ORGANIC LETTERS

2001
Vol. 3, No. 18
2863−2865

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

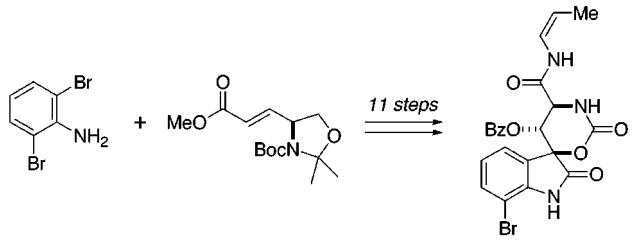
Masayuki Inoue, Hidetomo Furuyama, Hayato Sakazaki, and Masahiro Hirama*

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

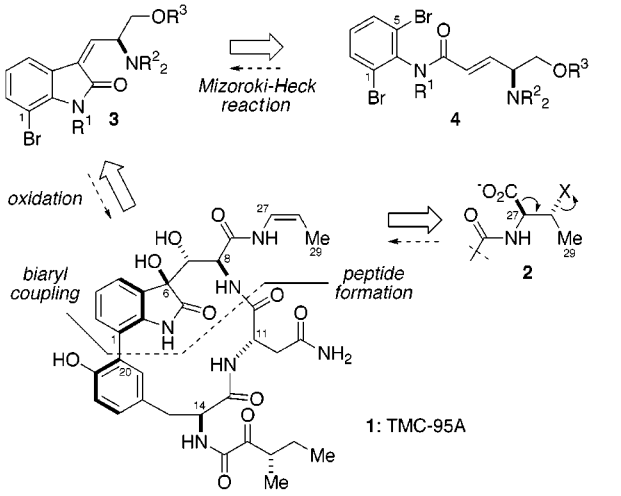
ABSTRACT



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

Scheme 1. Plan for Synthesis of TMC-95A



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(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.

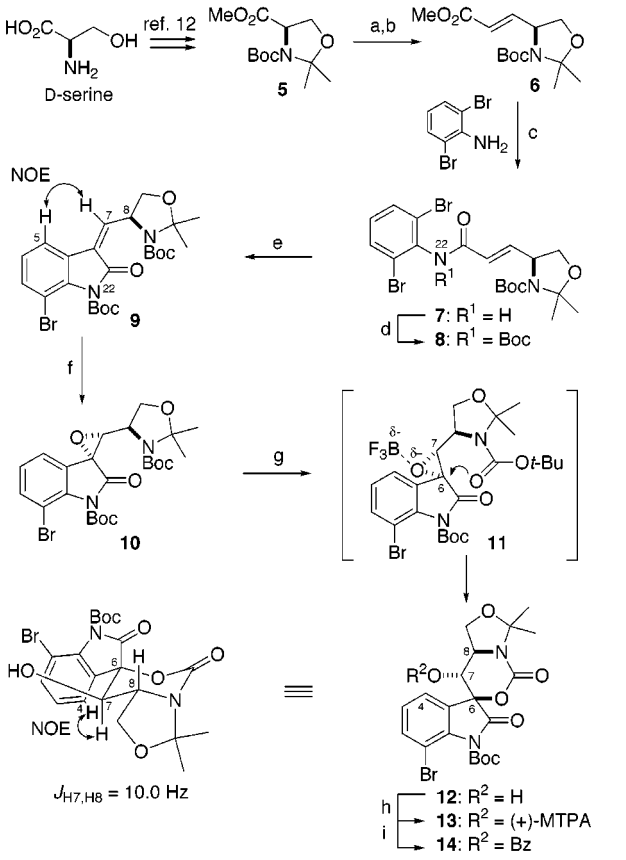
10.1021/ol016303v CCC: $20.00
Published on Web 08/11/2001

understanding the detailed biological function of proteasomes. Furthermore, proteasomes play important roles in the activation of NF-κB[7] and the processing of histocompatibility complex (MHC) class I ligands,[8] 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*)-1-propenylamine in the macrocyclic matrix. The biological importance, as well as the unique architecture, prompted us to undertake the total synthesis of **1**.[9] 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.[9a−c,10] The northern part can be further dissected so that the (*Z*)-1-propenylamine portion could be prepared by the decarboxylative 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**.[11]

As shown in Scheme 2, DIBAL reduction followed by Wittig reaction of a known ester **5**, which was derived from D-serine,[12] afforded α,β-unsaturated ester **6** in 71% overall yield.[13] Amidation of the ester **6** with 2,6-dibromoaniline in the presence of Me_3Al resulted in **7** (59% yield),[14] 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,[15] employing "ligandless" conditions[16] that involved a catalytic amount of $Pd_2(dba)_3$ in the presence of Et_3N, to afford the trisubstituted olefin **9** in 86% yield (*Z*:*E* > 20:1).[17]

Scheme 2[a]



