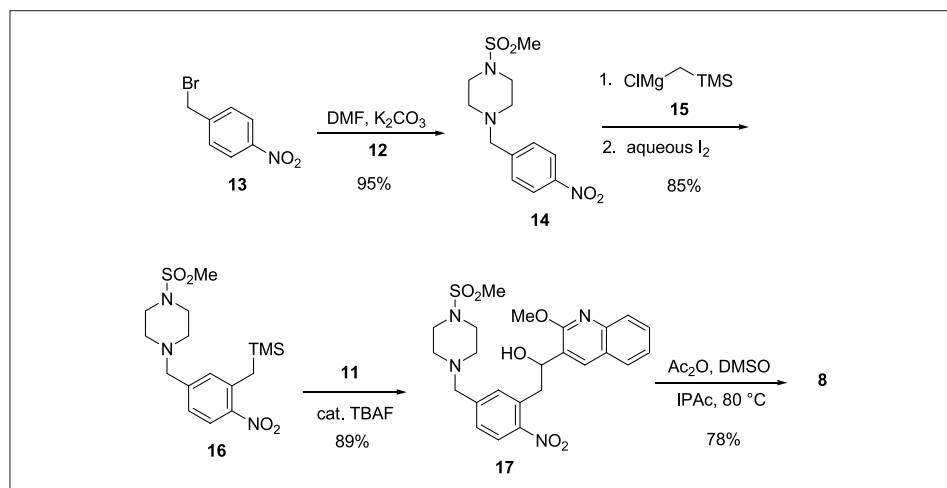
2.1. Nitro Ketone Reductive Cyclization Route

Reductive cyclization of 2-nitrobenzyl-carbonyl compounds is one of the oldest methods for the construction of indoles and indolinones [1][3][4]. The reductive cyclization of 2-nitrobenzyl ketones has been carried out with a variety of reagents including H_2/Pd , $H_2/RaNi$, $SnCl_2$, $Fe/AcOH$, $Zn/AcOH$, $TiCl_3/NH_4OAc$, and $Na_2S_2O_3$ [1][4]. However, the availability of starting materials has severely limited the util-

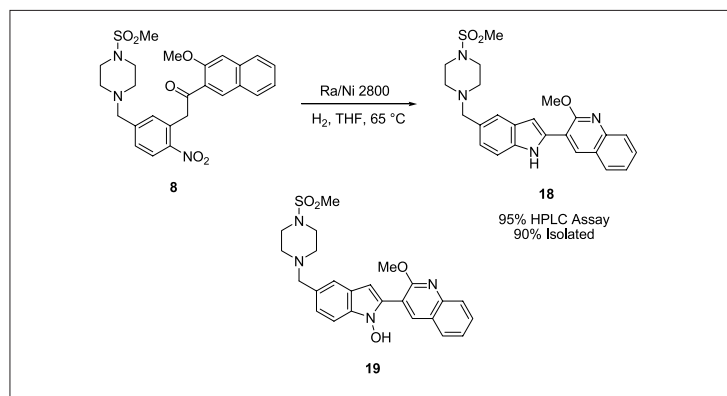
ity of this approach. Recent advances by the groups of Buchwald [12], Rawal [13], RajanBabu [14], and others [15] have given ready access to 2-nitrobenzyl ketones which are conveniently converted to substituted indoles. While these methods are noteworthy, there was still a need for alternative methods which provide highly functionalized 2-nitrobenzyl ketones and their subsequent conversion to indoles.

Our first goal was the development of an efficient high-yielding synthesis of nitroketone **8**, and our approach was inspired by the unique versatility of nitrobenzenes due to their ability to serve as nucleophilic and electrophilic partners [16]. The synthesis of **8** began by alkylation of readily available 4-nitrobenzyl bromide **13** with 1-methanesulfonylpiperazine **12** (Scheme 3) [17]. Reaction of **12** and **13** for 2 h in DMF in the presence of K_2CO_3 at room temperature afforded nitro derivative **14** in 95% isolated yield. Addition of trimethylsilylmethylmagnesium chloride **15** to a solution of **14** in THF at $-15^\circ C$ followed by oxidation of the resulting nitronate intermediate with DDQ [18] gave addition compound **16** in 85% yield. Alternatively, the oxidation could be carried out with *p*-chloranil and gave **16** in 83% yield. The corresponding workup of these reactions proved difficult to engineer on larger scale (>10 g) due to difficulty in removing DDQ or *p*-chloranil by-products. After extensive experimentation it was discovered that the oxidation of the nitronate intermediate was cleanly achieved with aqueous 1 N iodine solution which greatly simplified the workup and gave **16** in 85% yield. The higher purity of the crude stream of **16** allowed for its use in the subsequent reactions without the need for chromatography or further purification.

Treatment of a mixture of **16** and aldehyde **11** with a catalytic amount of TBAF furnished alcohol **17** in 89% yield [19]. Alcohol **17** was not isolated but used directly in the oxidation step without further



Scheme 3.



Scheme 4.

purification as a stream in isopropyl acetate (IPAc). Oxidation of **17** with Ac₂O/DMSO in IPAc at 80 °C gave ketone **8** which could be crystallized from the crude reaction mixture in 78% yield [20].

The reductive cyclization of **8** to indole **18** was accomplished under highly optimized conditions employing hydrogenation over Raney nickel in order to minimize the formation of hydroxyindole **19** (Scheme 4) [21]. Under most conditions screened, hydroxyindole **19** was the major product even upon prolonged reaction and the addition of excess catalyst [21]. The optimal conditions for the conversion of **8** to **18** involved the use of 40 wt% of Ra/Ni 2800 (H₂O), 40 psi H₂, and 65 °C in THF for 7.5 h and gave **18** in 95% HPLC assay yield. There was no detectable amount of **19** in the crude reaction mixture under these conditions. The isolation of **18** was simply a matter of filtering the catalyst, concentrating the filtrate, and adding MeOH, which precipitated the product in analytically pure form and in 90% isolated yield.

