# Stereocontrolled Synthesis of the Northern Part of Potent Proteasome Inhibitor TMC-95A

# LETTERS 2001 Vol. 3, No. 18 2863–2865

ORGANIC

## Masayuki Inoue, Hidetomo Furuyama, Hayato Sakazaki, and Masahiro Hirama\*

Department of Chemistry, Graduate School of Science, Tohoku University, and CREST, Japan Science and Technology Corporation (JST), Sendai 980-8578, Japan

hirama@ykbsc.chem.tohoku.ac.jp

Received June 20, 2001

### ABSTRACT



A protected version of the northern part of TMC-95A, a potent and selective proteasome inhibitor, was synthesized with full stereochemical control. Highlights of this synthesis include (i) a (Z)-selective Mizoroki–Heck reaction to construct the oxyindole portion, (ii) a diastereoselective epoxidation, (iii) a 6-endo selective epoxide opening by Boc carbonyl group to establish the stereochemistry of C6, and (iv) a 1,3-elimination reaction of the L-*allo*-threonine derivative under Mitsunobu conditions to afford the (Z)-1-propenylamine.

TMC-95A (**1**, Scheme 1) has been isolated from the fermentation broth of *Apiospora montagnei* Sacc. TC 1093,



which was derived from soil samples.<sup>1</sup> Despite the structural dissimilarity between **1** and other known inhibitors such as lactacystin,<sup>2</sup> epoxomicin,<sup>3</sup> other TMC series,<sup>4</sup> and peptide-derived molecules,<sup>5</sup> studies have shown that **1** can specifically inhibit 20S proteasome,<sup>1b</sup> the catalytic core of proteasome.<sup>6</sup> Thus, **1** may provide a unique insight into

(2) (a) Omura, S.; Fujimoto, T.; Otoguro, K.; Matsuzaki, K.; Moriguchi, R.; Tanaka, H.; Sasaki, Y. J. Antibiot. **1991**, 44, 113. (b) Fenteany, G.; Schreiber, S. L. J. Biol. Chem. **1998**, 273, 8545 and references therein.

(3) (a) Hanada, M.; Sugawara, K.; Kaneta, K.; Toda, S.; Nishiyama, Y.; Tomita, K.; Yamamoto, H.; Konishi, M.; Oki, T. *J. Antibiot.* **1992**, *45*, 1746. (b) Groll, M.; Kim, K. B.; Kairies, N.; Huber, R.; Crews, C. M. J. *Am. Chem. Soc.* **2000**, *122*, 1237 and references therein.

(4) TMC-86A, B and TMC-96: (a) Koguchi, Y.; Kohno, J.; Suzuki, S.i.; Nishio, M.; Takahashi, K.; Ohnuki, T.; Komatsubara, S. J. Antibiot. **1999**, 52, 1069. (b) Koguchi, Y.; Kohno, J.; Suzuki, S.-i.; Nishio, M.; Takahashi, K.; Ohnuki, T.; Komatsubara, S. J. Antibiot. **2000**, 53, 63. TMC-89A and B: (c) Koguchi, Y.; Nishio, M.; Suzuki, S.-i.; Takahashi, K.; Ohnuki, T.; Komatsubara, S. J. Antibiot. **2000**, 53, 967.

(5) For a recent review on proteasome inhibitors, see: Myung, J.; Kim, K. B.; Crews, C. M. *Med. Res. Rev.* **2001**, *21*, 245.

(6) For reviews on the biology of proteasomes, see: (a) Tanaka, K. J. Biochem. **1998**, *123*, 195. (b) Ciechanover, A. EMBO J. **1998**, *17*, 7151.

 <sup>(1) (</sup>a) Kohno, J.; Koguchi, Y.; Nishio, M.; Nakao, K.; Kuroda, M.;
Shimizu, R.; Ohnuki, T.; Komatsubara, S. J. Org. Chem. 2000, 65, 990.
(b) Koguchi, Y.; Kohno, J.; Nishio, M.; Takahashi, K.; Okuda, T.; Ohnuki,
T.; Komatsubara, S. J. Antibiot. 2000, 53, 105.

understanding the detailed biological function of proteasomes. Furthermore, proteasomes play important roles in the activation of NF- $\kappa$ B<sup>7</sup> and the processing of histocompatibility complex (MHC) class I ligands,<sup>8</sup> both of which are involved in mounting inflammatory immune responses, thus suggesting the use of TMC-95A and its analogues as potential antiinflammatory agents for treating autoimmune diseases. Notable structural features of **1** are the axially chiral biaryl group, the highly oxidized tryptophan, and the (*Z*)-1propenylamine in the macrocyclic matrix. The biological importance, as well as the unique architecture, prompted us to undertake the total synthesis of **1**.<sup>9</sup> Here we report the stereocontrolled synthesis of a protected version of the northern part of **1**.

