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Access to a Welwitindolinone Core Using Sequential Cycloadditions

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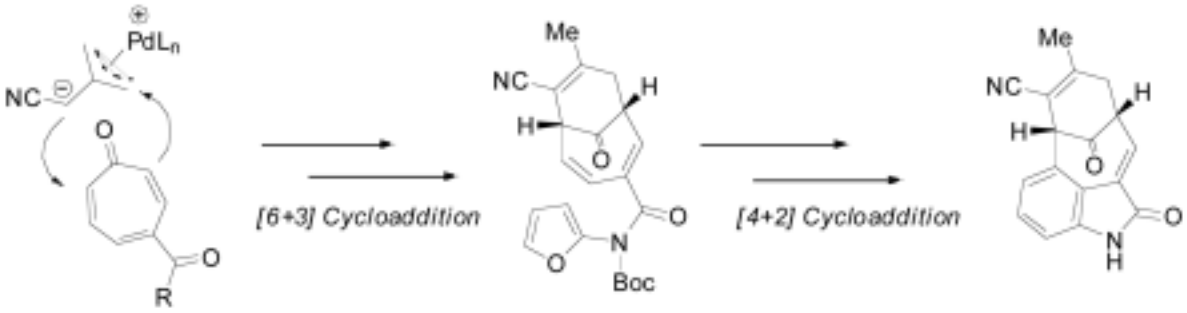
Abstract



A concise approach to the core skeleton of the welwitindolinone alkaloids was developed based on sequential cycloaddition reactions. First, a palladium catalyzed enantioselective [6 + 3] trimethylenemethane cycloaddition onto a tropone nucleus was used to generate the requisite bicyclo [4.3.1]decadiene. Subsequent modifications to the cycloadduct allowed for an intramolecular [4 + 2] cycloaddition to generate the oxindole and complete the core of the natural product family.

The palladium catalyzed trimethylenemethane (Pd-TMM) cycloaddition reaction represents a highly effective tool for the rapid synthesis of complex carbocycles.[1] A rather useful extension to the widely studied [3 + 2] cycloaddition to electron deficient olefins is a [6 + 3] cycloaddition to a tropone nucleus, providing access to functionalized bicyclo[4.3.1]decadienes.[2] Building upon our disclosures of enantioselective [3 + 2] Pd-TMM cycloadditions controlled using phosphoramidite ligands,[3] we have recently rendered the [6 + 3] cycloaddition enantioselective as well, thus enabling access to stereodefined bicyclo[4.3.1]decadienes in an efficient manner (Scheme 1).[4]

The advent of such methodology opens the door for a unique, enantioselective, synthesis of bioactive molecules possessing the [4.3.1] bicyclic motif. Of these, we chose to initiate a program to develop a synthesis of the welwitindolinone B & C class of marine alkaloids (**1**-**7**; Figure 1).[5] These particular compounds are characterized by a highly functionalized [4.3.1] bicyclic carbon skeleton containing an oxindole, two quaternary stereocenters, and multiple sensitive functional groups. While the bioactivity of these molecules varies, the more potent of these, *N*-methylwelwitindolinone C isothiocyanate (**1**), acts as a powerful antagonist for the over expression of P-glycoprotein, offering a potential therapeutic benefit against multiple drug resistant tumors.[6]

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Supporting Information Available Full characterization and NMR spectra of all new compounds is available free of charge at http://pubs.acs.org.

Although a total synthesis of any member of this class of compounds has yet to be accomplished,[7] several approaches to a core structure have been reported.[8] The majority of these syntheses rely on using an intact oxindole or indole moiety as a starting point, followed by stepwise construction of the bicyclo[4.3.1]decane core. In contrast, we envisioned a novel approach that would rely on a series of sequential cycloadditions to rapidly build the common core structure **8** (Scheme 2). Central to this theme was an enantioselective [6 + 3] cycloaddition that would rapidly construct the bicyclic fragment **10** from a suitable tropone (**11** or **12**) and the cyano TMM donor **13**. Based on work by Padwa,[9] an intramolecular [4 + 2] cycloaddition reaction between a pendent amidofuran and the endocyclic olefin would then be used to generate the oxindole core **8** in a single operation. This core structure could conceivably be elaborated to any of the natural products **1**-**7**.

