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Evolution of a Synthetic Strategy: Total Synthesis of (±)-Welwitindolinone A Isonitrile

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Abstract: An efficient and highly stereoselective total synthesis of the natural product (±)-welwitindolinone A isonitrile (**1**) is described. The bicyclo[4.2.0]octane core of **1** was established by a regio- and diastereoselective [2+2] ketene cycloaddition. The C12 quaternary center and vicinal stereogenic chlorine were installed in a single operation with excellent stereocontrol via a chloronium ion mediated semipinacol rearrangement. Described strategies for construction of the spiro-oxinole include a SmI_2−LiCl mediated reductive cyclization and a novel anionic cyclization that simultaneously constructs the spiro-oxindole and vinyl isonitrile moieties.

Introduction

In 1994, as a result of a screen for novel compounds displaying multiple drug resistance (MDR) reversing activity, Moore and co-workers reported the structural elucidation of the welwitindolinones, a family of unusual oxindole alkaloids isolated from the cyanobacteria *Hapalosiphon welwischii* and *Westiella intricate* (Figure 1, **1**−**7**).[1] Five years later, the structures of three additional highly oxidized welwitindolinones were reported (**8**−**10**).[2] Of the ten welwitindolinones isolated to date, nine comprise a bridged 3,4-oxindole carbon skeleton typified by *N*-methyl welwitindolinone C isothiocyanate (**7**), the compound responsible for the MDR reversing activity of the algal extracts. Interestingly, a single welwitindolinone, termed welwitindolinone A isonitrile (**1**), consisted of a unique carbon skeleton in which the oxindole is spiro-fused to a densely functionalized bicyclo[4.2.0]octane core. Despite their obvious differences, the homology of the relative stereochemistry at C12, C13, and C15 led Moore to speculate that **1** is the biogenetic precursor to **2**−**10**. While a number of synthetic strategies toward **7** have been reported in recent years,[3−9] Baran and Richter's biomimetic synthesis of **1** in 2005 was the first completed total synthesis of any member of this family of molecules.[10,11]

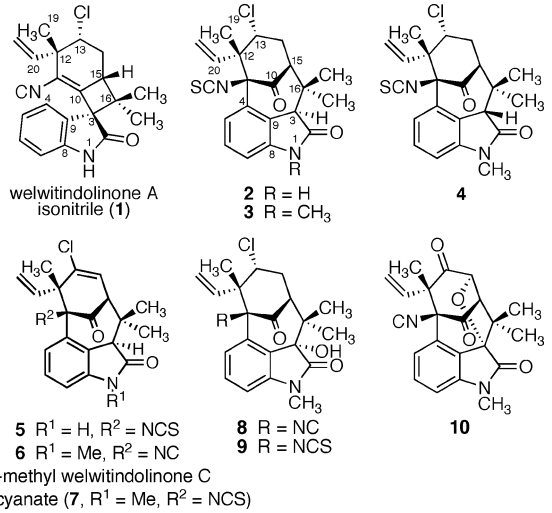

Figure 1. The welwitindolinone alkaloids.

Several years ago we initiated a general program for the synthesis of the welwitindolinones consisting of independent approaches to both the bridged 3,4-oxindole carbon-skeleton of **2**−**10**[9] and the spiro-cyclobutane oxindole core of **1**.[12] The latter approach resulted in a highly stereoselective synthesis of **1** that utilized an unprecedented anionic cyclization of an isocyano−isocyanate precursor to provide both the vinyl isoni-

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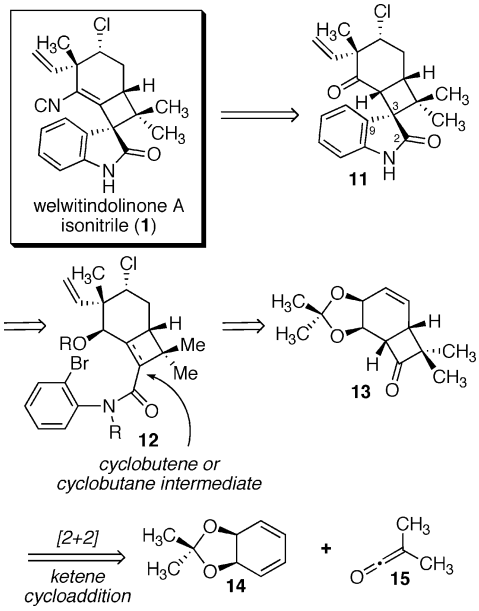
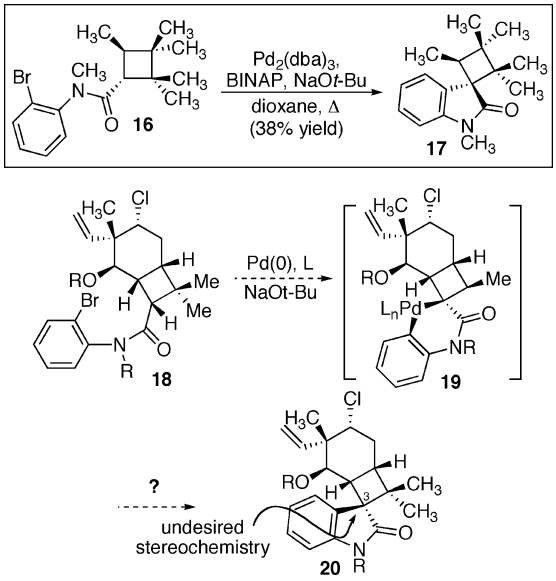
(1) Stratmann, K.; Moore, R. E.; Bonjouklian, R.; Deeter, J. B.; Patterson, G. M. L.; Shaffer, S.; Smith, C. D.; Smitka, T. A. *J. Am. Chem. Soc.* **1994**, *116*, 9935.
(2) Jimenez, J. I.; Huber, U.; Moore, R. E.; Patterson, G. M. L. *J. Nat. Prod.* **1999**, *62*, 569.
(3) Baudoux, J.; Blake, A. J.; Simpkins, N. S. *Org. Lett.* **2005**, *7*, 4087.
(4) Deng, H. B.; Konopelski, J. P. *Org. Lett.* **2001**, *3*, 3001.
(5) Holubec, A. A. *Progress Toward the Total Synthesis of the Welwitindolinone Alkaloids: Efficient Construction of the Carbocyclic Skeleton;* Yale University: New Haven, CT, 2000.
(6) Konopelski, J. P.; Deng, H. B.; Schiemann, K.; Keane, J. M.; Olmstead, M. M. *Synlett* **1998**, *10*, 1105.
(7) MacKay, J. A.; Bishop, R. L.; Rawal, V. H. *Org. Lett.* **2005**, *7*, 3421.
(8) Weiss, M. M. *Progress Toward a Total Synthesis of the Welwitindolinone Alkaloids*; Yale University: New Haven, CT, 2001.
(9) Wood, J. L.; Holubec, A. A.; Stoltz, B. M.; Weiss, M. M.; Dixon, J. A.; Doan, B. D.; Shamji, M. F.; Chen, J. M.; Heffron, T. P. *J. Am. Chem. Soc.* **1999**, *121*, 6326.
(10) Baran, P. S.; Richter, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 15394.
(11) Baran, P. S.; Maimone, T. J.; Richter, J. M. *Nature* **2007**, *446*, 404.
(12) Ready, J. M.; Reisman, S. E.; Hirata, M.; Weiss, M. M.; Tamaki, K.; Ovaska, T. V.; Wood, J. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1270.

Scheme 1



Scheme 2



trile and spiro-oxindole moieties in a single operation.[13] This paper describes the evolution of our synthetic strategy for **1** and highlights the advances in both methods and strategy that typically result from total syntheses of complex natural products.

Discussion

I. Retrosynthetic Considerations. From a retrosynthetic perspective, we initially expected that the potentially labile vinyl isonitrile of **1** would derive from ketone **11** in the final stage of the synthesis; thus **11** was considered a key synthetic intermediate (Scheme 1). For construction of **11**, we anticipated that the required bicyclo[4.2.0]octane carbon core would be accessible from a [2+2] ketene cycloaddition of known diene **14** and dimethylketene (**15**). With the core structure in place we would be in position to experimentally assess various methods for converting the derived ketone to **11**. Initial efforts focused on advancing tricycle **13** to a spiro-oxindole-containing intermediate (e.g., **11**). Strategically, this required formation of either the C3−C9 (aryl) bond or C3−C2 (acyl) bond in a key cyclization event. Given the numerous reports of methods for preparing 3,3-disubstituted oxindoles by formation of an sp^3-aryl carbon−carbon bond, we first considered strategies that would rely on cyclization of arylhalide intermediates such as **12**.

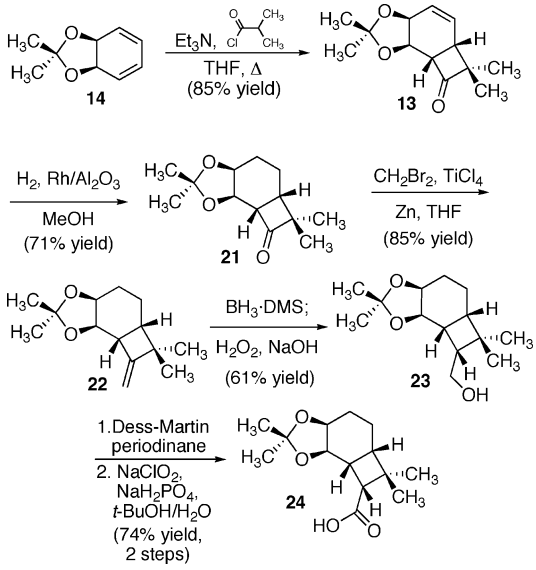
II. Construction of the Spiro-Oxindole by Formation of the C3-Aryl Bond. Of particular relevance to the cyclization of amide **12** is the work of Overman and co-workers, which has thoroughly demonstrated the utility of intramolecular Heck cyclizations for enantio- and diastereoselective preparation of a variety of 3,3-disubstitued oxindoles.[14−17] However, Heck cyclizations, particularly of hindered substrates, often require prolonged heating at elevated temperatures. Furthermore, in the context of our synthetic target (**1**), the requisite olefin would necessarily reside in a cyclobutene ring (see **12**, Scheme 1). Concern about the propensity of the cyclobutene substrate to undergo electrocyclic ring opening at the temperatures required for cyclization led us to consider alternative methods.[18]

At the outset of this project, Pd-catalyzed enolate arylation was just emerging as a powerful method for the construction of α-aryl carbonyl compounds. In 1998, Hartwig et al. reported the intramolecular α-arylation of amides to give oxindoles.[19] Importantly, this method is suitable for the preparation of several 3,3-disubstituted oxindoles and would not require a cyclobutene substrate. To test the feasibility of employing this method to access a hindered, spiro-cyclobutane oxindole such as **11**, model pentamethylated cyclobutyl-amide **16** was prepared.[20] Indeed, treatment of amide **16** with $Pd_2(dba)_3$ and BINAP in the presence of NaO*t*-Bu delivered a 10:1 mixture of diastereomers from which spiro-oxindole **17** was isolated in 38% yield (Scheme 2).

