Pergamon

Tetrahedron Letters 41 (2000) 9089–9093

TETRAHEDRON LETTERS

Enantioselective construction of the oxidized tryptophan fragment of proteasome inhibitors TMC-95A and TMC-95B

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Received 12 July 2000; revised 13 September 2000; accepted 20 September 2000

Abstract

The oxidized tryptophan analogue **5**, a proposed intermediate for a synthesis of the proteasome inhibitors TMC-95A and TMC-95B, is prepared using the condensation of oxindole **7** with the (*R*)-Garner aldehyde and stereoselective dihydroxylation of olefin **6** as key steps.

TMC-95A-D are four cyclic peptides containing L-tyrosine, L-asparagine, highly oxidized L-tryptophan, (*Z*)-1-propenylamine, and 3-methyl-2-oxopentanoic acid units.[1,2] These compounds were recently isolated from the fermentation broth of *Apiospora montagnei* Sacc. TC 1093, isolated from a soil sample. Biological studies indicated that these natural products, especially TMC-95A, exhibit potent inhibition activity towards proteasome ($IC_{50} = 5.4$ nM). The important biological activities displayed by TMC-95 A and TMC-95B and their unique structures stimulated us to embark on a program directed toward a total synthesis of these two compounds.

Our retrosynthetic analysis is shown in Fig. 1. The target molecule could be obtained by a Suzuki coupling[3] of the bromide **5** with the intermediate **E** and subsequent conversions, while the dihydroxy moiety in **5** could be introduced by a stereospecific dihydroxylation of olefin **6**. Further simplification gave oxindole **7** and the (*R*)-Garner aldehyde as two possible precursors. In this report, we wish to present our efforts for the synthesis of **5** by this strategy.

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0040-4039/00/$ - see front matter
PII: S0040-4039(00)01657-9

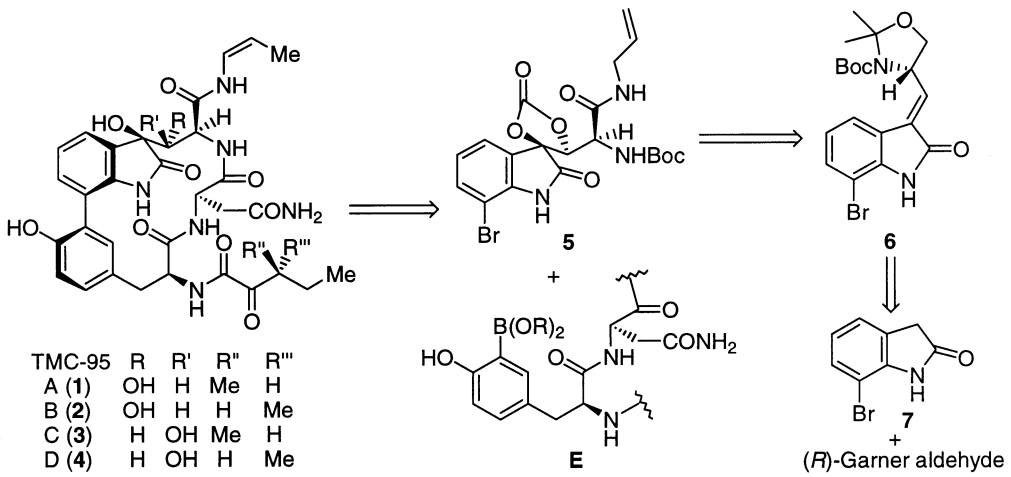
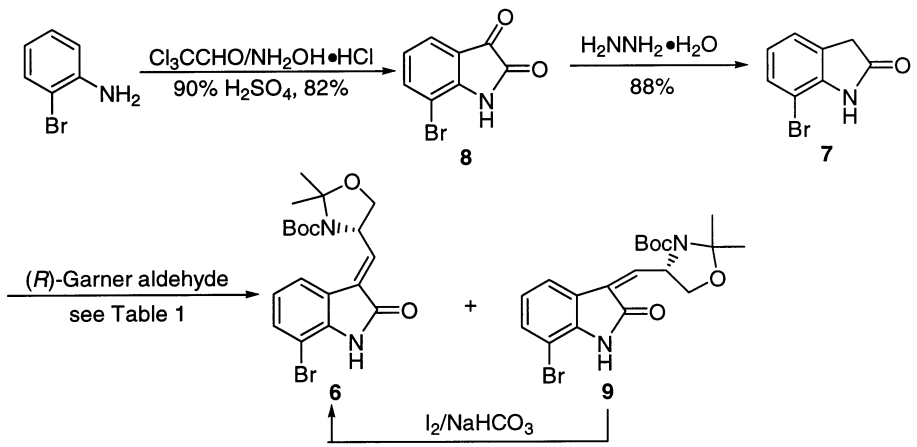


Figure 1.

