

Application of Reactive Enols in Synthesis: A Versatile, Efficient, and Stereoselective Construction of the Welwitindolinone Carbon Skeleton

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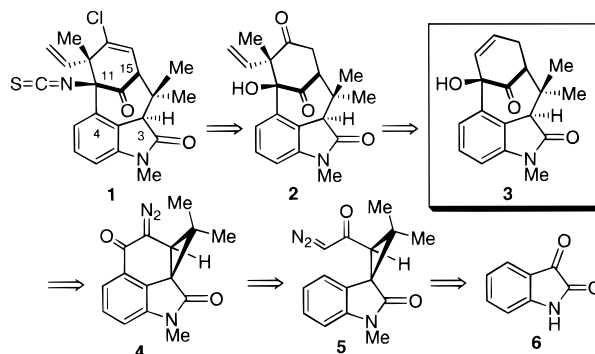
Recently, efforts to identify biologically important natural products from cyanobacteria resulted in the isolation of several welwitindolinone alkaloids, two of which have been identified as antagonists of the P-glycoprotein P-170 and hence as MDR-reversing agents.¹ As part of an ongoing synthesis directed toward the most potent congener, *N*-methylwelwitindolinone C isothiocyanate (**1**), we developed an efficient synthesis of **3**, a key intermediate that contains the complete carbon framework. Herein we report the details of our investigation.

From a retrosynthetic perspective we are focusing on a strategy wherein the chloroolefin and sensitive isothiocyanate will arise late in the sequence via interchange of a ketone and hydroxyl moiety, respectively, in intermediate **2** (Scheme 1). To access **2** the approach proceeds through **3** and, in turn, two α -diazo ketones, **4** and **5**. The more advanced of these, compound **4**, is a versatile intermediate from which several end-game scenarios are being explored. The second, diazo ketone **5**, serves as precursor to **4** and enables the use of aryl C–H insertion chemistry in assembling the 3,4-bridged oxindole core from isatin (**6**).

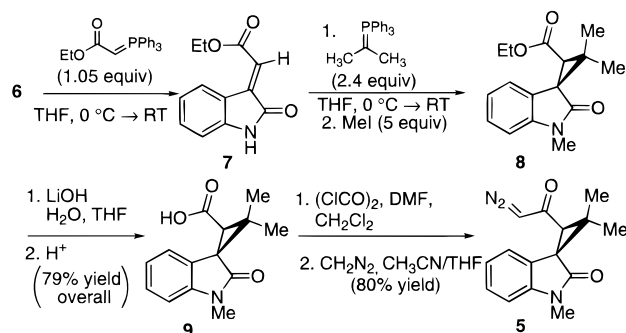
In the forward sense, isatin was found to be an excellent substrate for Wittig homologation with ethyl triphenylphosphoranylidene acetate.² The derived enoate (**7**) is produced in high yield and complete selectivity for the illustrated olefin isomer (Scheme 2). Sequential exposure of **7** to isopropyl triphenylphosphorane and MeI results in clean conversion to the corresponding gem-dimethyl cyclopropane **8**.³ Saponification of **8** furnishes acid **9** which,⁴ upon conversion to its acid chloride and treatment with diazomethane produces α -diazo ketone **5**.

Having established ready access to diazo ketone **5**, efforts to prepare **15** via aryl C–H insertion began.⁵ Initial studies illustrated that if $\text{Rh}_2(\text{TFA})_4$ is used as catalyst, **5** reacts to produce equimolar amounts of **14** and **15** along with a trace of spirocycle **11**. After considerable experimentation it was discovered that the norcadiene/cycloheptatriene interconversion leading to the undesired byproduct **14** (i.e., **13** \rightarrow **12**) can be suppressed in situ with the mildly Lewis acidic clay, Montmorillonite K10.⁶ Under these

