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Total synthesis of (±)-manzacidin D

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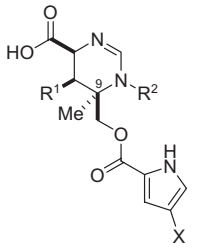
Abstract—We report herein the first total synthesis of the alkaloid manzacidin D, in 11 steps and 16% overall yield from commercially available glycine *tert*-butyl ester hydrochloride. Our synthesis demonstrates for the first time in a total synthesis the utility of two different methodologies. A highly diastereoselective iodocyclization of an olefinic isothiourea is used to induce stereocontrol at the quaternary centre, and to form the heterocyclic core. Conversion of a thiourea to the requisite formamidine is achieved in good yield using our modified procedure.

The manzacidins are a class of alkaloids having a cyclic amidine core (Fig. 1). Manzacidins A, B and C (**1a**, **b**, **c**) were isolated from the Okinawan sponge *Hymeniacidon* sp.[1] When first isolated, their tetrahydropyrimidine scaffold was considered unique. However, with the isolation of manzacidin D (**1d**) from the coralline demosponge *Astrosclera willeyana*,[2] and most recently compound **1e**, N-methyl manzacidin C, from the marine sponge *Axinella brevistyla*,[3] this family of natural products is expanding. Prior to this work, only manzacidins A and C, epimers at C-9, had been synthesized, by Ohfune and co-workers,[4] and by Wehn and DuBois.[5] It should be noted that the biological properties of the manzacidins have been little studied. Manzacidin D, in particular, has been tested against few targets[6] due to the scarcity of its supply, and a biological target against which it shows high potency has not yet been discovered. This situation makes manzacidin D a highly attractive target for synthesis and biological evaluation.



R^1	R^2	X		manzacidin
H	H	Br		A (**1a**)
OH	H	Br		B (**1b**)
H	H	Br	(9-*epi*)	C (**1c**)
H	Me	H		D (**1d**)
H	Me	Br	(9-*epi*)	N-methyl manzacidin C (**1e**)

Figure 1. The manzacidins.

Our retrosynthesis of manzacidin D is depicted in Figure 2. We expected to install the pyrrole carboxylate in the last step of the synthesis, according to Ohfune's precedent. The formamidine unit is derived from the corresponding isothiourea. The requisite hydroxyl group could be derived from an iodide. This intermediate could in turn be prepared by an iodocyclization reaction of the appropriate olefinic isothiourea, which we have shown to proceed with excellent diastereoselectivity and yield.[7] This disconnection greatly simplifies the

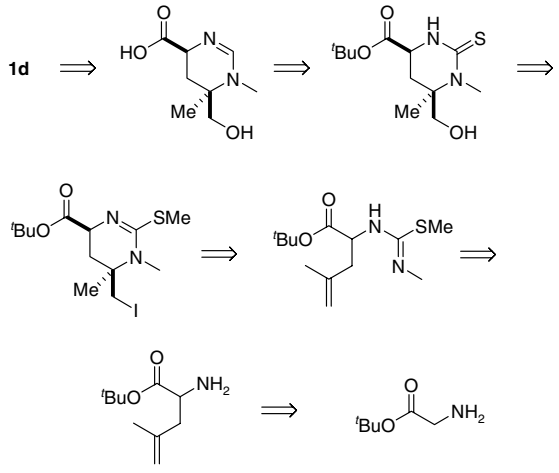


Figure 2. Retrosynthesis of Manzacidin D.

