A concise, total synthesis of the TMC-95A/B proteasome inhibitors

Brian K. Albrecht and Robert M. Williams*

Department of Chemistry, Colorado State University, Fort Collins, CO 80523

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A concise, total synthesis of the proteasome inhibitors TMC-95A/B has been accomplished. The synthesis features the use of an L-serine-derived *E*-selective modified Julia olefination reaction to ultimately control the stereochemical outcome of the highly oxidized tryptophan fragment. Additionally, the limited use of protecting groups at a late stage of the total synthesis allowed for its completion in an efficient manner.

Julia olefination | Suzuki biaryl coupling | Stille coupling

The ubiquitin-proteasome pathway is an ATP-dependent pathway discovered >20 years ago and is the major proteolytic pathway in the cytosol and nucleus of all eukaryotic cells (ref. 1 and references within). Initial studies focused on understanding the importance of this pathway in the regulation of cellular processes and benefited from biological studies in extracts of mammalian cells and genetic studies in yeasts (2). It was not until the development or isolation of cell-permeable proteasome inhibitors that the physiological roles of the proteasome were understood. These findings have shown that the proteasome catalyzes the degradation of the majority of mammalian proteins, both short- and long-lived (3, 4). The proteasomal degradation of a large variety of cellular proteins is vital to many of the intracellular processes such as cell-cycle progression, apoptosis, inflammation, immune surveillance, selective removal of misfolded or damaged proteins, and the regulation of metabolic pathways (ref. 1 and references within). Therefore, specific proteasome inhibitors are of great interest not only for use as a tool for understanding the ubiquitin-proteasome pathway but also as potential drug candidates.

In early 2000, Kohno and coworkers (5) reported the isolation of novel cyclic tripeptides TMC-95A–D (1–4) (Fig. 1). TMC-95A–D are potent proteasome inhibitors isolated from the fermentation broth of *Apiospora montagnei* Sacc. TC 1093, derived from soil samples. These natural products are unique cyclic peptides containing L-tyrosine, L-asparagine, a highly oxidized L-tryptophan, (Z)-1-propenylamide, and 3-methyl-2-oxopentanoic acid subunits. It has been shown that these compounds are biologically active against the chymotrypsin-like, trypsin-like, and peptidylglutamyl-peptide-hydrolyzing activities of the 20S proteasome. Recently, it was determined that TMC-95A displays noncovalent and reversible inhibition of the proteasome, a mode of action not observed with other inhibitors until recently (6).

The great interest emerging in the field of proteasome inhibition, the considerable biological activity, and the distinctive structures of the TMC-95 class of natural products have provided motivation to contemplate a total synthesis of these compounds that would be readily adaptable to preparing biologically active analogs (7–11). Indeed, immediately after the publication of the structures of these novel cyclic peptide natural products, significant synthetic activity in this field commenced (12, 13, †), resulting in total syntheses being reported by Lin and Danishefsky (14, 15) and Inoue *et al.* (16, 17).

Recently we reported a formal total synthesis of TMC-95A/B by intersecting a late-stage intermediate in the Danishefsky total synthesis (18). In that communication we reported the synthesis

Fig. 1. Structures of TMC-95A–D.

of the unprotected macrocyclic intermediate **5** (Fig. 2), and since that time, we have endeavored to elaborate this substance to TMC-95A/B in an efficient manner. Herein we report the realization of that goal along with a full account of our research program in this arena.

Materials and Methods

General Procedures. Unless otherwise noted, materials were obtained from commercial sources and used without purification. All reactions requiring anhydrous conditions were performed under a positive pressure of argon by using flame-dried glassware that was cooled under dry argon. Tetrahydrofuran (THF), dimethylformamide (DMF), and toluene were degassed with argon and passed through a solvent-purification system (J. C. Meyer, Glass Contour, Laguna Beach, CA) containing alumina or molecular sieves. Dichloromethane was distilled from CaH₂ before use. Column chromatography was performed on Merck silica gel Kieselgel 60 (230–400 mesh). Mass spectra were obtained on Fisons VG Autospec. HPLC data were obtained on a Waters 600 high-pressure liquid chromatograph. ¹H NMR, ¹³C NMR, and nuclear Overhauser effect (NOE) experiments were recorded on a Varian 300- or 400-MHz spectrometer. Chemical shifts (δ) were given in parts per million and recorded relative to the residual solvent peak unless otherwise noted. ¹H NMR were tabulated in the following order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet), coupling constant (in hertz), and number of protons. When a signal was deemed “broad,” it was noted as such. IR spectra were recorded on a Nicolet Avatar 320 Fourier transform IR spectrometer. Optical rotations were determined with a Rudolph Research Autopol III automatic polarimeter referenced to the D-line of sodium.

