Natural Product Synthesis

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Total Syntheses of the Elusive Welwitindolinones with Bicyclo[4.3.1] Cores

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indolyne · natural products · palladium · total synthesis · welwitindolinone

The welwitindolinones with bicyclo[4.3.1] cores are a class of natural products that have attracted tremendous interest from the synthetic community because of their fascinating structures and promising biological profiles. More than 15 research groups worldwide have reported progress toward these elusive natural products. This Minireview describes contemporary studies aimed at the total synthesis of these challenging targets, in addition to the two recently completed syntheses of welwitindolinones with bicyclo[4.3.1] cores reported by Rawal and Garg in 2011. Both of the completed efforts rely on C4–C11 bond constructions to access the congested bicyclic framework of these elusive natural products.

1. Introduction

The welwitindolinones (**1**–**10**, Figure 1) are an enticing family of oxindole-containing natural products that have drawn substantial interest from the scientific community. In 1994, Moore and co-workers described the isolation of many of these natural products, which were produced by the blue-green algae *Hapalosiphon welwitschii* and *Westiella intricata*. The discovery of additional welwindolinones, generated from *Fischerella muscicola* and *Fischerella major*, was subsequently reported in 1999.[1] These natural products were found to exhibit a wide range of biological activity, ranging from insecticidal or antimycotic properties, to the ability of **5** to reverse P-glycoprotein-mediated multiple drug resistance (MDR) to a variety of anticancer drugs in human cancer cell lines.[2] All of the welwitindolinones other than welwitindolinone A isonitrile (**1**) contain a 3,4-disubstituted oxindole with a bicyclo[4.3.1] decane core. In addition, these compounds feature compact, yet heavily substituted cyclohexyl rings, where at least five of the six carbon atoms on the ring are functionalized.

The combination of daunting structural features and promising biological activity have rendered the welwitindolinones attractive and highly sought after targets for total synthesis. Since the initial isolation of the welwitindolinones in 1994, at least 15 research groups worldwide have attempted to prepare these compounds by chemical synthesis.[3–13] Numerous dissertations and approaches toward these targets have been published (> 20). The exhaustive synthetic efforts have led to two syntheses of welwitindolinone A isonitrile (**1**), reported by the Baran[14] and Wood[15] groups. However, relatively less success has been realized in synthesizing welwitindolinones with bicyclo[4.3.1] cores.

A summary of successful strategies toward the bicyclic welwitindolinone core is presented in Figure 2. These efforts

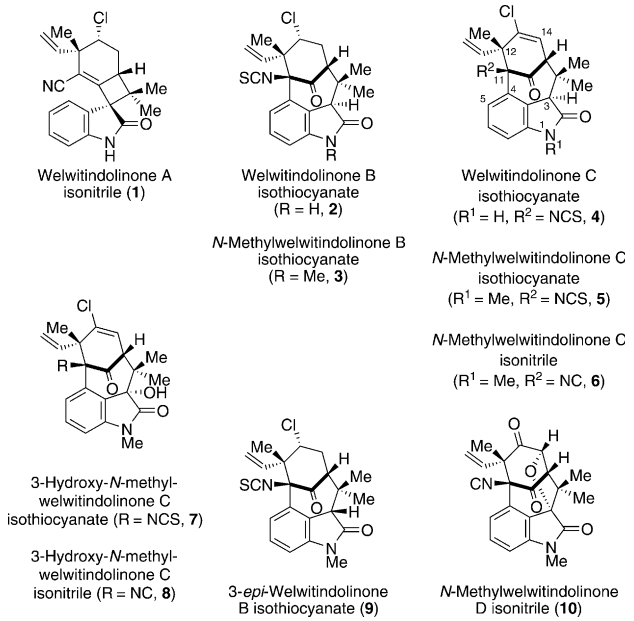

Figure 1. Welwitindolinone natural products **1**–**10**.

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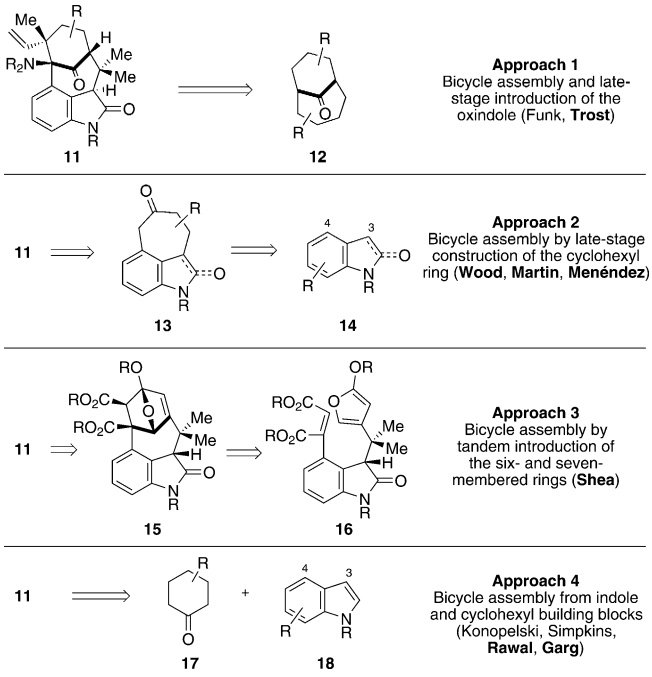

Figure 2. Synthetic approaches to the core scaffold of the welwitindolinone natural products with bicyclo[4.3.1] cores.

can be categorized into four approaches based on the order of ring assembly. Using Approach 1, Funk[3] and Trost[4] have targeted bicycle **11** by late-stage introduction of the oxindole unit from bicycle **12** with a bicyclo[4.3.1] core. Alternatively, Approach 2 by Wood,[5] Martin,[6] and Menéndez,[7] relies on accessing bicycle **11** by final introduction of the cyclohexyl ring from precursor **13**. In turn, the seven-membered ring would be built from a simpler indole or oxindole starting material **14**. Shea's ambitious approach to **11** (Approach 3) features tandem construction of the six- and seven-membered rings by using an intramolecular Diels–Alder cycloaddition (**11**⇒**15**⇒**16**).[8] Finally, in Approach 4, Konopelski,[9] Simpkins,[10] Rawal,[11] and Garg,[12] targeted bicycle **11** from suitably functionalized cyclohexyl and indole precursors **17** and **18**, respectively.