[a] (a) DIBAL, toluene, −78 °C; (b) $Ph_3P{=}CH_2CO_2Me$, CH_2Cl_2, 71% (2 steps); (c) 2,6-dibromoaniline, Me_3Al, toluene; then **6**, 0 °C to rt, 59%; (d) $(Boc)_2O$, Et_3N, DMAP, CH_2Cl_2, rt, 88%; (e) $Pd_2(dba)_3{\cdot}CHCl_3$ (0.2 equiv), Et_3N, THF−NMP (1:1), rt, 86%; (f) DMDO, CH_2Cl_2, rt; (g) $BF_3{\cdot}Et_2O$ (1.5 equiv), CH_2Cl_2, −78 to 0 °C, 87% (2 steps); (h) (+)-MTPACl, Et_3N, DMAP, CH_2Cl_2, rt, 98%; (i) BzCl, Et_3N, DMAP, CH_2Cl_2, 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** → **16** and/or **17**), followed by bond rotation (**16** → **18** and/or **17** → **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.[18]

Having secured the route to the oxyindole **9**, the α,β-unsaturated olefin was oxidized using 3,3-dimethyldioxirane (DMDO),[19] to yield epoxide **10** as a single diastereomer (Scheme 2). Interestingly, we discovered that activation of

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

(14) (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.

(15) 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.

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

(17) 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.

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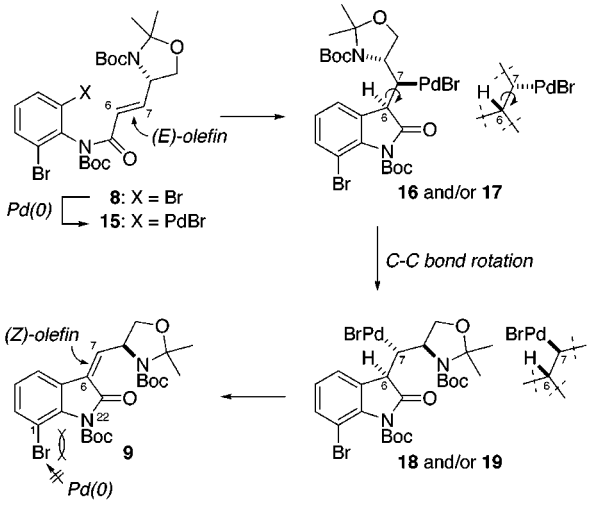
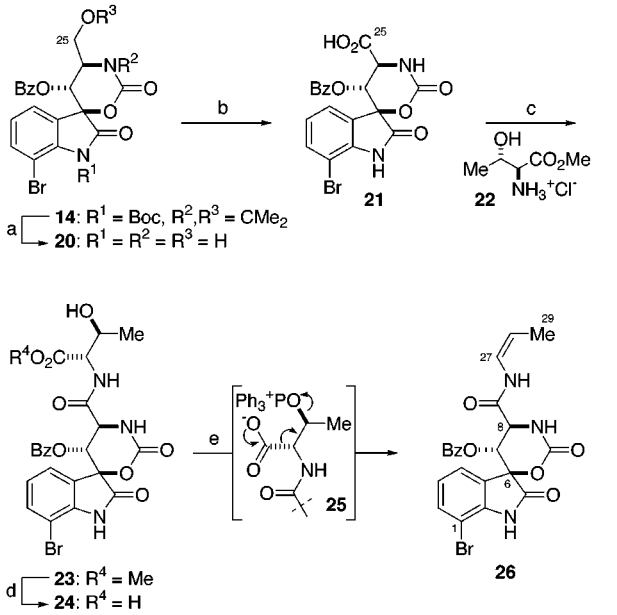
(19) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 1380.

Scheme 3. Proposed Mechanism of (*Z*)-Selective Mizoroki−Heck Reaction



Scheme 4[a]



[a] (a) TfOH (0.5 equiv), CF_3CH_2OH, 0 °C to rt, 64%; (b) CrO_3 (0.1 equiv), H_5IO_6, wet MeCN, 0 °C; (c) **22** (1.5 equiv), EDC, HOBt, NMM, DMF, 0 °C to rt, 60% (2 steps); (d) LiOH·H_2O, THF−H_2O (1:1), 0 °C; (e) DEAD, PPh_3, THF, −78 °C to rt, 40% (2 steps).

the epoxide of **10** with BF_3·Et_2O selectively provided a six-membered carbamate **12** with a concomitant loss of the *tert*-butyl group in 87% yield (2 steps).[20] 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 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_N2 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_3CH_2OH simultaneously removed the acetonide and Boc groups and generated the desired alcohol **20** in 64% yield.[21] Oxidation of the alcohol **20** using catalytic CrO_3 and H_5IO_6 as a reoxidant provided carboxylic acid **21**,[22] 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 α-alkoxy carboxylic acid **24**. Upon treatment of **24** with Mitsunobu conditions (Ph_3P, DEAD), the decarboxylative 1,3-elimination proceeded smoothly,[23] presumably through **25**, to yield the protected northern part of TMC-95A (**26**) in 40% yield (2 steps).[24]

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** → **10**), (iii) a 6-endo selective epoxide ring-opening reaction to establish the stereochemistry of C6 stereocenter (**10** → **12**), and (iv) a mild 1,3-elimination reaction of L-*allo*-threonine to build the (*Z*)-1-propenylamine (**24** → **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.

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

(23) 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, $CHCl_3$); IR (film) 3280, 1741, 1672, 1621, 1264, 1107, 708 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 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, d *J* = 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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 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 $C_{22}H_{19}BrN_3O_6$ [M + H^+] 500.0457, found 500.0433.