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Abbreviations: THF, tetrahydrofuran; DMF, dimethylformamide; NOE, nuclear Overhauser effect; BT, benzothiazole; PT, phenyl tetrazole; LiHMDS, lithium bis(trimethylsilyl)amide; DMPU, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone; RT, room temperature; EDCI, ethyl-dimethylaminopropyl carbodiimide hydrochloride; HOAt, 1-hydroxyazabenzotriazole.

*To whom correspondence should be addressed. E-mail: rmw@chem.colostate.edu.

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Fig. 2. Strategy to convert tetraol 5 into TMC-95A/B.

Complete experimental procedures and spectroscopic and analytical data including NMR spectra can be found in *Supporting Materials and Methods*, which is published as supporting information on the PNAS web site.

Results and Discussion

Synthetic Plan. Retrosynthetically, we reasoned that macrocycle 5 could be elaborated to TMC-95A/B (Fig. 3) and was derived from the building blocks 6–11. The highly oxidized tryptophan moiety was envisioned to be installed via a protected oxindole of type 6, which could ultimately come from L-serine (7) and a 7-substituted isatin 8. Stille coupling (19) was planned to form the biaryl bond linkage between the oxidized tryptophan and the bottom-half tyrosine portion, which in turn could come from commercially available 3-iodotyrosine (9) and 3-methyl-2-oxopentanoic acid sodium salt (10). Incorporation of an asparagine residue (11) and macrolactamization at the C10–N9 amide bond thus would afford macrocycle 5.

Total Synthesis of TMC-95A/B. The synthesis of TMC-95A/B began with the preparation of the highly oxidized tryptophan fragment. Initially, it was determined that treatment of 7-iodooxindole 12 [readily prepared from 7-iodoisatin via hydrazine reduction (20)] with either the Garner aldehyde 13 (21, 22) or the L-serine-derived OBO-ester aldehyde 14 (23) under condensation conditions produced oxindolones 15 and 16 (Scheme 1). Although these results proved to be very promising, Ma and Wu (13) and later Lin and Danishefsky (14, 15) reported a very similar

Scheme 1. Initial studies toward the highly oxidized tryptophan fragment.

transformation in their syntheses of the highly oxidized tryptophan fragment. It was therefore decided that an alternate and more efficient route to the highly oxidized tryptophan fragment should be developed.

Ultimately, it was found that a modified Julia olefination (24–26) proved to be an effective method to furnish an oxindolene derivative 6. The synthesis of the highly oxidized tryptophan fragment began with treatment of readily available *N*-benzyloxycarbonyl-L-serine methyl ester (17) under Mitsunobu (27) conditions with either 2-mercaptobenzothiazole or 1-phenyl-1*H*-tetrazole-5-thiol, diisopropyl azodicarboxylate, and PPh_3 to furnish *S*-heteroaromatic cysteine derivatives 18 (Scheme 2). Completion of the modified Julia sulfone coupling partners was accomplished by (i) reduction of the methyl ester with $\text{Ca}(\text{BH}_4)_2$, (ii) blocking of the carbamate nitrogen and the primary alcohol as the acetonide with 2,2-dimethoxypropane and *p*-toluenesulfonic acid, and (iii) oxidation (28) of the thioether to the sulfone 19. It should be noted that both the benzothiazole (BT) and phenyl tetrazole (PT) sulfone were prepared in like manner and similar yields.

With sulfones 19 in hand, we set out to determine the optimal reaction conditions necessary to couple sulfones 19 with readily available 7-iodoisatin (29–31) 20 that would give both a high-yielding and highly diastereoselective process (Table 1). It was found that conditions similar to those reported by Liu and Jacobsen (32) gave the best selectivity in the modified Julia olefination, furnishing the desired oxindolene 21. Under the same reaction conditions, we saw that the BT sulfone gave superior selectivity over that of the corresponding phenyl-tetrazole derivative (Table 1, entry 2 vs. 4). We also noticed that the more thermodynamically stable *E*-isomer can preferentially

Fig. 3. Retrosynthetic analysis of TMC-95A/B.