As outlined in Scheme 1, we started our synthesis from 2-bromoaniline, which was reacted with trichloroacetaldehyde to afford isatin **8**. Upon treatment with hydrazine, isatin **8** was reduced to oxindole **7** in 88% yield.[4] Condensation of **7** with the (*R*)-Garner aldehyde (~90% ee)[5] was attempted under several conditions that are summarized in Table 1. Initially, we tried to use piperidine as the catalyst and found that at high temperature the reaction gave coupling products in good yield (entry 1).[6] However, the rotation of the product **6** was zero, which meant that racemisation had occurred during the coupling reaction. A lower reaction temperature was still not satisfactory (entry 2). At this stage we studied stepwise coupling.[7] Thus, treatment of **7** with LHMDS followed by trapping the lithium enolate with the (*R*)-Garner aldehyde afforded the aldol condensation product. This product was converted into **6** and **9** in 54% yield upon treatment with TEA/MsCl. The ee value of **6** at this time was about 90% as detected by HPLC (entry 3). Further improvement of the reaction conditions provided **6** and **9** in 76% yield without any racemization (entry 6). The olefin **6** was predicted to be *E*-isomer and this was confirmed by further conversions discussed later. The *Z*-isomer **9** was converted into the *E*-isomer **6** with $I_2/NaHCO_3$ in 89% yield based on 42% recovery of **9**.



Scheme 1.

Table 1
Reaction conditions for condensation of **7** with the (*R*)-Garner aldehyde

Entry	Reaction conditions	Yield (%)[a]	**9**/**6**	ee% of **6**
1	Piperidine, EtOH, reflux	76	45/55	0
2	Piperidine, EtOH, rt	37	46/54	13
3	LHMDS (2 equiv.)/THF, −78°C, then TEA (4 equiv.), MsCl (3 equiv.), CH_2Cl_2, −60°C	54	44/56	~90
4	LDA (2 equiv.)/THF, −78°C, then TEA (4 equiv.), MsCl (3 equiv.), CH_2Cl_2, −60°C	62	41/59	~90
5	*n*-BuLi (2 equiv.)/THF, −78°C, then TEA (4 equiv.), MsCl (3 equiv.), CH_2Cl_2, −60°C	71	46/54	~90
6	*n*-BuLi (1.5 equiv.)/THF, −78°C, then TEA (2 equiv.), MsCl (1 equiv.), CH_2Cl_2, −60°C	76	44/56	~93

[a] Isolated yield.

Dihydroxylation of **6** was found to be another challenging step of our synthesis. Several oxidation systems were tried using our substrate **6** and most gave no products or provided the by-product, isatin **8**, in high yields (Table 2, entries 1–4). Fortunately, treatment of **6** with OsO_4/pyridine produced our desired product **10** in about 79% yield (entry 5). Protection of the diol **10** as its cyclic carbonate gave **11** in 91% yield. The carbonate **11** was crystalline and therefore we could determine its stereochemistry by X-ray analysis (Fig. 2). Thus we found that the configuration of **11** is 3*S*,1′*R*,2′*R*, which is the one required for synthesizing TMC-95A and TMC-95B. The stereochemistry in the dihydroxylation step is consistent with Fig. 3, the oxidant attacking the C–C double bond from the outer, less hindered face, to give the diol **10**. Next, the selective cleavage of the acetonide to form the alcohol **12** was attempted. We found that TMSI formed in situ[13] was the most effective catalyst for this transformation while CSA, TsOH, or Dowex-50W were not so good. Finally, Jones oxidation of **12** followed by amidation with allylamine gave **5** in 65% yield (Scheme 2).

Table 2
Dihydroxylation of **6**

Entry	Reaction conditions	Product	Yield (%)[a]
1	AD-mix-β, *t*-BuOH-H_2O, 0°C to rt[8]	**8** (0)	**10** (0)
2	OsO_4–NMO, THF/H_2O, rt[9]	**8** (73)	**10** (0)
3	$NaIO_4$/$RuCl_3{\cdot}xH_2O$, EtOAc/MeCN/H_2O, −10°C[10]	**8** (64)	**10** (31)
4	$KMnO_4$, EtOH/H_2O, −40°C[9,11]	**8** (40)	**10** (0)
5	OsO_4, pyridine, THF, 0°C[12]	**8** (10)	**10** (79)

[a] Isolated yield.

