Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 2881–2883

TETRAHEDRON LETTERS

Diastereoselective isothiourea iodocyclization for manzacidin synthesis

Jacqueline C. S. Woo and D. Bruce MacKay*

Merck Frosst Centre for Therapeutic Research, 16711 TransCanada Highway, Kirkland, QC, Canada H9H 3L1

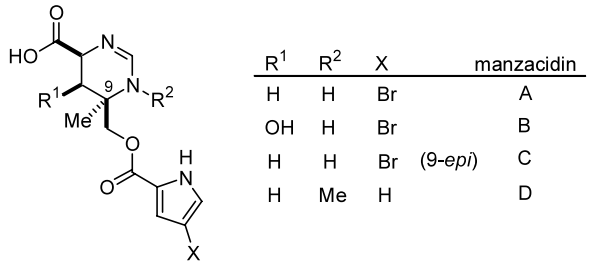
Received 10 December 2002; revised 14 February 2003; accepted 14 February 2003

Abstract—We have devised a novel strategy for the total synthesis of the manzacidins. Our approach utilizes an isothiourea iodocyclization strategy to directly form the heterocyclic core, and in the process induce stereoselectivity at the quaternary center. We have found that cyclization can be achieved using an isothiourea as the nucleophilic partner. Cyclization proceeds smoothly using IBr at low temperature, affording an advanced intermediate along our proposed route to manzacidin A in 92% yield. We have demonstrated the scope of the reaction by preparing several cyclic isothioureas, including an intermediate on our proposed route for the synthesis of manzacidin D.

Iodocyclizations of olefins with a wide variety of functional groups have been extensively studied.[1] Cyclizations involving carboxylic acids, carbonates and alcohols in particular have been widely used in natural product synthesis. By contrast, few examples of electrophilic cyclizations between olefins and isothioureas[2] or amidines[3] have been reported in the literature. Iodocyclizations in general often afford excellent diastereocontrol, but this had not yet been studied for isothioureas, prior to this work. We felt that this reaction would be ideally suited for synthesis of the manzacidins.

The manzacidins are a class of alkaloids having a novel cyclic amidine core (Fig. 1). Manzacidins A, B and C were isolated from the Okinawan sponge *Hymeniacidon* sp.,[4] while manzacidin D was isolated from the coralline demosponge *Astrosclera willeyana*.[5] Three of the four manzacidins contain a bromopyrrole residue. Manzacidins A and C, epimers at C-9, have been synthesized by Ohfune and co-workers,[6] and by Wehn and Du Bois,[7] while manzacidins B and D have not yet been synthesized.

Our retrosynthetic analysis is depicted in Figure 2. The bromopyrrole carboxylate was envisioned to be installed last in the synthesis by a straightforward esterification reaction, as had been done by Ohfune and co-workers. The requisite hydroxyl group could be derived from a halide. The formamidine unit could be



R^1	R^2	X		manzacidin
H	H	Br		A
OH	H	Br		B
H	H	Br	(9-*epi*)	C
H	Me	H		D

Figure 1. The manzacidins.

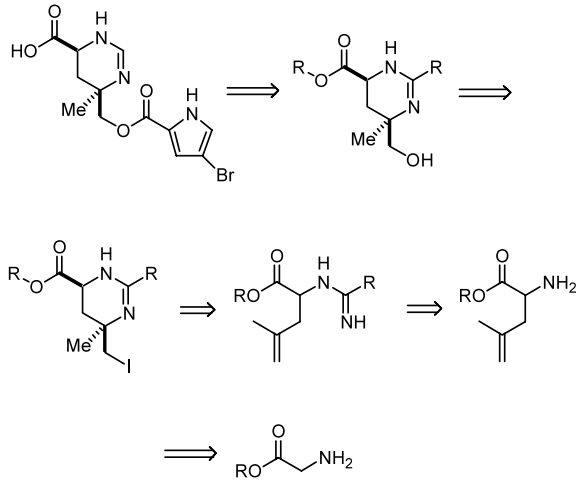


Figure 2. Retrosynthesis of manzacidin A.

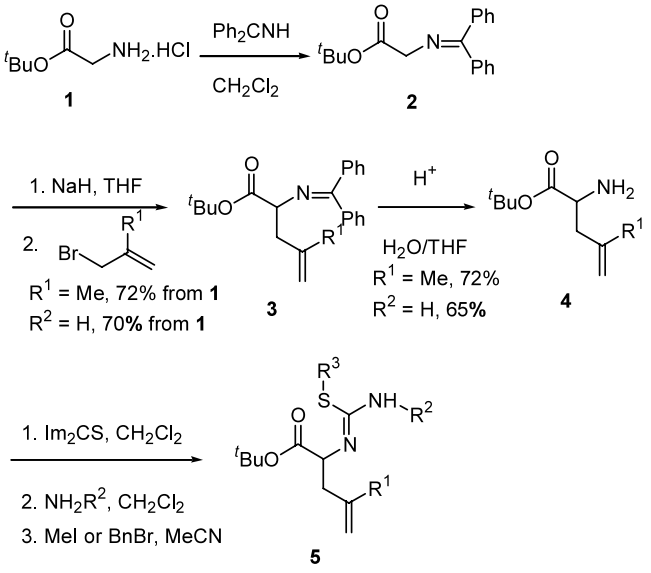
* Corresponding author.