Scheme 2. Preparation of the modified Julia sulfone. Reaction conditions: a, 2-mercaptobenzothiazole, diisopropyl azodicarboxylate, PPh_3 , THF, room temperature (RT) (89%); b, CaCl_2 , NaBH_4 , THF, 0°C to RT (95%); c, 2,2-dimethoxypropane, *p*-toluenesulfonic acid, CH_2Cl_2 , RT; d, $\text{Mo}_7\text{O}_{24}(\text{NH}_4)_6 \cdot 4\text{H}_2\text{O}$, H_2O_2 , EtOH (77%, two steps).

Table 1. Modified Julia olefination

Entry	Heterocycle (Het)	Conditions*	E/Z ratio [†]
1	PT	THF, NaHMDS, -78°C	1:1
2	PT	DMF, DMPU, LiHMDS, -45°C	2:1
3	BT	THF, NaHMDS, -78°C	1:1
4	BT	DMF, DMPU, LiHMDS, -78°C	2.5:1
5	BT	DMF, DMPU, LiHMDS, -45°C	3:1
6	BT	DMF, DMPU, LiHMDS, 0°C	5:1

NaHMDS, sodium bis(trimethylsilyl)amide.

*In all cases yields were at least 79%.

[†]E/Z ratios were determined by ¹H analysis of crude product mixtures.

be prepared with greater selectivity by increasing the reaction temperature. Ultimately the optimized reaction conditions were found to involve treating the BT sulfone **19a** and 7-iodoisatin with lithium bis(trimethylsilyl)amide (LiHMDS) in DMF/1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) (1:1) at 0°C, affording a 5:1 *E/Z* ratio of oxindolene **21** (Table 1, entry 6). It was also possible to separate the two isomers and then isomerize the undesired *Z*-isomer to the *E*-isomer under conditions reported by the Danishefsky group (14, 15).

With oxindolene **21** in hand, we considered numerous synthetic strategies that could be used to complete the total synthesis. Of those contemplated, two disconnections involving either C6–C7 oxidation to the diol or biaryl formation were seriously considered. Because our laboratory had previously developed a Stille coupling protocol for the preparation of a simplified TMC-95 biaryl (**33**) and studies have shown that the C6–C7 diol is somewhat labile (34, ‡), it was decided to form the biaryl bond before installation of the C6–C7 diol.

With aryl iodide **21** and aryl stannane **22** (33) in hand, attempts were made at constructing the biaryl moiety of the TMC-95 proteasome inhibitors under the Stille conditions discussed earlier. Despite extensive experimentation, we found that

Scheme 3. Attempted Stille coupling.

numerous combinations of Pd-catalyst and ligand gave unsatisfactory yields of the biaryl product **23** (Scheme 3). The best isolated yield of coupled product **23** was ≈20%, which was routinely accompanied by side products resulting from alkyl group transfer from the stannane (**24**) and reductive removal of the iodine atom (**25**). Because of the fact that the Stille coupling gave undesired side products and insufficient yields, we decided that the Suzuki (35) coupling protocol was the next logical choice for constructing the biaryl bond.

Preparation of the requisite boronic ester necessary for the Suzuki coupling began with the protection of commercially available 3-iodo-L-tyrosine **26**. Subjection of 3-iodo-L-tyrosine **26** to (i) thionyl chloride in methanol, (ii) di-*tert*-butyldicarbonate, and (iii) chloromethyl methyl ether and diisopropylethylamine afforded the fully protected tyrosine derivative **27** in near quantitative yield (Scheme 4). Conversion of the aryl iodide in **27** to the boronic ester **28** was accomplished via the Miyaura protocol (36). Treatment of boronic ester **28** under Suzuki conditions with aryl iodide **21** and K₂CO₃ in refluxing aqueous dimethoxyethane catalyzed by dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium smoothly installed the biaryl linkage yielding **23** in 90% yield.

Saponification of the methyl ester in **23** allowed for amide bond formation between the resulting carboxylic acid and L-asparagine benzyl ester mediated by ethyl-dimethylaminopropyl carbodiimide hydrochloride (EDCI) and 1-hydroxyazabenzotriazole (HOAt) to yield pseudotripeptide **29** in 98% yield over the two steps (Scheme 5). Pseudotripeptide **29** constitutes the complete carbon framework for the macrocyclic core. It is significant to note that the judicious choice of protecting groups has allowed for complete removal of all protecting groups in two simple transformations. With pseudotripeptide **29** in hand, we found that this was the ideal juncture in the synthesis for the oxidation to the C6–C7 diol. Subjection of **29** to OsO₄ in pyridine at 0°C allowed for the oxidation of the C6–C7 double bond with complete facial selectivity opposite to the allylic carbamate yielding diol **30** in 87% yield as a single diastereomer with the correct relative configuration.