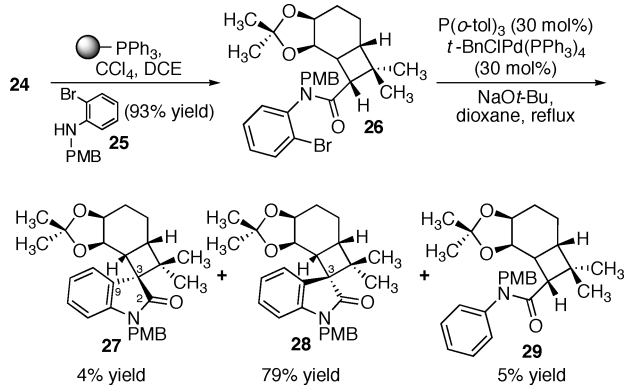
Having established the Pd-catalyzed enolate arylation as a suitable strategy for constructing sterically hindered spiro-oxindoles, we began to focus attention on the preparation of a substrate suited for advancement to **1**. At the outset of these studies it was recognized that the concave/convex nature of the requisite bicyclo[4.2.0]octane substrate (e.g., **18**) would likely direct aryl bond formation to the less hindered, convex face (via **19**) and lead to oxindole **20**, which possesses the undesired stereochemistry at C3. Hoping to overcome this intrinsic stereochemical bias by adjusting the ligands on palladium we proceeded with the preparation of a more advanced model cyclization substrate. To this end, treatment of acetonide **14** with excess isobutyryl chloride and triethylamine in refluxing THF provided tricyclic ketone **13** in 85% yield as a single regio- and diastereo-isomer (Scheme 3). Hydrogenation of the olefin furnished cyclobutanone **21**, which was subjected to Takai

(13) Reisman, S. E.; Ready, J. M.; Hasuoka, A.; Smith, C. J.; Wood, J. L. *J. Am. Chem. Soc.* **2006**, *128*, 1448.
(14) Dounay, A. B.; Hatanaka, K.; Kodanko, J. J.; Oestreich, M.; Overman, L. E.; Pfeifer, L. A.; Weiss, M. M. *J. Am. Chem. Soc.* **2003**, *125*, 6261.
(15) Ashimori, A.; Bachand, B.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **2000**, *122*, 192.
(16) Ashimori, A.; Overman, L. E. *J. Org. Chem.* **1992**, *57*, 4571.
(17) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945.
(18) Early experiments in our laboratory demonstrated that model cyclobutene Heck substrates were unstable to the reaction conditions.
(19) (a) Shaughnessy, K. H.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1998**, *63*, 6546. (b) For leading references on Pd-catalyzed arylation of carbonyl compounds, see: Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234−245 and references cited therein.
(20) See Supporting Information for details.

Scheme 3



Scheme 4



olefination conditions[21] to give *exo*-olefin **22**. Hydroboration/oxidation of olefin **22** smoothly provided primary alcohol **23**, which after a two-step adjustment of oxidation state, delivered carboxylic acid **24**.

Carboxylic acid **24** was subsequently coupled with PMB-protected *o*-bromoaniline **25** to give cyclization substrate **26** (Scheme 4). As illustrated in Table 1, exposure of amide **26** to the conditions originally reported by Hartwig (entry 1) provided a modest 29% yield of spiro-oxindoles **27** and **28** as a 1:6 mixture of diastereomers accompanied with a significant quantity of hydrodebromination product **29**; as anticipated the major isomer (**28**) results from carbon−carbon bond formation on the convex face of the bicyclic molecule. Further investigation of these conditions initially showed some promise with regard to overriding the intrinsic facial bias (Table 1, entry 2); however, subsequent screening of several palladium sources and ligands failed to produce favorable yields of the desired isomer (**27**) and led only to our improving the production of **28** (see Table 1 entry 9 and conditions illustrated in Scheme 4).[20]

Given our inability to identify a ligand system that would overcome the diastereofacial bias imparted by the bicyclic system, we turned to an alternative strategy wherein construction of the spiro-oxindole follows from cyclization via the C3-acyl bond (see Scheme 5).

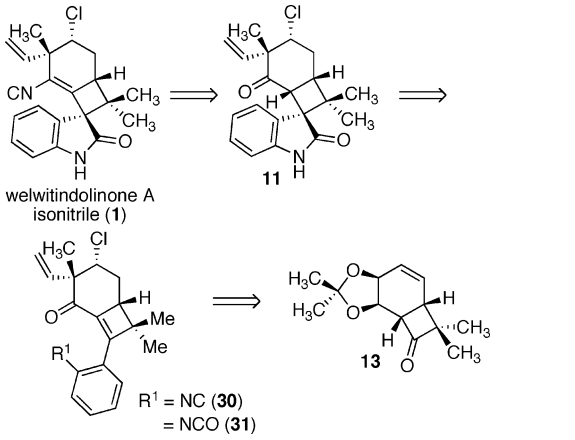
(21) Takai, K.; Kakiuchi, T.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 2668.

Table 1. Catalyst Screening[a]

	catalyst (mol %)	ligand (mol %)	conversion (%)	**27** (%)[b]	**28** (%)[b]	**29** (%)[b]
1	$Pd_2(dba)_3$ (30)	BINAP (45)	88	4	25	9
2	$Pd_2(dba)_3$ (40)	BINAP (30)	100	16	18	0
3	$Pd_2(dba)_3$ (70)	BINAP (100)	100	2	26	10
4	Pd(OAc)2 (30)	PCy_3 (30)	32	0	0	6
5	*t*-BnClPd$(PPh_3)_2$ (30)	PCy_3 (30)	60	0	0	22
6	*t*-BnClPd$(PPh_3)_2$ (30)	BINAP (40)	100	6	59	5
7	*t*-BnClPd$(PPh_3)_2$ (30)	Dppe (40)	100	3	59	5
8	*t*-BnClPd$(PPh_3)_2$ (30)	Dppe (40)	100	2	54	7
9	*t*-BnClPd$(PPh_3)_2$ (30)	(*o*-tol)$_3$P	100	4	79	5
10	*t*-BnClPd$(PPh_3)_2$ (30)		100	8	77	8
11	$Pd(PPh_3)_4$ (30)		100	10	65	8

[a] Conditions: Reactions were performed with 1.5 equiv of *t*-BuONa in refluxing dioxane [0.01 M]. [b] Isolated yield.

Scheme 5



III. A Second Generation Strategy: Development of a SmI_2/LiCl-Mediated Preparation of Spiro-Oxindoles. Our revised retrosynthetic strategy now called for the construction of spiro-oxindole **11** via the intermediacy of enone **30** or **31**, wherein an isonitrile or isocyanate would serve as *N*-acyl surrogates (Scheme 5). A survey of the literature provided limited precedent for this type of bond construction but did illustrate the viability of aryl isonitriles as acyl radical precursors.[22−25] Unfortunately, all examples required elevated temperatures (>80 °C) that were considered incompatible with the cyclobutene-containing substrate. However, we became intrigued with a report by Kim and co-workers detailing the SmI_2-mediated intermolecular reductive coupling of isocyanates and α,β-unsaturated esters to give amides.[26] While the Kim report described an *inter*molecular reaction, application to an *intra*molecular substrate (i.e., **31**) was expected to deliver spiro-oxindole **11** under very mild conditions.

To investigate this reaction, model substrate **33** (a nonisolated intermediate) was readily prepared by Pd-catalyzed Heck coupling of cyclohex-2-en-1-one with *o*-iodoaniline followed by treatment with phosgene and triethylamine (Scheme 6).

(22) Fukuyama, T.; Chen, X. Q.; Peng, G. *J. Am. Chem. Soc.* **1994**, *116*, 3127.
(23) For an alternative acyl radical precursor, see Herzon, S. B.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 5342.
(24) Tokuyama, H.; Fukuyama, T. *Chem. Record* **2002**, *2*, 37.
(25) Tokuyama, H.; Yamashita, T.; Reding, M. T.; Kaburagi, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **1999**, *121*, 3791.
(26) Kim, Y. H.; Park, H. S.; Kwon, D. W. *Syn. Comm.* **1998**, *28*, 4517.

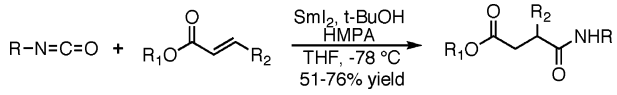
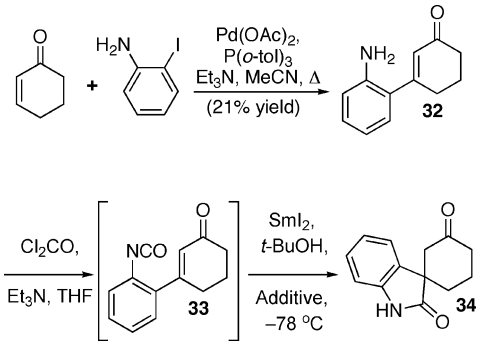


Table 2. Additive Screening[a]

entry	additive	yield **34** (%)[b]
1	none	5
2	NiI_2[c]	15
3	HMPA[d]	32
4	LiBr[e]	47
5	LiCl[e]	88

[a] Reactions carried out with 1 equiv **32**, 1 equiv *t*-BuOH, and 2.1 equiv SmI_2. [b] Isolated yield. [c] Run using 0.05 equiv. [d] Run using 6.2 equiv. [e] Run using 8.4 equiv.

Scheme 6

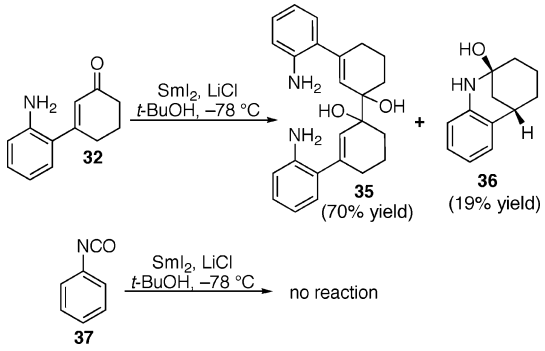


Unfortunately, exposure of the crude isocyanate to SmI_2 provided only trace amounts of the desired reductive cyclization product **34** (Table 2, entry 1). Subjection of isocyanate **33** to the conditions reported by Kim et al. (Table 2, entry 3) provided a modest increase to 32% yield.