In this Minireview, highlights of the various synthetic approaches to the bicyclic welwitindolinones are presented, with an emphasis on the most recent and promising studies that have been reported since the last pertinent review.[16] Specifically, the latest progress by Trost,[6] Wood,[5b] Martin,[6] Menéndez,[7] and Shea[8b] is featured, along with the recently completed syntheses of (±)-**10** and (−)-**5**, reported in 2011 by Rawal[11b] and Garg,[12b] respectively.

2. Recent Synthetic Studies Toward the Total Synthesis of Welwitindolinones with Bicyclo[4.3.1] Cores

2.1. Late-Stage Assembly of the Oxindole

One elegant strategy to assemble the core structure of the welwitindolinones relies on late-stage appendage of the oxindole to a preformed bicyclo[4.3.1] intermediate, as recently reported by Trost et al.[4] In this approach, a series of cycloadditions were used to assemble the core, and featuring a palladium-catalyzed trimethylenemethane (Pd-TMM) cycloaddition reaction (Scheme 1). For this (6+3) cycloaddition, tropone **20** was selected for the acceptor molecule and allylsilane **21** was chosen for the donor. Tropone **20** was accessed in three steps from cycloheptatriene **19**. Upon reaction with allyl silane **21** in the presence of [Pd(dba)$_2$] and phosphorous ligand **26**, the enantioselective (6+3) cycloaddition reaction occurred to deliver bicycle **22** in 94% *ee*. This impressive transformation is believed to proceed by way of an in situ generated π-allylpalladium intermediate.[17] The PMB ester **22** was then elaborated to amidofuran **23** in three steps. Upon heating **23** in toluene, a Diels–Alder cycloaddition occured to deliver oxabicycle **24**. Subsequent treatment with Yb(OTf)$_3$ unveiled oxindole **25**.

Although further elaboration of **25** has not yet been reported, this advanced species could possibly be used to

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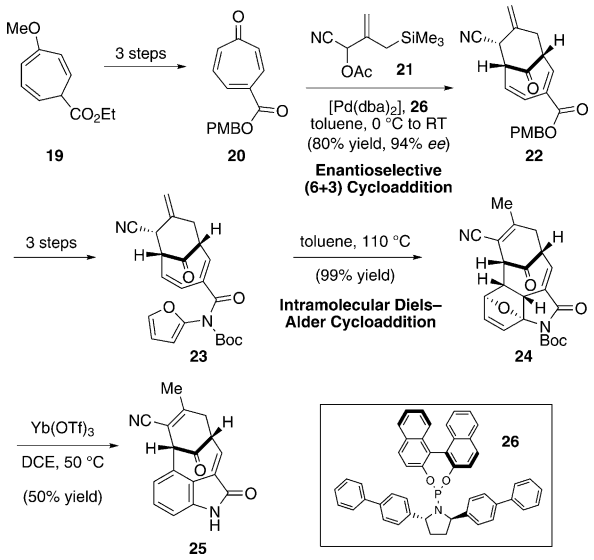
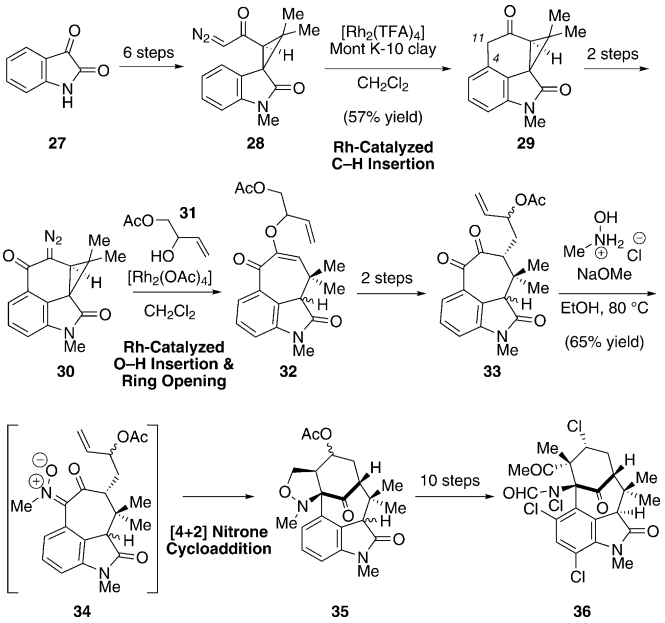


Scheme 1. Trost's approach to welwitindolinones **2**–**10**. dba = dibenzylideneacetone, DCE = 1,2-dichloroethane.



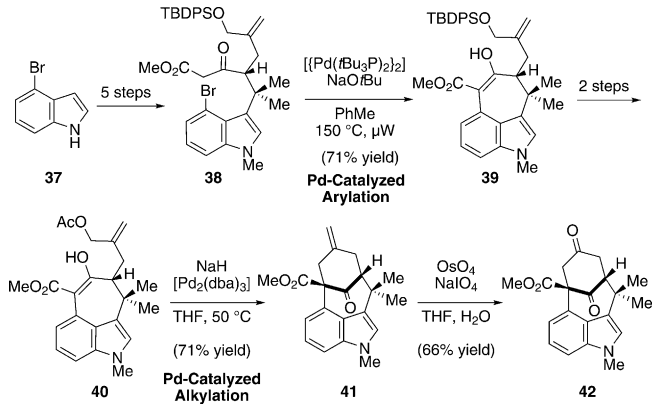
Scheme 2. Wood's progress toward **2**–**10** employing a Rh-catalyzed C–H insertion and a [4+2] nitrone cycloaddition. TFA = trifluoroacetate, OAc = acetate.

access all of the welwitindolinones with bicyclo[4.3.1] cores. Additionally, Trost's approach elegantly highlights the utility of the (6+3) cycloaddition methodology for building complex architectures. The route to **25** also showcases the distinctive ability of Pd catalysis, and notably π-allylpalladium chemistry, to provide intricate structural frameworks with high enantiomeric excess.

