

An Efficient Asymmetric Synthesis of
Manzacidin C

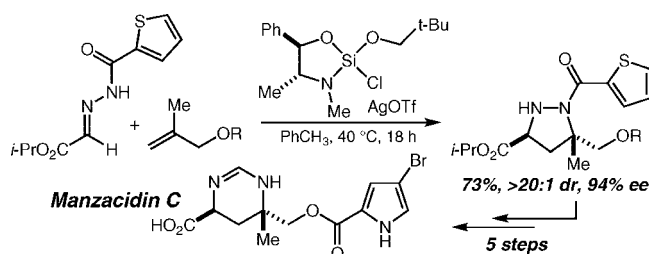
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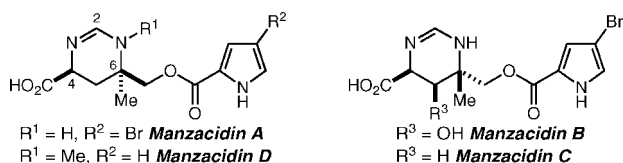
ABSTRACT



A brief synthesis of manzacidin C based on a chiral silane-promoted diastereo- and enantioselective acylhydrazone-alkene [3 + 2] cycloaddition reaction has been achieved. This synthesis is the first synthesis of any of the manzacidins wherein the C(4) and C(6) stereocenters are established in a single highly stereoselective step.

In 1991 Kobayashi and co-workers reported the isolation of manzacidins A, B, and C,¹ bromopyrrole alkaloids possessing an unusual 3,4,5,6-tetrahydropyrimidine ring, and in 1997, the isolation of manzacidin D, the debromo-*N*-methyl derivative of manzacidin A was reported (Scheme 1).² Because of the scarcity of these compounds, their full

Scheme 1



pharmacological profiles initially proved difficult to establish, but it has been shown that they possess activity as α -adrenoceptor blockers, antagonists of serotonergic receptors, and actomyosin ATPase activators.³

Because of their unusual structures and a desire to obtain significant quantities of them for more comprehensive biological profiling, the manzacidins have proven to be popular synthetic targets.⁴ Ohfuné reported syntheses of

manzacidin A and C that served to confirm the relative and establish the absolute stereochemistry of these compounds.⁵ There have been several additional syntheses of manzacidins A,⁶ C,^{5,7} and D,⁸ and very recently the first synthesis of manzacidin B was achieved that revised and established its relative and absolute stereostructure.⁹

Our interest in the synthesis of the manzacidins was elicited (1) by the observation that in none of the reported syntheses were the C(4) and C(6) stereocenters both estab-

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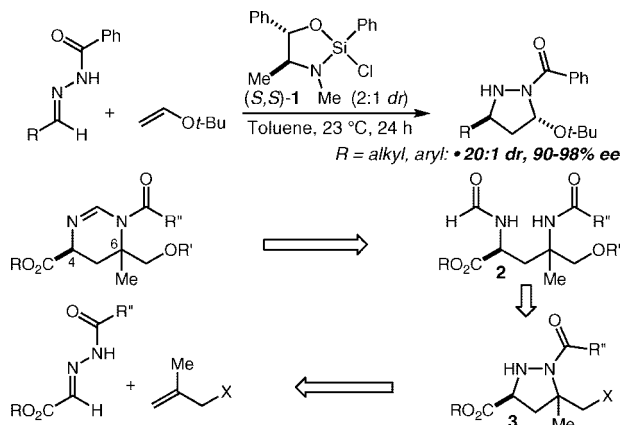
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lished in a single, experimentally straightforward, and diastereo- and enantioselective step and (2) by the possibility to accomplish exactly that suggested by our recently reported chiral silane Lewis acid (**1**) promoted acylhydrazone-enol ether [3 + 2] cycloaddition methodology (Scheme 2).¹⁰

