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Approaches to *N*-Methylwelwitindolinone C Isothiocyanate: Facile Synthesis of the Tetracyclic Core

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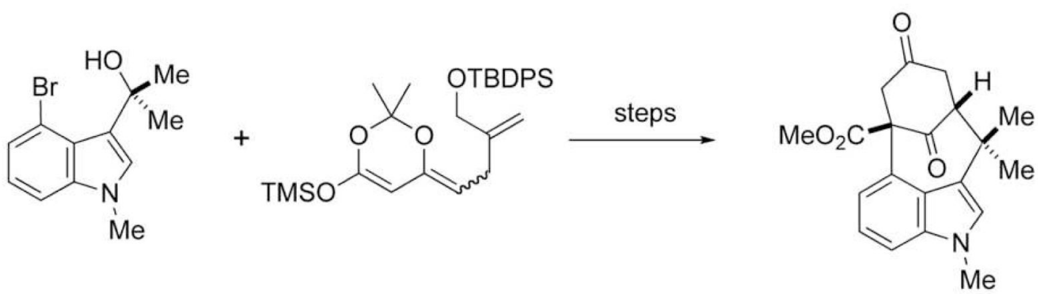
Abstract



The synthesis of a functionalized, tetracyclic core of *N*-methylwelwitindolinone C isothiocyanate is reported. The approach features a convergent coupling between an indole iminium ion and a highly functionalized vinylogous silyl ketene acetal followed by an intramolecular palladium-catalyzed cyclization that proceeds via an enolate arylation.

A series of novel indole alkaloids were isolated in 1994 by Moore and coworkers from the extracts of blue-green cyanobacteria *Hapalosiphon wetwitschii* and *Westiella intracta*. 1 These compounds, which were collectively named welwitindolinones, possess a unique skeletal framework and were isolated along with the structurally related fischerindoles and hapalindoles. A putative biogenetic relationship amongst these alkaloids has been proposed.[1] These natural products exhibit diverse biological activities, perhaps the most exciting of which is the ability of some to reverse multiple drug resistance (MDR) during chemotherapeutic treatment of cancer.[2]

As a result of their novel structures and exciting biological activities, the various welwitindolinones have captured the attention of many groups, whose efforts have been chronicled in a number of accounts.[3] Noteworthy are the elegant syntheses of welwitindolinone A isonitrile (**1**) independently reported by Baran [4] and Wood, [5] and of welwitindolinone A isothiocyanate (**2**) by Baran.[6] Another important member of this family is *N*-methylwelwitindolinone C isothiocyanate (**3**)Numerous efforts directed toward the synthesis

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Supporting Information Available Experimental procedures and ^{1}H and ^{13}C NMR spectra for all new compounds, plus CIF files representing X-ray coordinates for compounds **11** and **16** are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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of this challenging target have not yet reached fruition, [7] but the tetracyclic core has been prepared by several groups.[8b,g-k,m-o] We now report the details of some of our work in the area.

Our initial approach to *N*-methylwelwitindolinone C isothiocyanate (**3**)is outlined in retrosynthetic format in Scheme 1. We envisioned that the late stage intermediate **4**, which might be elaborated into **3** by a series of refunctionalizations and alkylations, might be accessible via a novel double allylic alkylation of the tricyclic keto ester **5**. The synthesis of **5** would then involve the cyclization of **6** via an enolate arylation, and compound **6** might be readily prepared by a Michael addition of *N*-methyl-4-bromooxindole (**7**).

In the event, 4-bromooxindole (**8**), prepared via a known procedure,[8] was selectively *N*-methylated using a method developed by Bordwell (Scheme 2).[9] Warming oxindole **7** in degassed sodium methoxide in methanol with excess methyl 3-methylcrotonate provided the adduct **9** in 74% yield. It was essential to rigorously exclude air in order to avoid extensive formation of the corresponding isatin derivative. The crossed Claisen condensation of **9** with the enolate of *tert*-butyl acetate afforded ketoester **10**. Because the *tert*-butyl ketoester group was prone to decarboxylation in future reactions, it was converted to the methyl ester **6**. The overall yield of **6** from **9** via this two-step procedure was superior to that obtained using methyl acetate in the crossed Claisen condensation with **9**.