Ideally, a tropone system bearing a 2-amino-5-ester substitution pattern, as in compound **12**, would provide the most straightforward synthetic approach. However, in order to attain high levels of regioselectivity for the TMM cycloaddition, the unusual isophthalimide group was required.[4] Unfortunately, this unstable protecting group led to numerous difficulties in carrying out further synthetic transformations. As a result, our attention turned to the potential of a late stage installation of the bridgehead amine using an intramolecular nitrenoid insertion into the C11-H bond.[10] This, in turn, enabled the use of a tropone lacking the 2-amino group (**11**), known to be highly successful in [6 + 3] cyclodadditions.[4]

Studies began with the construction of several 4-substituted tropones beginning from cycloheptatriene **14** (Scheme 3); easily prepared by the cyclopropanation/ring expansion of anisole.[11] Barium hydroxide mediated hydrolysis delivered acid **15**, which could be readily functionalized as desired.[12] Ideally, a tropone bearing the imidofuran ring (**19**) would offer the most straightforward approach. However, oxidation of the corresponding cycloheptatriene **16** to tropone **19** proved difficult. Use of a more electron deficient amidofuran possessing a methyl ester[9b] was then explored. Standard amide coupling conditions and *N*-methylation gave intermediate **17**, which was oxidized[13] to the tropone **20** in 54% overall yield. While the methyl ester would require eventual removal to generate the natural product series, it was thought that such an amidofuran would offer a method to access synthetic analogues, as well as providing an additional handle for the proposed nitrenoid insertion at C11. Nonetheless, to expand our synthesis options to allow for a later stage installation of the unsubstituted amidofuran, tropone **21** bearing the easily cleaved *p*-methoxybenzyl group (PMB) was also prepared in good yield from cycloheptatriene **18**.

Palladium catalyzed [6 + 3] cycloadditions of both tropones **20** and **21** were conducted using the (bis)biphenyl pyrrolidine ligand **L1**[14] (see Scheme 1). Tropone **20** reacted to give the desired cycloadduct **22** as a single regio- and diastereomer in 60% yield and high (94% ee) enantioselectivity (Scheme 4). Concurrently, the 4-PMB ester tropone **21** delivered the cycloadduct **23** in better yield (80%) and comparable enantioselectivity. Both cycloadducts **22** and **23** were independently carried forward to the natural product core to illustrate the effectiveness of our synthetic approach.

Already possessing the amidofuran, cycloadduct **22** was poised to undergo the anticipated [4 + 2] cycloaddition to generate the oxindole core. However, as predicted, a facile [3,3] sigmatropic rearrangement occurred upon heating.[4] To avoid this, chemoselective derivatizations of the exocyclic olefin, such as oxidation, were attempted yet remain a challenge for this synthetic route. Fortunately, isomerization of the double bond to the endocyclic position using catalytic DMAP proved facile, giving compound **24** in high yield (Scheme 5). Gratifyingly, heating this intermediate under microwave conditions promoted the intramolecular [4 + 2] cycloaddition to provide alcohol **25** as a single diastereomer,[15] albeit in moderate yield. While it was hoped that dehydration to the oxindole core would be

spontaneous, treatment of the unstable intermediate with the dehydrating agent developed by Burgess[16] proved necessary to give the completed core structure **26**.[17]

In considering the conversion of TMM adduct **23** to the core structure, the next stage of the synthesis called for installation of the amidofuran and a thermal [4 + 2] cycloaddition to generate the oxindole. As before, isomerization of the exocyclic olefin was readily accomplished with catalytic DMAP to give the α, β-unsaturated nitrile **27** in excellent yield (Scheme 6). Removal of the PMB group followed by coupling with *N*-Boc amidofuran **29**[9c] gave the Diels-Alder precursor **30** in good yield. Heating of imidofuran **30** in toluene at reflux temperature promoted the intramolecular cycloaddition to give oxabicycle **31** as a single diastereomer in almost quantitative yield. Not surprisingly, this cycloaddition occured at much lower temperature and with greatly improved yield as compared to the more electron deficient amidofuran system discussed above. The configuration was tentatively assigned as shown using ^{1}H NMR analysis. Somewhat surprisingly, however, this compound remained as the oxabicycle **31** and did not undergo dehydration to the oxindole even after prolonged reaction times.