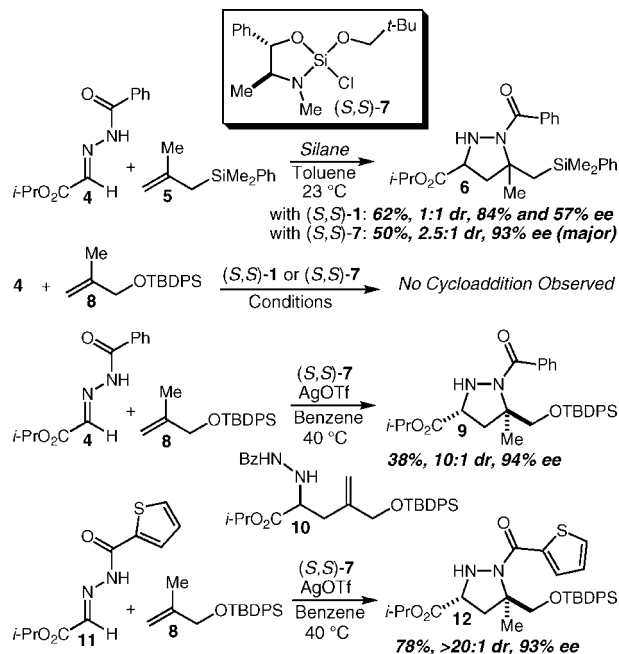
Scheme 2



Retrosynthetic analysis along these lines led in a straightforward fashion to diamide **2** and then to pyrazolidine **3**, which would arise from a cycloaddition between a glyoxylate-derived hydrazone and a methallyl alcohol ether or synthetic equivalent. It should be noted that the Maruoka^{6b} and Sibi^{6d} syntheses employ conceptually related enantioselective diazoester-methacrolein/methacrylate [3 + 2] cycloaddition reactions. While these reactions do establish the C(6) stereocenter, the C(4) stereocenter is established in a subsequent operation that is only moderately diastereoselective.

At the outset it seemed likely that methallylsilane derivatives (Scheme 2, X = SiR₃) might possess the requisite reactivity to engage in the [3 + 2] cycloaddition reaction, while also providing a functional equivalent for the requisite alcohol by way of a Tamao oxidation. Indeed, silane **1** was found to promote cycloaddition between hydrazone **4** and methallylsilane **5** to give **6** with promising enantioselectivity, albeit with no diastereoselectivity (Scheme 3). Our recently reported second-generation silane **7**¹¹ promoted the same reaction with at least measurable diastereoselectivity and excellent enantioselectivity (93% ee) for the major diastereomer.¹² Before taking on the optimization of these cycloadditions we became enamored of the idea that we might develop an effective cycloaddition using a simple methallyl alcohol as the dipolarophile. Such a cycloaddition would be “ideal” in that both stereocenters would be set in a single reaction, with every relevant carbon atom in the correct oxidation state, requiring no further manipulations other than a final global deprotection. In line with our expectations, however, treatment of hydrazone **4** with *tert*-

Scheme 3



butyldiphenylsilyl (TBDPS) methallyl alcohol (**8**) and silane **1** or **7** under a variety of conditions gave no cycloaddition product. In an effort to increase the activity of the silane Lewis acids, preactivation with AgOTf was considered, and indeed, treatment of (S,S)-**7** with AgOTf led to a Lewis acid that successfully promoted the reaction of **4** with **8** to give **9** in 38% yield and 94% ee (Scheme 3). Examination of the reaction mixture revealed the presence of at least one other product that was produced in significant (~20%) amounts: ene product **10**. Assuming a stepwise mechanism,¹³ this observation suggested that after initial attack of the alkene on the silane–hydrazone complex, the resulting carbocation partitions between ring closure to give **9** and elimination to give **10**. It seemed plausible in turn that modification of the benzoylhydrazone to a more electron-rich aroylhydrazone would increase the rate of ring closure while not impacting the rate of elimination. Gratifyingly, this line of reasoning led to the use of thienylhydrazone **11**, which upon cycloaddition with **8** and (S,S)-**7**/AgOTf gave **12** as a single diastereomer in 78% yield and 93% ee.