2.2. Nitro Styrene Reductive Cyclization Route

The widespread use of *ortho*-nitrostyrenes as synthetically useful intermediates has been limited by available methods for their preparation. Traditional approaches have relied on Wittig reactions of either 2-nitrobenzaldehydes or 2-nitro-phosphonium and phosphonate salts [22]. Alternatively, cross-coupling approaches involving 2-halonitrobenzenes or 2-nitrophenylstannanes have received considerable attention as an attractive method for the preparation of a range of *ortho*-nitrostyrenes [23]. Although each of these approaches offer certain advantages, they often require multiple steps for the construction of the appropriate starting materials and generally require purification by chromatography. In addition, these strategies have a high environmental burden since they suffer from poor atom economy and generate a significant amount of phosphorous or tin by-products.

The reductive cyclization of aromatic nitrostyrene compounds for the formation

of indoles has received considerable attention since the pioneering work of Cadogan *et al.* [24] and Sundberg *et al.* [25] who first described the formation of indoles *via* deoxygenation of aromatic nitrocompounds with trivalent phosphorus compounds (typically triethyl phosphite). While the Cadogan/Sundberg reaction is broad in scope, the extreme reaction conditions (>150 °C), formation of both N-hydroxy- and N-ethoxyindole byproducts, and the large amount of phosphorus waste render this transformation impractical for the process chemist. Transition metal catalyzed reductive cyclizations employing carbon monoxide as the stoichiometric reductant have recently emerged as a highly versatile method for the construction of indoles due to superior yields, diminished amounts of reaction by-products, and favorable environmental impact [23][26][27].

The preparation and reductive cyclization of nitrostyrene **9** is outlined in Scheme 5. Treatment of crude alcohol **17** with TFAA followed by elimination of the corresponding trifluoroacetate with DBU at 60 °C, in a one-pot operation, afforded exclusively *trans*-nitrostyrene **9** in 80% yield after direct crystallization from the crude reaction mixture. There was no detectable amount of any *cis*-nitrostyrene formed in the reaction mixture. The use of DBU for the elimination of the trifluoroacetate intermediate was also found to be crucial. When other amine bases were employed, little conversion to **9** was observed, and the use of aqueous bases

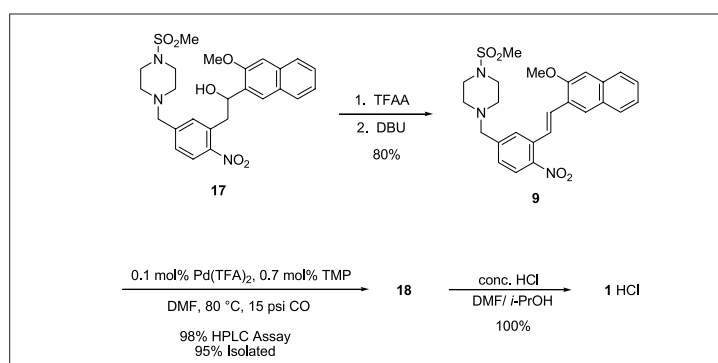
resulted in hydrolysis and alcohol **17** was re-isolated.

The reductive cyclization of **9** was extensively investigated with the aid of a parallel pressure reactor (PPR) in which optimization of all the reaction parameters (catalyst, ligand, solvent, temperature, pressure) could be conducted in an extremely rapid fashion [26]. The optimized reaction conditions employed 0.1 mol% Pd(TFA)₂, 0.7 mol% 3,4,7,8-tetramethylphenanthroline (TMP) in DMF at 80 °C, and 15 psi CO to give **18** in 98% HPLC assay yield. The isolation of **18** involved filtration of the catalyst and addition of MeOH to provide **18** in 95% yield.

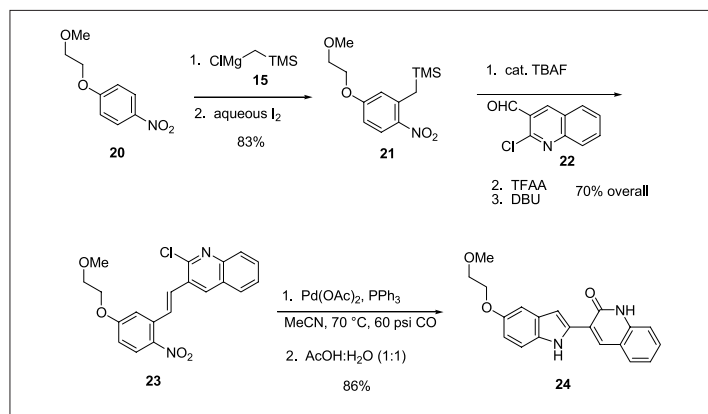
The deprotection of the masked quinolin-2-one moiety of **18**, prepared by either reductive cyclization of nitroketone **8** (Scheme 4) or nitrostyrene **9** (Scheme 5) was accomplished in a straightforward manner under acidic conditions. Reaction of **18** with concentrated HCl in DMF at 70 °C followed by the addition of IPA as an anti-solvent gave the crystalline KDR kinase inhibitor **1** as the desired HCl salt in quantitative yield. Compound **1** was prepared in six synthetic steps from readily available bulk chemicals in 56% overall yield for the nitroketone route and 60% overall yield for the nitrostyrene route. Due to the use of 40 wt% Ra/Ni and the presence of an oxidation step in the nitroketone route, the higher yielding nitrostyrene route was selected as the long-term manufacturing route for the preparation of **1**.

3. Application to Other KDR Kinase Inhibitors

Prior to the finalization of the manufacturing route to **1**, the above methodology was also utilized in the preparation of KDR kinase inhibitor **24** (Scheme 6) [28]. For example, addition of trimethylsilylmethylmagnesium chloride **15** to a solution of **20** [29] followed by oxidation with aqueous iodine afforded **21** in 83% yield. Treatment of a mixture of **21** and chloroquinoline **22** with a catalytic amount of TBAF furnished the



Scheme 5.



