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Aryllead(IV) Reagents in Synthesis: Formation of the C11 Quaternary Center of *N*-Methylwelwitindolinone C Isothiocyanate

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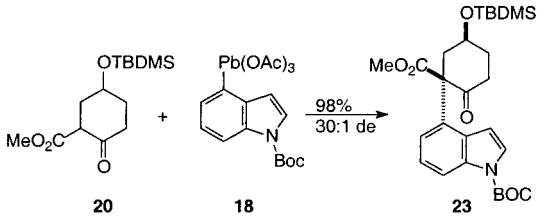
ABSTRACT



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The reaction of lead(IV) 4-indolyl triacetate with substituted methyl 2-oxo-1-cyclohexanecarboxylates has been investigated as a route to the natural product *N*-methylwelsitindolinone C isothiocyanate. Reaction of lead(IV) reagent 18 with *β*-ketoester 20 affords the desired coupled material in excellent yield and diastereoselectivity.

N-Methylwelwitindolinone C isothiocyanate **1** is the major indole alkaloid isolated from the lipophilic extract of *Hapalossiphon welwitschii W. & G. S. West* (UH strain IC-52-3, Stigonemataceae). In the isolation study, Moore and co-workers[1] found that **1** possessed antifungal activity and reversed P-glycoprotein-mediated multidrug resistance (MDR) in a vinblastine-resistant subline (SK-VLB) of a human ovarian adenocarcinoma line (SK-OV-3). The complete structural elucidation, including stereochemistry, of **1** rests on NMR and X-ray crystallographic analysis.

Compound **1** displays several distinctive architectural features. It contains four stereogenic centers, including one quaternary carbon (C12) and a fully substituted center at the adjacent (C11) carbon. There are four rings, including an oxindole system and a cyclohexanone linked to create a seven-membered ring. The compact structure includes a vinyl chloride functionality, the C11 isothiocyanate substituent, and the *gem*-dimethyl groups at C16.

As a result of its structural complexity and important biological activity, *N*-methylwelwitindolinone C isothiocyanate has been a target of synthetic interest. In particular, the Wood group has published elegant work on a synthetic strategy to the core structure of **1** using a rhodium carbenoid initiated Claisen rearrangement approach.[2] Herein, we present our observations on a convergent approach to this indole alkaloid.

Our original retrosynthetic plan is shown in Scheme 1.[3] The key reactions would be focused on formation of the seven-membered ring through the coupling of *β*-ketoester **2** with lead(IV) 4-indolyl triacetate **3** and subsequent use of an aldol-type condensation to form the C15−C16 bond. The synthesis of *β*-ketoester **2**, which possesses the C12 quaternary center with the correct absolute stereochemistry, has

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(3) Taken in part from: Deng, H.; Konopelski, J. P. 220th National Meeting of the American Chemical Society, Washington, DC, August 20−24, 2000, paper ORGN 11.

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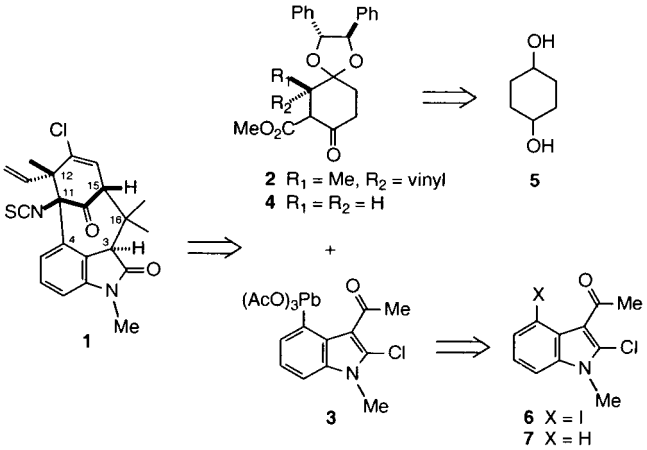
Scheme 1