At this stage, we decided to remove all the acid labile protecting groups, liberating the C14 amine, the C25 primary

[‡]¹H NMR at 393 K revealed the following retro-aldol cleavage:

Scheme 4. Suzuki biaryl formation. Reaction conditions: a1, SOCl_2 , MeOH, RT, 18 h; a2, di-*tert*-butyldicarbonate, saturated NaHCO_3 , CH_2Cl_2 , $0^\circ\text{C} \rightarrow \text{RT}$, ≈ 12 h; a3, chloromethyl methyl ether, diisopropylethylamine, CH_2Cl_2 , 0°C , 3 h, 95% (three steps); b, bis(pinacolato)diboron, KOAc, dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium, DMSO, 80°C , 4 h, 80–89%; c, **21**, K_2CO_3 , dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium, aqueous dime-thoxyethane, Δ 90%.

alcohol, and the C19 phenol with trifluoroacetic acid/ H_2O (1:1) (Scheme 5). Although we realized that the four free alcohols may prove to be problematic in both the incorporation of the ketoamide and the macrocyclization, the potential payoff in

Scheme 5. Preparation of the macrocyclic core. Reaction conditions: a1, LiOH, THF, H_2O , 0°C ; a2, $\text{H}_2\text{N-Asn-OBn}$, HOAt, EDCI, diisopropylethylamine, CH_2Cl_2 , 0°C , 4 h (98%, two steps); b, OsO_4 , pyridine, 0°C , 1 h, and then saturated NaHSO_3 , 87%; c, trifluoroacetic acid/ H_2O (1:1), RT, 4 h; d, 3-methyl-2-oxopentanoic acid sodium salt, HOAt, EDCI, THF, 0°C (98%, two steps); e, Pd black, H_2 , MeOH, RT, 6 h; f, EDCI, HOAt, CH_2Cl_2 , DMF (1:1), RT, 1 mM (49%, two steps).

Scheme 6. Selective oxidation of C25. Reaction conditions: a, SO_3 -pyridine, DMSO, CH_2Cl_2 (3:1), RT, 15 min; b, NaClO_2 , NaH_2PO_4 , 2-methyl-2-butene, $^t\text{BuOH}$, H_2O , RT, 5 h.

terms of efficiency motivated us to explore this approach. The resulting trifluoroacetic acid-amine salt was coupled to *d,l*-3-methyl-2-oxo-pentanoic acid sodium salt mediated by EDCI and HOAt, affording the corresponding amide **31** in $\approx 98\%$ yield over the two steps. The high yield in this reaction proved promising for the macrocyclization step, because there is no observable competing acylation of any of the free alcohols, and promised to obviate the need for protecting groups.

Hydrogenolysis of both the benzyl ester and the *N*-benzyloxy carbamate with palladium black afforded the requisite amino acid necessary for macrocyclization. The resulting amino acid was treated with EDCI and HOAt to yield the key unprotected macrocycle **5**. Crude ^1H NMR analysis showed that besides macrocycle **5**, there were no other macrocyclic compounds related to lactone formation or biaryl atropisomers.⁸

As stated earlier, although we were able to secure the structure of macrocycle **5** by intersecting a late-stage intermediate in the Danishefsky synthesis, it was felt that an efficient synthesis of TMC-95A/B could be accomplished via direct elaboration of macrocycle **5**. To realize this objective, selective oxidation of the C25 primary alcohol in the presence of the C7 secondary alcohol would need to be achieved. In addition and, even more problematic, the oxidative cleavage of the C6–C7 diol loomed as a potential pitfall. Initially, a selective oxidation of the primary alcohol directly to the necessary carboxylic acid using a platinum-catalyzed dehydrogenation reaction (37) was examined. Unfortunately, it was found that no reaction occurred or, if base was added, complete decomposition occurred.