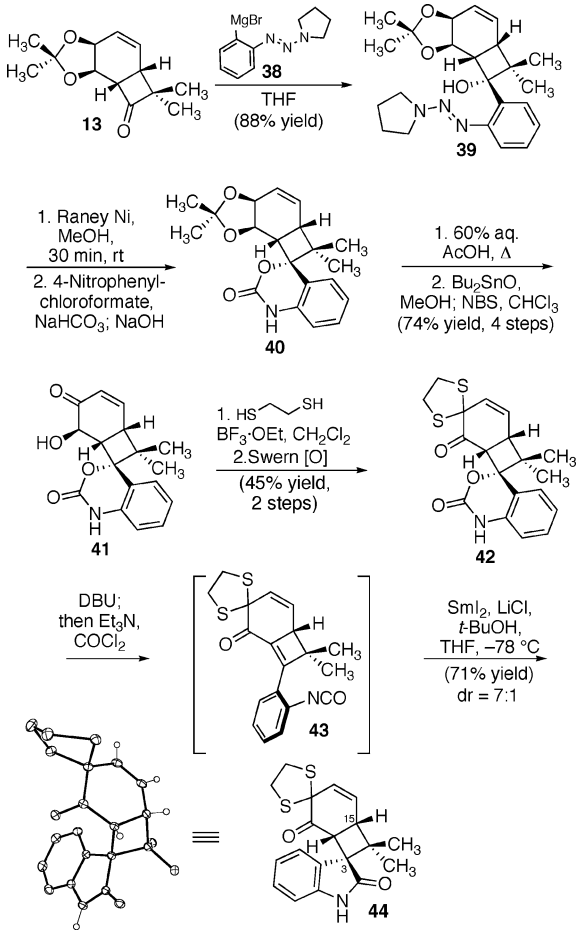
Despite the low yields, these initial results appeared promising. In an effort to further improve the chemical yield of **34**, other additives known to alter the reactivity of SmI_2 were screened (Table 2). Gratifyingly, treatment of the crude isocyanate **33** to a preformed mixture of SmI_2 and LiCl provided spiro-oxindole **34** in 88% yield. This increased reactivity is consistent with previous findings that the combination of SmI_2 and LiCl generates $SmCl_2$ in situ, a stronger reductant than SmI_2 alone (the $E_{1/2}$ for SmI_2/LiCl and SmI_2 are -1.78 V and -0.98 V, respectively).[27]

In considering the mechanism for cyclization, it was recognized that substrate **33** possesses two potential electron acceptors: the α,β-unsaturated ketone and the isocyanate. In an effort to distinguish which functional group is reduced by the SmI_2/LiCl mixture, two experiments were performed. In the first, aniline **32** (lacking the isocyanate functionality) was exposed to the optimized reaction conditions and found to furnish diol **35** (70% yield),[28] the product of pinacol dimerization, and aminal **36** (19% yield), the result of net-1,4-reduction of the enone (Scheme 7).[29] Alternatively, subjection of phenyl isocyanate (**37**, lacking a reactive enone) to the same reactions conditions resulted in no reaction. These results suggest that the conversion of isocyanate **33** to spiro-oxindole **34** proceeds first by reduction of the enone, followed by cyclization into the isocyanate.[30]

Scheme 7



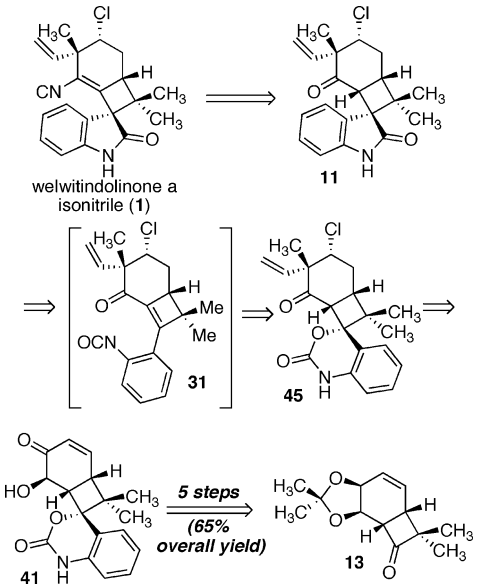
Scheme 8



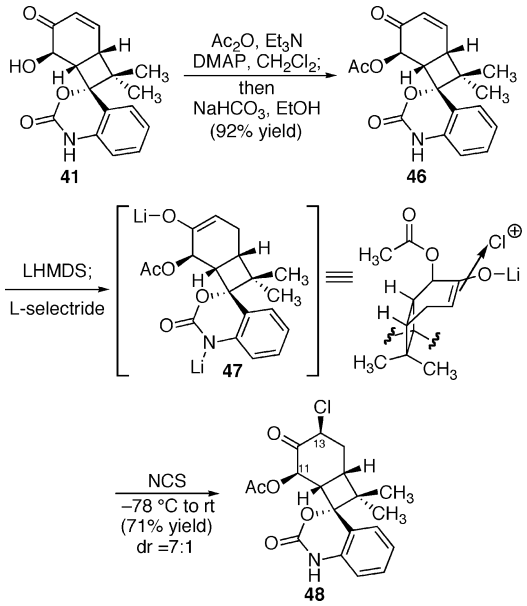
Although the mild conditions required for SmI_2/LiCl-mediated reductive cyclization suggested it would be tolerated by a highly functionalized substrate (e.g., **31**, Scheme 5), we sought confirmation and prepared a more relevant, cyclobutane-containing substrate (**43**, Scheme 8). To this end, cyclobutanone **13** was treated with triazene-protected aryl Grignard reagent **38** to give tertiary alcohol **39** in excellent yield as a single diastereomer. Reductive deprotection of the triazene, followed by urethane formation furnished **40**, which upon acidic hydrolysis of the acetonide and selective oxidation of the allylic alcohol provided hydroxy enone **41**. Using this efficient four-step sequence, multigram quantities of enone **41** could routinely be prepared from **39** with only a single chromatographic purification.

(27) (a) Miller, R. S.; Sealy, J. M.; Shabangi, M.; Kuhlman, M. L.; Fuchs, J. R.; Flowers, R. A. *J. Am. Chem. Soc.* **2000**, *122*, 7718. (b) On the basis of the emperical rules of House the reduction potentials of **33** and **43** are predicted to be 1.7 V and 1.8 V, respectively, see: House, H. O.; Huber, L. E.; Umen, M. J. *J. Am. Chem. Soc.* **1972**, *94*, 8471.
(28) Diol **35** was isolated as a mixture of diastereomers.
(29) On the basis of a theoretical yield of 50% for dimerization.
(30) It remains unclear whether the reductive cyclization of **33** to **34** occurs by a 1 or 2 e^- process.

Scheme 9



Scheme 10



Dithiolane protection of enone **41** followed by oxidation under Swern conditions provided ketone **42**, a masked substrate for our newly developed SmI_2/LiCl-mediated reductive cyclization protocol. In the event, treatment of ketone **42** with DBU effected smooth elimination of CO_2 to provide the corresponding aniline, which was converted in situ (Et_3N, $COCl_2$) to isocyanate **43**. Removal of the triethylamine salts and exposure of the crude isocyanate **43** to a preformed mixture of SmI_2/LiCl delivered spiro-oxindole **44** in 71% yield as a 7:1 mixture of diastereomers. The major diastereomer possessed C13/C15 relative stereochemistry consistent with bond formation on the less-hindered, convex face of **43** and was thus poised for advancement to **1**. This stereochemical assignment was confirmed by single-crystal X-ray diffraction.[31]

At this juncture, a more detailed retrosynthesis was devised (Scheme 9). While spiro-oxindole **44** was considered the most advanced synthetic intermediate en route to **1**, α-hydroxy enone **41**, which was easily accessible in multigram quantities (five steps and 65% overall yield) from cyclobutanone **13**, was envisioned to be an ideal substrate to explore the functionalization of the northern portion of the molecule. The illlustrated strategy relies on accessing oxindole **11** by employing the SmI_2/LiCl-mediated reductive cyclization on a completely functionalized aryl isocyanate (**31**). Aryl isocyanate **31** was envisioned to arise from urethane **45**, which we hoped to prepare from enone **41**. Though it was considered somewhat risky to delay construction of the spiro-oxindole to the end of the synthesis, the mild reaction conditions used for this key cyclization were expected to be compatible even with such an advanced intermediate.

IV. A Chloronium-Ion-Mediated Semipinacol Rearrangement. The focus of initial studies for advancing α-hydroxy enone **41** to isocyanate **31** was the stereoselective introduction of the C13 chlorine. To investigate this chemistry, the C11 secondary alcohol of **41** was first protected as the acetate (**46**, Scheme 10). Sequential treatment of **46** with LHMDS (to transiently protect the urethane as the lithium amide) and L-selectride regioselectively provided lithum enolate **47**, which was subsequently quenched with NCS to furnish α-chloroketone **48** in 71% yield as a 7:1 mixture of diastereomers. Unfortunately, analysis of the coupling constant and NOE data indicated that the major diastereomer contained the incorrect stereochemistry at C13.[32] This diastereoselectivity, while undesired, was not entirely unexpected as it resulted from trapping of the lithium enolate on the less hindered, convex face of the bicyclic ring system (see Scheme 10).

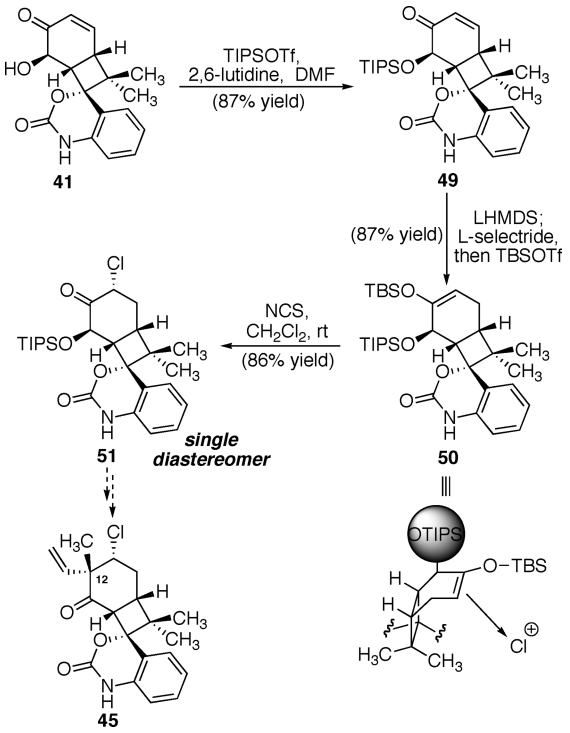
While α-acetoxy enone **46** could theoretically be advanced to the desired C13 epimer through a two-step sequence involving α-hydroxylation followed by chlorination with inversion of stereochemistry, it was postulated that protection of the C11 hydroxyl of enone **41** with a suitably large protecting group could over-ride the inherent facial bias of the bicyclic skeleton and promote chlorination of the concave face. Thus, α-hydroxy enone **41** was converted to the triisopropyl silyl ether **49** (Scheme 11). Subjection of silyl ether **49** to the conditions used previously (Scheme 10, LHMDS, L-selectride, then NCS) failed to provide significant quantities of chlorination product. However, after considerable experimentation it was found that conversion of enone **49** to *tert*-butyldimethylsilyl enol ether **50** and treatment with NCS at room-temperature provided α-chloroketone **51** in 86% yield as a *single* diastereomer possessing the desired stereochemistry at C13. While speculative, the selectivity in this reaction likely derives from the TIPS ether of **50** residing in the pseudoaxial position, a conformation which minimizes $A_{1,2}$ strain between the two large silyl groups. In this conformation, reaction by chloronium ion formation on the convex face of **50**, opposite of the large TIPS group, provides the observed diastereomer.