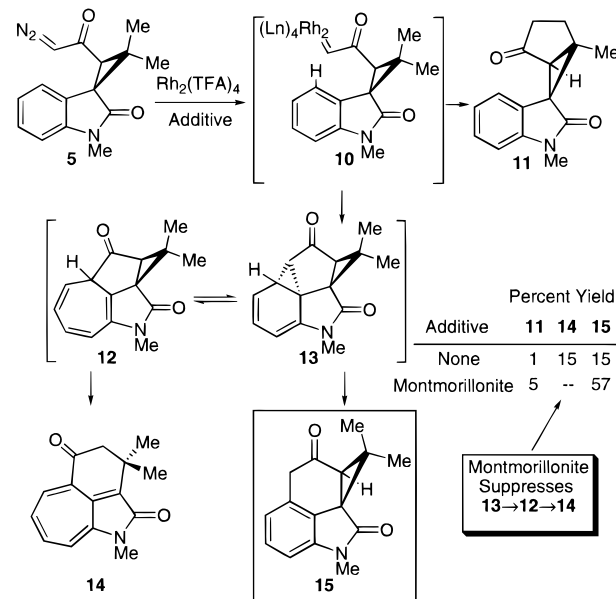
Scheme 1



Scheme 2



Scheme 3



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(1) (a) Stratmann, K.; Burgoyne, D. L.; Moore, R. E.; Patterson, G. M. L. *J. Org. Chem.* **1994**, *59*, 7219. (b) 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. (c) Smith, C. D.; Zilfou, J. T.; Stratmann, K.; Patterson, G. M. L.; Moore, R. E. *Mol. Pharm.* **1995**, *47*, 241.

(2) Brandman, H. A. *J. Heterocycl. Chem.* **1973**, *10*, 383.

(3) (a) Grieco, P. A.; Finkelhor, R. S. *Tetrahedron Lett.* **1972**, *36*, 3781.

(b) Krief, A.; Lecomte, P. *Tetrahedron Lett.* **1993**, *34*, 2695.

(4) This sequence is very amenable to large scale and has been used to produce several kilos of **9**.

(5) For leading references relevant to the C–H insertion chemistry of **5**, see: (a) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091. (b) Wenkert, E.; Liu, S. *Synthesis* **1992**, 323. (c) Taber, D. F.; Petty, E. H. *J. Org. Chem.* **1982**, *47*, 4808.

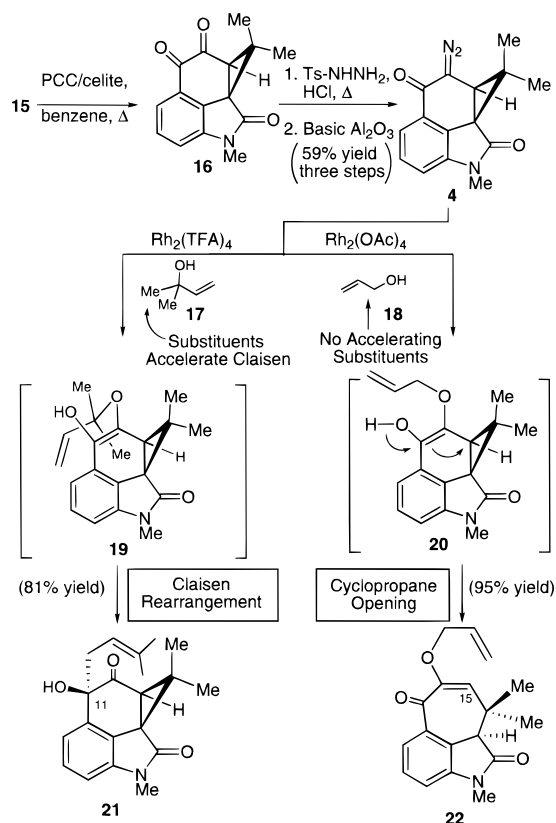
(6) We have found that Montmorillonite K10 also suppresses the formation of cycloheptatrienes in the aryl C–H insertions of α -diazo esters. These results will be published elsewhere.

conditions yields of the desired aryl C–H insertion product improved nearly 4-fold to 57% (Scheme 3).

On the basis of recent discoveries in our laboratories,⁷ we devised a strategy for advancing **15** that calls for the preparation of α -diazo ketone **4** (Scheme 4). To this end, we found that **15** could be readily oxidized to α -diketone **16** which, upon treatment with TsNHNH_2 and base, undergoes regioselective diazotization at the homobenzylic position to furnish **4**. In accord with our previous studies, the rhodium carbenoid derived from **4** was found

(7) Wood, J. L.; Moniz, G. A.; Pflum, D. A.; Stoltz, B. M.; Holubec, A. A.; Dietrich, H.-J. *J. Am. Chem. Soc.* **1999**, *121*, 1748.

Scheme 4



to rapidly couple with allylic alcohol substrates to furnish enol intermediates.⁸ Depending upon the nature of the allylic alcohol, the derived enol either undergoes Claisen rearrangement or cyclopropane opening (cf., **4** \rightarrow **21** and **4** \rightarrow **22**, Scheme 4). Thus, when substrate alcohols contain substituents that accelerate Claisen rearrangement (e.g., **17**),⁹ the incipient enol furnishes an α -hydroxy ketone. In contrast, with allyl alcohol (**18**) the rate of ring-opening exceeds that of the Claisen rearrangement, and the reaction furnishes only **22**.

