Bridgehead enolates and bridgehead alkenes in a welwistatin model series†

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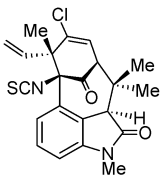
Bridgehead metallation is possible in a ketone having the welwistatin skeleton, and this facilitates installation of the isothiocyanate function present in the natural product, and also enables synthesis of remarkable bridgehead alkenes.

The welwitindolinones are a small group of oxindole alkaloids, first isolated from blue–green algae by Moore and co-workers in 1994.[1,2] Of the seven structures originally reported, one compound, *N*-methylwelwitindolinone C isothiocyanate (**1**), also later dubbed welwistatin, has provoked special synthetic interest, due both to its fascinating molecular architecture and its apparent ability to reverse multi-drug resistance (MDR).[3] Despite widespread interest in the development of routes towards **1** no total synthesis has emerged to date.[4,5]

In a previous report we described a four-step synthesis of a simple model compound **2**, having the characteristic [4.3.1]-skeleton of welwistatin, starting from commercial 4-bromoindole.[6] We also showed that the indole bridge present in ketone **2** could be converted into an oxindole resembling that in welwistatin **1**.



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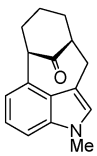
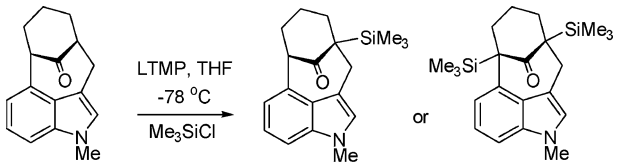


2

The extremely concise access to ketone **2** makes further controlled embellishment of this system a very attractive option for the preparation of more advanced model compounds related to **1**, and potentially for a synthesis of the natural product itself. Foremost amongst our aspirations for ketone **2** in this regard were the installation of the bridgehead isothiocyanate (possibly implicated as the 'warhead' function in the MDR reversal activity), and introduction of an additional functional group 'handle' into the cyclohexanone ring. Herein we describe our progress in these directions, which have uncovered some remarkable transformations of **2**, involving regiocontrolled bridgehead substitutions, and access to unusual bridgehead alkenes.

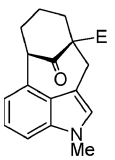


2 **3** 56% (1 eq of base) **4** 68% (3 eq of base)

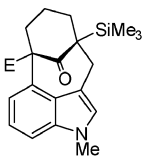
Scheme 1 Silylation of bridged ketone **2**.

We started the exploration of the enolate reactivity of **2** by probing the regiochemistry of enolate silylation using lithium tetramethylpiperidide (LTMP) as base (LDA effected only ketone reduction), Scheme 1. Treatment of **2** with around one equivalent of LTMP gave silylketone **3** cleanly, with no trace of the alternative product silylated at the benzylic bridgehead position. Increasing the amount of base led to formation of bis-silylated ketone **4**, which could be generated in good yield by employing 3–5 equivalents of base.

Although the regiochemistry of the bridgehead substitution leading to **3** was not the desired outcome for welwistatin, we examined the scope of this substitution process with a range of alternative electrophiles, leading to ketones **5–10**.



5 E = Me (72%)
6 E = Bn (73%)
7 E = prenyl (57%)
8 E = CO^{t}Bu (85%)
9 E = CH(OH)Ph (51%)
10 E = SePh (88%)



11 E = CO_2Me (58%)
12 E = SePh (74%)

Thus, the putative bridgehead enolate was successfully alkylated with reactive alkyl halides, acylated, added to benzaldehyde or selenylated in good to excellent yields.[7]

More interesting in terms of substitution at the required position for installation of the isothiocyanate function present in **1**, was the finding that silylketone **3** could be further substituted at the benzylic bridgehead position, *e.g.* to give ketoester **11** or selenide **12**. We considered that desilylation of

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† Electronic supplementary information (ESI) available: Experimental procedures and spectroscopic data for new compounds. CCDC 698859 (enone **16**) and 698860 (enone **18**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b820674k

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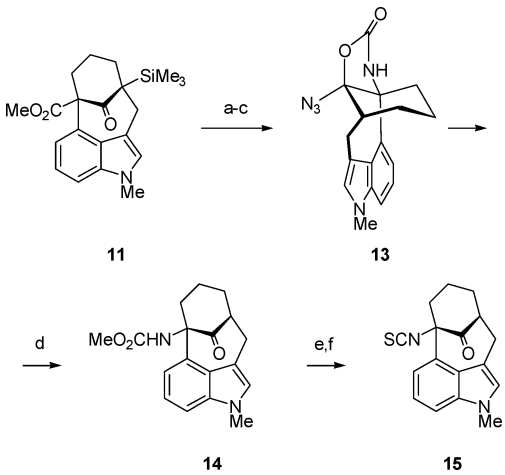