Pleased with our ability to control the diastereoselectivity of the chlorination event, we considered methods to install the all carbon quaternary center at C12. After contemplating sequences to convert chloroketone **51** to urethane **45**, we decided to pursue a more streamlined strategy in which the quaternary center and vicinal stereogenic chlorine would be incorporated simultaneously. Specifically, we recognized that one approach to

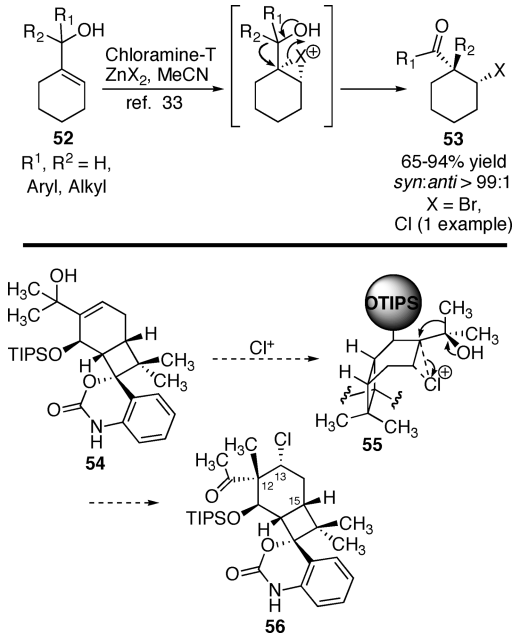
(31) See Supporting Information for crystallographic details.

(32) See Supporting Information for details.

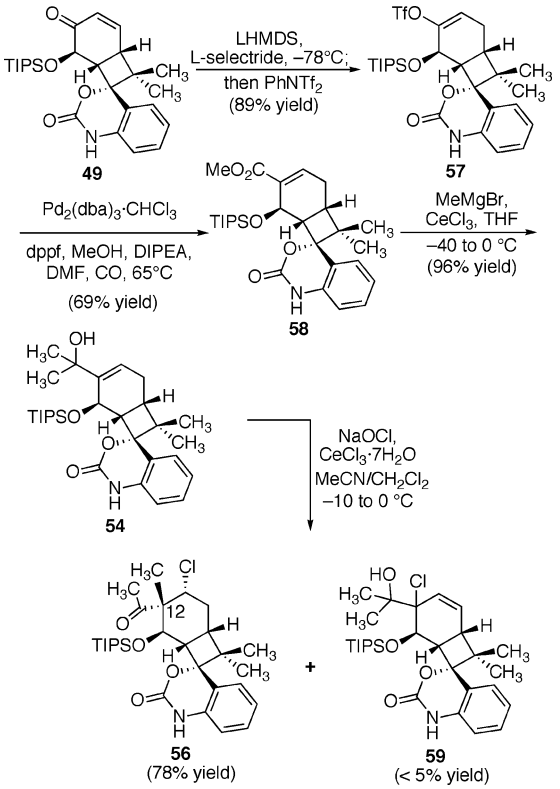
Scheme 11



Scheme 12



Scheme 13



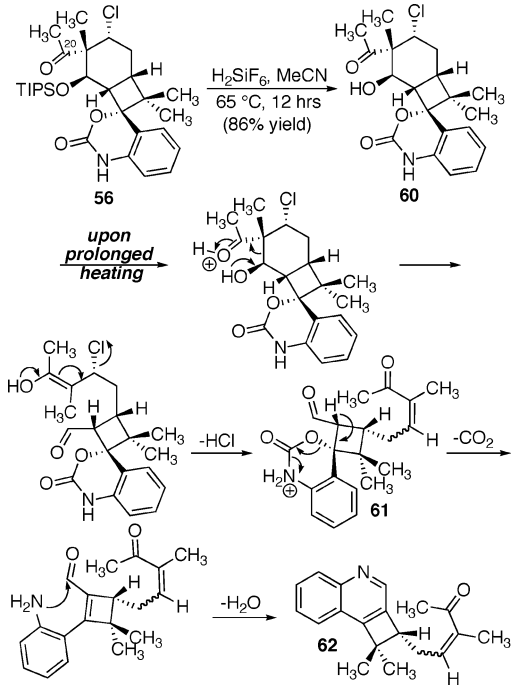
construct α-halo quaternary centers is the semipinacol rearrangement of tertiary allylic alcohols (Scheme 12, **52** → **53**).[33] In analogy to the Lewis-acid-mediated semipinacol rearrangement of epoxyl alcohols,[34] the diastereoselectivity is a result of stereospecific alkyl migration *anti* to the chloronium ion. It was therefore anticipated that treatment of tertiary alcohol **54** with a source of electrophilic chlorine would provide chloroketone **56** with the desired relative stereochemical relationship between carbons C12 and C13 (Scheme 12). Furthermore, the diastereoselective chlorination of structurally similar silyl enol ether **50** to give chloroketone **51** (Scheme 9) led us to hypothesize that reaction via chloronium ion formation on the concave face of **54** (producing intermediate **55**), would result in chloroketone **56** wherein the relative stereochemistry between C12, C13, and C15 is correct for advancement to **1** (Scheme 12).

To implement this strategy, tertiary allylic alcohol **54** was prepared by a sequence which commenced by treating α-siloxy ketone **49** with LHMDS (to deprotonate the urethane) followed by L-selectride then *N*-phenyltriflimide to give enol triflate **57** in 89% yield (Scheme 13). Subsequent exposure of triflate **57** to $Pd_2(dba)_3$ and 1,1′-bis(diphenylphosphino)ferrocene (dppf) in the presence of methanol, DIPEA and carbon monoxide furnished enoate **58** (69% yield). Subjection of enoate **58** to excess methyl magnesium bromide and anhydrous cerium trichloride provided tertiary allylic alcohol **54**, the required semipinacol rearrangement substrate.

Initial screening of tertiary alcohol **54** with the conditions described by Wang (chloramine-T, $ZnCl_2$, MeCN) provided minor quantities (<15%) of the rearrangement product **56**; however, separation from chloramine-T byproducts was difficult. Switching to NaOCl/AcOH as the chlorine source improved the overall conversion, unfortunately formation of multiple byproducts was observed. Use of $CeCl_3$ in biphasic CH_2Cl_2/H_2O and cooling the reaction to 0 °C significantly improved the yield of **56** to 50%. Upon further optimization, using MeCN as the solvent and maintaining the reaction temperature between −10 and 0 °C provided chloroketone **56** in 78% isolated yield as a *single* diastereomer.[35]

(33) Wang, B. M.; Song, Z. L.; Fan, C. A.; Tu, Y. Q.; Chen, W. M. *Synlett* **2003**, *10*, 1497.
(34) Marson, C. M.; Walker, A. J.; Pickering, J.; Hobson, A. D.; Wrigglesworth, R.; Edge, S. J. *J. Org. Chem.* **1993**, *58*, 5944.
(35) The stereochemistry was assigned by extensive nOe experimentation, for example, irradiation of the psuedo-axial H13 showed significant enhancements of the bridgehead H15, $H14_{eq}$, and H19 (methyl protons) (see Supporting Information for details).

Scheme 14

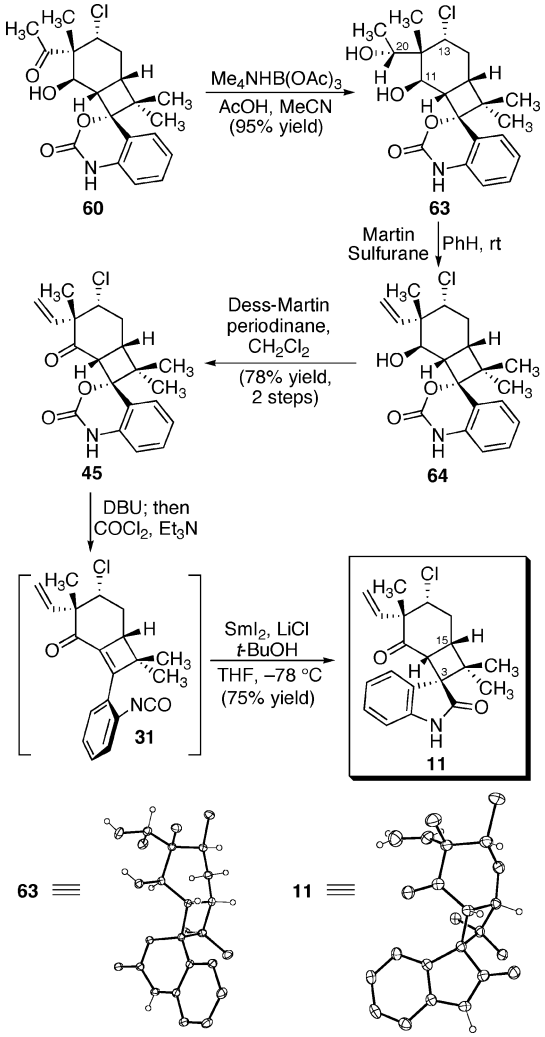


In this remarkable reaction, the relative stereochemistry of the C12 quaternary center and vicinal chlorine are simultaneously set with excellent stereocontrol. Analysis of the ^{1}H NMR spectrum of the crude product mixture indicated that the mass balance was a mixture of several minor byproducts (<2% yield per byproduct); the major and only cleanly isolable byproduct was olefin **59** (<5% yield), resulting from competitive deprotonation α to the chloronium ion.[36]

With chloroketone **56** in hand, attention turned to accessing fully functionalized reductive cyclization substrate **45** (see Scheme 9) by converting the C20 ketone to the requisite vinyl functionality. Disappointingly, all attempts to reduce ketone **56** resulted in recovery of starting material. Reasoning that the TIPS protecting group was blocking access to the C20 ketone, **56** was desilylated by treatment with fluorosilicic acid in warm acetonitrile to give hydroxy ketone **60** (Scheme 14).[37] Interestingly, prolonged heating (>12 h) resulted in formation of cyclobutane quinoline **62**.[38] This unanticipated byproduct likely arises by acid-mediated retro-aldol/chloride elimination to give putative intermediate **61**, followed by CO_2 extrusion and intramolecular condensation.

To avoid complications that could arise by the retro-aldol pathway illustrated in Scheme 14, hydroxy ketone **60** was reduced with $Me_4NHB(OAc)_3$ to give diol **63** (Scheme 15). Fortuitously, diol **63** crystallized from $CDCl_3$, and single-crystal X-ray diffraction provided definitive proof of the assigned stereochemistry at C12 and C13 set by the semipinacol rearrangement. Exposure of diol **63** to Martin sulfurane[39] resulted in selective dehydration of the C20 alcohol, furnishing the required vinyl moiety of **1**. Subsequent oxidation of alcohol

Scheme 15



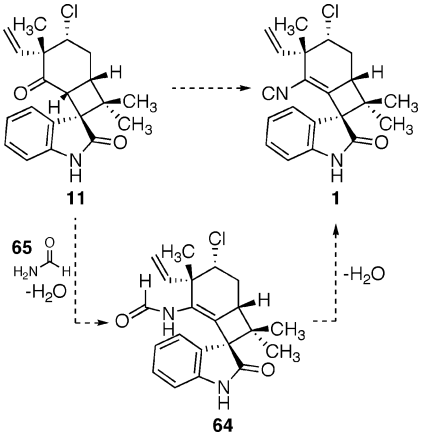
64 using Dess−Martin periodinane[40] furnished ketone **45** and set the stage for the previously developed SmI_2/LiCl-mediated reductive cyclization.

