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Synthesis of Functionalized Cyclohexenone Core of Welwitindolinones via Rhodium- Catalyzed [5+1] Cycloaddition

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Abstract

The cyclohexenone core of welwitindolinones was synthesized by a Rh(I)-catalyzed [5+1]-cycloaddition of an allenylcyclopropane with CO. A penta-substituted cyclopropane was prepared successfully by a Rh(II)-catalyzed intramolecular cyclopropanation of alkenes with chlorodiazooacetates.

Indole alkaloid welwitindolinones (e.g. **1–3**, Scheme 1) and related natural products were isolated from blue-green algae *Hapalosiphon welwitschii* and *westiella intricata*.¹ *N*-Methylwelwitindolinone C isothiocyanate **1** reversed the drug-resistance of cancer cells in the presence of various anticancer drugs, including actinomycin D, colchicine, daunomycin, taxol, and vinblastine.² Because of the challenging structures and their interesting biological activity, numerous synthetic efforts have been devoted to the synthesis of welwitindolinone Cs³ and related natural products, such as welwitindolinone A.⁴ Recently, research groups of Rawal⁵ and Garg⁶ independently accomplished elegant syntheses of welwitindolinone Cs and their oxidized congeners.

In most previous strategies for welwitindolinone Cs, functional groups on the six-membered ring especially the vinyl chloride group were introduced or proposed to be introduced at late

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Supporting Information Available ¹HNMR, ¹³CNMR, IR, HRMS for starting materials and products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

stage, which was often challenging.⁷ We envisioned that a Rh-catalyzed [5+1] cycloaddition of allenylcyclopropane **5** with CO might afford the fully functionalized cyclohexenone core **4** efficiently. Alternatively, [5+1] cycloaddition of allenylcyclopropane **8** may yield cyclohexenone **7**. Closing of the sevenmembered ring may be realized by addition to the isopropylidene group in intermediate **4** through strategy **a** or α -arylation of the ketone group in intermediate **6** through strategy **b**.

We recently developed a stereoselective method for the synthesis of highly functionalized cyclohexenones via Rhcatalyzed [5+1] cycloaddition of allenylcyclopropanes derived from 1,3-acyloxy migration of propargyl esters.^{8,9} We examined the regioselectivity for the cleavage of the cyclopropane ring and found that the C-C bond adjacent to an electron-rich aryl group or away from a quaternary carbon was selectively cleaved.^{8,10} This provided the basis for the proposed regioselective [5+1] cycloaddition of cyclopropanes **5** or **8**.

The synthesis began with the preparation of allylic alcohol **11** from commercially available 4-cyanoindole **9** through a sequence of methylation, reduction, olefination, and reduction. Esterification and diazo compound formation were achieved in one step using reagent **12**.¹¹ Chlorination of diazo compound **13** yielded an unstable halodiazoacetate that was directly used in the cyclopropanation reaction. Based on a previous report,¹² Du Bois' Rh₂(esp)₂ was an efficient catalyst for mediating intermolecular cyclopropanation of alkenes and halodiazoacetates.¹³ We also found that Rh₂(esp)₂ was superior to other rhodium catalysts such as Rh₂(OAc)₄ for this intramolecular cyclopropanation. The best isolated yield we obtained for product **15**, however, was only about 20%. We suspected that the electron-rich indole ring might interfere with the electrophilic cyclopropanation. Substrates with an electronwithdrawing group on the indole nitrogen were then examined.

Boc-protected indole **16** was prepared in two steps from 4-cyanoindole indole **9** (Scheme 3). Diazoacetate **17** could be synthesized according to protocols described in Scheme 2. Chlorination followed by intramolecular cyclopropanation using Rh₂(esp)₂ catalyst afforded bicyclic product **19** in 50–60% yield after two steps starting with 1.2–4.4 g of diazo compound **17**. This represents the first successful example of intramolecular cyclopropanation of alkenes with chlorodiazoacetates and the reaction could be scaled up to several grams.

Opening of the lactone and protection of the resulting primary alcohol afforded Weinreb amide¹⁴ **20**. Addition of propynyl magnesium bromide to this amide then yielded ynone **21**, which was reduced to a mixture of two diastereomeric propargyl alcohols. Attempts to prepare allene **22** through a S_N2' reaction led to either decomposition when the leaving group was mesylates/triflate or no reaction when the leaving was acetate.¹⁵ Eventually, displacement of a sulfoxide leaving group¹⁶ proved to be fruitful and provided the desired allene **22** in 80% yield from ynone **21**.

With allenylcyclopropane **22** in hand, we then tried the [5+1] cycloaddition under different conditions. After screening various solvents (toluene, xylene, DCE, CHCl₃, dioxane), catalysts ([Rh(CO)₂Cl]₂, [Rh(COD)₂Cl]₂, [RhCl(PPh₃)₃], Ir(CO)₂Cl]₂), CO pressure (1 atm, 2 atm, and 5 atm), and temperature, we were able to isolate 60% yield of the desired [5+1] cycloaddition product **23** under conditions shown in Scheme 5. The cyclopropane C-C bond adjacent to the indole ring and away from the quaternary carbon was selectively cleaved during the cycloaddition. The relative stereochemistry of the product and the regioselectivity for the cleavage of cyclopropane C-C σ -bond were determined by nOe and HMBC, respectively.¹⁷

In summary, we have developed an efficient strategy to access the cyclohexenone core of welwitindolinone Cs. Highly sterically congested penta-substituted cyclopropanes were prepared successfully by an intramolecular cyclopropanation of trisubstituted alkenes with chlorodiazoacetates. The [5+1] cycloaddition product **23** has a cyclohexenone core with most of the required functionalities for welwitindolinone Cs including a quaternary carbon, a vinylchloride group, an indole ring, and a ketone group with an isopropylidene substituent. Efforts to complete the synthesis of welwitindolinone Cs and their analogues by installing the second quaternary carbon and closing the seven-membered ring are currently underway in our laboratory,¹⁸ in addition to the study of [5+1] cycloaddition of other allenylcyclopropanes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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17. See Supporting Information for details.
18. Initial attempts to close the seven-membered ring by Lewis acid mediated direct cyclization of intermediate **23** were not successful.

Scheme 1.
Proposed Strategies for Welwitindolinones

Scheme 2. Intramolecular Cyclopropanation of an Alkene Substituted with a *N*-Methyl Indole

Scheme 3.
Intramolecular Cyclopropanation of an Alkene Substituted with a *N*-Boc protected Indole

Scheme 4.
Preparation of Penta-substituted Allenylcyclopropane

Scheme 5.

Rh-catalyzed [5+1] cycloaddition of Allenylcyclopropane and CO