Scheme 6.

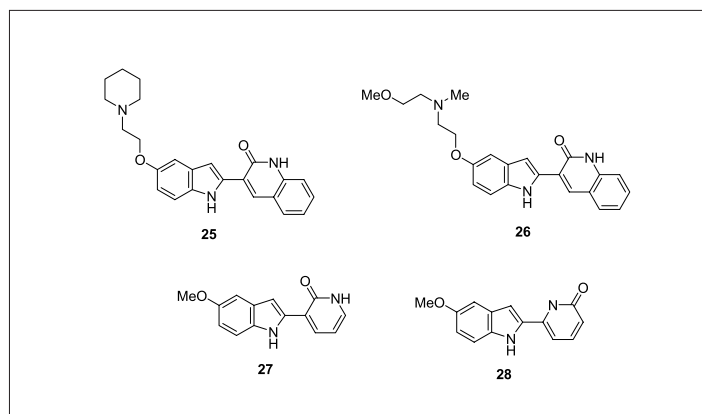
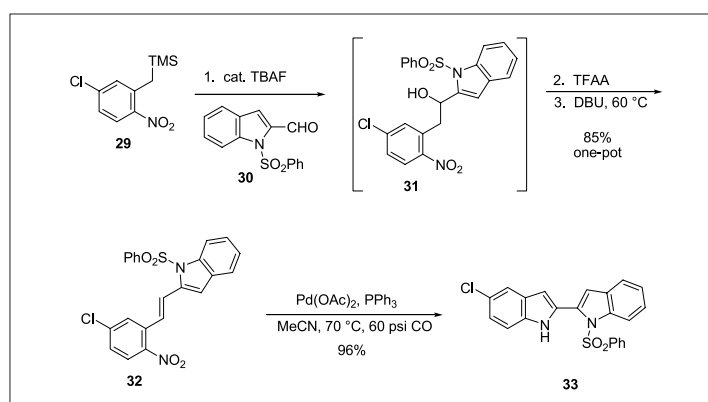


Fig. 2.



Scheme 7.

desired alcohol which was used crude in the elimination reaction without purification. Reaction with TFAA followed by elimination of the trifluoroacetate intermediate with DBU gave nitrostyrene **23** in 70% overall yield from **21**. Palladium-catalyzed reductive cyclization under Söderberg conditions (6 mol% Pd(OAc)₂, 24 mol% PPh₃, CO (6 atm), 70 °C) [23] gave the corresponding indole in 94% yield. The quinolinone functionality was unmasked by hydrolysis of the chloroquinoline in 1:1 AcOH/water [7] and gave **24**, which crystallized from the crude reaction mixture and was isolated in 91% yield. This same sequence of transformations was also successfully employed in the preparation of KDR kinase inhibitors **25–28** (Fig. 2) [28].

4. Preparation of Indolo[2,3-*a*]carbazole Aglycons, Glycosides, and Indigo Azines

The indolo[2,3-*a*]carbazole ring system constitutes the core skeleton of a family of structurally unique natural products possessing a wide range of biological activity [30]. Indolocarbazole glycosides with either one or two glycosidic linkages have been shown

to be potent inhibitors of protein kinase C and topoisomerases and exhibit antitumor activity [30][31]. In addition, the aglycons have been shown to be potent and selective inhibitors of human cytomegalovirus [32]. The potency and selectivity of the indolocarbazoles depends on the arrangement of substituents about the aglycon as well as the nature of the carbohydrate moiety. Often the aromatic substituents are displayed in an unsymmetrical manner, which presents a formidable challenge to current synthetic methods. As an outgrowth of the KDR program, the ability to assemble highly functionalized 2-arylindoles rapidly from readily available starting materials prompted us to investigate this methodology for the preparation of unsymmetrical 2,2'-biindoles and their elaboration of indolo[2,3-*a*]carbazole aglycons and glycosides [33].

The first challenge was preparation of the *ortho*-nitrostyrenes. Reaction of a mixture of the known TMS-nitro compound **29** [18] and indole carboxaldehyde **30** with a catalytic amount of TBAF afforded the desired alcohol **31** which was not isolated (Scheme 7). Direct addition of TFAA to the reaction mixture was followed by elimination of the corresponding trifluoroacetate with DBU at 60 °C and afforded exclu-

sively the highly crystalline *trans*-nitrostyrene **32** in 85% overall yield for the one-pot transformation. Reductive cyclization of **32** gave biindole **33** in 96% yield. The reaction sequence was general and provided access to an array of diversely substituted symmetrical and unsymmetrical nitrostyrenes and biindoles in modest to excellent yield for each synthetic step (Table 1).

With the biindoles in hand, our focus turned to the preparation of tjipanazole alkaloids I, D, B, and E (Scheme 8). While the preparation of the indolocarbazole ring system of the tjipanazole alkaloids from 2,2'-biindoles was unprecedented, an operationally trivial procedure for incorporation of the two-carbon fragment with the correct oxidation state was developed [34]. For example, reaction of biindoles **36** and **39** with (dimethylamino)-acetaldehyde diethyl acetal in acetic acid [35] provided tjipanazoles I (**53**) and D (**54**) in 79 and 71% yields respectively. In similar fashion, reaction of biindole **42** under the identical reaction conditions gave indolocarbazole **55** in 73% yield. This synthetic strategy was particularly noteworthy as it gave access to unsymmetrical indolocarbazole aglycons in just three synthetic operations from readily available starting materials.

The installation of the carbohydrate moieties and the completion of the total syntheses of tjipanazoles E and B was accomplished by glycosylation of **39** in a biphasic mixture of MTBE and 45% aqueous KOH and Aliquat 336 followed by hydrogenation [36]. Reaction of **39** with α -D-glycolopyranosyl chloride (**56**) [36] under these conditions furnished tjipanazole E (**57**) as a single anomer in 77% overall yield from **39**. In like fashion, tjipanazole B (**59**) was obtained as a single anomer from α -D-xylopyranosyl chloride (**58**) [37] in 66% overall yield. The synthetic sequence outlined in Scheme 8 allowed for the first reported total syntheses of tjipanazoles E and B *via* the high-yielding, stereoselective

glycosidation of the respective indolocarbazole aglycon.