0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)00431-3

derived from a suitable precursor. In practice, a methyl isothiourea was chosen for this position. The key to our retrosynthesis is to construct this intermediate via a iodocyclization of the olefin precursor. We felt that such a cyclization would prove highly stereoselective, given ample literature precedent employing related functional groups such as carbamates and carbonates.[1a] A second advantage of this disconnection is that it simplifies the synthesis, since the cyclization precursor can be prepared by alkylation of a protected glycine.

Synthesis of the amine precursor was performed in straightforward fashion as shown in Scheme 1. Commercial glycine *tert*-butyl ester hydrochloride **1** was protected as its benzophenone imine derivative **2**. Alkylation proceeded smoothly in good yield over two steps.[8] Deprotection of the benzophenone imine was potentially problematic due to the sensitivity of the *gem*-disubstituted olefin as well as the *tert*-butyl ester to acid, but conditions were found where selective deprotection to **4** occurred (HCl, THF/H_2O, 0°C, 5 min). Isothiourea cyclization substrates **5** were prepared easily from **4** according to literature procedure (Table 1).[9]

With the requisite substrates in hand, we next turned our attention to the key iodocyclization. We first investigated the cyclization of isothiourea substrate **5a**, which proved facile under a variety of conditions (Table 2). Cyclization of **5a** proceeded readily using iodine (entries 1–4) with moderate stereoselectivity.

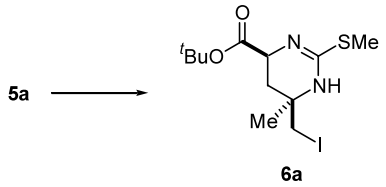


Scheme 1.

Table 1. Preparation of isothioureas

Compound	R^1	R^2	R^3	Yield (%) from **4**
5a	Me	H	Me	66
5b	Me	H	Bn	34
5c	H	H	Me	67
5d	Me	Me	Me	35

Table 2. Iodocyclization of alkenyl isothiourea **5a**[a]



Entry	Reagent(s)	Temp. (°C), time	Yield% (d.r.)[b]
1	I_2	rt, 1.5 h	78 (9:1)
2	I_2, pyridine[c]	rt, 3.5 h	77 (9:1)
3	I_2	0, 16 h	85 (9:1)
4	I_2, MeCN	0, 16 h	82 (5:1)
5	NIS	rt, 16 h	80 (8:1)
6	IBr	rt, 10 min	91 (9:1)
7	IBr	0, 1.5 h	95 (11:1)
8	IBr	−78, 2 h	95 (>20:1)
9	IBr, toluene	−78, 16 h	Incomplete reaction
10	ICl	−78, 2 h	87 (7:1)

[a] Except where noted, all cyclizations were performed in CH_2Cl_2, using 1.5 equiv. of iodinating reagent.
[b] Diastereomeric ratios were determined by 400 MHz NMR of crude reaction mixtures.
[c] 10 equiv. pyridine in CH_2Cl_2 were used.

Addition of pyridine had been reported for cyclization of primary thioureas,[2] but in this system, its only effect was to retard the rate of product formation (entry 2). Use of MeCN instead of CH_2Cl_2 (entry 4) gave lower stereoselectivity and a longer reaction time. The greater reactivity of IBr and ICl allowed reactions to be performed at −78°C (entries 7–10). Optimized conditions with IBr at −78°C in CH_2Cl_2 (entry 8) gave excellent yield and diastereoselectivity.

We propose that the observed diastereoselectivity can be rationalized by considering a chair-like transition state for attack on the iodonium ion, where the ester and iodonium ion sit in a *pseudo*-equatorial position, and the methyl group is oriented *pseudo*-axially (Fig. 3). Similar models have been proposed to explain allylic and homoallylic induction for iodocyclization of thioimidates.[10]

Having established optimal conditions for cyclization, we decided to examine the scope of this transformation with substrates **5b–d** (Scheme 2). Cyclization again proceeded readily for all three substrates. Substitution of a benzyl group at sulfur for substrate **5b** did not affect the stereoselectivity, but proceeded in lower yield. Reducing the nucleophilicity of the olefin by employing a terminal olefin in substrate **5c** did not impede cyclization. Finally, substitution on nitrogen is tolerated by

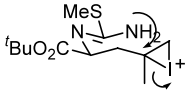
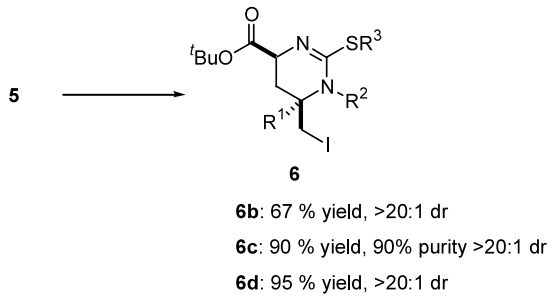


Figure 3. Proposed transition state.