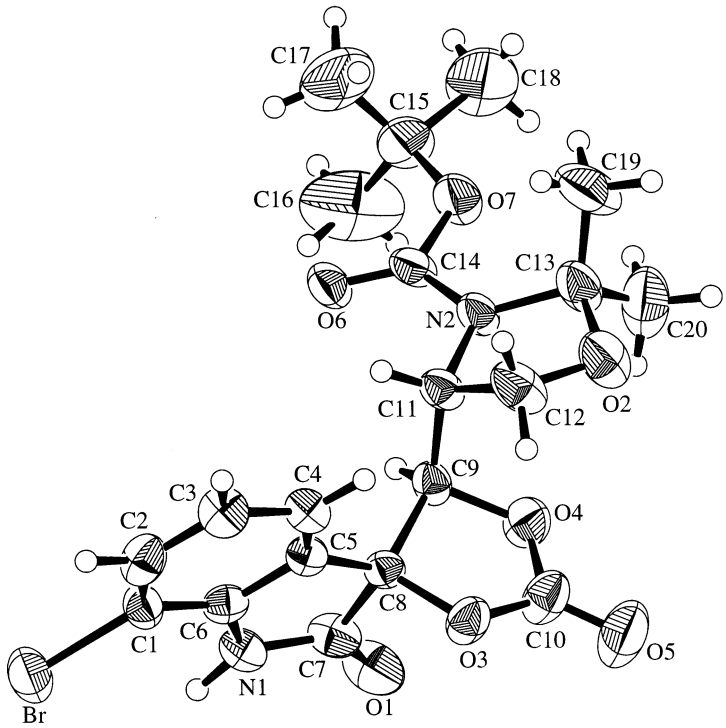


Figure 2.

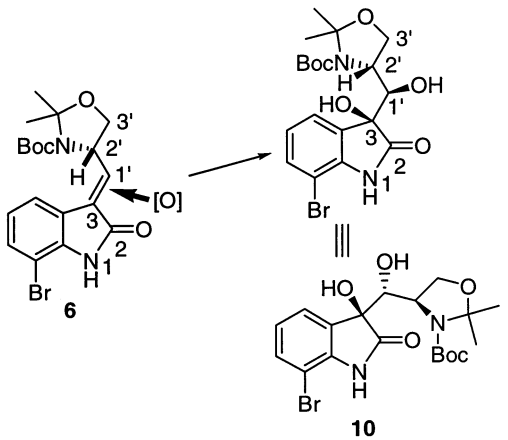
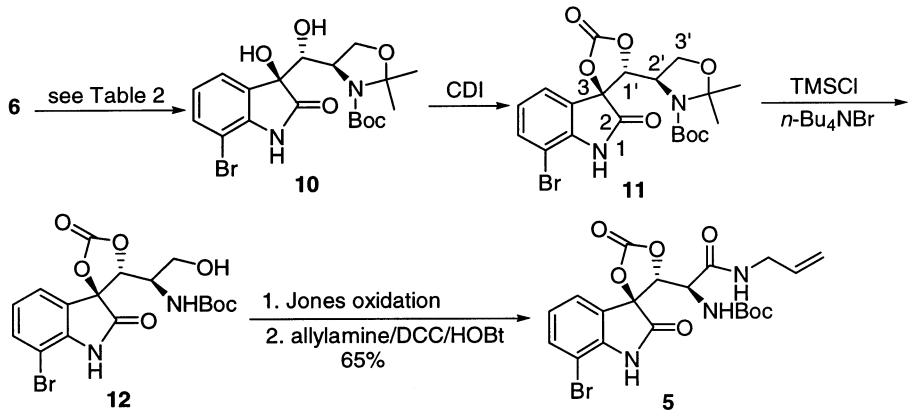


Figure 3.

In conclusion, we have developed a method to prepare the oxidized tryptophan fragment of TMC-95A and TMC-95B. Further efforts for the total synthesis of these two natural products as well as structure-activity relationship studies are underway in our laboratory.



Scheme 2.

Aknowledgements

The authors are grateful to the Chinese Academy of Sciences, National Natural Science Foundation of China (grant 29725205), and Qiu Shi Science & Technologies Foundation for their financial support.

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