Scheme 2 Synthesis of isothiocyanate **15**. (a) TBAF, THF, 87%; (b) LiI, pyridine, 88%; (c) DPPA, Et_3N, CH_2Cl_2 reflux then toluene 90 °C, 63%; (d) NaOMe, MeOH, 87%; (e) Me_3SiI, CH_2Cl_2 reflux then MeOH reflux, 90%; (f) thiocarbonyldi-2(1*H*)-pyridone, DMAP, CH_2Cl_2, 76%.

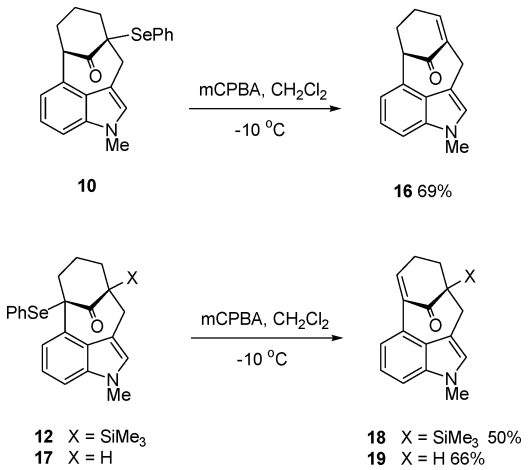
11 and manipulation of the methyl ester function by means of a Curtius rearrangement sequence would provide access to simple isothiocyanate models related to **1**. In this way the bridgehead silicon substituent present in ketone **3** would act as a temporary blocking group. These expectations were realised, although not without an initial unexpected detour, as shown in Scheme 2.

Desilylation and ester hydrolysis proceeded routinely to give a bridgehead carboxylic acid, which was then treated with diphenylphosphoryl azide along the lines described by Rawal *et al.* in their synthesis of a related welwistatin model isocyanate.[5e] To our surprise the product lacked both of the expected ketone and isocyanate functional groups, and ultimately proved to be azido oxazolidinone **13**.[8]

This compound could be further processed by oxazolidinone ring-opening and carbamate removal to give a bridgehead amine. Treatment of this compound with thiocarbonyldiimidazole generated only minor amounts of the desired isothiocyanate due to incomplete conversion of the imidazolyl thiourea intermediate. By contrast, the less commonly employed reagent 1,1′-thiocarbonyl-2,2′-pyridone gave clean and efficient conversion to the desired isothiocyanate **15**.[9]

We were also interested to see if elimination of the bridgehead selenides **10** and **12** might provide a means to further elaborate the cyclohexane ring. To this end we effected selenoxide *syn*-elimination reactions by reaction of the selenides **10**, **12** and **17** with mCPBA in dichloromethane at −10 °C, Scheme 3.

These reactions led to the formation of the bridgehead alkenes **16**, **18** and **19** in good yields. Although the sum of the bridging atoms in these systems (the so-called *S*-value, here 8) is large enough that these alkenes are not strictly anti-Bredt in nature, the accommodation of a cyclohexenone into systems that already posses a rigid methyleneindole bridge appears remarkable.[5g,10] Indeed, alkenes **18** and **19** appeared highly improbable, based on simple molecular models. Thankfully, crystalline samples were obtained for **16** and **18**, and X-ray crystallography secured the proposed structures and provided further insight into the shape and conformation of these unusual systems Fig. 1 and 2.[11]



Scheme 3 Selenoxide eliminations to give bridgehead alkenes.

In each case the cyclohexenone adopts a distinctive boat conformation in which conjugation of the carbonyl function with the newly introduced C=C bond appears compromised. In accord with this are the observed stretching frequencies of the C=O group in **16** and **19** of around 1710 cm^{-1}, and also the chemical shift of the 'enone' β C–H, which in each of the bridgehead enones is at least 0.5 ppm upfield compared to cyclohexenone. The most remarkable feature of these molecules is the geometry of the planarised bridgehead carbon—C12 in **16**, C14 in **18**—where there are marked

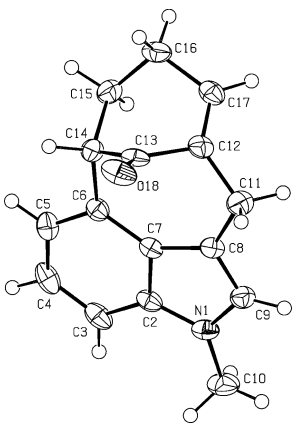


Fig. 1 X-Ray structure of enone **16**.