In the event, we were gratified to find that treatment of ketone **45** with DBU smoothly effected the elimination of CO_2 and provided the corresponding aniline, which was converted in situ to isocyanate **31** ($Et_3N/COCl_2$). Upon removal of the triethylamine salts, cooling to −78 °C and subjection to a preformed mixture of SmI_2/LiCl, spiro-oxindole **11** was isolated in 75% yield as a single diastereomer. The stereochemical assignment of oxindole **11** was confirmed by X-ray crystallographic analysis and is consistent with bond formation at C3 occurring on the less hindered, convex face of the bicyclic molecule. Importantly, there was no detection of products wherein the C13 chlorine had been reduced under the reaction conditions, an observation which is consistent with literature reports that SmI_2/LiCl mixtures reduce enones significantly faster than alkyl chlorides.[27]

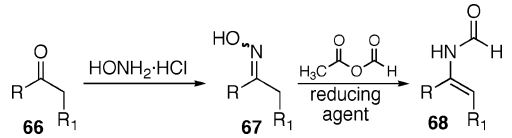
V. Attempts to Convert Ketone 11 to Welwitindolinone A Isonitrile (1). Having developed an efficient and stereoselective preparation of highly functionalized spiro-oxindole **11** (17 steps and 10.3% overall yield from cyclohexadiene **14**), completion of (±)-welwitindolinone A (**1**) isonitrile required only conversion of the C11 ketone to the corresponding vinyl

(36) Attempts to assign the C12 stereochemistry of byproduct **59** using nOe techniques were inconclusive, and **59** was unstable to recrystallization conditions.
(37) Pilcher, A. S.; Deshong, P. *J. Org. Chem.* **1993**, *58*, 5130.
(38) Compound **62** was isolated as a single olefin isomer, however the bond geometry was not confirmed.
(39) Martin, J. C.; Arhart, R. J. *J. Am. Chem. Soc.* **1971**, *93*, 4327.
(40) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

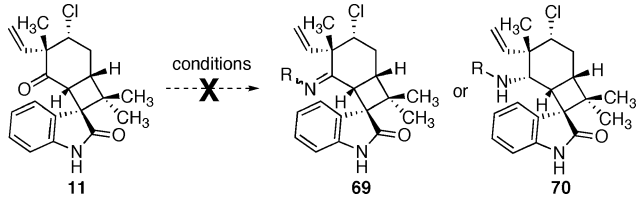
Scheme 16



Scheme 17



Scheme 18

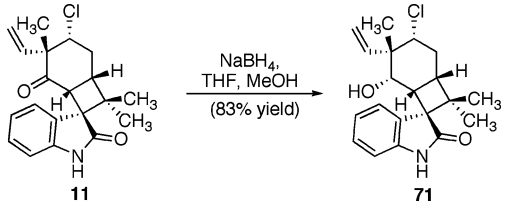


isonitrile (see, **11** → **1**, Scheme 16). Noting that the carbonyl carbon of **11** and isonitrile-bearing carbon of **1** are in the same oxidation state, formally the conversion of ketone **11** to vinyl isonitrile **1** should require condensation with 1 equiv of formamide (**65**) and the net loss of 2 equiv of water (Scheme 16). However, in a practical sense this straightforward approach is limited by the poor nucleophilicity of formamide.

Given that dehydration of vinyl formamides is facile and can be accomplished under mild conditions,[41−43] a variety of routes to convert ketones to vinyl formamides have been developed for the purpose of synthesizing vinyl isonitriles. One such method was developed by Barton et al., wherein a ketone (**66**) is first converted to the corresponding oxime (**70**, Scheme 17), a transformation which is generally high yielding and applicable to a variety of substrates.[42] Subsequent treatment of the oxime **67** with $Ti(OAc)_3$ in the presence of acetic formic anhydride (AFA) delivers the enamide (**68**). Recent advances have shown that commercially available and inexpensive iron(0) can be used as the reductant instead of $Ti(OAc)_3$.[44,45]

Initial efforts to convert ketone **11** to **1** focused on application of the aforementioned Barton sequence. Unfortunately, ketone **11** proved to be remarkably unreactive; all efforts to access oxime **69** (Scheme 18, R = OH) using a variety of conditions simply resulted in the recovery of starting material or, under

Scheme 19



extreme conditions (i.e., heating >150 °C), decomposition. For example, heating ketone **11** in neat pyridine with 100 equiv of hydroxylamine hydrochloride in a microwave reactor at 100 °C for 12 h provided only recovered starting material! Attempts to condense other amine sources documented to be successful with sterically hindered substrates also failed to provide any detectable quantities of product.[46] Interestingly, under all conditions evaluated, there was no evidence of Cl-elimination, suggesting that the C13-Cl is locked in a pseudo-equatorial position by the conformationally rigid bicyclic skeleton.

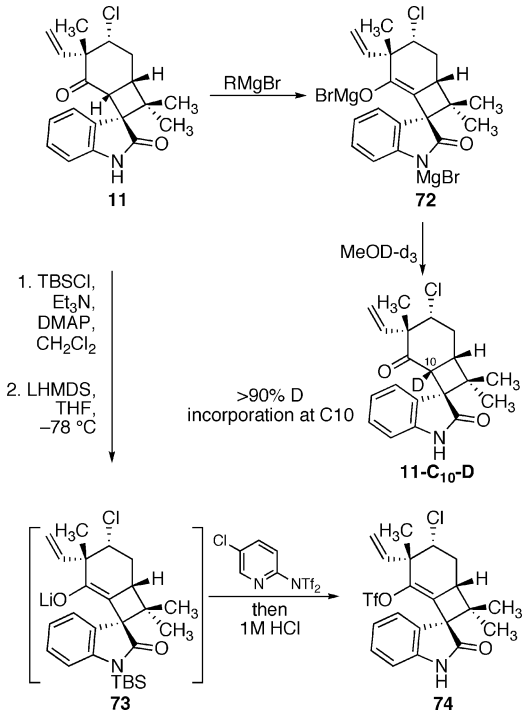
To determine whether iminium ion formation was occurring, but disfavored under equilibrium conditions, **11** was subjected to reductive amination conditions that had been successfully employed with similar ketones in the synthesis of related fischerindoles.[47] Ketone **11** again failed to produce any amine product **70** (R = H). These results suggested that iminium ion formation was strongly disfavored for ketone **11**. Alternatively, it is conceivable that iminium ion formation occurs, but the intermediate is too hindered for hydride reduction; however, the observation that ketone **11** undergoes facile $NaBH_4$ reduction to a single diastereomer of alcohol **71** suggests this is unlikely (Scheme 19).

Further probing of the general reactivity of ketone **11** revealed that exposure to a variety of carbon-based nucleophiles (e.g., Grignard reagents, organolithiums) also results in the recovery of starting material. Suspecting that competitive enolization was responsible for the lack of reactivity, deuterium-trapping experiments were conducted. Indeed, treatment of **11** with vinylmagnesium bromide followed by quenching with CD_3OD provided **11**-C10-D with near quantitative deuterium incorporation. Recognizing that welwitindolinone A isonitrile (**1**) contains Δ^{10-11} unsaturation, we sought to capitalize on the facile enolization of ketone **11** by trapping with triflating reagents. In the event, *N*-silylation of ketone **11** followed by treatment with LHMDS cleanly generated the bridgehead lithium enolate (**73**), which could be quenched with Comins' reagent to give vinyl triflate **74** (Scheme 20).[48] With vinyl triflate **74** in hand, investigations of metal-catalyzed amidation reactions were undertaken.

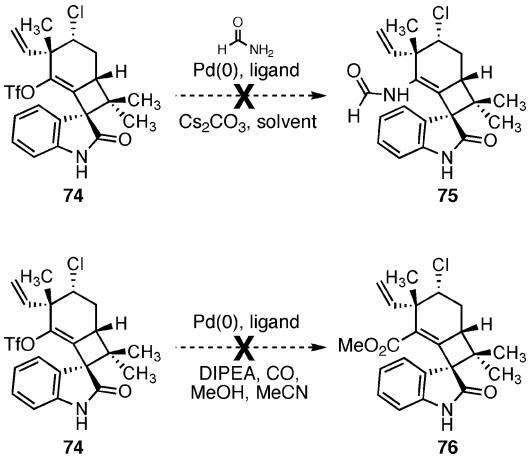
In recent years, there have been numerous reports detailing Pd-catalyzed coupling of vinyl triflates[49] and vinyl tosylates[50−52] with amides or carbamates to give enamide products. While the Pd-catalyzed amidations were found to be quite general with respect to the amide partner, until recently, they had been limited

(41) Baldwin, J. E.; Oneil, I. A. *Synlett* **1990**, *10*, 603.
(42) Barton, D. H. R.; Bowles, T.; Husinec, S.; Forbes, J. E.; Llobera, A.; Porter, A. E. A.; Zard, S. Z. *Tetrahedron Lett.* **1988**, *29*, 3343.
(43) Creedon, S. M.; Crowley, H. K.; McCarthy, D. G. *J. Chem. Soc., Perkin Trans. 1* **1998**, *6*, 1015.
(44) Burk, M. J.; Casy, G.; Johnson, N. B. *J. Org. Chem.* **1998**, *63*, 6084.
(45) Yoshida, M.; Watanabe, T.; Ishikawa, T. *Heterocycles* **2001**, *54*, 433.
(46) For a table of failed conditions for the conversion of **11** to **69** or **70**, see the Supporting Information.
(47) Baran, P. S.; Richter, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 7450.
(48) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299.
(49) Wallace, D. J.; Klauber, D. J.; Chen, C. Y.; Volante, R. P. *Org. Lett.* **2003**, *5*, 4749.
(50) Klapars, A.; Campos, K. R.; Chen, C. Y.; Volante, R. P. *Org. Lett.* **2005**, *7*, 1185.
(51) Movassaghi, M.; Ondrus, A. E. *J. Org. Chem.* **2005**, *70*, 8638.
(52) Willis, M. C.; Brace, G. N.; Holmes, I. P. *Synth. Stuttg.* **2005**, *19*, 3229.