2.2. Late-Stage Construction of the Cyclohexyl Ring

Another attractive route toward construction of the bicyclo[4.3.1] core of the welwitindolinones relies on initial formation of the seven-membered ring followed by assembly of the cyclohexyl ring. As mentioned above, Wood, Martin, and Menéndez et al. all designed their syntheses around this general strategy (Scheme 2). In Wood's route,[5b] isatin (**27**) was converted into diazoketone **28** by using a six-step sequence. The C4–C11 bond was then constructed through a rhodium-catalyzed C–H insertion[18] to provide tetracycle **29**. Further elaboration afforded diazoketone **30** over two steps. Subsequent treatment with $[Rh_2(OAc)_4]$ and allylic alcohol **31** initiated O–H insertion along with tandem ring expansion to furnish tricycle **32**, which possesses the necessary seven-membered ring. Two additional steps allowed access to allylic acetate **33**. Upon treatment of **33** with *N*-methylhydroxylamine hydrochloride and sodium methoxide, [4+2] nitrone cycloaddition occurred to forge the bicyclo[4.3.1] core. Presumably the conversion of **33** into cycloadduct **35** proceeds through intermediate **34**. After extensive experimentation, the authors were able to access alkyl chloride **36** from **35**.

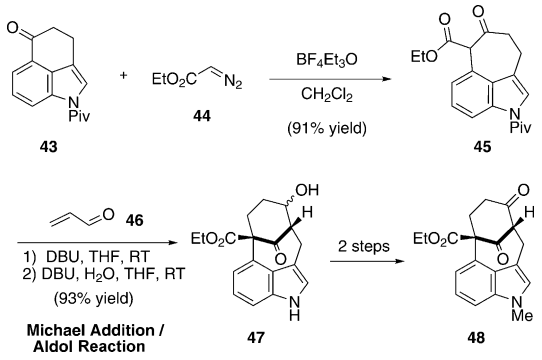
Martin's efforts to construct the bicyclo[4.3.1] system through sequential installation of the seven- and six-membered rings are highlighted in Scheme 3.[6] Starting with 4-bromoindole (**37**), a five-step sequence delivered β-ketoester **38**. Next, a palladium-catalyzed cyclization was employed to



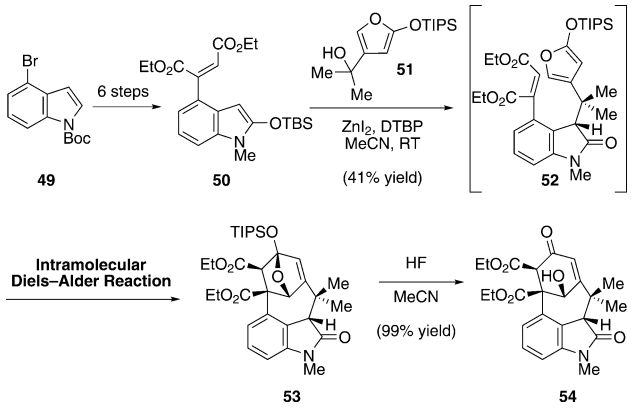
Scheme 3. Martin's approach to welwitindolinones **2**–**10** featuring Pd-catalyzed transformations. THF = tetrahydrofuran.

furnish **39**, which contains the necessary seven-membered ring. After elaborating to allylic acetate **40**, treatment with $[Pd_2(dba)_3]$ and sodium hydride provided bicycle **41** through intramolecular trapping of a π-allylpalladium intermediate. Lemieux–Johnson oxidation of the olefin furnished dione **42**, which possesses the welwitindolinone bicyclic core.

As shown in Scheme 4, the Menéndez group also devised a very concise means to assemble the bicyclic structure of the welwitindolinones.[7] Kornfeld's ketone (**43**)[19] underwent ring expansion with ethyl diazoacetate (**44**) to deliver β-ketoester **45**. In turn, **45** was subjected to a one-pot, tandem Michael addition/aldol reaction using propenal (**46**) and DBU to yield keto alcohol **47**. Methylation of the indole nitrogen atom followed by oxidation of the alcohol provided indolyl bicycle **48**.



Scheme 4. Menéndez's route toward **2**–**10** using a tandem Michael addition/aldol condensation sequence. Piv = pivaloyl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.



Scheme 5. Shea's route toward **2**–**10** employing an intramolecular Diels–Alder reaction. DTBP = 2,6-di-*tert*-butylpyridine, TIPS = triisopropylsilyl.

Each of the approaches discovered by Wood, Martin, and Menéndez provide smooth access to the bicyclic welwitinodolinone core, which sets the stage for late-stage elaboration. More importantly, lessons involving synthetic strategies and methods can be extracted from each group's efforts. Wood's use of C–H insertion chemistry (**28**→**29**, Scheme 2) and subsequent fragmentation chemistry to install the seven-membered ring, serves as a reminder that unconventional disconnections often provide exciting routes to complex structures. Wood's nitrone cycloaddition (**33**→**35**, Scheme 2) provides further support of this notion, and cleverly builds the six-membered ring, while installing the troublesome C11 nitrogen substituent. Martin's approach to the welwitindolinones highlights the power of Pd catalysis in building quaternary stereocenters and sterically congested frameworks by the assembly of carbon–carbon bonds (Scheme 3). The specific use of Pd–enolate chemistry provides an example of modern Pd catalysis greatly enabling complex molecule synthesis. Finally, Menéndez's application of a tandem Michael addition/aldol reaction (**45**→**47**, Scheme 4) to assemble the welwitindolinone bicyclo[4.3.1] core demonstrates that classical chemistry may still provide simple, yet elegant solutions to challenging synthetic problems.

2.3. Tandem Assembly of the Seven- and Six-Membered Rings

Another bold approach to the core of the welwitindolinones is to assemble the seven- and six-membered rings in a tandem process. To this end, Shea et al. implemented a [4+2] cycloaddition to assemble the welwitindolinone bicycle (Scheme 5).[8b] Bromoindole **49** was elaborated to silylketene aminal **50** in six steps. In turn, **50** underwent a ZnI_2-promoted alkylation with silyloxyfuran **51** to deliver intermediate **52**, which immediately reacted in an intramolecular Diels–Alder (IMDA) cycloaddition to yield oxabicyclic oxindole **53**. Treatment of this compound with HF then unveiled ketoalcohol **54**. Shea's route is exceedingly concise, as it provides a highly functionalized oxindole-appended bicyclo[4.3.1] core in only eight steps from indole **49**. The approach not only highlights the utility of the IMDA reaction, but also demonstrates the effectiveness of cascade reactions for constructing complex architectures. Moreover, Shea's use of intermediates containing anti-Bredt olefins (i.e., **53**) reminds us that our commonly accepted rules concerning structure and stability are not insurmountable.

