Concise and very efficient synthesis of the *N*-methylwelwistatin tetracyclic core based on an anionic domino process†

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An efficient synthesis of the *N*-methylwelwistatin tetracyclic core in only two steps from Kornfeld's ketone is described, whose key transformation involves the generation of a fused bicyclo[4.3.1]decane ring system through a one-pot sequence comprising a Michael-intramolecular aldolization anionic domino process and a DBU-promoted hydrolysis of the *N*-pivaloyl protecting group. Besides providing the most efficient synthesis of the welwistatin core to date, this method has the advantage of installing an oxygenated function at the welwistatin D ring.

The welwitindolinones are a family of structurally novel oxindole alkaloids from marine cyanobacteria. The first members of this group were isolated in 1994 by Moore and coworkers from the lipophilic extracts of *Hapalosiphon welwitschii* and *Westiella intricata*.[1] These extracts contained 3,4-bridged oxindoles, most notably *N*-methylwelwitindolinone C isothiocyanate, also known as *N*-methylwelwistatin **1**, and a spirocyclobutane oxindole derivative with antifungal properties called welwitindolinone A isonitrile **2** (Fig. 1). Subsequent work led to the isolation of some other oxidized welwitindolinones from several *Fischerella* species.[2]

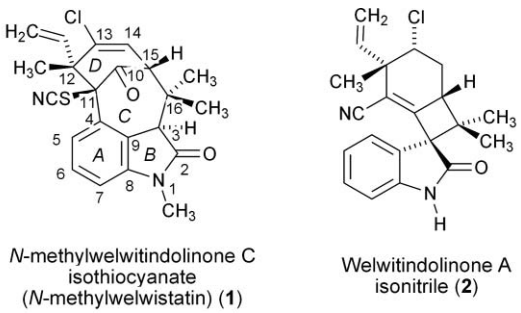
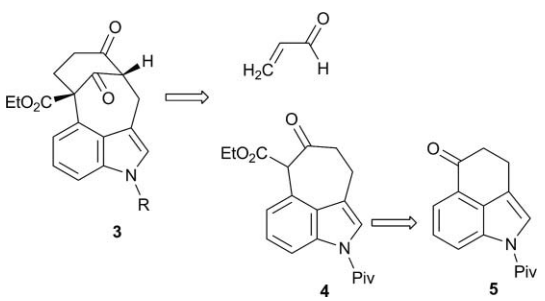


Fig. 1 Structures of representative welwitindolinones.

N-Methylwelwistatin can be considered as the biologically most relevant of the welwitindolinones. First, it inhibits the glycoprotein P-170-mediated resistance of MCF-7/ADR tumor cells to commonly used anticancer drugs at 10^{-7} M concentrations,[3] representing a potency 20- to 100-fold that of verapamil, the reference MDR reversor.[4] Furthermore, *N*-methylwelwistatin also behaves as an antimicrotubule agent that acts by inhibiting the polymerization of tubulin.[5] Since P-gp-overexpressing cells show virtually no resistance to welwistatin due to its MDR reversal properties, this natural product can be considered as a good lead compound in the chemotherapy of drug-resistant tumors.

The biological relevance of the welwitindolinones, combined with their unique and challenging structures, makes them very attractive synthetic targets, although work in this field has started to gather momentum only in recent years. While the groups of Baran and Wood have completed total syntheses of welwitindolinone A isonitrile **2**[6] and again the group of Baran has described the synthesis of welwitindolinone A isothiocyanate,[7] *N*-methylwelwistatin (**1**) has not been prepared synthetically so far. One of the main challenges to be overcome in this endeavour is the construction of the unprecedented ring system comprising a bicyclo[4.3.1]decane about an oxindole.[8] Some syntheses of the welwistatin tetracyclic core have been disclosed,[9,10] which normally start from indole or oxindole derivatives and involve as the key step a ring-closing metathesis that creates the 12–13 bond,[9a] an intramolecular arylation (4–11 bond),[9b] an intramolecular aldol reaction (15–16 bond),[9c] intramolecular Diels–Alder reactions (10–15/13–14[9e] or 10–11/12–13[9h] bonds), and a Pd-catalyzed alkylation (11–12 bond).[9i] Two of the syntheses differ from all the others in that they create the indole system at a late stage.[9d,g] With one exception,[9c] these routes are quite lengthy, requiring 6–16 steps to construct the tetracyclic system, and, again with one exception,[9a] they start from non-commercially available or very expensive starting materials like 4-bromoindole. Furthermore, some of these literature syntheses lead to systems lacking functionalization at ring D.[9b,c,f]

We describe here a new route based on the retrosynthetic analysis summarized in Scheme 1, which involves the initial preparation of a suitable ABC fragment, followed by construction of the D ring at a later stage by creation of the 11–12 and 14–15 bonds. Thus, our plan for the synthesis of **3**, a highly functionalized derivative of the welwistatin core, involves as the key step a Michael-intramolecular aldol sequence from compound **4**, which would be prepared by ring expansion from Kornfeld's ketone **5**. This starting material is readily available in multigram amounts (two steps and 89% yield from commercially available starting



Scheme 1 Retrosynthetic analysis of the welwistatin core.