Scheme 20



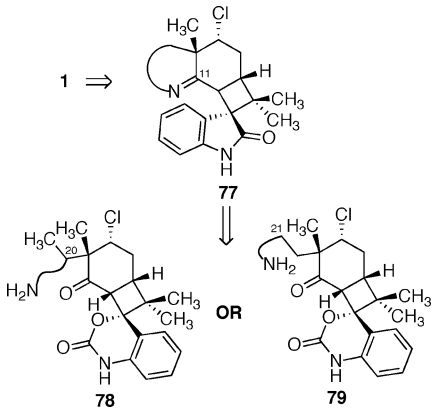
Scheme 21



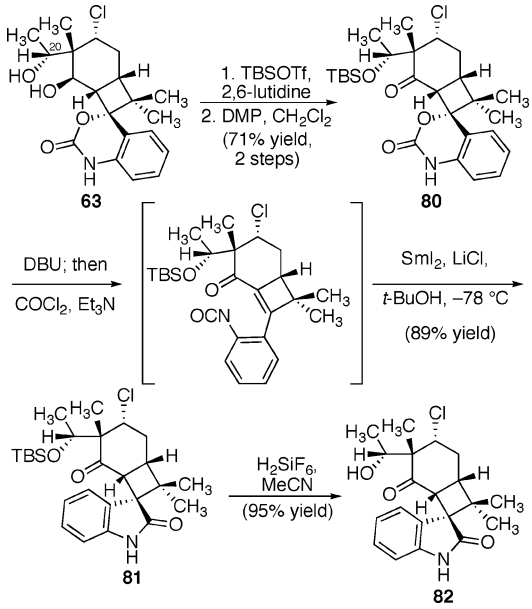
to activated vinyl triflates or tosylates.[52] Unfortunately, attempts to couple vinyl triflate **74** and formamide (**65**) using a number of catalysts, ligands, and solvents failed to produce any observable quantities of vinyl formamide **75** (Scheme 21).[53] At low temperatures (<80 °C), the vinyl triflate **74** could be recovered; however, at higher temperatures decomposition of the starting material was observed. Even the use of stoichiometric palladium and ligand failed to provide any trace of desired product or any byproducts indicative of oxidative addition. On the basis of the success earlier in the synthesis for promoting Pd-catalyzed CO-insertion of sterically hindered vinyl triflate **57** (see Scheme 13), vinyl triflate **74** was also subjected to a variety of Pd-catalyzed CO-insertion conditions. The complete failure of these latter reactions suggested that vinyl triflate **74** was too hindered to undergo oxidative addition to palladium, and once again other routes were evaluated.

(53) At the time of this work, there were no examples of Pd-catalyzed amidation of unactivated vinyl triflates.

Scheme 22



Scheme 23

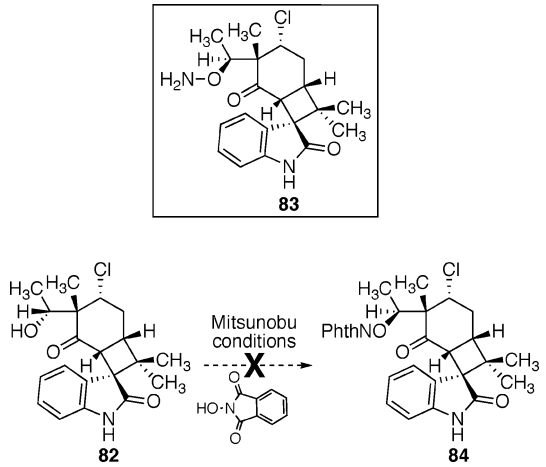


VI. An Intramolecular Condensation Approach. Unable to advance ketone **11** or various derivatives to **1** via intermolecular reactions (presumably due to steric and entropic factors) we began to consider strategies involving the *intra*molecular condensation of tethered amine nucleophiles (see Scheme 22). It was envisioned that our current route to ketone **11** could easily be modified to incorporate the required tethers at either C20 (e.g., **78**) or C21 (e.g., **79**). Of particular interest was tethered amine **78**, which was envisioned to arise in a straightforward manner by selective functionalization of the less-hindered C20 alcohol of diol **63** (see Scheme 15).

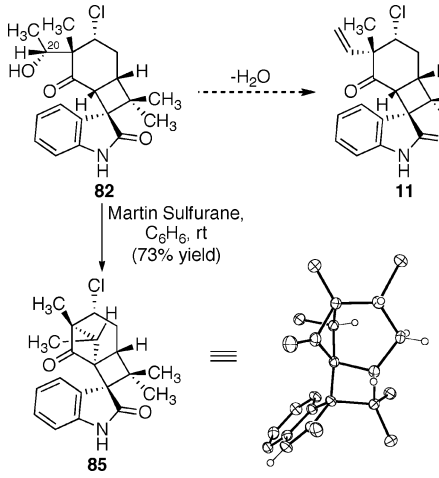
Functionalization of diol **63** commenced by selective monoprotection of the C20 hydroxyl as the TBS ether, and oxidation of the remaining C11 alcohol with Dess−Martin periodinane to provide ketone **80** (Scheme 23).[40] Exposure of ketone **80** to our previously optimized conditions for SmI_2/LiCl-mediated oxindole formation provided oxindole **81** in 91% yield, once again with complete stereocontrol of C3 spiro-center. The silyl protecting group was subsequently removed using fluorosilicic acid to give hydroxy ketone **82**, a substrate well-suited for nitrogen incorporation.

Because hydroxylamines are known for their exceptional nucleophilicity, and N−O bond cleavage can be carried out under a variety of conditions, initial efforts focused on prepara-

Scheme 24



Scheme 25

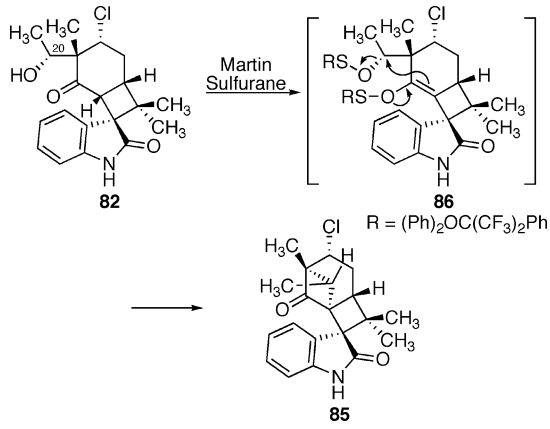


tion of hydroxylamine derivative **83** (Scheme 24).[54−57] To incorporate the hydroxylamine, hydroxy ketone **82** was treated with *N*-hydroxyphthalimide under a variety of Mitsunobu conditions; disappointingly, starting material was recovered unchanged. Subsequent attempts to effect alternative cyclizations with carbamate-derivatives or silyl tethered amines were also unsuccessful.

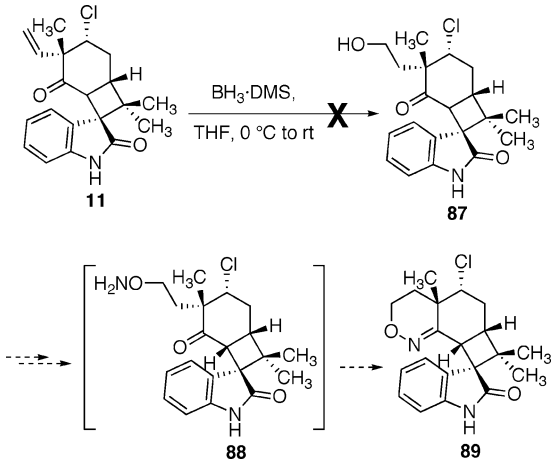
In addition to evaluating tether attachment, we briefly explored the feasibility of eventually dehydrating derivatives of **82** to the requisite olefin (i.e., **11**) (Scheme 25). In the event, it was found that exposure of a benzene solution of ketone **82** to Martin sulfurane provided a single, less polar product in 73% yield. While low-resolution mass spectrometry (ES+) indicated the correct mass (*m*/*z* calcd for $C_{20}H_{22}ClNNaO_2$ $[M+Na]^+$ 366.1, found 366.1), analysis of the ^1H NMR spectrum clearly indicated that the product of this reaction was *not* known ketone **11**. Notably, there were no vinyl protons; instead, the C10 α-keto bridgehead proton signal had disappeared, and the H20 carbinol signal had shifted upfield by approximately 1.2 ppm.

On the basis of extensive spectroscopic studies (NMR: ^1H, ^{13}C, ^1H-^1H COSY, DEPT, HMQC), the structure was ultimately assigned as the pentacyclic ketone **85**. This assignment was

Scheme 26



Scheme 27



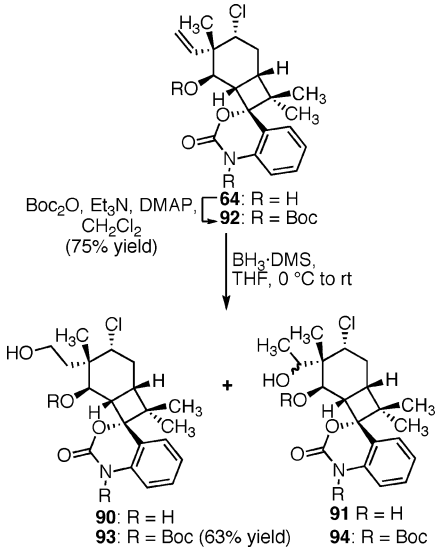
further corroborated by IR spectroscopy, which showed strong carbonyl stretching frequencies at 1703 and 1780 cm^{-1}, the latter of which is consistent with literature values for cyclobutanones.[58] The proposed structure was eventually confirmed by single-crystal X-ray analysis. A proposed mechanism for formation of this structurally intriguing compound is shown in Scheme 26. As excess Martin sulfurane was used, activation of the secondary alcohol was accompanied by Lewis acid promoted enolization of the ketone to give enolate **86**. Subsequent intramolecular nucleophilic displacement would then deliver cyclobutanone **85**.[59]

The difficulties encountered in efforts to access and cyclize tethered amine substrates from hydroxy ketone **82** were postulated to derive from the sterically hindered environment of the C20 neopentyl alcohol. As a result, we turned our attention to a primary hydroxylamine tether (e.g., **88**, Scheme 27).

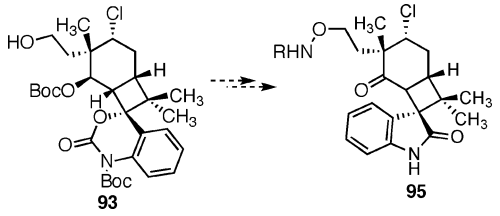
Unfortunately, attempts to access alcohol **87** directly by hydroboration of the olefin in oxindole **11** were unproductive; the starting material was recovered unchanged using mild conditions or went to multiple uncharacterized products under more forcing conditions (Scheme 27). However, by turning to an earlier olefin substrate, alcohol **64**, we were gratified to find that treatment with BH_3·DMS in THF and warming from 0 °C

(54) Aschwanden, P.; Kvaerno, L.; Geisser, R. W.; Kleinbeck, F.; Carreira, E. M. *Org. Lett.* **2005**, *7*, 5741.
(55) Curran, D. P.; Fenk, C. J. *Tetrahedron Lett.* **1986**, *27*, 4865.
(56) Curran, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 5826.
(57) Curran, D. P.; Singleton, D. H. *Tetrahedron Lett.* **1983**, *24*, 2079.
(58) Pretsch, E.; Buhlmann, P.; Affolter, C. *Structure Determination of Organic Compounds*, 3rd ed.; Springer-Verlag: Berlin, 2000.
(59) While the observed stereochemistry is consistent with an S_N2 mechanism (inversion at C20), it is also possible an S_N1 mechanism could be at work.