Keywords: Manzacidin; Iodocyclization; Isothiourea; Thiourea; Formamidine.
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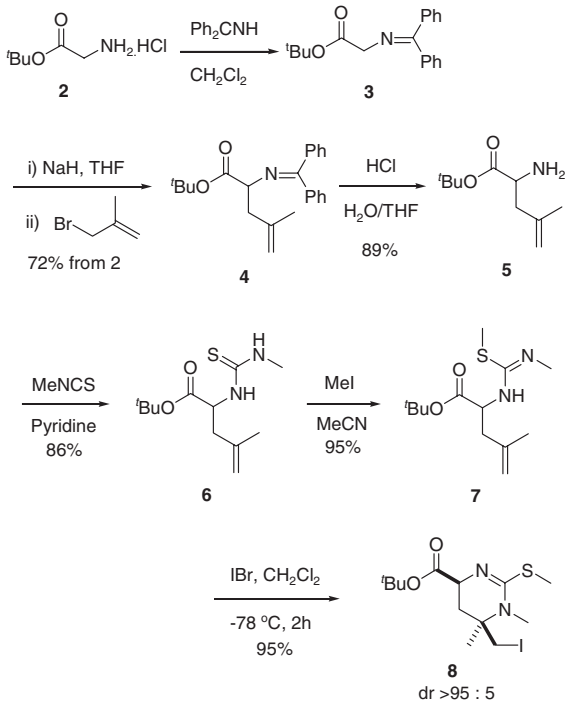
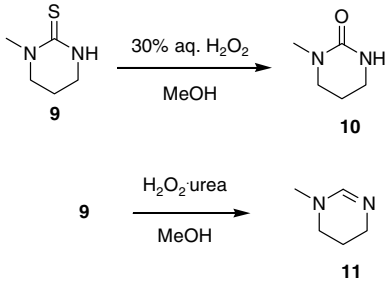


Scheme 1.

synthesis, since the acyclic isothiourea can be derived from an allylated glycine ester. This intermediate can be prepared from a glycine ester.

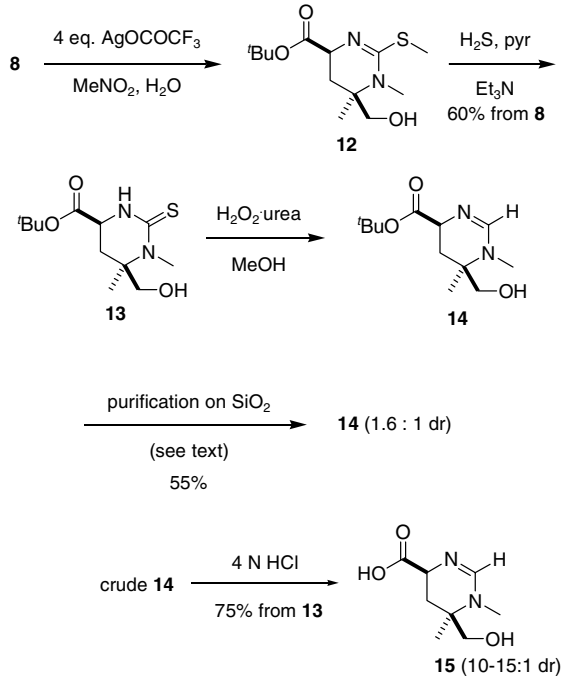
Synthesis of the cyclic isothiourea **8** is presented in Scheme 1. Protection of glycine *t*-butyl ester hydrochloride **2** as its benzophenone imine and alkylation with methallyl bromide affords the alkylated imine **4**, in good yield over two steps.[8] Acid mediated deprotection of the imine is potentially complicated by the sensitivity of the *t*-butyl ester to hydrolysis and of the olefin moiety to potential isomerization; however, we found that exposure of **4** to aqueous acid at 0 °C for 5 min gave an excellent yield of amine **5**. Conversion of amine **5** to thiourea **6** proceeded smoothly using methyl isothiocyanate. Preparation of isothiourea **7** proceeded in virtually quantitative yield, and cyclization of this compound using our procedure afforded **8** in excellent yield with high diastereocontrol. The diastereoselectivity was assessed as greater than 95:5 by analysis of the crude reaction mixture by 400 MHz ^{1}H NMR. The stereochemistry of the iodocyclization product was confirmed by NOESY analysis; cross-peaks were seen between the methyl group of the newly-formed quaternary centre and the proton α to the carbonyl, both of which take up pseudoaxial positions in the ring.