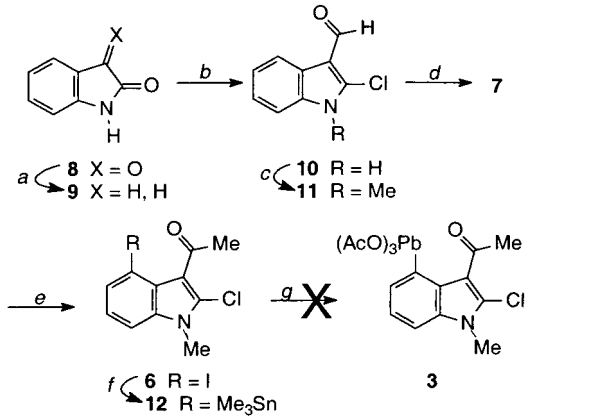


been completed.[4] It arises from simple β-ketoester **4** and requires two successive conjugate additions to the intermediate α,β-unsaturated ketoesters to afford the desired C12 center. β-Ketoester **4** is prepared from 1,4-cyclohexanediol **5**. The plan for synthesis of the unprecedented indole lead(IV) reagent **3** was envisioned to proceed from 4-iodo-3-acetylindole **6** which, in turn, comes from 3-acetylindole **7**.[5] The use of a 2-chloro substituent on the indole ring allows for easy hydrolysis to the oxindole in the latter stages of the synthesis.[6]

The key reaction in this sequence would be the coupling of organolead compound **3** with β-ketoester **2** to form the C11 quaternary center. Aryllead(IV) reagents are an excellent choice for establishment of a quaternary center,[5,7,8] and access to an indole-based reagent would expand the chemistry of these aryl cation equivalents to this class of medicinally important compounds. The reactions proceed under very mild conditions, and yields tend to be very high. Our group, as well as others, has applied this methodology toward the total synthesis of natural products.[9,10]

Our approach to indole fragment **3** is illustrated below (Scheme 2) and is based on our previous published work directed toward the total synthesis of the marine natural product diazonamide A.[9] Isatin **8** was treated with hydrazine to form the corresponding hydrazone, followed by Wolff–Kishner reduction to give oxindole **9** in 95% yield.[11] Vilsmeier chloroformylation with $POCl_3$, DMF, and pyridine provided 2-chloro-3-formylindole **10**.[12] Methylation with NaH/KH/MeI furnished compound **11**.[13] Treating **11** with

Scheme 2[a]



[a] (a) (1) NH_2NH_2, MeOH, reflux, (2) NaOEt, EtOH, reflux, 98%; (b) $POCl_3$, DMF, pyridine, $CHCl_3$, 0 °C to rt, 76%; (c) NaH, KH, MeI, THF, reflux, 97%; (d) (1) MeMgBr, THF, (2) TPAP, NMO, 96%; (e) (1) $Tl(TFA)_3$, TFA, (2) I_2, CuI, DMF, 78%; (f) Sn_2Me_6, toluene, $PdCl_2(PPh_3)_2$, reflux, 50%; (g) $Pb(OAc)_4$, $Hg(OAc)_2$, $CHCl_3$, 40 °C.

MeMgBr followed by immediate oxidation with TPAP/NMO yields *N*-methyl-2-chloro-3-acetylindole **7** in 96% yield. Oxidation utilizing DDQ gave the same product but required longer reaction time and led to more difficult product purification. This four-step procedure affords **7** in much greater overall yield than does the more direct two-step method.[14]

All attempts to obtain the desired lead reagent at the 4-position of the indole nucleus by a direct plumbation approach failed.[15] Therefore, organothallium chemistry was utilized to functionalize the 4-position of the indole ring system.[16,17] Compound **7** was treated with thallium(III) trifluoroacetate (TTFA) in TFA, which resulted in efficient thallation at the C4 position of the indole. After evaporation of the TFA solvent under vacuum, iodination with iodine and copper iodide gave the desired *N*-methyl-3-acetyl-2-chloro-4-iodoindole **6** in 78% yield for the two steps.

With compound **6** in hand, the conditions for iodo-tin exchange were investigated. Direct lithium-iodo exchange with *t*-BuLi/Bu_3SnCl afforded only deiodinated product. Iodo-tin exchange was achieved to give compound **12** in 50% yield by refluxing **6** with hexamethylditin in toluene in the presence of catalytic $PdCl_2(PPh_3)_2$ or $Pd(PPh_3)_4$.[18] The reaction did not proceed as well with $Pd(OAc)_2$. The final step to the desired indole lead(IV) reagent was the transfor-