It will be noted that **12** is the opposite enantiomer to that required for a synthesis of manzacidin C.¹⁴ Indeed, the relative and absolute stereochemistry of **12** (and of **9**) was assigned by its conversion to *ent*-manzacidin C by the route described below. The cycloaddition of **11** and **8** was therefore carried out with the enantiomeric silane (R,R)-**7** and AgOTf to provide *ent*-**12** in 73% yield as a single diastereomer in

(13) We have established a stepwise mechanism for the acylhydrazone-enol ether cycloaddition reaction. See ref 10.

(14) This result was unexpected and is a reversal of the absolute sense of induction observed when hydrazone **4** is engaged in Friedel–Crafts reactions (see : Shirakawa, S.; Berger, R.; Leighton, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 2858). The mechanistic basis for this reversal, possibly associated with the use of AgOTf, is under investigation.

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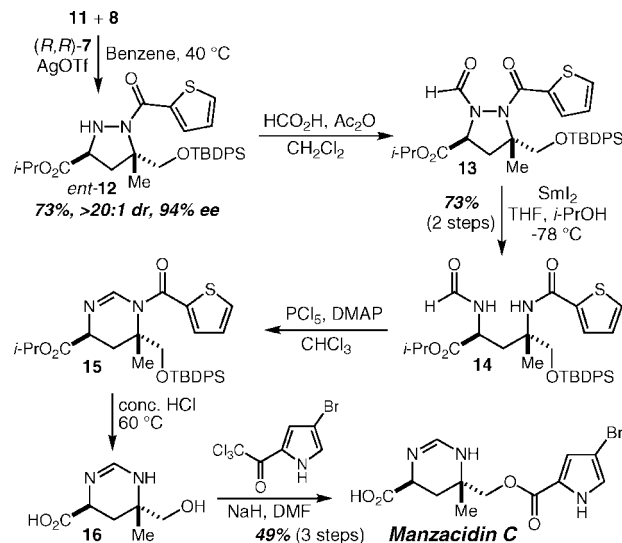
(12) The relative and absolute stereochemistry of the diastereomers of **6** has not been rigorously established.

94% ee (Scheme 4). Formylation of hydrazide *ent*-**12** proceeded smoothly to give **13** and provided the final carbon atom for the synthesis of the tetrahydropyrimidine ring. Hydrazide reduction with SmI₂ was straightforward and gave bisamide **14** in 73% yield over two steps. The task of devising a dehydrative cyclization of **14** proved nontrivial and required extensive screening of dehydrating agents, bases, and reaction conditions.¹⁵ Among the problems encountered were a propensity for epimerization of the C(4) stereocenter, cyclization onto the thienyl amide instead of the formamide, and instability of the desired product to silica gel chromatography. Eventually it was found that the combination of PCl₅ and 4-dimethylaminopyridine (DMAP) in CHCl₃ was effective in promoting the desired cyclization with minimal epimerization to give **15**. Subjection of **15** directly to global deprotection with concentrated HCl gave **16** and was followed by installation of the bromopyrrole side chain according to the procedure of Ohfuné⁵ to give manzacidin C in 49% yield over the three-step sequence from **14**. Full spectral comparison (¹H and ¹³C NMR, IR, MS, optical rotation) confirmed the identity of our synthetic material.

A brief, efficient, and stereocontrolled synthesis of manzacidin C has been achieved (6 steps from **11** and **8** in 26% overall yield). The synthesis inspired the discovery that the AgOTf-modified silane **7** has significantly greater activity, which in turn led to a significant expansion in the scope of our acylhydrazone-alkene [3 + 2] cycloaddition and made possible the cycloaddition between **11** and **8**, a reaction that establishes both stereocenters of the target in a single highly diastereo- and enantioselective step.

(15) A similar cyclization was carried out by Du Bois and Wehn, and they describe similar observations. See ref 6a.

Scheme 4



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Supporting Information Available: Experimental procedures, characterization data, and stereochemical proofs. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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