The key remaining challenge in our synthesis involved conversion of the isothiourea to a formamidine. We first investigated metal-promoted reductions, since we envisioned this would be a facile process.[9,10] To our dismay, in no experiments were we able to successfully carry out the transformation on either model substrates, or for cyclic isothioureas closer to our required substrate. In general, reactions were extremely sluggish, affording only starting material or slow hydrolysis even upon refluxing. We turned our attention to a reaction that has been studied only sporadically,[11] desulfurization of a thiourea (which we would generate from an isothiourea) under oxidative conditions, to accomplish overall conversion of isothiourea to formamidine in two steps. Yields quoted in the literature for this synthetic method are highly variable, and transformation of the corresponding six-membered ring substrate has not been reported.[12] In the event, exposure of tetrahydropyrimidinethione **9** to aqueous peroxide afforded only the hydrolysis product tetrahydropyrimidinone **10** (Scheme 2). By contrast, employing urea hydrogen peroxide adduct affords the desired tetrahydropyrimidine **11** cleanly as the only product observed by NMR.



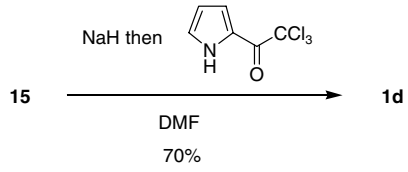
Scheme 2.

Having established a reasonable plan for installing the formamidine unit, we proceeded to test it in our synthesis (Scheme 3). In previous studies we had found that solvolysis of an iodide differing only from **8** by the absence of the N-methyl group proceeded readily with one



Scheme 3.

equivalent of silver trifluoroacetate.[7] By contrast, **8** underwent slow reaction, and required 16 h and 4 equiv of silver salt to drive the reaction. Furthermore, **12** was not stable upon storage, and needed to be used immediately. Treatment of **12** with hydrogen sulfide under basic conditions regenerated thiourea **13**. Exposure of **13** to our developed conditions afforded **14**, which showed less than 5% epimerization by crude ^{1}H NMR analysis. This is the first demonstration of this reaction in a synthetic sequence with so high a degree of complexity. Upon purification on SiO_2, however, **14** was isolated as a 1.6:1 mixture of diastereomers. It should be noted that ammonia was required as an additive to the eluent to elute this highly polar compound, and it is possible that this basic environment led to the epimerization of the stereocentre α to the carbonyl. Due to the crucial importance of reducing the acidity at this position, we decided to deprotect the crude ester; once formed, the resultant zwitterion **15** should thus have no mechanism to epimerize. In the event, **15** was isolated in 75% yield over two steps from **13** following ion exchange chromatography, with a minimal amount of epimerization. The diastereomeric purity of **15** varied somewhat between different reactions, but was always in the range of 10–15 to 1.



Scheme 4.

With our requisite amidino-alcohol **15** in hand, we expected conversion to manzacidin D to proceed in straightforward fashion. Indeed, this proved to be the case (Scheme 4). Using conditions slightly modified from those of Ohfune and co-workers,[13] we obtained manzacidin D **1d** in good yield following ion exchange and preparative HPLC. Manzacidin D has been stored for five months at 4 °C as its TFA salt without significant decomposition.

In summary, we have devised an efficient synthesis of manzacidin D, with an average yield per step above 80%. This route allowed facile preparation of sufficient material for biological screening against new targets. Perhaps more importantly, the route is sufficiently flexible to allow preparation of various analogues of manzacidin D for biological testing. Both of these opportunities are currently being explored, and we will report our results in due course.

Acknowledgements

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12. Imidazoline has been prepared in 53% yield from imidazolidine-2-thione, along with 15% hydrolysis by-product 2-imidazolidone; see Ref. 11c.
13. The equivalents of NaH (60% dispersion in mineral oil) and trichloromethyl ketone were increased to 3.0 and 3.2, respectively, and the compound was purified by ion exchange (Dowex 50×4, 100–200 mesh, H^+ form, elution with H_2O then 1 M aq NH_4OH).