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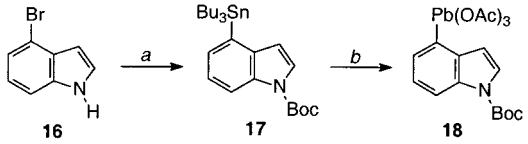
mation of **12** to **3** by tin−lead exchange. Compound **12** was reacted with lead tetraacetate and catalytic mercury(II) according to Pinhey's procedure.[19] No desired indole lead triacetate was formed. Changing the mercury catalyst to the more active mercury(II) trifluoroacetate also failed to give any product.[20] Only starting material was recovered from the reaction.[21]

Simplifying the system, we focused on the synthesis of *N*-protected 4-indolestannanes without functional groups at the 3-position, as shown in Scheme 3. By modification of

Scheme 3[a]

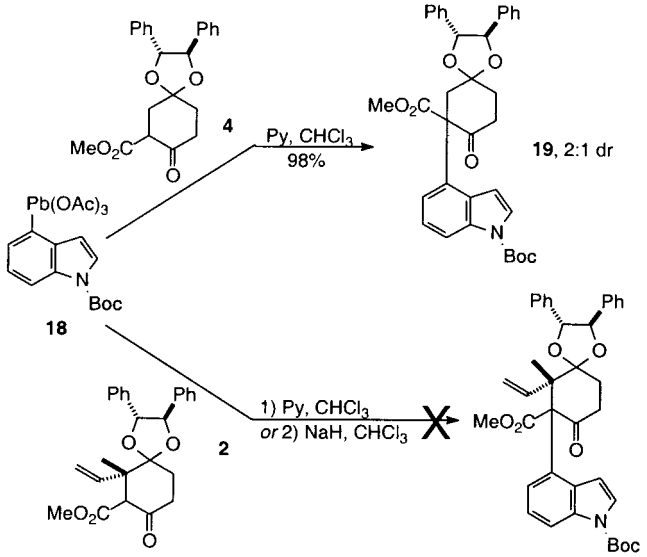


[a] (a) (1) KH, *t*-BuLi, Bu_3SnCl, (2) Boc_2O, DMAP, 70%; (b) $Hg(TFA)_2$ (1%), $Pb(OAc)_4$, 90%.

the literature procedure,[22] 4-bromoindole **16**, which is commercially or synthetically available, was treated with KH to deprotonate the indole nitrogen, thereby blocking both the 2- and 3-positions of the indole ring from deprotonation. *tert*-Butyllithium was added to generate the dianion by bromolithium exchange. Quenching the dianion with tri-*n*-butyltin chloride gave the desired lead(IV) 4-indolyltri-*n*-butylstannane. Without purification, the crude product was protected with a Boc group to afford compound **17**.[23] In this way, indolestannane **17** could be prepared in 70% yield on a large scale. To our delight, treatment of **17** with lead(IV) tetraacetate and catalytic mercury(II) trifluoroacetate afforded the unprecedented 4-indole lead triacetate **18** in over 90% yield. The reddish product is very stable in the air and can be stored at 4 °C for months without decomposition. Simple aryllead compounds were reported to decompose after a month.[5]

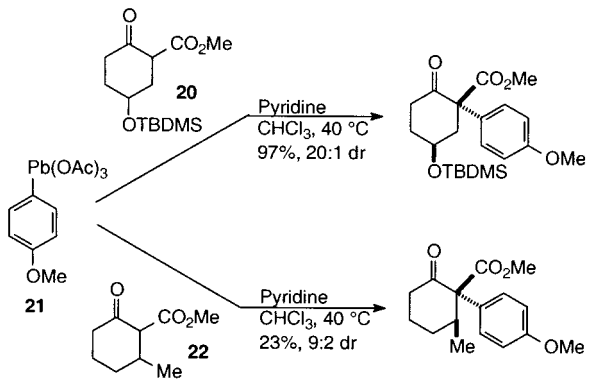
With this indole lead triacetate in hand, the coupling reaction of β-ketoesters **2** and **4** with **18** were carried out. Coupled product **19** was generated in almost quantitative yield from the simple β-ketoester **4** in 2:1 diastereoselectivity. These results could be obtained either with isolation of **18** or directly from **17** without isolation of the aryllead(IV) reagent. However, no corresponding coupled product was produced from β-ketoester **2** reacting with **18** under a variety of conditions (Scheme 4).