The next stage of the synthesis required the palladium catalyzed cyclization of the enolate of the ketoester **6** (Scheme 3). Although use of *bis*-*tert*-butyl-2-biphenyl phosphine as a ligand [10] provided the cyclized β-ketoester, which existed in its enol form **11**, in 58% yield, significant amounts of unreacted **6** were invariably recovered; the structure of **11** was established by X-ray crystallography. On the other hand, use of a combination of commercially available tri-*tert*-butylphosphine palladium dimer [11] and either palladium bisdibenzylideneacetone or chlorobisallylpalladium dimer a ratio of 2:1 as suggested by Fu[12]> gave the enol **11** 88% yield. These reactions are sensitive to the presence of oxygen, and the best results were obtained with a freezepump-thaw protocol.

The synthetic plan then anticipated the conversion of **11** into the tetracyclic intermediate **15** via a palladium catalyzed double allylic alkylation using the known bisallylic carbonate **12**. However, when **11** was allowed to react with **12** in the presence of base and a number of Pd (0) catalysts, none of the desired **15** was obtained. Somewhat surprisingly **14** was the only product isolated.[13] This alternate mode of cyclization is presumably the consequence of the more acidic proton on the oxindole ring. A change of strategy that would obviate this deleterious cyclization was thus warranted.

Reasoning that the undesired cyclization mode would not be accessible to the indole analog of **13**, **11** was tranformed into **16**, which like **11** existed in its enolic form as confirmed via X-ray crystallography, in modest yield by reduction and dehydration (Scheme 4). Palladium-catalyzed alkylation of **16** with **12** afforded allylic carbonate **17**; however, all attempts using various bases to enolize the ketone function in **17** under the reaction conditions were unsuccessful. Interestingly, when **17** was treated with $ZnCl_2$ in the presence of a Pd(0) catalyst, **18** was formed in 51% yield. [14] When this reaction was performed in the absence of the palladium catalyst, **18** was again isolated, albeit in only 28% yield.

Because the problem we encountered involved forming the C(14)–C(15) bond *after* forming the C(11)–C(12) bond, it occurred to us that reversing the order of these two bond constructions might be a viable alternative. This revised approach then dictated the intermediacy of a substrate such as **19**, which could be formed by cyclization of the β-keto ester **20** (Scheme 5). Our first attempts to prepare **20** involved the alkylation of the dianion of **10** with a suitably substituted allyl halide (*Path A*), but these efforts were to no avail. We also envisioned that **20** might be accessed by *Path B*, a process that would involve capture of the stabilized

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carbocation generated from **21** with a π-nucleophile such as **22**. At the time we conceived of this approach there was little precedent for such a construction.[15] Shortly after we had conducted this reaction, Rawal reported a similar process using a *N*-protected indole in his work directed toward the welwitindolinones.7g, m Since our original discovery, we have found this reaction to be more generally useful for preparing heteroaryl propanoic acid derivatives.[16]

In order to examine the feasibility of forming **20** via *Path B*, the vinylogous silyl ketene acetal **22** was first prepared (Scheme 6). Accordingly, the *bis*-anion of *tert*-butylacetoacetate (**23**) was alkylated with the allylic bromide **24**, which was easily prepared in two steps from the corresponding diol, to furnish **25**. Dioxanone formation to give **26** and subsequent silylation of the dienolate derived from **26** gave **22**, which because of instability was used without further purification, as inconsequential mixture (1.5:1) of isomeric olefins.