Due to the pronounced physiological activities of many indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazoles, which continue to attract the synthetic efforts of academic and pharmaceutical researchers, our 2,2'-biindoles bearing a phenylsulfonyl group were examined as suitable substrates for the synthesis of unsymmetrical indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazoles (Scheme 9) [38]. It was reasoned that N-sulfonylbiindoles would provide significant advantages in the [4+2]

cycloaddition with various dienophiles due to the electron-withdrawing nature of the sulfonyl group, which would facilitate the formation of the [4+2] adducts by accelerating the rate of cyclization (*i.e.* **64** to **65**). Reaction of **33** with N-benzylmaleimide in chlorobenzene (150 °C, sealed tube, 12 h) gave **61** as the single reaction product, which crystallized from the crude reaction mixture in 50% yield. Interestingly, the phenylsulfonyl group was absent from the isolated product. It was speculated that addition of the dienophile to the 3-position of

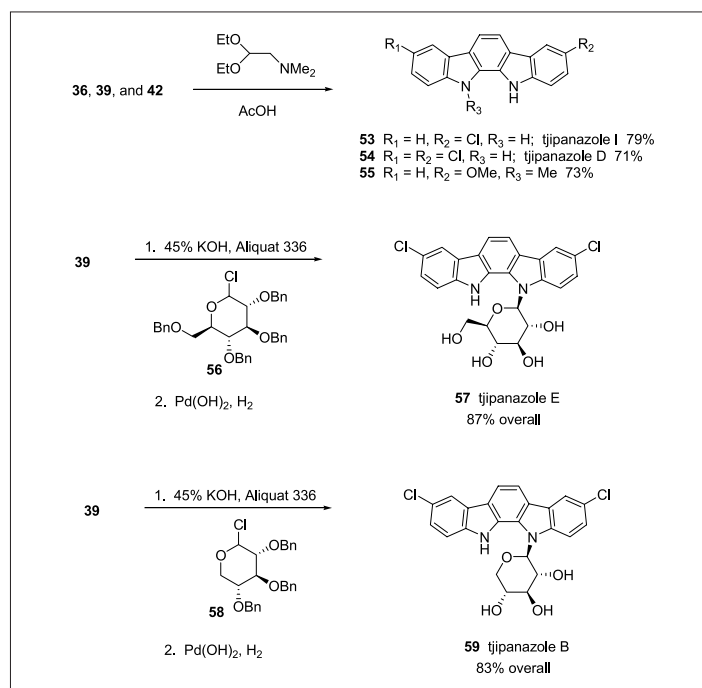
the unsubstituted indole ring gave intermediate **64**. Rapid cyclization to **65**, which is facilitated by the phenylsulfonyl group, was followed loss of the phenylsulfonyl group as part of the aromatization process. Dehydrogenation of **66** led to the product **61**. In similar fashion, reaction of **33** with N-methylmaleimide afforded **62** in 47% yield, and reaction of **60** with N-phenylmaleimide gave **63** in 42% yield.

Access to indigo azines was also realized by reaction of **39** with diethylazodicarboxylate (DEAD). For example, reaction of symmetrically substituted 2,2'-biindole **39** with DEAD at 150 °C in a sealed tube for 12 h gave 5,5'-dichloroindigo azine derivative **67** as the only identifiable product in 39% yield (Scheme 10). Under the identical reaction conditions, reaction of biindole **60** with DEAD afforded **68** in 43% isolated yield. The isolation of these azine products with the N-sulfonyl group still attached to the indole core indicated that an alternative

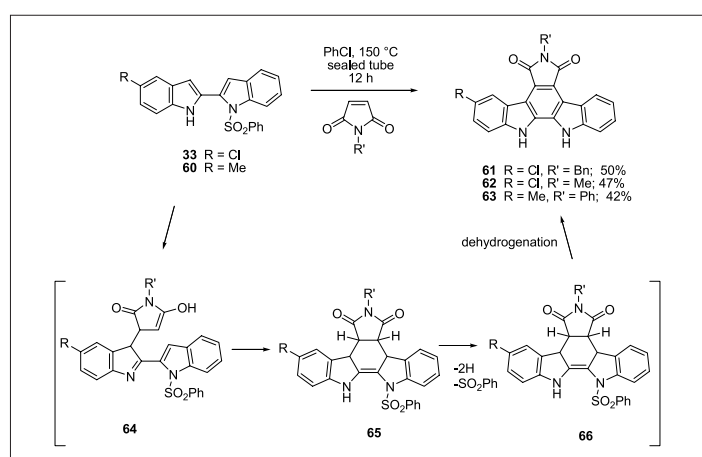
Table 1. Preparation of nitrostyrenes and biindoles

Aldehyde	Styrene (% yield)	Biindole (% yield)
	35 (51%) ^a	36 (68%)
	38 (33%) ^a	39 (68%)
	41 (43%)	42 (84%)
	43 (60%)	44 (69%)
	45 (62%)	46 (63%)
	48 (25%)	49 (94%)
	51 (60%)	52 (71%)

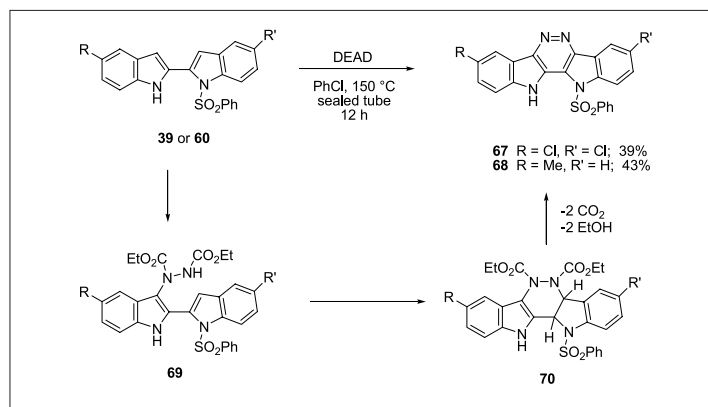
^a The Boc group was cleaved under the reaction conditions.