Scheme 4



Independent studies in our laboratory on aryllead(IV) coupling diastereoselectivity were concurrent with these experiments.[24] As shown in Scheme 5, β-ketoester **20** reacts

Scheme 5



with aryllead(IV) reagent **21** to afford excellent yield and selectivity, whereas 6-methyl derivative **22** reacts with **21** in only 23% yield. Our continuing studies on this coupling reaction indicate that silyloxy groups at C5 of the methyl 2-oxo-1-cyclohexanecarboxylate nucleus give uniformly high selectivity and yield, whereas alkyl substituents at C6 of the same system afford poor yields of coupling products and large amounts of recovered starting material.

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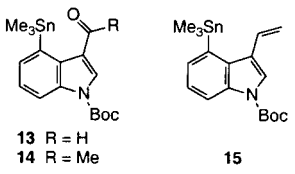
(21) In separate experiments, **13**−**15** were prepared and also failed to afford tin−lead exchange products. It is believed that steric and/or electronic factors arising from the close proximity of the C4 and C3 substituents on the indole nucleus are involved.



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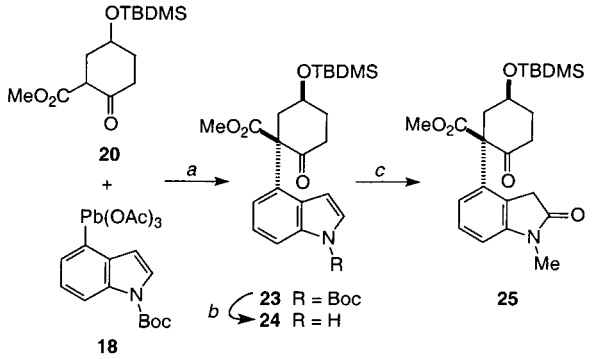
Given the poor results in the reaction of **21** with **22**, it is not surprising that β-ketoester **2**, with the C12 quaternary center adjacent to the reaction site, did not afford product. Likewise, the lack of stereocontrol in the reaction of **18** with **4** echoed similar results obtained in our published work[24] and made this approach less attractive. Fortunately, compound **20** proved to be an ideal coupling partner. Under standard conditions, the reaction of **20** with **18** gave a 30:1 mixture of diastereomers in almost quantitative yield (Scheme 6). This is one of the highest selectivities yet observed in our laboratory and likely reflects the larger size of **18** relative to **21**. The success of this reaction in both yield and stereoselectivity portends well for an enantioselective synthesis based on introduction of the correct absolute stereochemistry into the β-ketoester fragment.

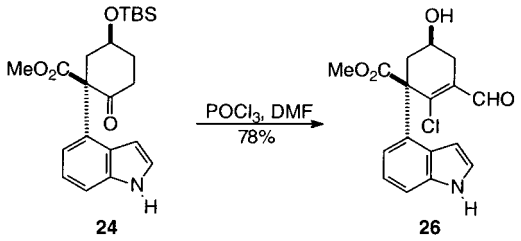
Scheme 6



a) Pyridine,$CHCl_3$, 40 °C, 98%; *b*) 200 °C, 90%;
c) 1) KOH, MeI, Bu_4NI, THF, 85%; 2) NBS, *t*-BuOH; 65%

Deprotection of the indole nitrogen proved to be more challenging than originally imagined. Neither acid nor base conditions could be found that were compatible with the other functionalities in the molecule. However, heating compound **23** neat at 200 °C for 4 h gave cleanly deprotected indole product **24** in 90% yield.[25] Oxindole formation also required extensive investigation. Methylation of the indole nitrogen under phase transfer conditions proceeded without complication. Standard literature procedures for oxindole formation involving strong acid treatment gave complicated mixtures of products, as did treatment with dimethyldioxirane (DMDO).[26] Success was achieved with the combination of NBS and *t*-BuOH.[27] Under these conditions, the transformation of **23** to **25** occurred in 70% yield without purification of **24**.

Compound **25** is the basis for our continuing studies toward *N*-methylwelwitindolinone C isothiocyanate. Preliminary work suggests that the C3 position of the indole is extremely hindered. For example, while reaction under Vilsmeier conditions ($POCl_3$, DMF) proceeds well in the transformation of **9** to **10**, the same reaction conditions imposed on **24** affords **26**, the product of ketone, not indole, reaction. Reactions of compound **26**, as well as related compounds, are under study and will be reported in due course.



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

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