As outlined in Scheme 1, the structure of 1 can be retrosynthetically divided into two fragments that could be reassembled to the macrocyclic structure by a peptide bond formation and a Pd(0)-catalyzed biaryl coupling.<sup>9a-c,10</sup> The northern part can be further dissected so that the (*Z*)-1-propenylamine portion could be prepared by the decarboxy-lative 1,3-elimination of carboxylate **2**. The oxidized tryptophan moiety could be synthesized by the oxidation of **3**, which in turn could be prepared by an intramolecular Mizoroki–Heck reaction of dibromide **4**.<sup>11</sup>

As shown in Scheme 2, DIBAL reduction followed by Wittig reaction of a known ester **5**, which was derived from D-serine,<sup>12</sup> afforded  $\alpha,\beta$ -unsaturated ester **6** in 71% overall yield.<sup>13</sup> Amidation of the ester **6** with 2,6-dibromoaniline in the presence of Me<sub>3</sub>Al resulted in **7** (59% yield),<sup>14</sup> followed by protection of the N22-amide with a Boc group to produce **8** in 88% yield. After numerous conditions were screened, intramolecular Mizoroki–Heck reaction of **8** was reliably and reproducibly carried out at room temperature,<sup>15</sup> employing "ligandless" conditions<sup>16</sup> that involved a catalytic amount of Pd<sub>2</sub>(dba)<sub>3</sub> in the presence of Et<sub>3</sub>N, to afford the trisubstituted olefin **9** in 86% yield (*Z*:*E* > 20:1).<sup>17</sup>

(7) Palombella, V. J.; Rando, O. J.; Goldberg, A. L. Maniatis, T. Cell **1994**, 78, 773.

(10) For recent reviews on biaryl synthesis, see: (a) Lloyd-Williams, P.; Giralt, E. *Chem. Soc. Rev.* **2001**, *30*, 145. (b) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263.

(11) For excellent reviews on Mizoroki-Heck reactions, see: (a) Link, J. T.; Overman, L. E. Intramolecular Heck Reactions in Natural Product Chemistry. In *Metal-catalyzed Cross-coupling Reactions*; Diedrich, F., Stang, P. J., Eds.; Wiley-VCH Verlag GmbH: Weihheim, 1998; pp 231–269. (b) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (c) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379.

(12) (a) Garner, P.; Park, J. M. J. Org. Chem. 1987, 52, 2361. (b) Garner, P.; Park, J. M. Org. Synth. 1992, 70, 18.

(13) The numbering of compounds in this paper corresponds to that of TMC-95A.

(16) Madin, A.; Overman, L. E. Tetrahedron Lett. 1992, 33, 4859.



<sup>*a*</sup> (a) DIBAL, toluene, -78 °C; (b) Ph<sub>3</sub>P=CH<sub>2</sub>CO<sub>2</sub>Me, CH<sub>2</sub>Cl<sub>2</sub>, 71% (2 steps); (c) 2,6-dibromoaniline, Me<sub>3</sub>Al, toluene; then **6**, 0 °C to rt, 59%; (d) (Boc)<sub>2</sub>O, Et<sub>3</sub>N, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, rt, 88%; (e) Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> (0.2 equiv), Et<sub>3</sub>N, THF–NMP (1:1), rt, 86%; (f) DMDO, CH<sub>2</sub>Cl<sub>2</sub>, rt; (g) BF<sub>3</sub>·Et<sub>2</sub>O (1.5 equiv), CH<sub>2</sub>Cl<sub>2</sub>, -78 to 0 °C, 87% (2 steps); (h) (+)-MTPACl, Et<sub>3</sub>N, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, rt, 98%; (i) BzCl, Et<sub>3</sub>N, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, rt, 83%.