2.4. Linkage of Cyclohexyl and Indole Building Blocks To Assemble the Bicyclo[4.3.1] Core

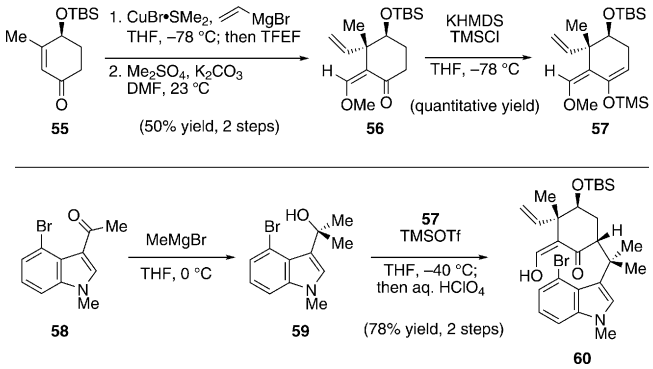
An alternative approach to the formation of the bicyclic structure of the welwitindolinones is through the linkage of cyclohexyl and indole building blocks. Rawal[11b] and Garg[12b] have each reported recent efforts using this strategy, which have culminated in completed total syntheses. The details of these studies are described in depth in the subsequent sections of this Minireview.

3. Rawal's Total Synthesis of (±)-N-Methylwelwitindolinone D Isonitrile and Related Studies

3.1. Assembly of the Bicyclo[4.3.1] Core

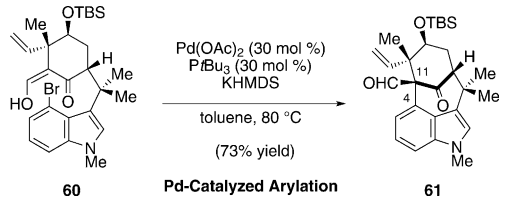
In 2011, Rawal et al. reported the first total synthesis of any welwitindolinone with a bicyclo[4.3.1] core.[11b] Their synthetic route relies upon a palladium-catalyzed enolate coupling to form the key C4–C11 bond found in the bicyclic welwitindolinones, as well as an uncommon aldoxime rearrangement to ultimately form the isonitrile moiety.

Starting from known enone **55**,[20] a sequence involving vinyl cuprate addition, quenching with 2,2,2-trifluoroethylformate (TFEF), and subsequent O-methylation provided the vinylogous ester **56** (Scheme 6).[21] Next, formation of TMS enol ether **57** proceeded smoothly to complete one of the coupling fragments. The remaining coupling partner was swiftly prepared from 4-bromo-*N*-methyl-3-acetylindole (**58**). Treatment of ketone **58** with methylmagnesium bromide furnished tertiary alcohol **59**.[22] Upon reaction of **59** and crude silyl enol ether **57**, Lewis acid mediated alkylative coupling occurred to provide vinylogous acid **60** as a single diastereomer.



Scheme 6. Coupling of the indole and cyclohexyl fragments. DMF = dimethylformamide, TFEF = 2,2,2-trifluoroethylformate, KHMDS = potassium hexamethyldisilazide, TMS = trimethylsilyl, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl.

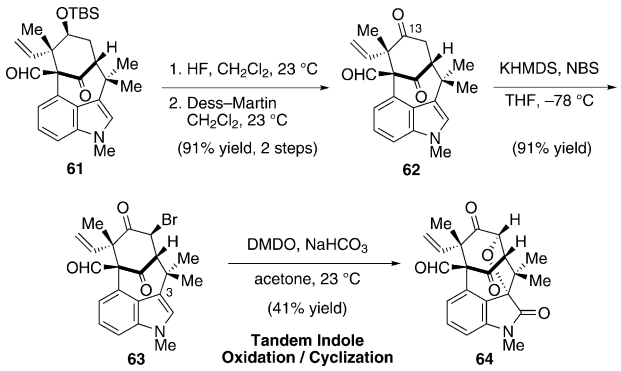
It was expected that a palladium-catalyzed enolate coupling could be employed to forge the congested C4–C11 bond and build the critical bicyclo[4.3.1] core (Scheme 7).[23] An exhaustive search of palladium sources, ligands, solvents, and bases revealed $Pd(OAc)_2$, tri-*tert*-butylphosphine, KHMDS, and toluene to be the optimal conditions for the desired transformation. At 80 °C, formation of bicycle **61** took place in 73 % yield and set the stage for the completion of the total synthesis. It should be noted that Rawal et al. have described a complementary method for assembling the C4–C11 bond in welwitindolinone model studies using a Mn-promoted oxidative cyclization.[11d]



Scheme 7. Pd-catalyzed enolate coupling to assemble the bicyclo[4.3.1] core.

3.2. Introduction of the Tetrahydrofuran Ring

Following formation of the bicycle, focus shifted to construction of the last ring of the natural product: the spiro-fused tetrahydrofuran. Desilylation of **61** followed by Dess–Martin oxidation smoothly delivered diketone **62** (Scheme 8). It was thought that α bromination of the C13 ketone would provide a suitable intermediate to be intercepted by an in situ generated 3-hydroxyoxindole moiety. Electrophilic bromination was expected to occur on the less hindered side of **62**, toward the one-carbon bridge of the bicycle, properly orienting the halide for subsequent displacement. Gratifyingly, regio- and stereoselective bromination occurred upon sequential treatment of ketone **62** with KHMDS and *N*-bromosuccinimide (NBS) to give bromodiketone **63**. Oxidation of the indole with dimethyldioxirane (DMDO) provided the desired tetrahydrofuran-containing product **64**. This ambitious step presumably proceeds through the cyclization of a 3-hydroxyoxindole intermediate, just as the authors had intended.

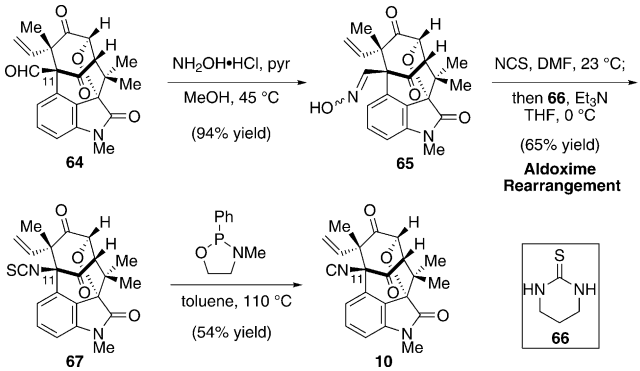


Scheme 8. Synthesis of late-stage intermediate **64**. Dess–Martin = 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one, NBS = *N*-bromosuccinimide, DMDO = dimethyldioxirane.