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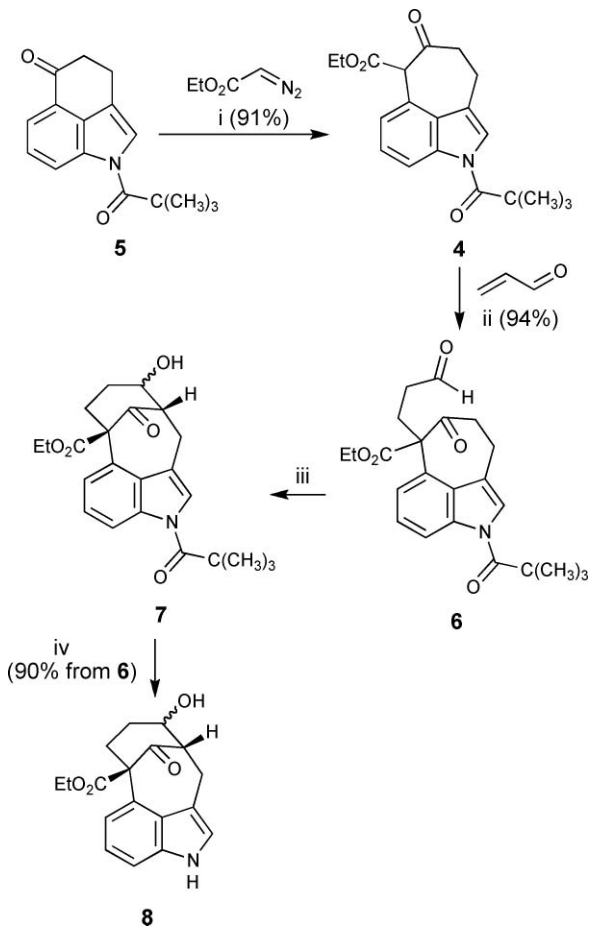
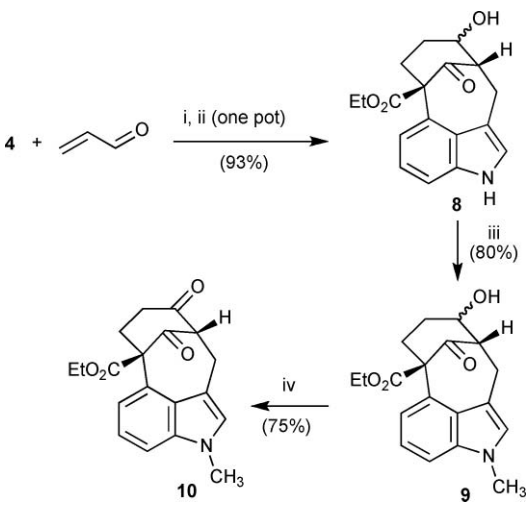
materials, in our hands) through an intramolecular Friedel–Crafts cyclization of 3-(1-pivaloyl-3-indolyl)propionic acid, where the pivaloyl group is essential to direct the regioselectivity of the reaction in favour of the less nucleophilic, but also less hindered, C-4 position.[11] The mandatory presence of a pivaloyl group on indole nitrogen was the cause for some concern in the planning stage, since there are few methods in the literature for indole *N*-depivaloylation[11,12] and they normally involve the use of strong bases or reducing agents, which could lead to unwanted reactions in our substrates. The presence of the ester group was prompted by the fact that it has been shown to be a suitable precursor for a bridgehead nitrogen function in related situations, *via* the Curtius rearrangement.[9b,13]