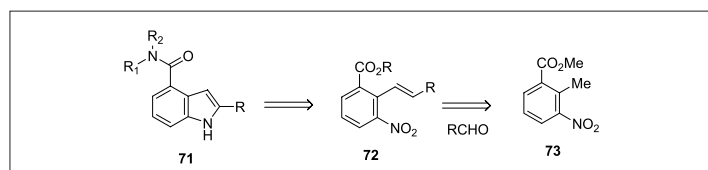
Scheme 8.



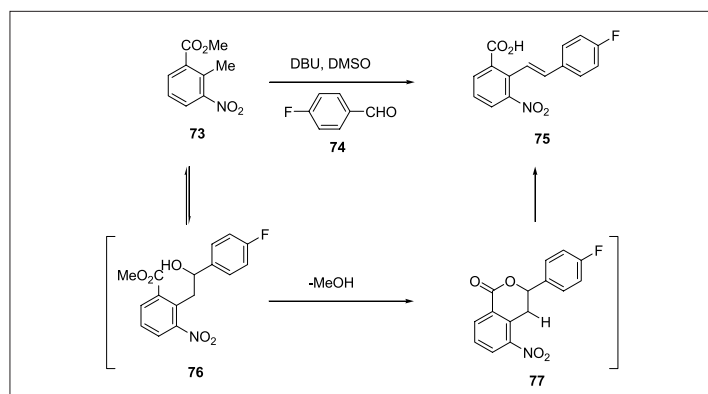
Scheme 9.



Scheme 10.



Scheme 11.



Scheme 12.

reaction mechanism was operating. It was postulated that addition of **39** to DEAD was followed by rapid re-aromatization of the indole ring to give intermediate **69**. Indeed, when the reaction was conducted in toluene for shorter periods of time (3 h), intermediate **69** could be isolated (56–62%) and only trace amounts of **67** were present. Ring closure of **69** to intermediate **70** leads to aromatization and decarboxylation to give **67**. The primary driving force for the overall sequence from **69** to **67** was aromatization of the C-ring.

5. Preparation of 2-Arylindole-4-carboxylic Amide Derivatives

Indole-4-carboxylic amide derivatives possess a wide range of biological activity including CC chemokine receptor 5 (CCR5) antagonists [39], serotonin (5-HT) subtype 2A receptor antagonists [40], muscarinic M2 receptor antagonists [41], bradycardic agents [42], histone deacetylase inhibitors [43], p38 α mitogen activated protein kinases (MAPK) inhibitors [44], matrix metalloproteinases (MMPs)

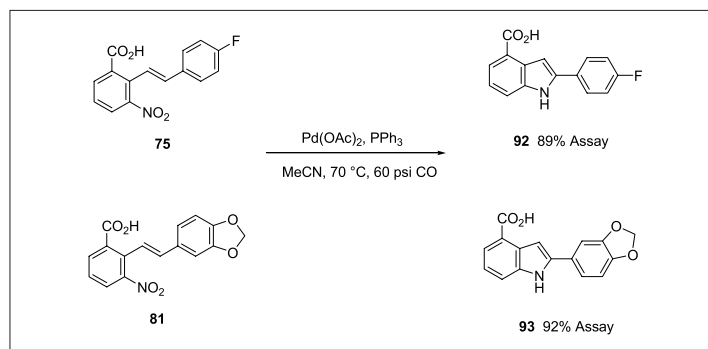
inhibitors [45], and poly(ADP-ribose) polymerase-1-inhibitors [46]. Typically indoles of this subclass have been prepared from commercially available indole-4-carboxylic acid or 4-bromoindole [47], both of which are expensive reagents and require extensive manipulation if a more substituted pharmacophore is needed. It was recognized that access to indoles of type **71** would feature reaction of commercially available methyl 2-methyl-3-nitrobenzoate **73** with a substituted aldehyde followed by reductive cyclization (Scheme 11) [48]. Nitrobenzene **73** was an extremely attractive raw material and would allow for the preparation of indoles of type **71** in a remarkably straightforward manner.

In order to access indoles of class **71**, an efficient synthesis of nitrostyrenes of type **72** was imperative. It was previously demonstrated that reaction of *ortho*-nitrotoluenes with aromatic aldehydes in the presence of DBU in DMSO was a reversible process and only modest to good yields of the corresponding nitro alcohols were obtained [26]. Based on the juxtaposition of the methyl ester with the reacting center and its capacity to serve as an