As previously demonstrated by Padwa,[9d] the electron withdrawing properties of the Boc group were likely preventing the spontaneous opening and dehydration of the oxabicycle. Thus, removal of the Boc group was expected to lead directly to the formation of the desired oxindole. Interestingly, while confirming the hypothesis, the common removal technique employing TFA also led to hydrolysis of the nitrile to provide primary amides **32** and **33** (Table 1). Several alternate reagents ($BF_3{\cdot}OEt_2$, BCl_3, bromocatechol borane, $[Rh(COD)Cl]_2$[9d] were also examined without much success. Ultimately, two useful conditions were identified; Burgess reagent could be used to dehydrate and leave the Boc group intact to generate oxindole **34** and, alternatively, use of catalytic $Yb(OTf)_3$ could deliver the *N*-H oxindole core **35** as a single component in moderate yield.

In summary, a particularly concise strategy for the synthesis of the core of several welwitindolinone alkaloids derives from the combination of the asymmetric [6 + 3] Pd-TMM cycloaddition to form the bridged [4.3.1]bicycle with the [4 + 2] cycloaddition-dehydration to form the oxindole bicycle. The examples presented provided the complete tetracyclic ring system in less than 10 steps beginning with anisole. Efforts are underway to elaborate these intermediates and complete the synthesis of several of the more bioactive members in this group of natural products.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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14. A commercially available phosphoramidite (Aldrich Chemical Co. Inc., Catalog #665290) could also be used, although it gave low *ee*. See Supporting Information.
15. Due to the unstable nature of intermediate 25, the configuration was not rigourously established.
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17. A single step conversion of intermediate **24** to oxidole **26** was also possible using the Burgess reagent at high temperature, however, purification of the product was difficult.

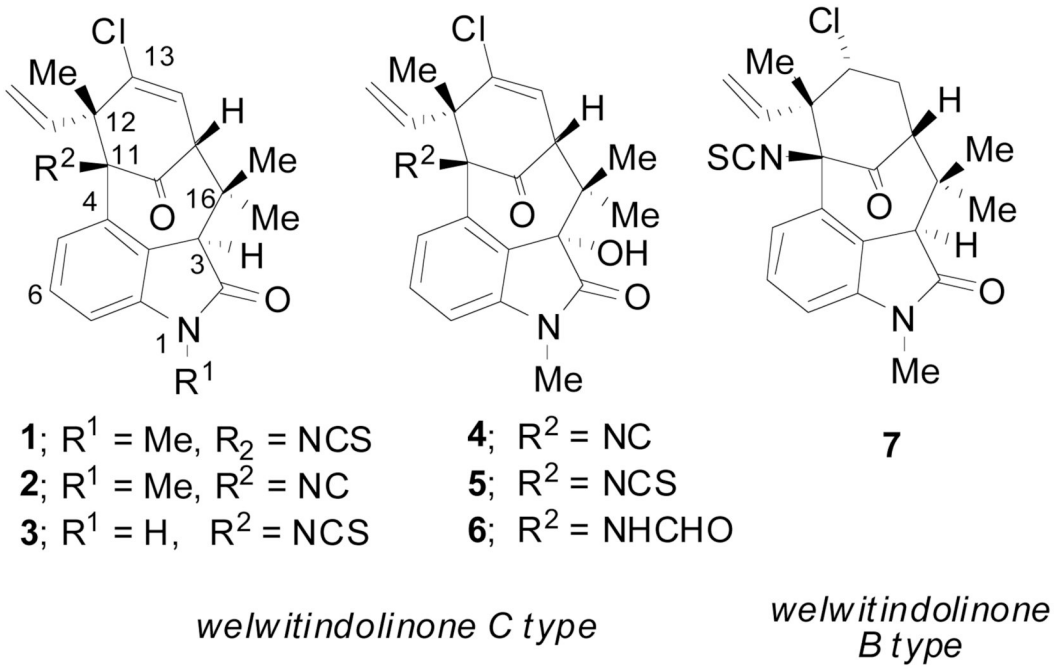
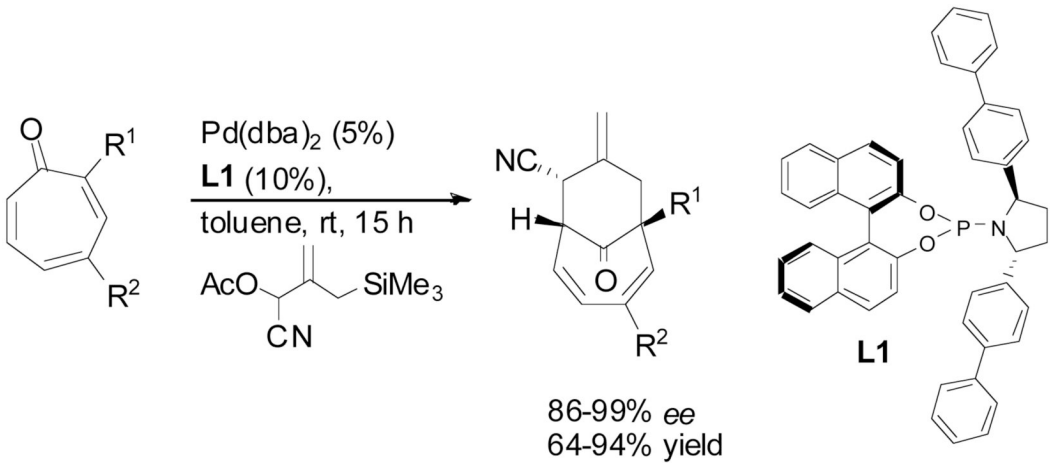
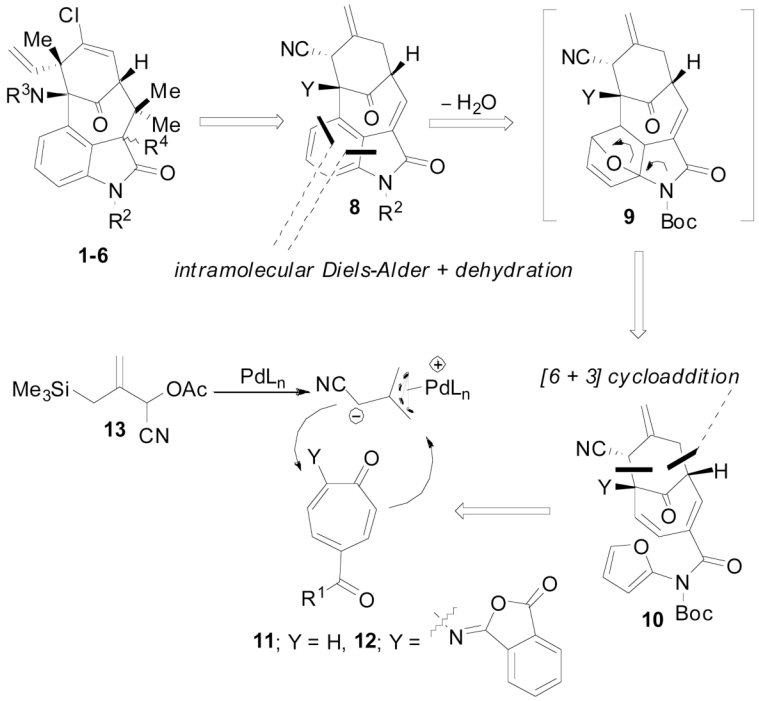