Scheme 28



Scheme 29



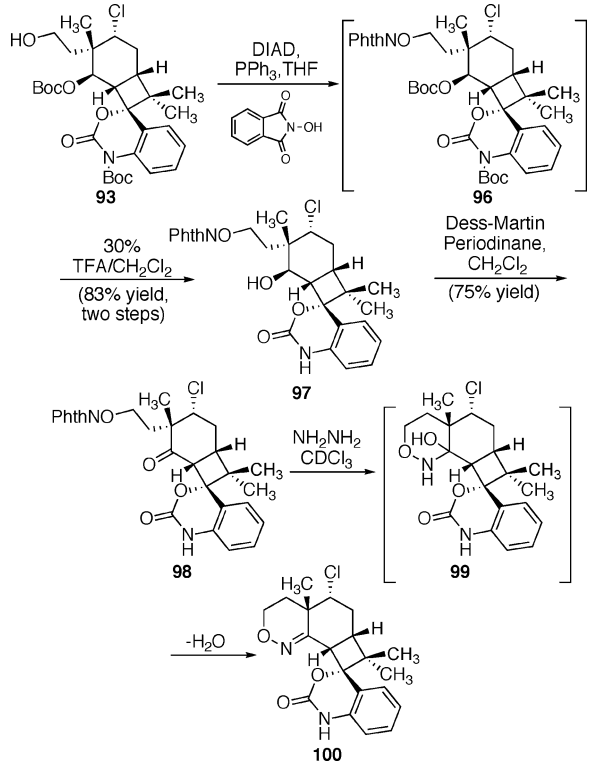
to room-temperature provided the desired primary alcohol **90**, albeit in low yield (ca. 25% by ^{1}H NMR) owing to competitive formation of a diastereomeric mixture of the secondary alcohol regioisomer (**91**, Scheme 28).[60]

This poor regioselectivity was surprising considering the high levels of regiocontrol generally found for primary olefin substrates in hydroboration reactions.[61,62] Screening a number of dialkylboranes known to increase the regioselectivity of hydroboration failed to result in significant improvement.[63] Suspecting that the free alcohol could be acting as a directing group to favor Markovnikov addition,[64] alcohol **64** was converted to bis-Boc derivative **92** and subjected to the same hydroboration conditions (Scheme 28). Thus, exposure of **92** to BH_3·DMS provided a much improved 63% isolated yield of primary alcohol **93** along with <10% of minor regioisomer **94**. The balance of the mass was starting material and small quantities of Boc-deprotected products.

VII. Synthesis of a Tethered Hydroxylamine Substrate. With primary alcohol **93** in hand, efforts turned to the synthesis of oxindole **95** (Scheme 29) by installation of the required hydroxylamine and construction of the spiro-oxindole using our SmI_2/LiCl-mediated reductive cyclization.

Primary alcohol **93** proved to be an excellent substrate for Mitsunobu reaction with *N*-hydroxyphthalimide, providing phthalimide-protected hydroxylamine derivative **96**, which upon treatment with trifluoroacetic acid gave free alcohol **97** in 83%

Scheme 30



yield over two steps (Scheme 30). Subsequent oxidation of alcohol **97** proceeded smoothly with Dess-Martin periodinane[40] to give ketone **98**. As a proof-of-concept for the intramolecular condensation, phthalimide **98** was deprotected by treatment with hydrazine hydrate in deuterated chloroform at room temperature. After 30 min, ^{1}H NMR showed complete conversion to a new product proposed to be hemiacetal **99**. Furthermore, upon removal of the hydrazine by rotary evaporation and standing in fresh $CDCl_3$ overnight, hemiacetal **99** underwent complete conversion to oxazine **100**.

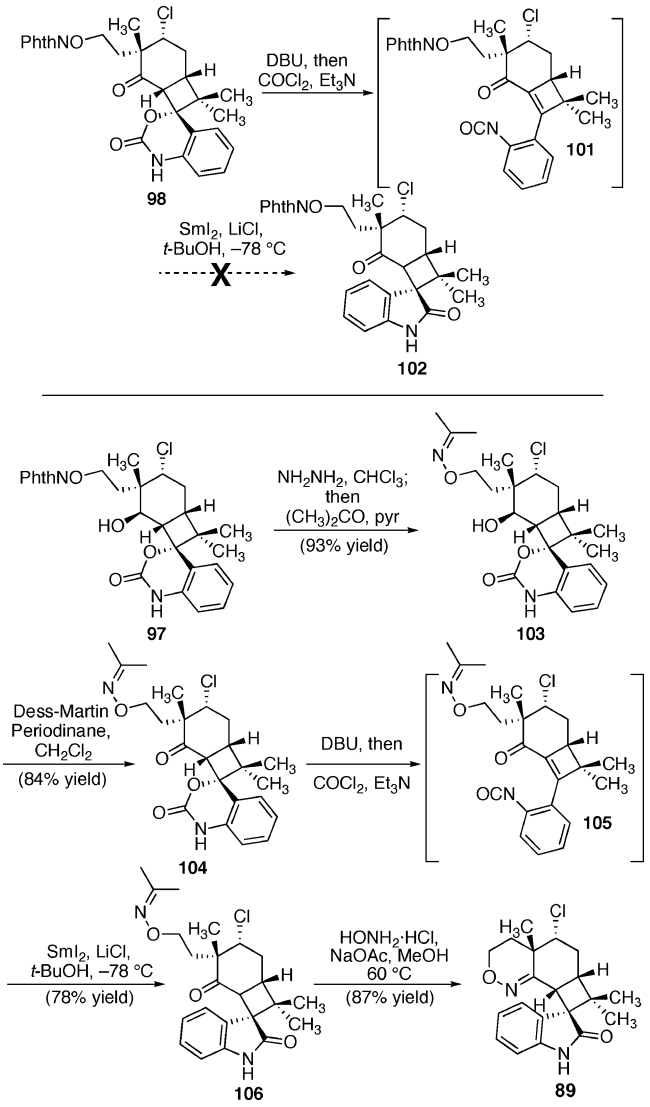
Pleased by the mild conditions under which oxazine formation occurred, methods for accessing oxindole **89** were evaluated. Treatment of ketone **98** with DBU followed by phosgene and triethylamine provided the required aryl isocyanate (**101**, Scheme 31). Unfortunately, subjection of the crude isocyanate to our optimized reaction conditions (SmI_2/LiCl, *t*-BuOH, −78 °C) provided products resulting from N−O bond cleavage and none of the desired spiro-oxindole **102**.

While this result was initially frustrating, the electron-withdrawing nature of the phthalimide protecting group was deemed responsible for the facile reduction of the N−O bond. Previous experiments had shown that oxime ethers were stable to the SmI_2/LiCl at low temperatures; therefore protection of the hydroxylamine functionality as an oxime ether (i.e., **103**, Scheme 31) was expected to render the N−O bond inert to the SmI_2/LiCl conditions. In the event, oxime **103** was prepared in excellent yield by treating alcohol **97** with hydrazine hydrate in chloroform for 30 min, then, after removal of excess hydrazine by rotary evaporation, dissolution of the residue in acetone.

Oxidation of the derived alcohol (**103**) with Dess−Martin periodinane[40] provided ketone **104** which, when exposed to DBU followed by phosgene was converted to isocyanate **105**. Gratifyingly, subjection of the crude isocyanate to a preformed

(60) The major diastereomer is identical by ^{1}H NMR to compound **63**.
(61) Brown, H. C., W. A. *Hydroboration*, Benjamin: New York, 1962.
(62) Brown, H. C. *Science* **1980**, *210*, 485.
(63) Screening of dialkylboranes included: Et_2BH, $(Cy)_2BH$, 9-BBN, catechol borane. With Et_2BH, regioselection was comparable to BH_3, while the other three reagents provided no reaction at ambient or elevated temperatures.
(64) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93* (4), 1307.

Scheme 31



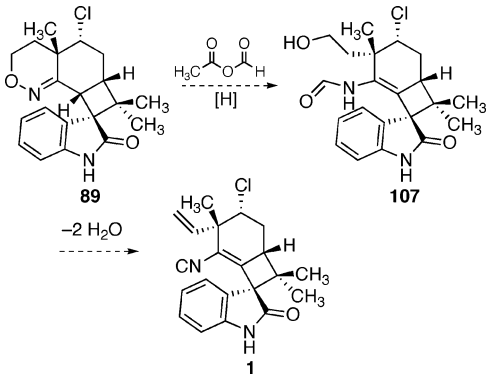
mixture of SmI_2/LiCl furnished spiro-oxindole **106** in 78% yield. Having devised an appropriate sequence of transformations to access hydroxylamine derivative **106**, our attention turned to formation of the critical C11−nitrogen bond. To this end, treatment of a methanolic solution of oxindole **106** with hydroxylamine hydrochloride (to scavenge liberated acetone) cleanly provided oxazine **89** in 87% yield (Scheme 31).

With access to oxindole **89**, the first intermediate in the synthesis to contain both the oxindole and the requisite C11 nitrogen functionality, end-game strategies were reconsidered. Formally, transformation of oxindole **89** to **1** would require reductive formylation of the oxazine to give formamide **107**, followed by simultaneous loss of two molecules of water to provide (±)-welwitindolinone A isonitrile (**1**, Scheme 32).

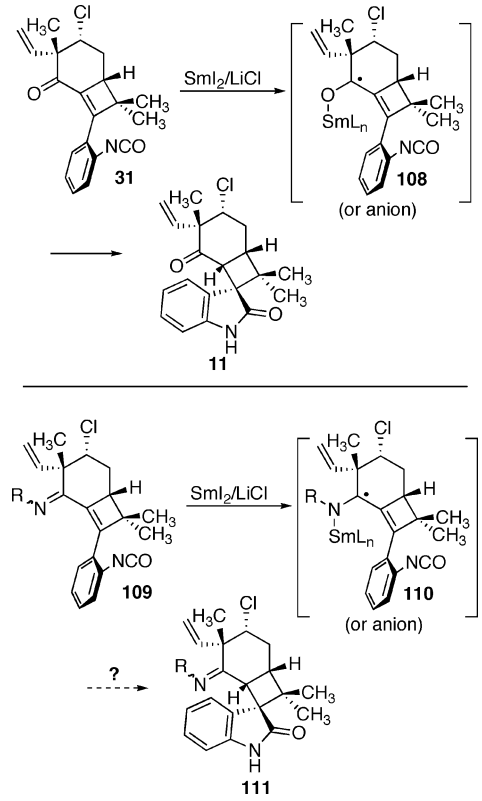
Unfortunately, in analogy to ketone **11**, oxazine **89** proved to be extraordinarily unreactive. Implementation of a number of reductive conditions reported in the literature to cleave similar N−O bonds failed to provide any significant reduction products.[55−57] In addition, attempts to reduce the C−N double bond with hydride sources were unproductive.[65] At this time,

(65) Conditions included: $NaBH_4$/TFA, $NaBH_3CN/H^+$, $NaBH(OAC)_3$, LAH, DIBAL, $LiEt_3BH$, Raney Ni/$B(OH)_3$.