As shown in Scheme 2, homologation of the cyclohexanone fragment in Kornfeld's ketone **5** to give the welwistatin ABC fragment **4** was achieved regioselectively and in 91% yield by its treatment with ethyl diazoacetate in the presence of triethyloxonium tetrafluoroborate.[14] Treatment of **4** with acrolein in the presence of potassium carbonate suspended in THF afforded a 94% yield of the Michael adduct **6**, which was cyclized to **7** in the presence of 1.5 equivalents of DBU. Although the reaction lacked diastereoselectivity, this was of no consequence to the synthetic plan since the stereocenter adjacent to the hydroxyl group is lost during subsequent stages of the sequence. In the course of these studies, we found that some experiments afforded small amounts of the deprotected compound **8**, which was attributed to the generation of hydroxide from DBU and traces of water in the reaction medium. Subsequent experimentation showed that it was possible to achieve complete hydrolysis of the pivaloyl protection to give **8** from **6** in a single synthetic operation and 90% overall yield by addition of water and an additional amount of DBU to the reaction mixture containing compound **7**, followed by prolonged stirring at room temperature.



Scheme 2 Initial route leading to the welwistatin core. Reagents and conditions: i. BF_4^+ EtO_3^- (2 eq), CH_2Cl_2, 4 °C, 24 h. ii. K_2CO_3, THF, r.t., 1 h. iii. DBU (1.5 eq), THF, r.t., 4 h. iv. DBU (2.5 eq), H_2O (2 eq), r.t., 18 h.

Although the sequence summarized in Scheme 2 represented a very efficient synthesis of a D ring-functionalized welwistatin tetracyclic core, we felt that a further improvement would be possible if the Michael addition-intramolecular aldol sequence leading to the bicyclo[4.3.1]decane system could be performed in a domino process.[15] This expectation was based on the related transformation of alkyl 2-oxocyclopentane-carboxylates into bicyclo[3.2.1]octan-8-ones by reaction with α,β-unsaturated aldehydes under basic conditions,[16,17] but it remained to be established if this literature result could be extended to the preparation of a bicyclo[4.3.1]decane fragment fused to an indole system. In the event, after assaying several bases, we were gratified to find that the desired transformation could be carried out under the conditions previously employed for the intramolecular aldol addition, namely stirring at room temperature in THF containing DBU. Furthermore, this anionic domino process could also be combined with the hydrolysis of the pivaloyl group in the presence of water-DBU to give a 93% yield of **8** in a one-pot sequence starting from **4**. Compound **8** was further elaborated by chemoselective N-methylation under phase-transfer catalysis to give **9**, followed by oxidation of the hydroxyl group in the presence of TPAP[18] to give **10** (Scheme 3). The successful preparation of this compound confirms that our route has the advantage of allowing the introduction at the D ring of functionalities suitable for further elaboration towards the natural product.



Scheme 3 Improved, one-pot access to a *N*-deprotected derivative of the welwistatin core and its subsequent elaboration. Reagents and conditions: i. DBU (1.5 eq), THF, r.t., 12 h. ii. DBU (2.5 eq), H_2O (2 eq), r.t., 18 h. iii. ICH_3 (1.5 eq), HSO_4^- BuN_4^+, 50% aq. KOH–CH_2Cl_2, r.t., 14 h. iv. TPAP (5 mol%), NMO (1.5 eq), 4 Å MS, CH_3CN, r.t., 3 h.

The stereochemical assignments of compounds **6–10** were based on NOESY experiments. The results of two representative examples are shown in Fig. 2, where the observed NOE effects prove the *cis* arrangement between the substituents placed at the bridgehead positions.

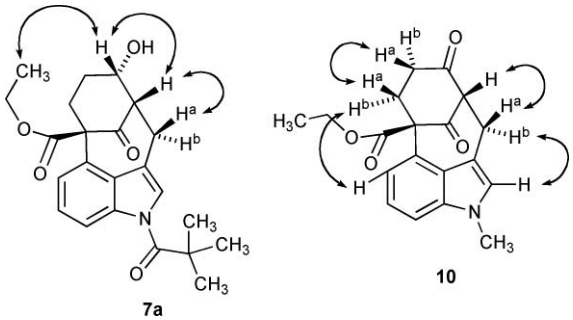


Fig. 2 NOE effects used in the stereochemical assignment of compounds **7b** and **10**.

In conclusion, we have developed the most efficient synthesis of the welwistatin core to date, consisting of a two-step route that involves a domino Michael-aldol-*N*-deprotection process as the key step and proceeds in 85% overall yield from Kornfeld's ketone. As an additional advantage, this route installs a hydroxy group at the C-14 position of the welwistatin D ring that will allow its further manipulation, which is planned to proceed by two α,β-unsaturation generation/conjugate addition sequences for the generation of the quaternary center ar C-12.

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