3.3. Late-Stage Aldoxime Rearrangement and Completion of the Total Synthesis

With the end in sight, the final obstacle was to convert the C11 aldehyde substituent into the desired isonitrile. To this end, Rawal and co-workers smoothly converted aldehyde **64** into oxime **65** (Scheme 9). Subsequent treatment of **65** with *N*-chlorosuccinimide (NCS) and propylenethiourea **66** gave isothiocyanate **67** in 65 % yield.[24] Finally, desulfurization using *N*-methyl-*P*-phenyl-1,3,2-oxazaphospholidine delivered (±)-*N*-methylwelwitindolinone D isonitrile (**10**).[25] The last steps are notable in that both C11 isothiocyanate and isonitrile moieties are accessible, as these functional groups appear in all members of the bicyclic welwitindolinones (i.e., **2**–**10**).

Rawal's elegant route to (±)-**10**, which proceeds in only twelve steps from enone **55**, provided the first total synthesis of a welwitindolinone with a bicyclo[4.3.1] core. The synthesis highlights the remarkable ability of Pd catalysis to build

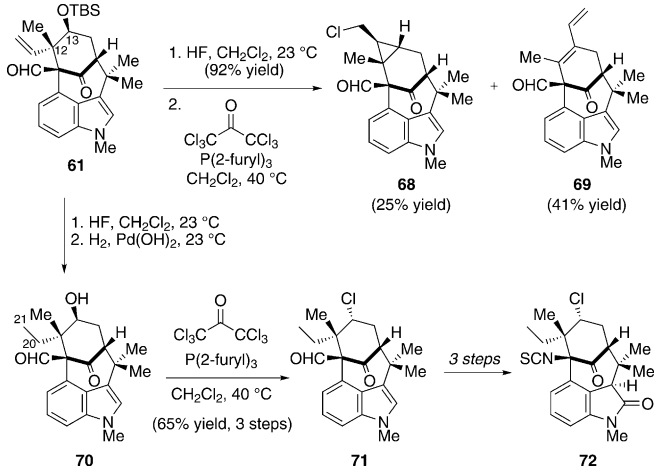


Scheme 9. Completion of the total synthesis of (±)-**10**. pyr = pyridine, NCS = *N*-chlorosuccinimide.

complex molecular frameworks, as seen similarly in the works of Trost and Martin, respectively. Notably, even very sterically congested systems, such as the vicinal quaternary stereocenters present in intermediate **61**, may be assembled by metal-catalyzed transformations. Rawal's use of a late-stage aldoxime rearrangement to install the bridgehead nitrogen substituent (**65**→**67**, Scheme 9) underscores the impressive utility of classic chemistry in a remarkably complex setting.

3.4. Unexpected Late-Stage Reactivity and the Synthesis of 20,21-Dihydro-N-methylwelwitindolinone B Isothiocyanate

Shortly after disclosing their synthesis of **10**, the Rawal group reported a concise approach to the non-natural compound 20,21-dihydro-*N*-methylwelwitindolinone B isothiocyanate.[11c] This route commenced with aldehyde **61**, an intermediate used in the synthesis of (±)-**10** (Scheme 10). It was envisioned that installation of the alkyl chloride would be possible by nucleophilic displacement of an activated hydroxy group. However, following desilylation of TBS ether **61**, treatment with tri(2-furyl)phosphine (TFP) and hexachloroacetone did not produce the desired alkyl chloride. Instead, methylcyclopropyl chloride **68** and diene **69** were seen as the major products.[26] The authors hypothesized that an interaction between the π system of the vinyl group attached to C12 and an intermediate carbocation at C13 ultimately led to these undesired products. Thus, the offending vinyl group was removed by hydrogenation. Exposure of intermediate **70** to the same chlorination conditions then furnished **71**, containing the desired alkyl chloride. Indolyl aldehyde **71** was then elaborated to **72**, the non-natural dihydro derivative of *N*-methylwelwitindolinone B isothiocyanate, through three additional steps. Although the natural product *N*-methylwelwitindolinone B isothiocyanate has yet to be synthesized, the formation of the undesired products **68** and **69** serves as a reminder of the unexpected side reactions that often occur when manipulating intricate late-stage compounds.

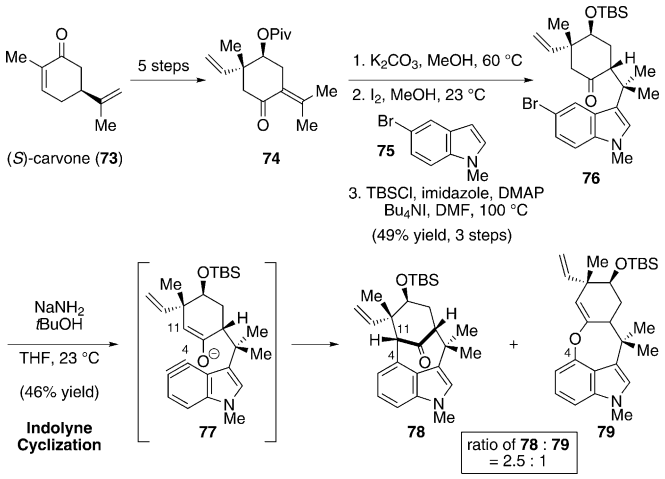


Scheme 10. Synthesis of non-natural welwitindolinone **72**. furyl = 2-furanyl.

4. Garg's Total Synthesis of (−)-N-Methylwelwitindolinone C Isothiocyanate

4.1. Indolyne Cyclization to Assemble the Bicyclo[4.3.1] Core

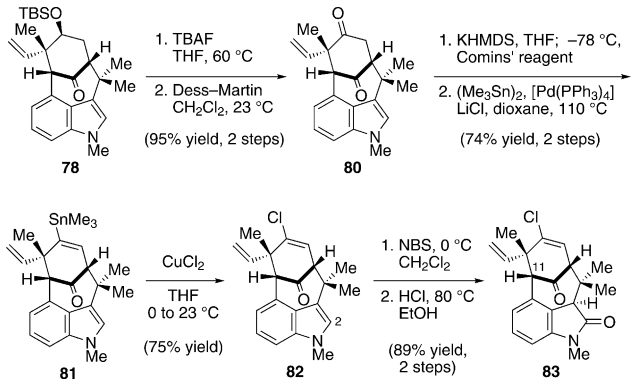
The Garg group reported the enantiospecific total synthesis of (−)-*N*-methylwelwitindolinone C isothiocyanate (**5**) in 2011,[12b] which hinged upon a challenging indolyne[27,28] cyclization to construct the C4–C11 bond of the bicycle.[29] (*S*)-Carvone (**73**) was elaborated to known enone **74** by using Natsume's five-step procedure reported in the enantiomeric series (Scheme 11).[30] Enone **74** underwent pivalate cleavage, followed by iodine-catalyzed conjugate addition with 5-bromo-*N*-methylindole (**75**).[31] Subsequent TBS protection afforded TBS ether **76** in 49% yield over three steps. Silyl ether **76** represents the key intermediate for construction of the bicyclic core. Gratifyingly, the cyclization was effected by a 3:1 $NaNH_2$/*t*BuOH complex base mixture[32] to give indolyne adducts **78** and **79** in a 46% combined yield. Both products are presumed to arise from transient intermediate **77**. Although *O*-arylated product **79** was observed, the major product **78** contained the desired bicyclo[4.3.1] core found in welwitindolinones **2**–**10**.