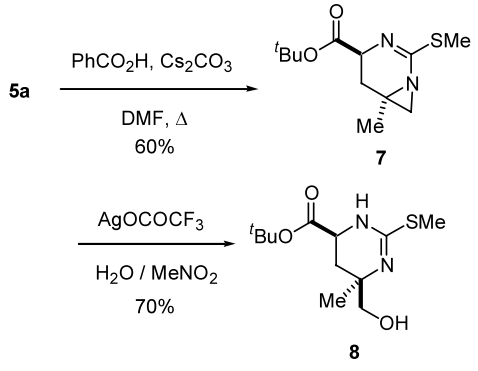


Scheme 2.

the reaction, giving substituted cyclic isothiourea **6d**, in excellent yield and diastereoselectivity. We were particularly gratified by this result, since we envisage that **6d** can be converted to manzacidin D.

The following procedure is typical for the cyclization experiments: To a 0.1 M solution of isothiourea in CH_2Cl_2 at −78°C was added IBr (1.5 equiv.). The flask was wrapped with foil, and stirred in the dark at −78°C for 2 h. The solution was warmed to rt, washed with 1N NaOH and two portions H_2O. The organic phase was dried over Na_2SO_4, filtered and concentrated in vacuo. The purity and diastereomeric ratio were assessed by 400 MHz ^1H NMR. Except where noted, the product was >95% pure. The compounds prepared in this study were found to be somewhat unstable upon storage for several days, and characterization needed to be completed immediately upon preparation.

Finally, conversion of the iodide to a functional group suitable for our synthesis was investigated (Scheme 3). Considering the ester linkage of the manzacidins, we attempted displacement with benzoate, as a model for the bromopyrrole carboxylate. To our surprise, however, intramolecular attack predominated, affording the bicyclic product **7**, along with recovered **5a**. This ring system has not been previously observed, and warrants further study, although we chose not to pursue its



Scheme 3.

conversion to manzacidin A. Solvolysis promoted by silver salts afforded alcohol **8**.

In conclusion, we have succeeded in forming the core ring system of manzacidins A and D using a diastereoselective isothiourea cyclization. We are currently investigating the conversion of compound **8** to manzacidin A, conversion of **6d** to manzacidin D, and the chemistry of the novel ring system of **7**, and we will report our results in due course.

Acknowledgements

The authors thank Merck Frosst Centre for Therapeutic Research for support of this work. J.C.S.W. thanks NSERC for generous financial support. We thank Dr. Yves Gareau (Merck Frosst) for helpful discussion.

References

1. For a recent two-part review of iodocyclization, see: (a) Frederickson, M.; Grigg, R. *Org. Prep. Proc. Intl.* **1997**, *29*, 33; (b) ibid, p. 63.
2. Creeke, P. I.; Mellor, J. M. *Tetrahedron Lett.* **1989**, *30*, 4435.
3. For examples of cyclizations of amidines mediated by: (a) acid, see: Partridge, M. A.; Smith, A. *J. Chem. Soc., Perkin 1* **1973**, 453; (b) electrophilic halogen sources, see: (i) Hunt, P. A.; May, C.; Moody, C. J. *Tetrahedron Lett.* **1988**, *29*, 3001; (ii) Ershova, I. I.; Yu, I.; Staninets, V. I. *Ukr. Khim. Zh.* **1977**, *43*, 884; (iii) Chern, J.-W.; Shiau, C.-Y.; Lu, G.-Y. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 571; (c) electrophilic selenium sources, see: Engman, L. *J. Org. Chem.* **1993**, *58*, 2394.
4. Kobayashi, J.; Kanda, F.; Ishibashi, M.; Shigemori, H. *J. Org. Chem.* **1991**, *56*, 4574.
5. Jahn, T.; Konig, G. M.; Wright, A. D. *Tetrahedron Lett.* **1997**, *38*, 3883.
6. Namba, K.; Shinada, T.; Teramoto, T.; Ohfune, Y. *J. Am. Chem. Soc.* **2000**, *122*, 10708.
7. Wehn, P. M.; Du Bois, J. *J. Am. Chem. Soc.* **2002**, *124*, 12950.
8. Note that this transformation can also be carried out enantioselectively using a chiral phase transfer catalyst, see: Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 6519.
9. (a) Moynihan, H. A.; Roberts, S. M.; Weldon, H.; Allcock, G. H.; Anggard, E. E.; Warner, T. D. *J. Chem. Soc., Perkin Trans. 1* **1994**, 769; (b) Esser, F.; Pook, K.-H.; Carpy, A.; Leger, J.-M. *Synthesis* **1994**, 77.
10. Takahata, H.; Takamatsu, T.; Yamazaki, T. *J. Org. Chem.* **1989**, *54*, 4812. See also: Takahata, H.; Takamatsu, T.; Chen, Y.-S.; Ohkubo, N.; Yamazaki, T.; Momose, T. *J. Org. Chem.* **1990**, *55*, 3792 and references cited therein.