The requisite indole fragment **29** was then prepared from 4-bromoindole (**27**) by a procedure developed by Rapoport (Scheme 7). [17] *N*-Methylation of **27** with dimethylcarbonate[18] followed by acetylation at C(3) of **27** afforded ketone **28**. [19] Reaction of **28** with methylmagnesium bromide provided the unstable tertiary alcohol **21**, which was immediately treated with the crude vinylogous silyl ketene acetal **22** in the presence of TMSOTf to form **29** in 35% yield over two steps. Heating **29** with methanol unveiled an intermediate ketoester **20** (R = TBDPS), which underwent palladium catalyzed cyclization to give **30** in 71% yield from **29**. The silyl ether was cleaved with triethylamine hydrofluoride, but the subsequent acetylation of the resulting alcohol was complicated by competing reaction with the enolized ketone to give an enol acetate. After some experimentation, we discovered that selective acetylation of the alcohol could be achieved by the action of acetyl chloride in the presence of collidine at –78 ° C to furnish **31** in 52% overall yield from **30**. Cyclization of the sodium enolate derived from **31** was achieved utilizing $Pd_2(dba)_3$ to deliver the desired tetracycle **32** in 71% yield. Oxidative cleavage of the exocyclic olefin under Johnson-Lemieux conditions gave the dione **33**.

In preparing **33**, we have thus developed a facile entry to the tetracyclic scaffold found in *N*-methylwelwitindolinone C isothiocyanate (**3**). The synthesis features the coupling of an indole-stabilized carbocation with a vinylogous silyl ketene acetal as a π -nucleophile together with a palladium-catalyzed enolate arylation and a palladium-catalyzed allylic alkylation. Efforts toward the application of this approach and variants thereof to the total synthesis of **3** are in progress and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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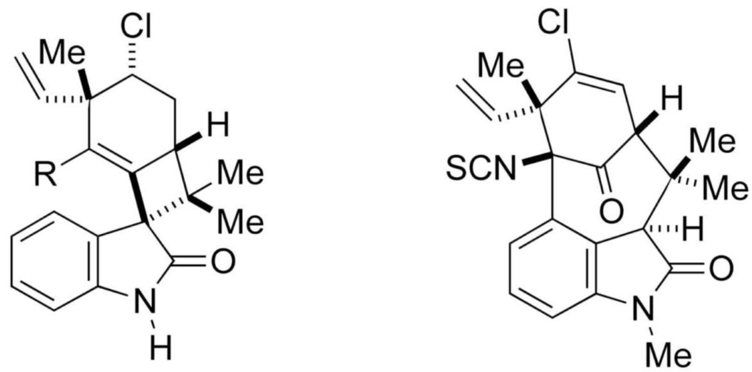

1: R = NC
2: R = NCS

3

Figure 1.
Structures of Welwitindolinone A Isocyanate (**1**), Welwitindolinone A Isothiocyanate (**2**) and *N*-Methylwelwitinolidone C Isothiocyanate (**3**).

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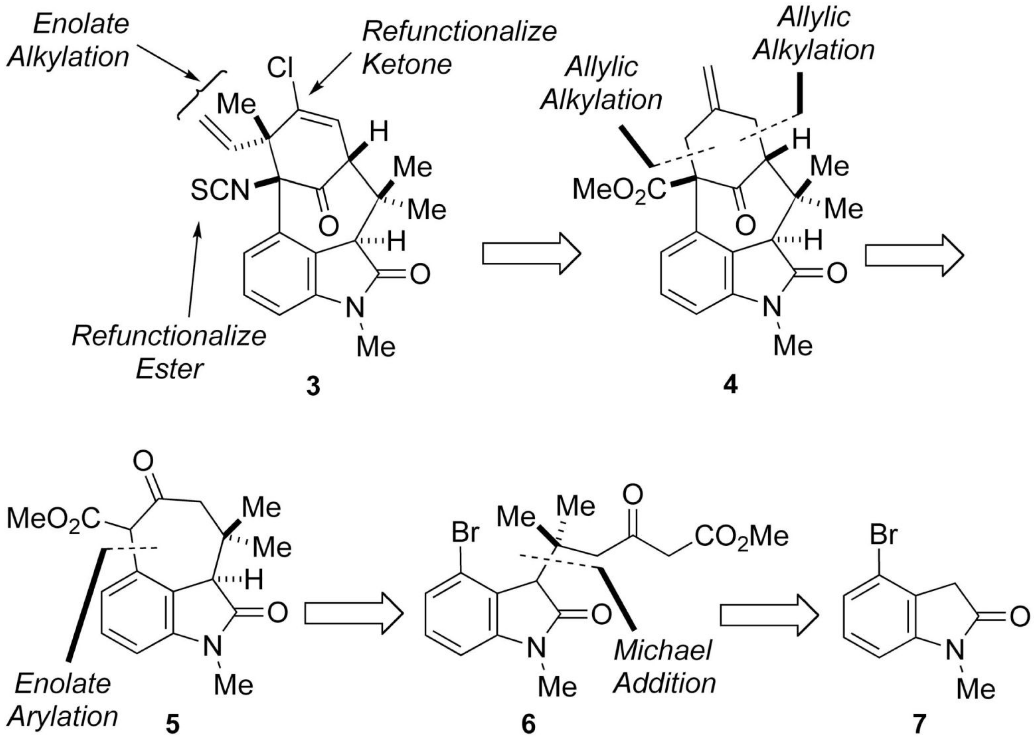