Importantly, the routes producing **21** and **22** can both be viewed as eventually leading to **1**. The former provides a stereocontrolled means of homologating C(11), while the latter unveils the seven-membered ring and sets the stage for homologation of C(15). Focusing on the former, we began exploring allylic alcohol substrates that would allow direct access to the vicinal quaternary centers embedded in the cyclohexene core of **1**. During these investigations we discovered that exposure of **4** to **23** in the presence of $\text{Rh}_2(\text{TFA})_4$ results in formation of **24** and **25** under remarkably mild conditions (Scheme 5). Unfortunately, these compounds proved very difficult to handle, and all attempts to isolate them or advance crude reaction mixtures induced facile α -ketol rearrangements that furnish **26** and **27**.¹⁰

(8) Trapping studies have confirmed the intermediacy of enols in the current study, see Supporting Information for details.

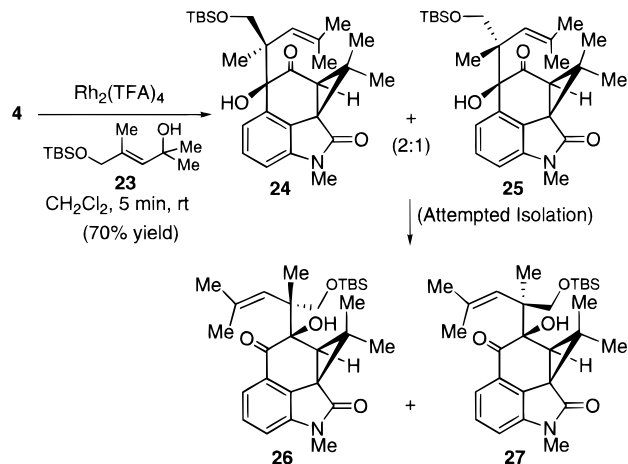
(9) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423 and references therein.

(10) This propensity for rearrangement is also observed for compound **21** but can be suppressed by in situ trapping of either **19** or **21** as the corresponding trifluoroacetate, see Supporting Information for details. Attempts to trap **24** and **25** in a similar fashion failed.

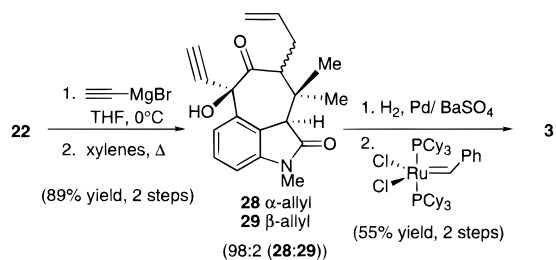
(11) Similar experiments initiated with vinyl Grignard reagents were found to proceed with poor stereoselectivity.

(12) Although ring-closing metathesis has been widely used in synthesis, its application in constructing medium-sized bridged carbocycles is less common. For a recent discussion, see: Morehead, A., Jr.; Grubbs, R. *Chem. Commun.* **1998**, 275.

Scheme 5



Scheme 6



Unable to circumvent the deleterious rearrangements of **24** and **25**, we turned attention to advancing **22**. In these studies we found that exposure of **22** to ethynyl Grignard results in the stereoselective formation of a product which, upon heating, rearranges to a 98:2 mixture of ketones **28** and **29** (Scheme 6).¹¹ Exposure of the major isomer (**28**) to H_2 in the presence of Lindlar's catalyst followed by treatment of the derived olefin with Grubbs's catalyst provides **3**.¹²

In summary, we have developed an efficient and stereoselective synthesis (15 steps) of the complete carbon skeleton present in several welwitindolinone alkaloids. In the course of this synthetic endeavor we discovered the remarkable affects of Montmorillonite K10 clay on aryl C-H insertion reactions and have further established the utility of reactive enol intermediates derived from the interaction of α -keto rhodium carbenoids with alcohols. In addition to completing the synthesis of *N*-methylwelwitindolinone C isothiocyanate, we are continuing investigations into the general affects of Montmorillonite clay on rhodium carbenoid-mediated reactions and other uses of carbenoid-derived reactive enols.

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Supporting Information Available: Spectral and experimental data pertaining to all new illustrated compounds (i.e., **3***, **5**, **8**, **9**, **11***, **14***, **15***, **16**, **21**, * **22**–**26***, **27**–**29***) and isolable intermediates generated en route but not illustrated. Note, (*) denotes the inclusion of data pertaining to a crystallographically based structure proof (PDF). An X-ray crystallographic file in CIF format. This material is available free of charge via the Internet at <http://pubs.acs.org>.