Scheme 11. Indolyne cyclization to assemble the bicyclo[4.3.1] core. DMAP = 4-dimethylaminopyridine.

4.2. Introduction of the Vinyl Chloride and Oxindole Functional Groups

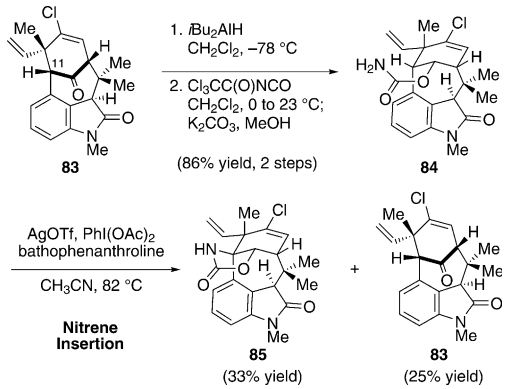
Having quickly assembled the bicyclic scaffold, efforts were focused on formation of the vinyl chloride and oxindole (Scheme 12). Following desilylation of **78**, Dess–Martin oxidation smoothly delivered diketone **80**. A two-step procedure involving triflation and palladium-catalyzed stannylation afforded vinyl stannane **81**.[33] Subsequent treatment of stannane **81** with $CuCl_2$ provided vinyl chloride **82**.[34] Next, the required indole oxidation was achieved by a sequence involving bromination, followed by acid hydrolysis to deliver oxindole **83**.[29]



Scheme 12. Synthesis of late-stage intermediate **83**. TBAF = tetrabutylammonium fluoride, Comins' reagent = *N*-(5-chloro-2-pyridyl)-bis(trifluoromethanesulfonimide), dioxane = 1,4-dioxane.

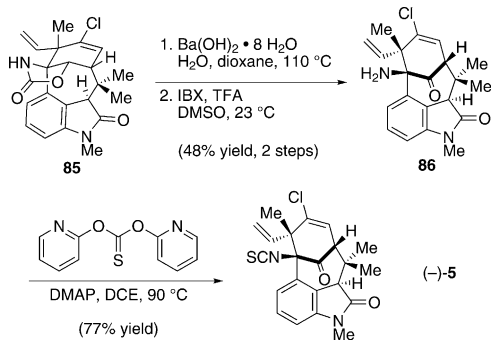
4.3. Nitrene Insertion for Bridgehead Functionalization and Completion of the Total Synthesis of (−)-5

The final hurdle to complete the synthesis required introduction of the C11 isothiocyanate substituent. Efforts to do so through intermolecular processes were found to be unsuccessful. However, Garg and co-workers envisioned the adjacent ketone could serve as a functional group handle to perform intramolecular nitrene C–H insertion into the sterically congested C11 bridgehead.[35] To this end, reduction of ketone **83** with iBu$_2$AlH, followed by carbamoylation furnished carbamate **84**, the key substrate for C–H insertion (Scheme 13). Commonly used conditions to form five-membered oxazolidinones using Rh catalysis returned ketone **83** rather than providing the desired product.[36] Gratifyingly, more fruitful results were obtained by using Ag catalysis.[36b,c] Treatment of carbamate **84** with AgOTf, bathophenanthroline, and PhI(OAc)$_2$ in CH_3CN at elevated temperatures furnished the desired oxazolidinone **85** in 33% yield. Ketone **83** was also recovered, which could be recycled through the synthetic sequence.



Scheme 13. Nitrene insertion to functionalize C11. bathophenanthroline = 4,7-diphenyl-1,10-phenanthroline.

The final steps of the total synthesis of **5** are shown in Scheme 14. Base-mediated hydrolysis of the carbamate, followed by IBX oxidation afforded amino ketone **86**. Finally, introduction of the isothiocyanate provided **5** in 77% yield. The total synthesis of (−)-**5** proceeds in 17 steps from known carvone derivative **74** and sets the stage for further welwitindolinone syntheses using related approaches.



Scheme 14. Completion of the total synthesis of (−)-**5**. IBX = 2-iodoxybenzoic acid, DMSO = dimethylsulfoxide.

Garg's enantiospecific synthesis of *N*-methylwelwitindolinone C isothiocyanate (**5**) uses a balance of classical and modern chemistry to reach the final target. The implementation of indolyne chemistry to build the sterically congested [4.3.1] bicycle (**76**→**78**, Scheme 11) demonstrates that arynes, despite their long history and high reactivity, remain valuable synthetic intermediates for the assembly of complex frameworks. The late-stage nitrene insertion to functionalize the bridgehead carbon atom (**84**→**85**, Scheme 13) is one of only a few examples of modern C–H activation chemistry in extraordinarily complex settings.[37]

5. Conclusions

In summary, the bicyclic welwitindolinones have garnered tremendous attention from the chemical community because of their wide range of biological properties and challenging structural features. With the numerous research groups working on these compounds worldwide, a variety of ambitious synthetic approaches have been disclosed. The combination of classical chemistry and new synthetic innovations has led to striking progress in the field, along with many lessons that may be useful in future synthetic studies. Beyond the ambitious approaches and recently completed syntheses described here, it is certain that further breakthroughs in the welwitindolinone arena will be unveiled in due course.[38]

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[1] a) K. Stratmann, R. E. Moore, R. Bonjouklian, J. B. Deeter, G. M. L. Patterson, S. Shaffer, C. D. Smith, T. A. Smitka, *J. Am. Chem. Soc.* **1994**, *116*, 9935–9942; b) J. L. Jimenez, U. Huber, R. E. Moore, G. M. L. Patterson, *J. Nat. Prod.* **1999**, *62*, 569–572.