Scheme 1.
Initial Retrosynthetic Proposal

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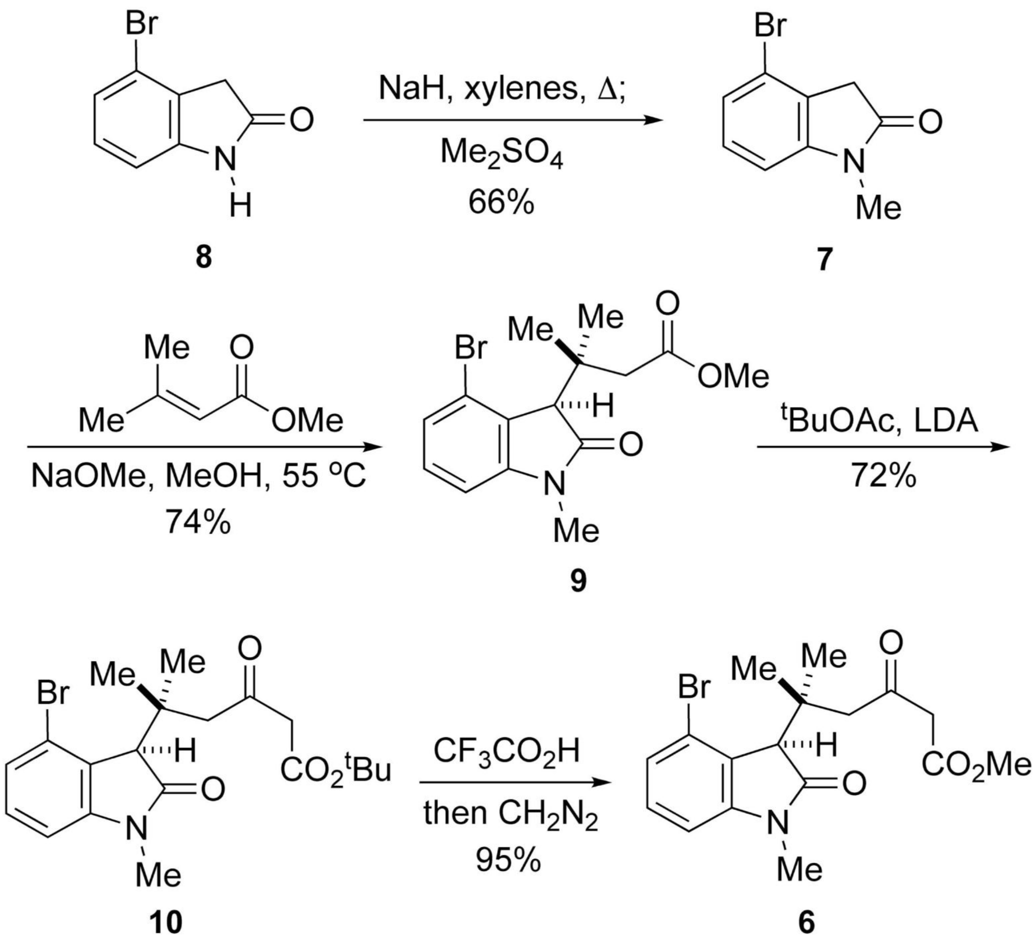

Scheme 2.