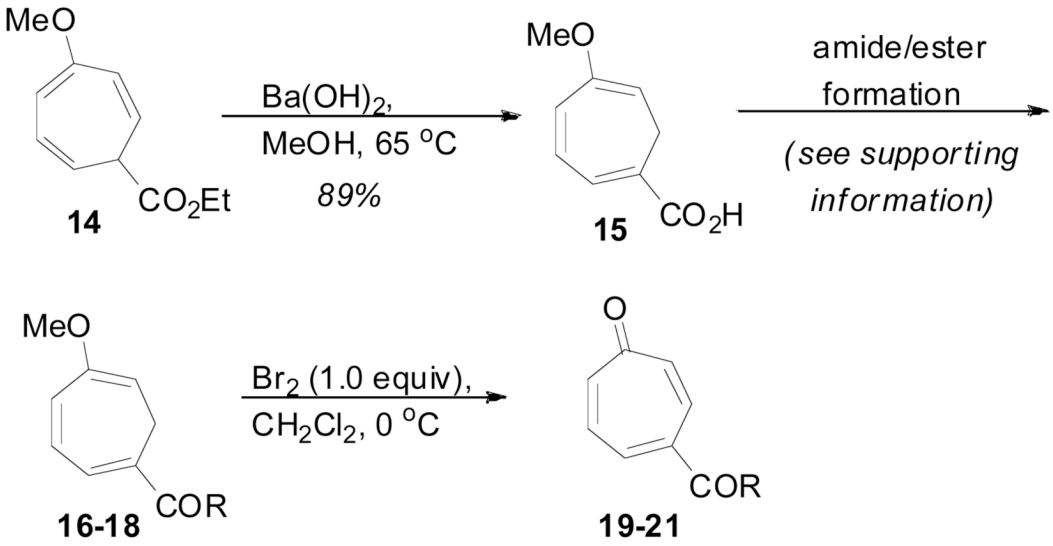
Figure 1.
Selected Welwitindolinone B & C Alkaloids