As shown in Scheme 3, the (Z)-selectivity of this facile intramolecular cyclization can be explained by the *syn*insertion of the alkyl palladium into (*E*)-olefin ( $15 \rightarrow 16$ and/or 17), followed by bond rotation ( $16 \rightarrow 18$  and/or 17  $\rightarrow 19$ ), and *syn*-elimination of the C6-hydride to provide predominantly (Z)-oxyindole 9 (Scheme 3). The bulky Boc group protecting the N22-amide of 9 can explain the lack of further Pd(0)-insertion into the C1-bromide of 9, which would cause undesirable side reactions, and maintain the catalytic cycle.<sup>18</sup>

Having secured the route to the oxyindole **9**, the  $\alpha$ , $\beta$ unsaturated olefin was oxidized using 3,3-dimethyldioxirane (DMDO),<sup>19</sup> to yield epoxide **10** as a single diastereomer (Scheme 2). Interestingly, we discovered that activation of

<sup>(8)</sup> Rock, K. L.; Gramm, C.; Rothstein, L.; Clark, K.; Stein, R.; Dick, L.; Hwang, D.; Goldberg, A. L. *Cell* **1994**, *78*, 761.

<sup>(9)</sup> For synthetic studies on TMC-95 from other laboratories, see: (a) Lin, S.; Danishefsky, S. J. Angew. Chem., Int. Ed. **2001**, 40, 1967. (b) Albrecht, B. K.; Williams, R. M. Tetrahedron Lett. **2001**, 42, 2755. (c) Ma, D.; Wu, Q. Tetrahedron Lett. **2001**, 42, 5279. (d) Ma, D.; Wu, Q. Tetrahedron Lett. **2000**, 41, 9089.

<sup>(14) (</sup>a) Lipton, M. F.; Basha, A.; Weinreb, S. M.Org. Synth. **1980**, *59*, 49. (b) Overman, L. E.; Paone, D. V.; Stearns, B. A. J. Am. Chem. Soc. **1999**, *121*, 7702.

<sup>(15)</sup> Reaction temperature is crucial for the regioselectivity of this cyclization. For instance, the E/Z ratio of **9** was decreased to 3/1 when the reaction was conducted at 50 °C.

<sup>(17)</sup> While this paper was in preparation, we noticed that Lin and Danishefsky (see ref 9a) planned a similar route to this involving Heck cyclization of a closely related substrate.

<sup>(18)</sup> Macor, J. E.; Ogilvie, R. J.; Wythes, M. J. Tetrahedron Lett. 1996, 37, 4289.

<sup>(19)</sup> Danishefsky, S. J.; Bilodeau, M. T. Angew. Chem., Int. Ed. Engl. 1996, 35, 1380.



the epoxide of 10 with BF<sub>3</sub>·Et<sub>2</sub>O selectively provided a sixmembered carbamate 12 with a concomitant loss of the tertbutyl group in 87% yield (2 steps).<sup>20</sup> The observed selectivity was reasoned that, because of the electronic assistance of the aromatic group, the C6–O bond of 11 would be more susceptible to cleavage than the C7-O bond. The stereostructure of 12 was unambiguously assigned using the coupling constant ( $J_{H7,H8} = 10.0 \text{ Hz}$ ) and the observed NOE between H4 and H7. The results indicate that not only did the epoxidation selectively occur from the opposite side of the C8–NRBoc group of 9, but the resulting epoxide in 10 was opened via an S<sub>N</sub>2 pathway. The enantiomeric excess of 12 was calculated to be 94% after derivatization to its (+)-MTPA ester 13. For further synthetic manipulations, the secondary alcohol of 12 was protected as its benzoate ester to furnish 14 in 83% yield.

Before building the (*Z*)-1-propenylamine moiety, deprotection and oxidation of the C25-hydroxyl were necessary (Scheme 4). Thus, treatment of **14** in the presence of a catalytic amount of TfOH in CF<sub>3</sub>CH<sub>2</sub>OH simultaneously removed the acetonide and Boc groups and generated the desired alcohol **20** in 64% yield.<sup>21</sup> Oxidation of the alcohol **20** using catalytic CrO<sub>3</sub> and H<sub>3</sub>IO<sub>6</sub> as a reoxidant provided carboxylic acid **21**,<sup>22</sup> which was then coupled with L-*allo*threonine methyl ester **22** by the action of EDC and HOBt, resulting in amide **23** (60%, 2 steps). Subsequent saponification of methyl ester **23** led to  $\alpha$ -alkoxy carboxylic acid **24**. Upon treatment of **24** with Mitsunobu conditions (Ph<sub>3</sub>P,