Preparation of Ketoester **6**

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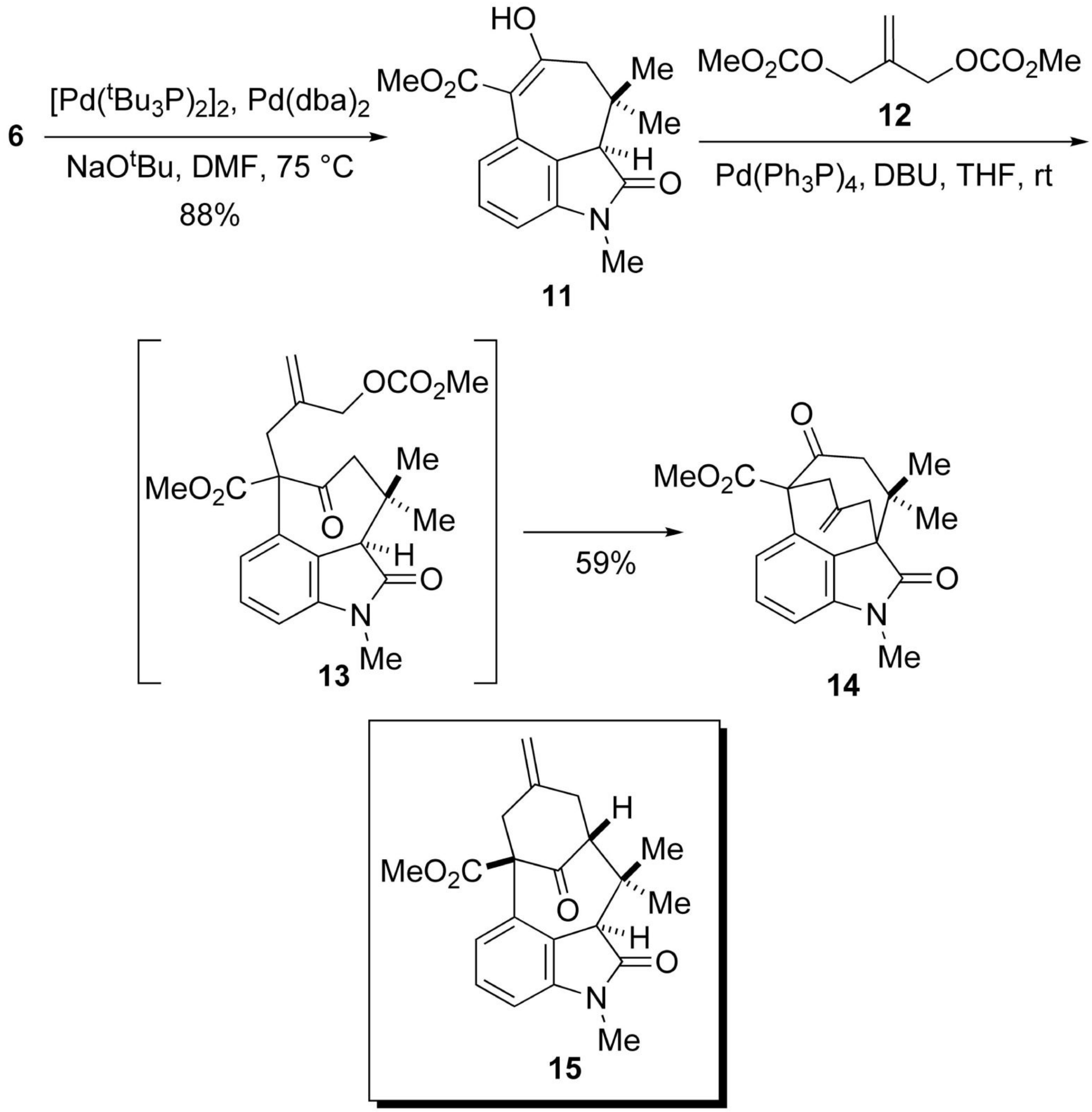