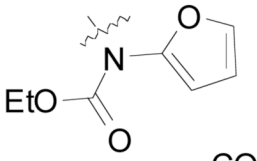
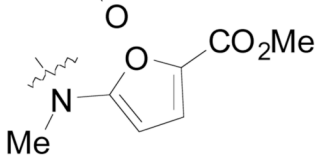


Scheme 1
Enantioselective Pd-TMM [6 + 3] Cycloadditions

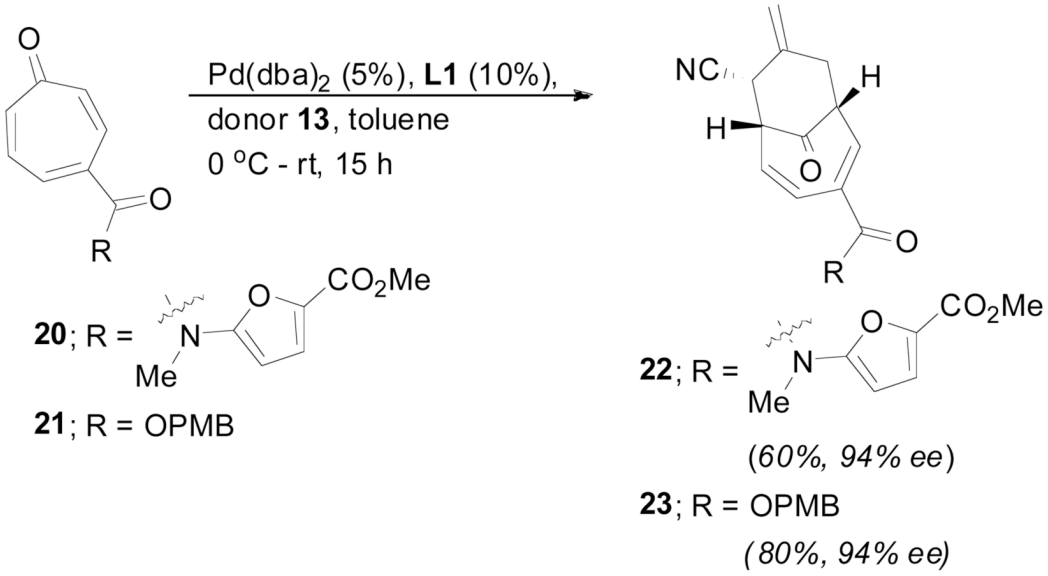


Scheme 2
Retrosynthetic Analysis

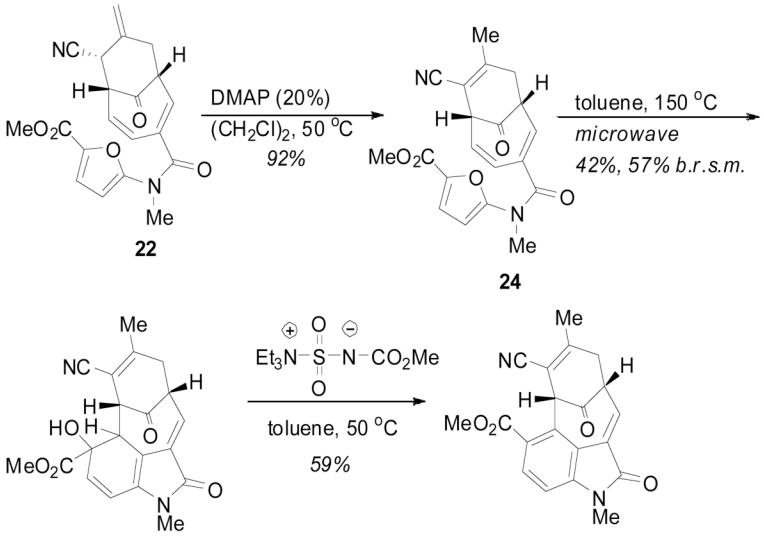


cycloheptatriene	R	tropone	yield
16		**19**	*0%*
17		**20**	*54% (three steps)*
18	OPMB	**21**	*58% (two steps)*