Other direct oxidation methods of the primary alcohol to the carboxylic acid were considered, including the 2,2,6,6-tetramethyl-1-piperidinyloxy (free radical)/ NaClO_2 / NaOCl combination; unfortunately, no desired carboxylic acid product was observed (38). Finally, after exhaustive experimentation [Swern oxidation (39), SO_3 -pyridine, Dess–Martin periodinane (40), *o*-iodoxybenzoic acid (41, 42), and other 2,2,6,6-tetramethyl-1-piperidinyloxy systems (43)], it was found that a two-step protocol proved successful in obtaining the desired carboxylic acid. Thus, treating macrocycle **5** with SO_3 -pyridine in DMSO- CH_2Cl_2 afforded the desired aldehyde as an inseparable complex mixture of aldehyde, plus C6 and C7 lactol isomers (Scheme 6). Fortunately, subjection of this mixture to NaClO_2 and NaH_2PO_4 in the presence of 2-methyl-2-butene to produce desired carboxylic acid **32**.

With carboxylic acid **32** in hand, all that remained was the incorporation of the *cis*-propenyl amide. There were several avenues that we chose to investigate for this transformation. Initially, we decided to test the method developed by Stille and Becker (44), which involved a transition-metal-mediated process wherein allyl amides are converted to the corresponding enamides in which the *cis*-configuration predominates. Coupling of

⁸Lin and Danishefsky (14, 15) showed that the atropisomeric outcome follows the C6 stereochemistry.

Scheme 7. Completion of TMC-95A/B. Reaction conditions: a, *L*-*allo*-treonine-benzyl ester hydrochloride, EDCI, HOAt, diisopropylethylamine, CH_2Cl_2 , DMF, 0°C , 16 h, 49% (from 5); b, Pd black, MeOH, H_2 [1 atm (1 atm = 101.3 kPa)], RT; c, diisopropyl azodicarboxylate, PPh_3 , DMF, THF, RT, 70% (two steps).

allyl amine with the carboxylic **32** readily provided the corresponding allyl amide. Unfortunately, all attempts to isomerize this product proved futile.

Next, the Peterson olefination method developed by the Fürstner laboratory (ref. 45 and references therein) that utilizes hydroxyalkyl silanes for the preparation of enamides was evaluated. The requisite strong base used in this Peterson olefination protocol was anticipated to be too harsh for the sensitive functionality present in the TMC-95 macrocyclic core. Therefore, we examined the liberation of a masked alkoxide under mild conditions as a means to trigger the desired olefination. The literature revealed that fluoride-based deprotection of a *tert*-butyldimethylsilyl ether unleashes an alkoxide species reactive enough to suffer facile Peterson olefination to yield an enamide as reported in the synthesis of crocacin D (46). Although we were able to conduct this reaction on a very simplified substrate, we were unable to produce TMC-95A/B after subjection of the corresponding hydroxyalkyl silyl amide with a variety of fluoride sources.

Based on the aforementioned setbacks, we evaluated the enamide preparation developed by Pansare and Vederas (47) and used by Inoue *et al.* (16, 17) in their synthesis of TMC-95A. Treatment of carboxylic acid **32** with *L*-*allo*-threonine-benzyl ester hydrochloride salt (48) mediated by EDCI and HOAt afforded the corresponding amide **33** in 49% overall yield from **5** (Scheme 7). Hydrogenolysis of the benzyl ester in **33** with palladium black under an atmosphere of hydrogen produced the resultant carboxylic acid. Subjection of this material to Mitsunobu conditions afforded TMC-95A/B in 70% yield for the

two steps. The individual diastereomers TMC-95A and TMC-95B were separated by HPLC to collect analytical data on each. The synthetic samples of TMC-95A and TMC-95B and the natural materials proved identical by ^1H NMR, ^{13}C NMR, mobility on TLC, mobility on HPLC, optical rotation, and high-resolution mass spectrometry.

Conclusions

A concise and efficient total synthesis of TMC-95A/B has been accomplished. The synthesis was completed in 22 total steps with only 18 steps in the longest linear sequence. It should be noted that this is a very short and efficient total synthesis of these natural substances and is an approach to commence with *L*-serine instead of *D*-serine. Our synthesis features an *E*-selective modified Julia olefination to form the key oxindolene. It has been found that this transformation is also a viable route to other β,γ -unsaturated protected amino alcohols. The synthesis recorded here constitutes an efficient strategy that is amenable to the preparation of a variety of analogs due to being highly convergent and requiring minimal protecting group manipulations.

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