Scheme 3.
Attempted Preparation of Tetracycle **15**

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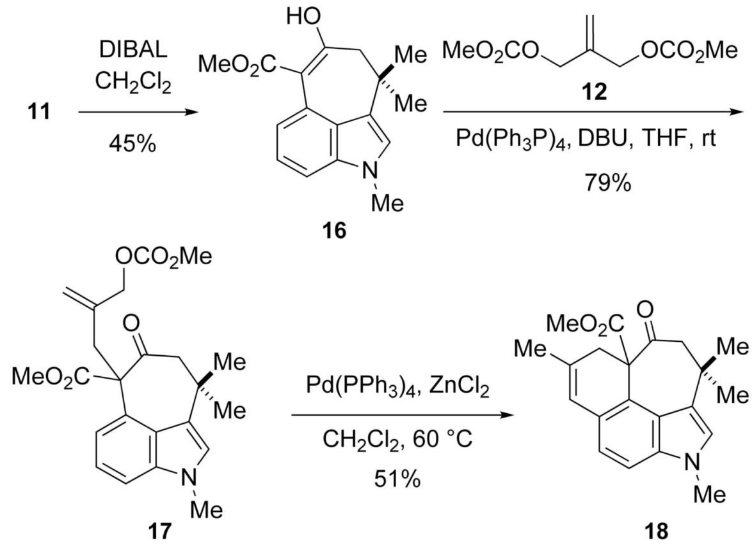

Scheme 4.

Attempted Preparation of an Indolic Tetracycle

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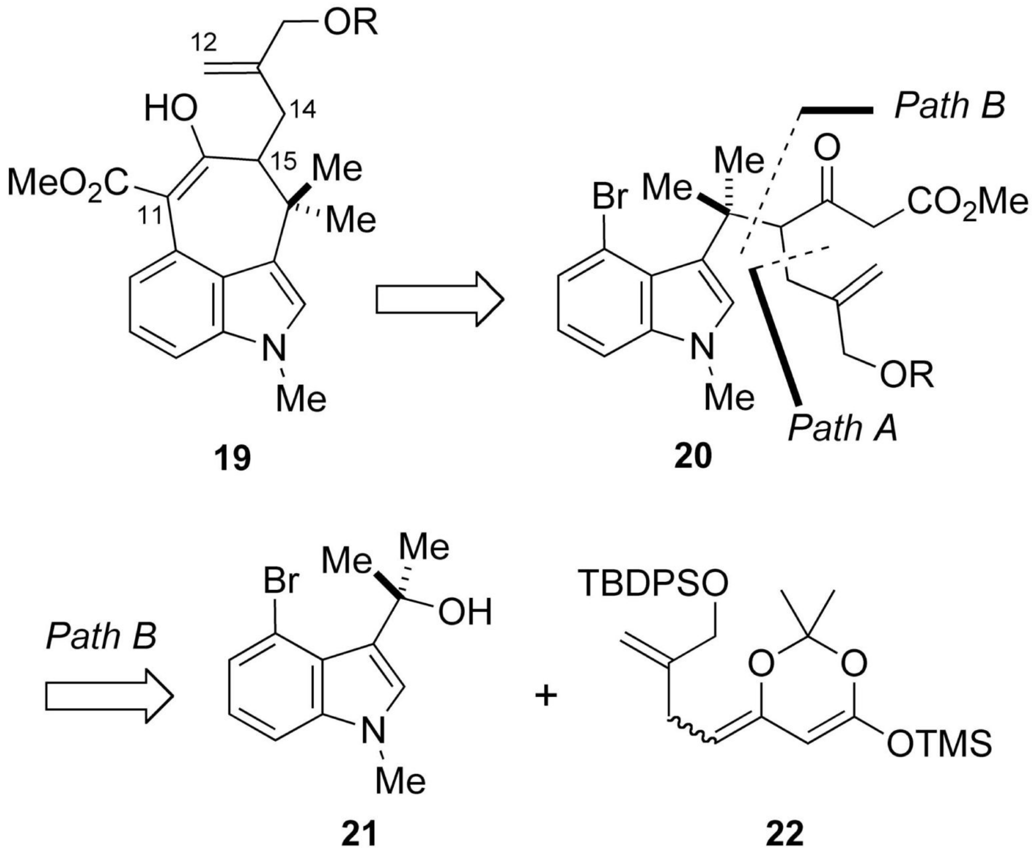

Scheme 5.