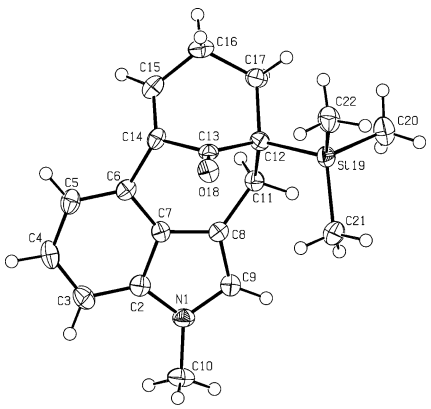
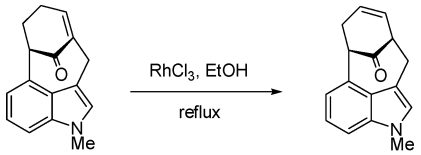


Fig. 2 X-Ray structure of enone **18**.



16 20 53%

Scheme 4 Alkene transposition.

distortions from ideal trigonal planar geometry. In **16** the angles subtended at C12 range from 114.43(11) to 128.59(13)° and sum to 358.10°; C12 lies 0.113 Å out of the C11–C13–C17 plane. The geometry at C14 in **18** is even more distorted, with angles ranging from 111.96(15) to 130.99(17)° and summing to 357.87°; C14 lies 0.120 Å out of the C6–C13–C15 plane.

We also found that these enones could not be coerced into Michael addition chemistry, either using soft heteroatom nucleophiles, such as thiolate (PhSH, Et_3N, CH_2Cl_2 at reflux) or organocuprate reagents. Our disappointment at the reluctance of these bridgehead alkenes to react with nucleophiles might be compensated if they could instead be reacted with electrophilic reagents. However, the co-existence of a much more reactive nucleophilic indole in these systems dictates that conversion into oxindoles should be carried out *prior* to attempting electrophilic additions to the bridgehead alkenes. Such studies are ongoing.

Finally, we were interested to attempt isomerisation of the bridgehead enones. Treatment of **16** with mild bases such as DBU or NaOMe did not result in isomerisation of the bridgehead α,β-unsaturated ketone into a less strained β,γ-unsaturated isomer. However, treatment of **16** with $RhCl_3$ in EtOH at reflux for 24 h resulted in quite clean isomerisation to give the transposed enone **20**, Scheme 4.[12]

This isomerisation moves the ring alkene into the position required for welwistatin, making the sequence of bridgehead selenylation, elimination and isomerisation a new possibility for installation of the vinyl chloride found in the natural product.

We expect that the alkene function in **20** could serve as a very useful handle for preparing more advanced welwistatin models and synthetic intermediates, and we will report on further progress in due course.

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8 We are not aware of direct precedent for this type of structure. This structure was subsequently confirmed by X-ray crystallography; further details will be published elsewhere. The undesired excursion *via* the azide **13** could be avoided by removal of excess azide salts from the intermediate acyl azide prior to thermolysis in toluene, providing easy access to **15**.

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11 For both structures displacement ellipsoids are drawn at the 50% probability level. Crystal data for enone **16**. $C_{16}H_{15}NO$, FW = 237.29, monoclinic, space group $P2_1/c$, a = 9.7651(14), b = 14.083(2), c = 10.0083(14) Å, β = 117.807(2)°, U = 1217.4(3) Å^3, Z = 4, D_c = 1.295 Mg m^{-3}, μ(Mo-Kα) = 0.081 mm^{-1}, T = 150(2) K. 2788 unique reflections (R_{int} = 0.106). Final R_1 [2263 $I > 2\sigma(I)$] = 0.0492, w$R2$ (all data) = 0.134. Enone **18**: $C_{19}H_{23}NOSi$, FW = 309.47, orthorhombic, space group $Pna2_1$, a = 23.565(2), b = 10.8079(10), c = 6.5185(6) Å, U = 1660.2(4) Å^3, Z = 4, D_c = 1.238Mg m^{-3}, μ(Mo-Kα) = 0.143 mm^{-1}, T = 150(2) K. 3751 unique reflections (R_{int} = 0.039). Final R_1 [2929 $I > 2\sigma(I)$] = 0.0349, w$R2$ (all data) = 0.0741.

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