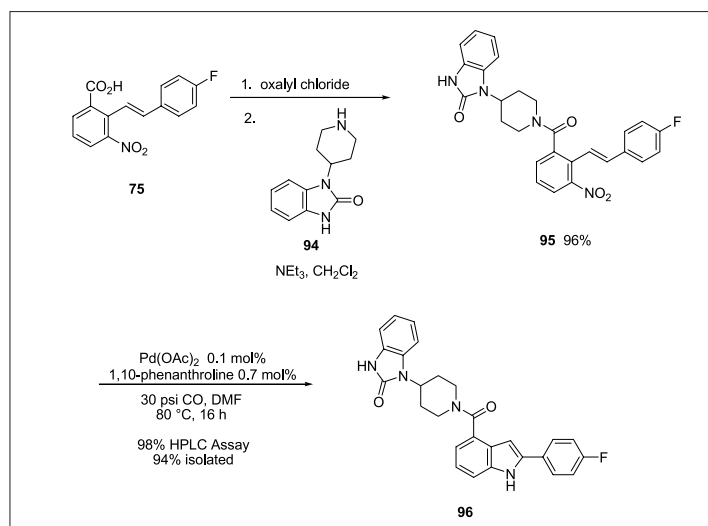
intramolecular electrophilic trap of the intermediate nitro alcohol, reaction of **73** with aromatic aldehydes was anticipated to lead to the formation of a lactone intermediate (*i.e.* **77**). Reaction of **73** with 1.5 equiv. of 4-fluorobenzaldehyde **74** under optimized reaction conditions (2 equiv. of DBU, DMSO, 12 h rt then heat to 50 °C for 30 min) afforded nitrostyrene benzoic acid **75** in 90% HPLC assay yield. Under these reaction conditions, none of the intermediate lactone **77** was observed in the crude reaction mixture. After an extractive workup to remove excess **74**, the product could be obtained in analytically pure form and in 84% isolated yield by crystallization from MeOH/water. The overall sequence involved deprotonation of nitrotoluene **73** by DBU followed by addition to **74** to give nitro alcohol **76**, which underwent intramolecular cyclization to lactone **77** (Scheme 12). Further deprotonation of **77** by DBU was followed by elimination of the carboxylate anion to furnish the nitrostyrene benzoic acid product upon workup. This sequence was extremely general and provided access to a structurally diverse array of nitrostyrene benzoic

Table 2. Preparation of nitrostyrene benzoic acid derivatives

Entry	Aldehyde	Nitrostyrene
1		 79 61%
2		 81 68%
3		 83 88%
4		 85 79%
5		 87 82%
6		 89 90%
7		 91 82%



Scheme 13.



Scheme 14.

acids in good to excellent yield (Table 2). In addition, the *trans*-nitrostyrene benzoic acids were the exclusive products with no detectable amounts of the corresponding *cis*-isomers being formed. Furthermore, electron-donating and electron-withdrawing groups on the aromatic aldehyde participated equally well.

For the preparation of indoles of subclass 71 bearing an amido-substituent in the four position of the indole ring, a two-step sequence involving either reductive cyclization of the *ortho*-nitrostyrenes followed by amide formation or amide formation followed by reductive cyclization was required. Initial efforts were focused on reductive cyclization of the nitrostyrene benzoic acids (Scheme 13). For example, reductive cyclization of 75 and 81 under the conditions discovered by the Söderberg group [23] (6 mol% Pd(OAc)₂, 24 mol% PPh₃, MeCN, 70 °C, 60 psi CO, 16 h) afforded indole carboxylic acids 92 and 93 in 89% and 92% HPLC assay yields, respectively. Unfortunately, the isolation of 92 and 93 in pure form was plagued by both solubility issues and the difficulty in removing the excess triphenylphosphine and triphenylphosphine oxide and the isolated yields of 92 and 93 were <50% after crystallization. Due to this difficulty, our attention turned to con-

version of the benzoic acid moiety to the required amide functionality prior to reductive cyclization.

Treatment of nitrostyrene benzoic acid 75 with oxalyl chloride in the presence of a catalytic amount of DMF in CH₂Cl₂ afforded the intermediate acid chloride which was not isolated (Scheme 14). Reaction with 4-(2-keto-1-benzimidazoliny) piperazine 94 in the presence of NEt₃ gave, after workup, amido nitrostyrene 95 as a highly crystalline solid and in 96% isolated yield. Reductive cyclization of 95 under highly optimized reaction conditions utilized in the KDR program gave indole 96 in 98% HPLC assay yield. In this case, isolation of 96 was simply a matter of filtration of the catalyst through Celite followed by addition of 1M H₃PO₄ which precipitated the product in analytically pure form and in 94% isolated yield. The use of 1 M H₃PO₄ for the isolation of the product aided in the removal of trace amounts of 1,10-phenanthroline and was mild enough that sensitive functionalities such as a Boc-protecting group were preserved (Table 3, entry 3). The sequence whereby the appropriately substituted nitrostyrene benzoic acid was converted to an amide followed by reductive cyclization provided an extremely high yielding means of preparing a diverse array

Table 3. Preparation of 2-arylindole-4-carboxylic amide derivatives

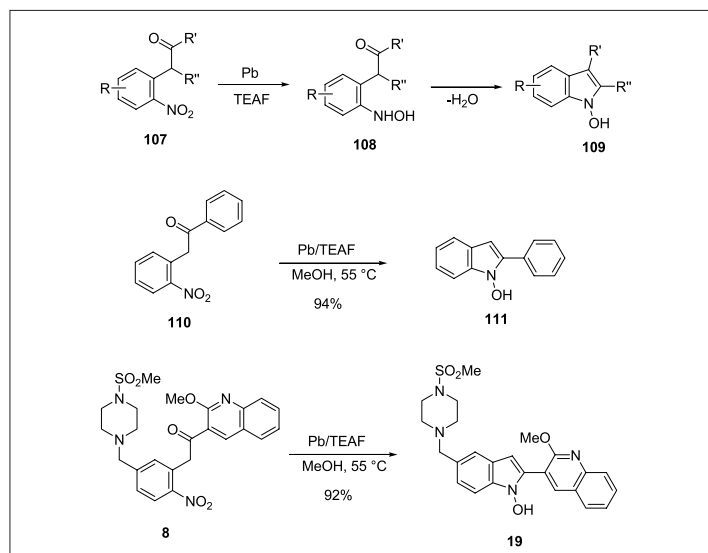
Acid	Amide	Indole
75		
	97 99%	98 93%
83		
	99 98%	100 94%
81		
	101 98%	102 95%
81		
	103 97%	104 92%
89		
	105 99%	106 91%

of highly functionalized 'drug-like' 2-arylindole-4-carboxylic amides (Table 3.)