A Revised Retrosynthetic Analysis

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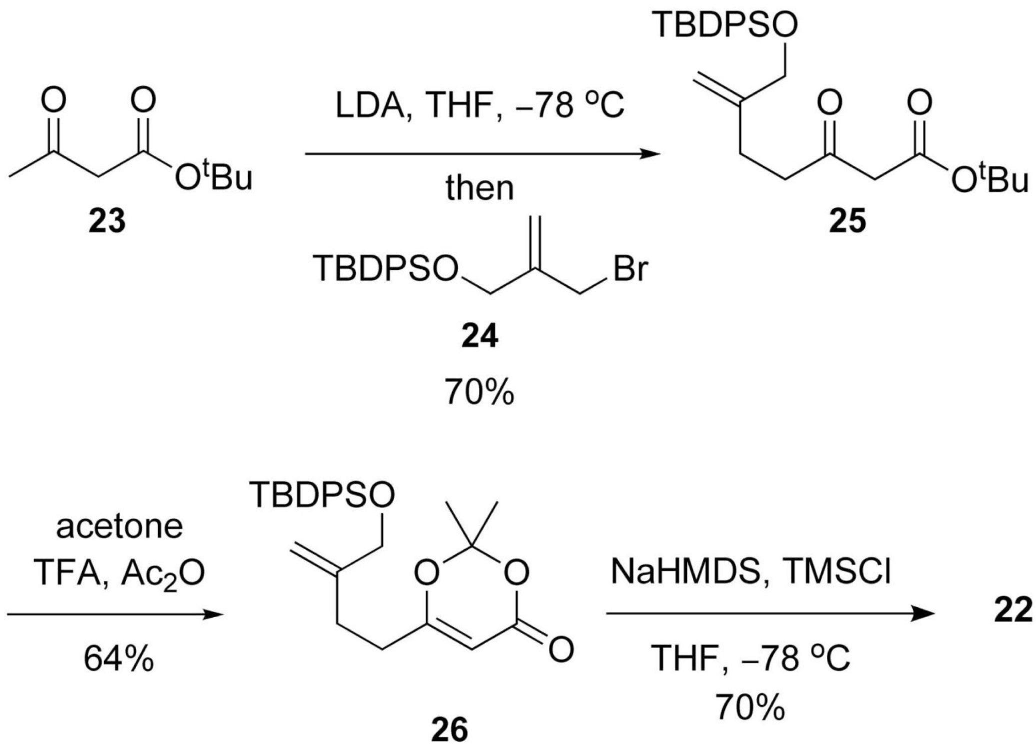

Scheme 6.
Preparation of Vinylogous Silyl Ketene Acetal **22**.

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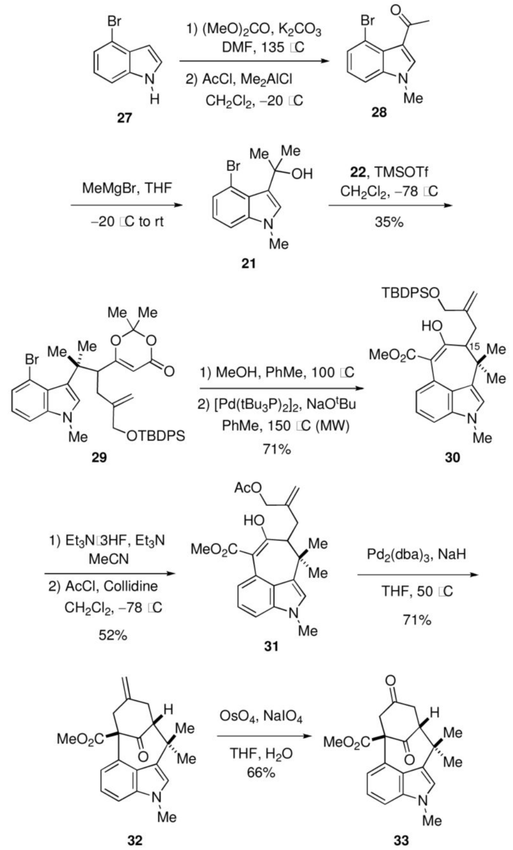

Scheme 7.
Preparation of the Welwitindolinone C Skeleton