[2] a) C. D. Smith, J. T. Zilfou, K. Stratmann, G. M. L. Patterson, R. E. Moore, *Mol. Pharmacol.* **1995**, *47*, 241–247; b) X. Zhang, C. D. Smith, *Mol. Pharmacol.* **1996**, *49*, 288–294.

[3] T. J. Greshock, R. L. Funk, *Org. Lett.* **2006**, *8*, 2643–2645.

[4] B. M. Trost, P. J. McDougall, *Org. Lett.* **2009**, *11*, 3782 – 3785.
[5] a) J. L. Wood, A. A. Holubec, B. M. Stoltz, M. M. Weiss, J. A. Dixon, B. D. Doan, M. F. Shamji, J. M. Chen, T. P. Heffron, *J. Am. Chem. Soc.* **1999**, *121*, 6326 – 6327; b) D. B. Freeman, A. A. Holubec, M. W. Weiss, J. A. Dixon, A. Kakefuda, M. Ohtsuka, M. Inoue, R. G. Vaswani, H. Ohki, B. D. Doan, S. E. Reisman, B. M. Stoltz, J. J. Day, R. N. Tao, N. A. Dieterich, J. L. Wood, *Tetrahedron* **2010**, *66*, 6647 – 6655.
[6] R. W. Heidebrecht, Jr., B. Gulledge, S. F. Martin, *Org. Lett.* **2010**, *12*, 2492 – 2495.
[7] M. Ruiz, P. López-Alvarado, J. C. Menéndez, *Org. Biomol. Chem.* **2010**, *8*, 4521 – 4523.
[8] a) R. Lauchli, K. J. Shea, *Org. Lett.* **2006**, *8*, 5287 – 5289; b) J. A. Brailsford, R. Lauchli, K. J. Shea, *Org. Lett.* **2009**, *11*, 5330 – 5333.
[9] a) J. P. Konopelski, H. Deng, K. Schiemann, J. M. Keane, M. M. Olmstead, *Synlett* **1998**, 1105 – 1107; b) H. Deng, J. P. Konopelski, *Org. Lett.* **2001**, *3*, 3001 – 3004; c) J. Xia, L. E. Brown, J. P. Konopelski, *J. Org. Chem.* **2007**, *72*, 6885 – 6890.
[10] a) J. Baudoux, A. J. Blake, N. S. Simpkins, *Org. Lett.* **2005**, *7*, 4087 – 4089; b) V. Boissel, N. S. Simpkins, G. Bhalay, *Tetrahedron Lett.* **2009**, *50*, 3283 – 3286; c) V. Boissel, N. S. Simpkins, G. Bhalay, A. J. Blake, W. Lewis, *Chem. Commun.* **2009**, 1398 – 1400.
[11] a) J. A. MacKay, R. L. Bishop, V. H. Rawal, *Org. Lett.* **2005**, *7*, 3421 – 3424; b) V. Bhat, K. M. Allan, V. H. Rawal, *J. Am. Chem. Soc.* **2011**, *133*, 5798 – 5801; c) V. Bhat, V. H. Rawal, *Chem. Commun.* **2011**, *47*, 9705 – 9707; d) V. Bhat, J. A. MacKay, V. H. Rawal, *Org. Lett.* **2011**, *13*, 3214 – 3217; e) V. Bhat, J. A. MacKay, V. H. Rawal, *Tetrahedron* **2011**, *67*, 10097 – 10104.
[12] a) X. Tian, A. D. Huters, C. J. Douglas, N. K. Garg, *Org. Lett.* **2009**, *11*, 2349 – 2351; b) A. D. Huters, K. W. Quasdorf, E. D. Styduhar, N. K. Garg, *J. Am. Chem. Soc.* **2011**, *133*, 15797 – 15799.
[13] For other elegant strategies and approaches, see: a) T. Kaoudi, B. Ouiclet-Sire, S. Seguin, S. Z. Zard, *Angew. Chem.* **2000**, *112*, 747 – 749; *Angew. Chem. Int. Ed.* **2000**, *39*, 731 – 733; b) M. E. Jung, F. Slowinski, *Tetrahedron Lett.* **2001**, *42*, 6835 – 6838; c) P. López-Alvarado, S. García-Granda, C. Ivarez-Rúa, C. Avendaño, *Eur. J. Org. Chem.* **2002**, 1702 – 1707; d) J. M. Richter, Y. Ishihara, T. Masuda, B. W. Whitefield, T. Llamas, A. Pohjakallio, P. S. Baran, *J. Am. Chem. Soc.* **2008**, *130*, 17938 – 17945.
[14] P. S. Baran, J. M. Richter, *J. Am. Chem. Soc.* **2005**, *127*, 15394 – 15396.
[15] S. E. Reisman, J. M. Ready, A. Hasuoka, C. J. Smith, J. L. Wood, *J. Am. Chem. Soc.* **2006**, *128*, 1448 – 1449.
[16] For reviews of earlier routes toward the welwitindolinones, see: a) C. Avendaño, J. C. Menéndez, *Curr. Org. Synth.* **2004**, *1*, 65 – 82; b) L. E. Brown, J. P. Konopelski, *Org. Prep. Proced. Int.* **2008**, *40*, 411 – 445.
[17] B. M. Trost, P. R. Seoane, *J. Am. Chem. Soc.* **1987**, *109*, 615 – 617.
[18] T. Ye, M. A. McKervey, *Chem. Rev.* **1994**, *94*, 1091 – 1160.
[19] E. C. Kornfeld, E. J. Fornefeld, G. B. Kline, M. J. Mann, D. E. Morrison, R. G. Jones, R. B. Woodward, *J. Am. Chem. Soc.* **1956**, *78*, 3087 – 3114.
[20] a) J.-M. Galano, G. Audran, H. Monti, *Tetrahedron* **2000**, *56*, 7477 – 7481; b) J.-P. Uttaro, G. Audran, J.-M. Galano, H. Monti, *Tetrahedron Lett.* **2002**, *43*, 2757 – 2760; c) E. Palombo, G. Audran, H. Monti, *Synlett* **2006**, 403 – 406; d) K. C. Nicolaou, H. Li, A. L. Nold, D. Pappo, A. Lenzen, *J. Am. Chem. Soc.* **2007**, *129*, 10356 – 10357.
[21] G. H. Zayia, *Org. Lett.* **1999**, *1*, 989 – 991.
[22] Compound **58** was prepared in 76% yield over four steps from 2-bromo-6-nitrotoluene; see: H. Maehr, J. M. Smallheer, *J. Org. Chem.* **1981**, *46*, 1752 – 1755; see also ref. [11a].