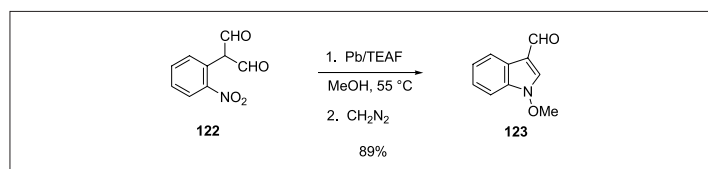
6. Preparation of N-Hydroxyindoles

N-Hydroxyindoles and their derivatives have received considerable attention in recent years [49]. The biological role of N-hydroxyindoles is still an area of active investigation since they have been shown to possess biological activity in certain cases. In addition, biologically inactive indoles have been rendered biologically active when their N-hydroxyindole analogues were examined. The preparation of N-hydroxyindoles has been somewhat limited by currently available methods for their preparation which suffer from low yields and competing side reactions. Even though the Somei 'tungstate method' [50] has addressed some of these limitations, the ability to assemble highly functionalized N-hydroxyindoles rapidly from simple precursors prompted our investigations in this area [51]. It was envisioned that reductive cyclization of suitably substituted *ortho*-nitrobenzyl ketone would be an attractive method for their preparation.

Although the reductive cyclization of *ortho*-nitrobenzyl ketones or aldehydes to



Scheme 15.



Scheme 16.

N-hydroxyindoles have been reported under a variety of conditions [52], these reaction conditions were generally intolerable to many functional groups, low yielding, and substrate limited. In many cases, further reduction of the *N*-hydroxyindole products to the corresponding indoles was competitive giving rise to multiple reaction products. Inspired by an observation of Gowda, who reported the reduction of nitro compounds to azo derivatives with Pb/triethylammonium formate (TEAF) [53], we envisioned that capture of the intermediate *N*-hydroxyaniline **108** by an adjacent carbonyl would provide *N*-hydroxyindoles **109** in a straightforward manner (Scheme 15).

Treatment of nitroketone **110** [54] with Pb/TEAF in MeOH at 55 °C for 12 h gave 2-phenyl-*N*-hydroxyindole **111** as the sole reaction product which was isolated in 94% yield. There was no detectable amount of 2-phenylindole in the crude reaction mixture as evidenced by both HPLC and NMR. When the highly functionalized intermediate **8** which was utilized in the synthesis of KDR kinase inhibitor **1** was subjected to the identical reaction conditions, *N*-hydroxyindole **19** was obtained in 92% yield. This method proved to be extremely general and allowed for the preparation of a number of substituted *N*-hydroxyindoles in good to excellent yield (Table 4). In all cases, isolation of the products was achieved by filtration of the insolubles, concentration of the solvent, and filtration through a small

plug of silica gel to afford the products as stable crystalline solids.

The methodology was further highlighted by the two-step preparation of 1-methoxyindole-3-carboxaldehyde **123**, a natural product isolated from the Cruciferae family of plants and extensively utilized as a building block for the synthesis of other natural products (Scheme 16) [55][56]. Lead-promoted reductive cyclization of commercially available 2-nitromalondialdehyde **122** was followed by methylation of the corresponding *N*-hydroxyindole with CH₂N₂ and afforded **123** in 89% overall yield. Although this methodology utilizes stoichiometric lead, the rapid assembly of the product *N*-hydroxyindoles coupled with the fact that the products are obtained essentially lead-free renders this approach particularly attractive.

7. Preparation of 2-Aryl-5-Substituted-2,3-Dihydrobenzofurans

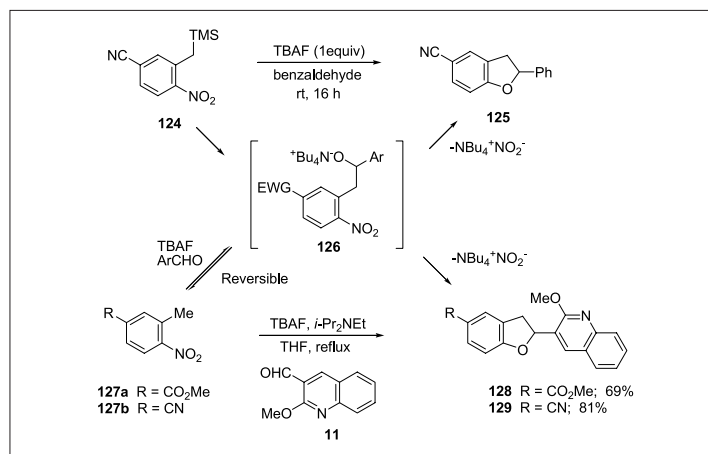
The 2,3-dihydrobenzofuran ring system constitutes the core skeleton of an increasing number of neolignan natural products that possess a range of biological activity [57]. In addition, 2,3-dihydrobenzofurans have been developed for treatment of traumatic and ischemic CNS injury [58], and are reported to be useful in the treatment of arteriosclerosis, hepatopathy, and cerebrovascular disease [59]. While there are a multitude of methods for the

Table 4. Preparation of *N*-hydroxyindoles

Entry	Ketone	<i>N</i> -OH Indole
1		 113 92%
2		 115 95%
3		 117 94%
4		 119 71%
5		 121 66%

preparation of 2,3-dihydrobenzofurans, strategies which provide rapid access to the 2,3-dihydrobenzofuran ring system not accessible through current synthetic techniques are invaluable. Our approach was guided by the work of Bartoli and our own related work with nitrotoluenes. Bartoli discovered that reaction of 4-cyano-1-nitro-2-[(trimethylsilyl)-methyl]benzene (**124**) with benzaldehyde in the presence of an equimolar amount of TBAF gave 5-cyano-2,3-dihydro-2-phenylbenzofuran **125** in 70% yield [19]. Based on our own observations, it was apparent that TBAF might be basic enough to promote the direct formation of the expected tetrabutylammonium alkoxide intermediate **126** from unfunctionalized *ortho*-nitrotoluenes **127**. The direct use of simple and often commercially available *ortho*-nitrotoluenes for the preparation of highly substituted 2,3-dihydrobenzofurans would greatly simplify the Bartoli two-step protocol. It was against this background that a thorough investigation of the Bartoli methodology utilizing *ortho*-nitrotoluenes was initiated [60].