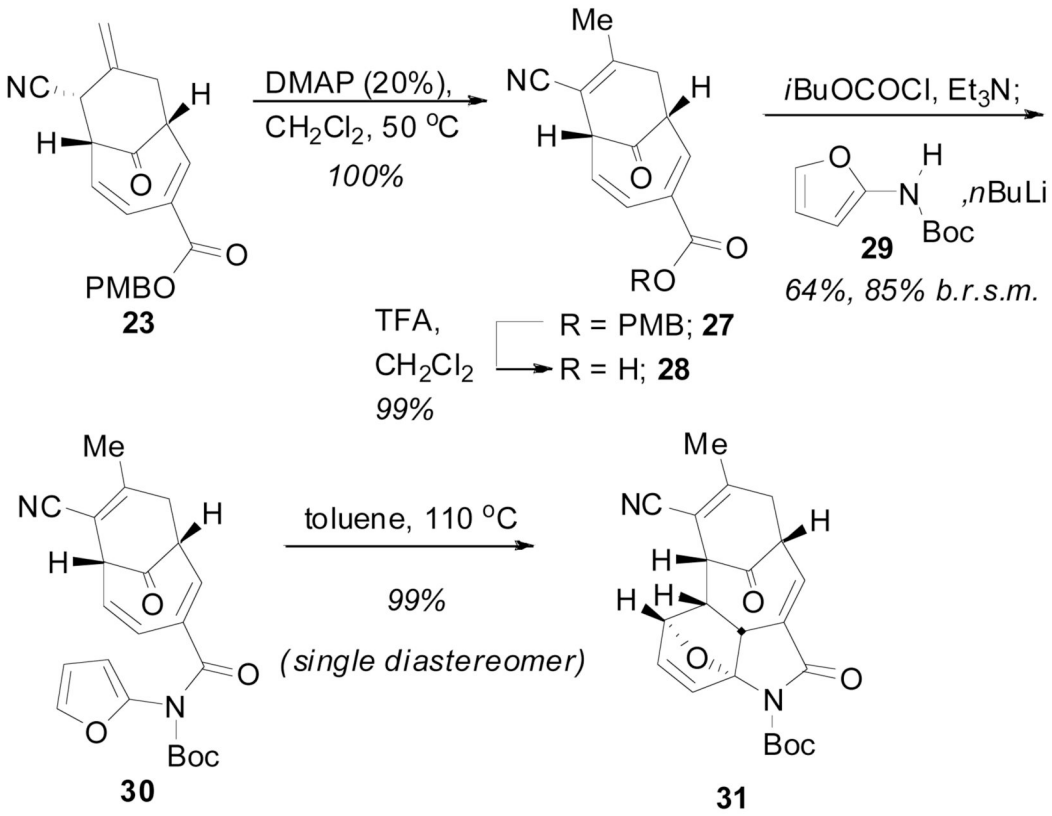
Scheme 3
Preparation of the Tropone Intermediates



Scheme 4
Asymmetric [6 + 3] Cycloadditions



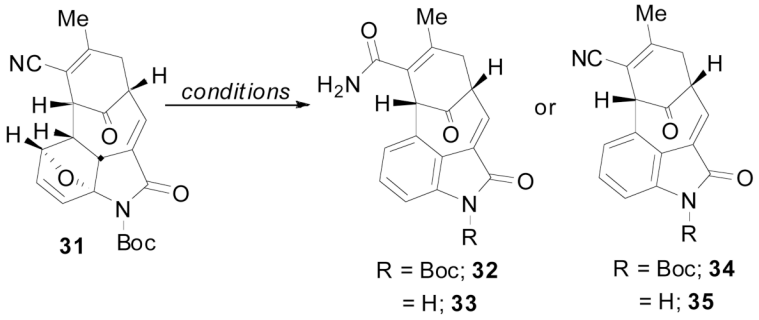
Scheme 5
Elaboration of Adduct **22**



Scheme 6
Elaboration of Adduct **23**

Table 1

Completion of Oxindole Core



reagents	compound	yield
TFA	**32** & **33**	not determined
$BF_3 \cdot OEt_3$	**34** & **35**	18% & 34%
Burgess Reagent	**34**	48%
$Yb(OTf)_3$	**35**	50%