[23] For a model system study of this transformation, see ref. [11a].
[24] a) K. J. Nyoung, E. K. Ryu, *Tetrahedron Lett.* **1993**, *34*, 8283 – 8284; b) J. N. Kim, K. S. Jung, H. J. Lee, J. S. Son, *Tetrahedron Lett.* **1997**, *38*, 1597 – 1598.
[25] T. Mukaiyama, Y. Yokota, *Bull. Chem. Soc. Jpn.* **1965**, *38*, 858 – 859.
[26] Homoallylic systems rearranging to the methylcyclopropyl moiety has been extensively studied; see: a) M. Hanack, H.-J. Schneider, *Angew. Chem.* **1967**, *79*, 709 – 720; *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 666 – 677; b) H. G. Richey, Jr., *Carbonium Ions*, *Vol. 3* (Eds.: G. A. Olah, P. v. R. Schleyer), Wiley-Interscience, New York, **1972**, p. 1201; c) T. Nagasawa, Y. Handa, Y. Onoguchi, K. Suzuki, *Bull. Chem. Soc. Jpn.* **1996**, *69*, 31 – 39; d) R. E. Taylor, F. C. Engelhardt, M. J. Schmitt, *Tetrahedron* **2003**, *59*, 5623 – 5634.
[27] For seminal indolyne studies, see: a) M. Julia, Y. Huang, J. Igolen, *C. R. Seances Acad. Sci. Ser. C* **1967**, *265*, 110 – 112; b) J. Igolen, A. Kolb, *C. R. Seances Acad. Sci. Ser. C* **1969**, *269*, 54 – 56; c) M. Julia, F. Le Goffic, J. Igolen, M. Baillarge, *Tetrahedron Lett.* **1969**, *10*, 1569 – 1571; d) M. Julia, F. Le Goffic, J. Igolen, M. Baillarge, *C. R. Seances Acad. Sci. Ser. C* **1967**, *264*, 118 – 120; e) M. Julia, J. Igolen, A. Kolb, *C. R. Seances Acad. Sci. Ser. C* **1971**, *273*, 1776 – 1777.
[28] For recent studies involving indolyes, see: a) S. M. Bronner, K. B. Bahnck, N. K. Garg, *Org. Lett.* **2009**, *11*, 1007 – 1010; b) P. H.-Y. Cheong, R. S. Paton, S. M. Bronner, G.-Y. J. Im, N. K. Garg, K. N. Houk, *J. Am. Chem. Soc.* **2010**, *132*, 1267 – 1269; c) G.-Y. J. Im, S. M. Bronner, A. E. Goetz, R. S. Paton, P. H.-Y. Cheong, K. N. Houk, N. K. Garg, *J. Am. Chem. Soc.* **2010**, *132*, 17933 – 17944; d) S. M. Bronner, A. E. Goetz, N. K. Garg, *J. Am. Chem. Soc.* **2011**, *133*, 3832 – 3835; e) K. R. Buszek, D. Luo, M. Kondrashov, N. Brown, D. VanderVelde, *Org. Lett.* **2007**, *9*, 4135 – 4137; f) N. Brown, D. Luo, D. VanderVelde, S. Yang, A. Brassfield, K. R. Buszek, *Tetrahedron Lett.* **2009**, *50*, 63 – 65; g) K. R. Buszek, N. Brown, D. Luo, *Org. Lett.* **2009**, *11*, 201 – 204; h) N. Brown, D. Luo, J. A. Decapo, K. R. Buszek, *Tetrahedron Lett.* **2009**, *50*, 7113 – 7115; i) A. N. Garr, D. Luo, N. Brown, C. J. Cramer, K. R. Buszek, D. VanderVelde, *Org. Lett.* **2010**, *12*, 96 – 99.
[29] For model system studies of the desired transformation, see ref. [12a].
[30] M. Sakagami, H. Muratake, M. Natsume, *Chem. Pharm. Bull.* **1994**, *42*, 1393 – 1398.
[31] S.-Y. Wang, S.-J. Ji, T.-P. Loh, *Synlett* **2003**, *15*, 2377 – 2379.
[32] P. Caubere, *Acc. Chem. Res.* **1974**, *7*, 301 – 308.
[33] W. D. Wulff, G. A. Peterson, W. E. Bauta, K.-S. Chan, K. L. Faron, S. R. Gilbertson, R. W. Kaesler, D. C. Yang, C. K. Murray, *J. Org. Chem.* **1986**, *51*, 277 – 279.
[34] S. M. E. Simpkins, B. M. Kariuki, C. S. Aricó, L. R. Cox, *Org. Lett.* **2003**, *5*, 3971 – 3974.
[35] a) H. M. L. Davies, J. R. Manning, *Nature* **2008**, *451*, 417 – 424; b) F. Collet, C. Lescot, C. Liang, P. Dauban, *Dalton Trans.* **2010**, *39*, 10401 – 10413.
[36] For intramolecular nitrene C–H insertions through carbamate substrates, see: a) C. G. Espino, J. Du Bois, *Angew. Chem.* **2001**, *113*, 618 – 620; *Angew. Chem. Int. Ed.* **2001**, *40*, 598 – 600; b) Z. Li, D. A. Capretto, R. Rahaman, C. He, *Angew. Chem.* **2007**, *119*, 5276 – 5278; *Angew. Chem. Int. Ed.* **2007**, *46*, 5184 – 5186; c) Y. Cui, C. He, *Angew. Chem.* **2004**, *116*, 4306 – 4308; *Angew. Chem. Int. Ed.* **2004**, *43*, 4210 – 4212.
[37] For an impressive example of a nitrene C–H insertion used in late-stage alkaloid total synthesis, see: A. Hinman, J. Du Bois, *J. Am. Chem. Soc.* **2003**, *125*, 11510 – 11511.
[38] During the production of this manuscript, additional welwitindolinones have been reported, see a) K. M. Allen, K. Kobayashi, V. H. Raval, *J. Am. Chem. Soc.* **2012**, *134*, 1392 – 1395; b) K. W. Quasdorf, A. D. Huters, M. W. Lodewyk, D. J. Tantillo, N. K. Garg, *J. Am. Chem. Soc.* **2012**, *134*, 1396 – 1399.