<sup>*a*</sup> (a) TfOH (0.5 equiv), CF<sub>3</sub>CH<sub>2</sub>OH, 0 °C to rt, 64%; (b) CrO<sub>3</sub> (0.1 equiv), H<sub>5</sub>IO<sub>6</sub>, wet MeCN, 0 °C; (c) **22** (1.5 equiv), EDC, HOBt, NMM, DMF, 0 °C to rt, 60% (2 steps); (d) LiOH·H<sub>2</sub>O, THF-H<sub>2</sub>O (1:1), 0 °C; (e) DEAD, PPh<sub>3</sub>, THF, -78 °C to rt, 40% (2 steps).

DEAD), the decarboxylative 1,3-elimination proceeded smoothly,<sup>23</sup> presumably through **25**, to yield the protected northern part of TMC-95A (**26**) in 40% yield (2 steps).<sup>24</sup>

In conclusion, we have attained a highly stereocontrolled synthesis of **26** through (i) (*Z*)-selective Mizoroki–Heck reaction of dibromide **8** to construct the oxyindole portion, (ii) a diastereoselective epoxidation procedure  $(9 \rightarrow 10)$ , (iii) a 6-endo selective epoxide ring-opening reaction to establish the stereochemistry of C6 stereocenter  $(10 \rightarrow 12)$ , and (iv) a mild 1,3-elimination reaction of L-*allo*-threonine to build the (*Z*)-1-propenylamine ( $24 \rightarrow 26$ ). Further studies directed toward the total synthesis of TMC-95A, including derivatization of **26** to a suitable form for coupling with a southern part, are currently underway in our laboratory.

### OL016303V

<sup>(20)</sup> For a related approach for forming a six-membered carbamate, see: Urabe, H.; Aoyama, Y.; Sato, F. *Tetrahedron* **1992**, *48*, 5639.

<sup>(21) (</sup>a) Kobayashi, S.; Reddy, R. S.; Sugiura, Y.; Sasaki, D.; Miyagawa, N.; Hirama, M. J. Am. Chem. Soc. **2001**, *123*, 2887. (b) Holcombe, J. L.; Livinghouse, T. J. Org. Chem. **1986**, *51*, 111.

<sup>(22)</sup> Zhao, M.; Li, J.; Song, Z.; Desmond, R.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 5323.

<sup>(23)</sup> Pansare, S. V.; Vederas, J. C. J. Org. Chem. **1989**, 54, 2311. (24) Physical data of **26**:  $[\alpha]^{25}_{D} + 86.0$  (c 0.62, CHCl<sub>3</sub>); IR (film) 3280, 1741, 1672, 1621, 1264, 1107, 708 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  1.08 (3H, dd, J = 7.5, 1.5 Hz, H29), 4.72 (1H, dq, J = 9.0, 7.5 Hz, H28), 5.31 (1H, d, J = 9.5 Hz, H8), 6.02 (1H, d, J = 9.5 Hz, H7), 6.43 (1H, ddd, J = 10.5, 9.0, 1.5 Hz, H27), 6.96 (1H, s, amide-NH), 6.99 (1H, dd, J = 8.5, 7.5 Hz, H3), 7.36 (1H, dJ = 8.5 Hz, H4), 7.44 (2H, dd, J = 8.0, 7.5 Hz, Bz), 7.50 (1H, d, J = 7.5 Hz, H2), 7.59 (1H, t, J = 7.5 Hz, Bz), 7.93 (2H, d, J = 7.5 Hz, Bz), 8.83 (1H, d, J = 10.5 Hz, amide-NH), 9.57 (1H, s, amide-NH); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  10.7, 52.5, 66.5, 80.7, 103.9, 109.9, 120.8, 124.6, 125.1, 125.2, 127.8, 128.8, 130.0, 134.3, 134.6, 141.2, 151.4, 163.9, 165.2, 173.6; MALDI-TOF MS calcd for C<sub>22</sub>H<sub>19</sub>BrN<sub>3</sub>O<sub>6</sub> [M + H<sup>+</sup>] 500.0457, found 500.0433.