After extensive reaction optimization, it was discovered that reaction of a mixture of nitrotoluene **127a** and aldehyde **11** in the presence of 1.5 equiv. of TBAF and 2 equiv. of Hünig's base in refluxing THF for 3 h furnished 2,3-dihydrobenzofuran **128** in 69% yield (Scheme 17). The use of Hünig's base served to remove the liberated HF from the reaction mixture and was cru-



Scheme 17.

Table 5. Preparation of 2,3-dihydrobenzofurans

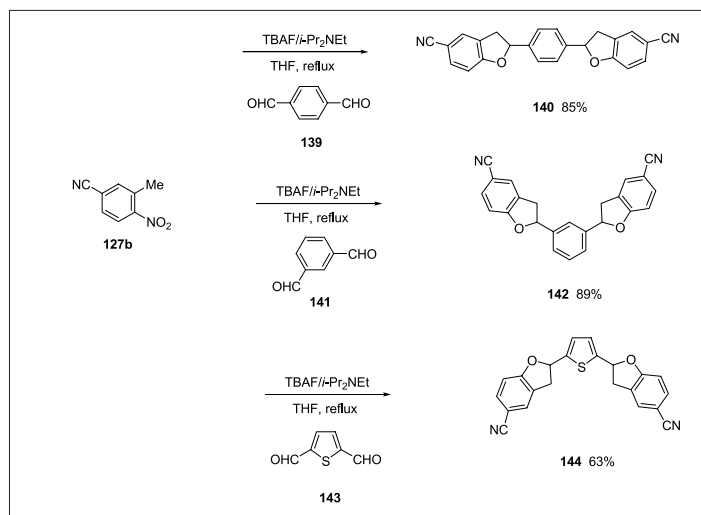
Nitrotoluene	Aldehyde	2,3-dihydrobenzofuran
127a		 131 85%
127a		 132 82%
127a		 133 68%
127b		 135 88%
127b		 136 79%
127b		 138 93%

cial for obtaining high yields. In addition, the addition of **127a** to aldehyde **11** was observed to be reversible; however, conducting the reaction in refluxing THF drives the reaction to completion in several hours. In similar fashion, reaction of **127b** with **11** provided **129** in 81% yield. The one-pot operation was general and provided access to a structurally diverse array of substituted 2,3-dihydrobenzofurans in good to excellent yields (Table 5).

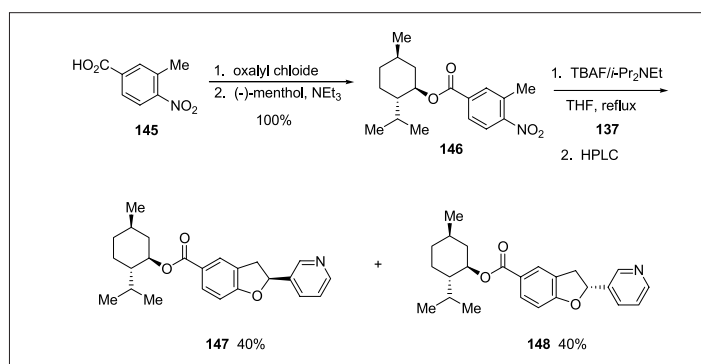
This methodology was also successfully applied toward the synthesis of dimeric 2,3-dihydrobenzofurans as outlined in Scheme 18 [61]. For example, reaction of 2 equiv. of **127b** with terephthalaldehyde **139** gave dimer **140** that crystallized from the crude reaction mixture in analytically pure form and in 85% isolated yield. In like fashion, reaction of **127b** with isophthalaldehyde **141**

or 2,5-thiophenedicarboxaldehyde **143** afforded dimers **142** and **144** in 89% and 63% yields, respectively.

Due to the reversibility of the process, the methodology does not lend itself to the one-pot asymmetric synthesis of 2,3-dihydrobenzofurans. However, chiral 2,3-dihydrobenzofurans are obtained in just three steps by using (–)-menthol as a chiral auxiliary (Scheme 19) [61]. For example, preparation of menthyl ester **146** (100%) was followed by treatment with TBAF in the presence of aldehyde **137** and gave a 1:1 mixture of **147** (40%) and **148** (40%). The individual diastereomers were then separated by HPLC. Thus chiral 2,3-dihydrobenzofurans are also accessible through this methodology involving readily available benzoic acid **145**, (–)-menthol, and an appropriately substituted aldehyde fol-



Scheme 18.



Scheme 19.

lowed by chromatography of the individual diastereomers by HPLC.

8. Conclusions

The novel methodology discovered in the development of the long-term manufacturing route of KDR kinase inhibitor **1** has led to a successful research program aimed at taking advantage of the underlying versatility of nitrobenzenes. The use of readily available nitrobenzene and nitrotoluene compounds for the rapid construction of highly functionalized indoles and 2,3-dihydrobenzofurans is an extremely powerful method that will continue to see growth as a practical and efficient means of preparing these highly valued pharmacophores. The addition of trimethylsilyl nitro compounds

and *ortho*-nitrotoluenes to various aromatic aldehydes provides an intermediate alcohol which can either be oxidized to the corresponding nitroketone or undergo elimination to a nitrostyrene. Palladium-catalyzed reductive cyclization of these intermediates leads to substituted indoles. In certain cases, the intermediate nitroalcohol can be trapped leading to 4-substituted nitrostyrene benzoic acids and 2,3-dihydrobenzofurans. Often the products are obtained in a minimal number of synthetic transformations and generally do not require the use of chromatography. Due to the extremely low catalyst/ligand loadings for many of the nitrostyrene reductive cyclizations, final API products can generally be isolated with low levels of residual palladium (< 20 ppm). In addition, these methodologies are exceptionally mild and tolerant of a wide range of functional groups. Potential applications to parallel and diversity oriented synthesis are also possible.

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