Scheme 32



Scheme 33



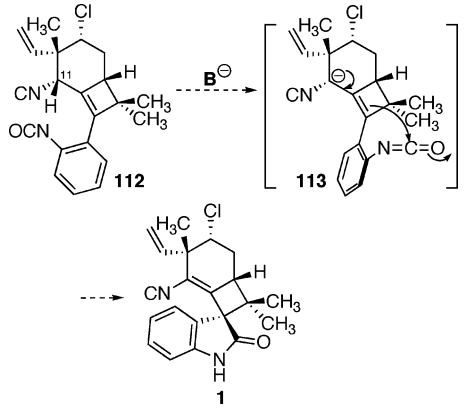
due in part to the fact that preparation of oxazine **89** now required 23 steps and there was no clear route from **89** to **1**, we again considered alternative end-game scenarios.

VIII. Completion of the Synthesis of 1. Although nonproductive, our efforts to convert ketone **11** to (±)-welwitindolinone A isonitrile (**1**) did illustrate the need to incorporate the C11 nitrogen *prior* to oxindole formation. Thus, we considered the possibility of utilizing nitrogen-containing substrates to access analogues of **11** via the SmI_2/LiCl-mediated reductive cyclization protocol (cf., **31** → **11** and **109** → **111** in Scheme 33).[66−68]

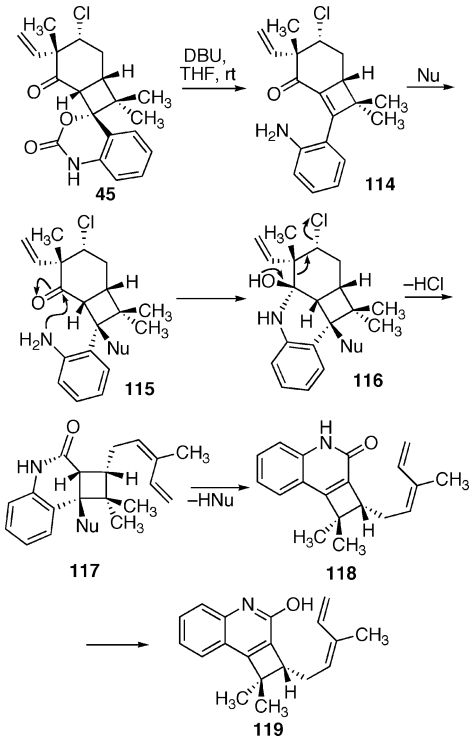
However, the difficulties encountered while attempting to functionalize ketone **11** and oxazine **89** caused great concern about the prospect of converting imine **111** to **1**. Instead, consideration of the mechanistic details illustrated in Scheme 33 led us to recognize that an intermediate similar to **110** could

(66) Dahlen, A.; Hilmersson, G. *Chem.—Eur. J.* **2003**, *9*, 1123.
(67) Knettle, B. W.; Flowers, R. A. *Org. Lett.* **2001**, *3*, 2321.
(68) Shiraishi, H.; Kawasaki, Y.; Sakaguchi, S.; Nishiyama, Y.; Ishii, Y. *Tetrahedron Lett.* **1996**, *37*, 7291.

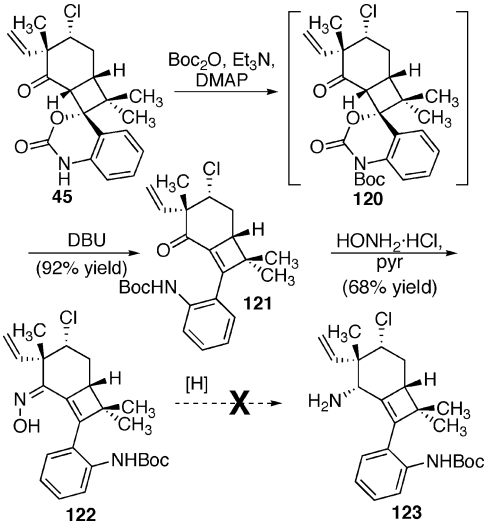
Scheme 34



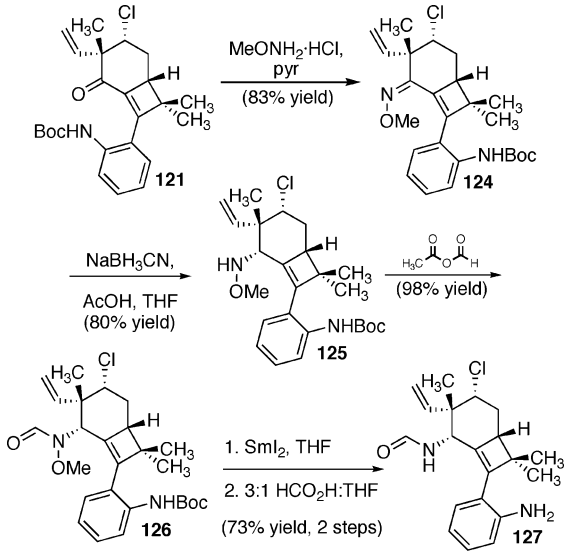
Scheme 35



Scheme 36



Scheme 37



be accessed by taking advantage of the known propensity for alkyl isocyanides to undergo α-deprotonation when exposed to strong base.[69] In this scenario, access to **1** would entail the preparation of isocyano-isocyanate **112**, which was envisioned to undergo cyclization upon deprotonation via the intermediacy of anion **113** (Scheme 34).

Of the many intermediates we had prepared that could potentially give rise to isocyano-isocyanate **112**, we initially focused on aniline **114**, the CO_2-elimination product derived from ketone **45** (Scheme 35). Unfortunately, aniline **114** was unstable to a variety of conditions, including silica gel chromatography. While initially puzzling, our eventual isolation of byproduct **119** upon exposure of aniline **114** to DMAP was enlightening.[70] As illustrated in Scheme 35, conversion of aniline **114** to hydroxyquinoline **119** is proposed to proceed first by nucleophilic attack at the enone of **114** to provide intermediate **115**, wherein the aniline nitrogen is positioned to undergo ring closure to the corresponding hemiaminal (**116**). Subsequent Grob-type fragmentation of **116** to diene **117** followed by aromatization then delivers hydroxyquinoline **119**.[71] Notably, this reaction only requires a catalytic nucleophile and is consistent with the observed formation of the same product (**119**) under different conditions.[72]

In light of the proposed mechanism for the rearrangement of **114** to hydroxyquinoline **119**, protection of the aniline nitrogen was expected to disfavor formation of hemiacetal **116**, thus preventing the deleterious Grob-type fragmentation. Conversion of carbamate **45** to *N*-Boc-imide **120** followed by in situ treatment with DBU at room-temperature delivered *N*-Boc-aniline **121** in 92% yield (Scheme 36). As predicted, **121** was a stable intermediate and readily purified by silica gel chromatography.

Having accessed enone **121**, efforts next focused on installing the C11 nitrogen. Unfortunately, attempts to affect the direct reductive amination of **121** employing $NH_4OAc/NaBH_3CN$

(69) Hoppe, D. *Angew. Chem., Int. Ed.* **1974**, *13*, 789.
(70) Exposure of a dichloromethane solution of aniline **114** to DMAP followed by Et_3N and methyl chloroformate for 10 min provided hydroxyquinoline **119** in 65% yield.
(71) Grob, C. A. *Angew. Chem., Int. Ed.* **1969**, *8*, 535.
(72) Subjection of aniline **114** to TMSCN also provides hydroxyquinoline **119**.

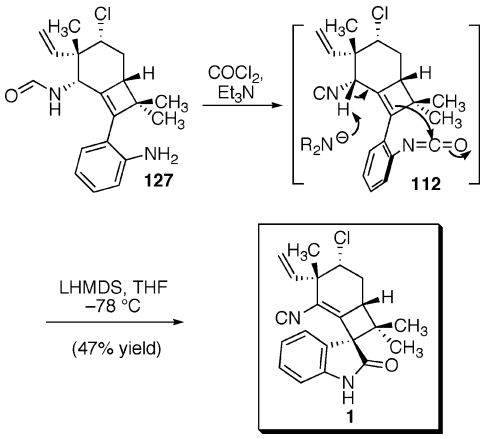
failed to provide amine **123**.[73] Resorting to a two step method, enone **121** was readily converted to oxime **122** and represented the first successful installation of the required C11-nitrogen bond in an intermolecular reaction manifold. However, we were disappointed to find that exposure of oxime **122** to a variety of hydride sources failed to provide the desired amine (**123**). In contrast, advancement of **121** to the corresponding methyl oxime (**124**) followed by exposure to $NaBH_3CN$/AcOH resulted in the smooth formation of methoxylamine **125** (Scheme 37). Subsequent formylation of **125** with acetic formic anhydride (AFA) provided a near quantitative yield of methoxyamide **126** which, upon sequential exposure to SmI_2[74] followed by formic acid, underwent N−O bond cleavage and Boc-deprotection to furnish aniline **127**.

In the final-ring closing event, treatment of formamide **127** with excess phosgene and triethylamine promoted simultaneous dehydration of the formamide to the isocyanide and conversion of the aniline to the isocyanate to deliver isocyano-isocyanate **112** (Scheme 38). Upon removal of the triethylamine salts by filtration and drying in vacuo, we were delighted to find that treatment of **112** with excess LHMDS at −78 °C provided **1** in 47% yield.[13] However, attempts to further optimize the reaction by changing the base or rigorously drying the intermediate isocyano/isocyanate **112** did not significantly improve the yield of **1**.

Conclusions

A synthesis of (±)-welwitindolinone A (**1**) from readily accessible cyclohexadiene **14** has been developed. Notably, this synthesis furnishes a 2.5% overall yield of **1** with an average yield of 81% and features a chloronium ion mediated semipinacol rearrangement of tertiary alcohol **54** to simultaneously install the C12 quaternary center and C13 stereogenic chlorine with excellent stereocontrol. Furthermore, the spiro-oxindole and vinyl isonitrile moieties were accessed in a single operation by means of an unprecedented anionic cyclization of isocyano−isocyanate **112**, providing (±)-welwitindolinone A isonitrile (**1**) as a single diastereomer. Though not utilized in the successful total synthesis, this work also resulted in the discovery of a mild SmI_2/LiCl-mediated synthesis of spiro-oxindoles.

Scheme 38



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Supporting Information Available: Experimental and characterization details. This material is available free of charge via the Internet at http://pubs.acs.org.

JA076663Z

(73) The ^{1}H NMR spectrum for the crude reaction mixture indicated that reduction of ketone **121** to the corresponding alcohol had occured.
(74) Keck, G. E.; Wager, T. T.; McHardy, S. F. *Tetrahedron* **1999**, *55*, 11755.