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Total Synthesis of (*R*)-Telomestatin

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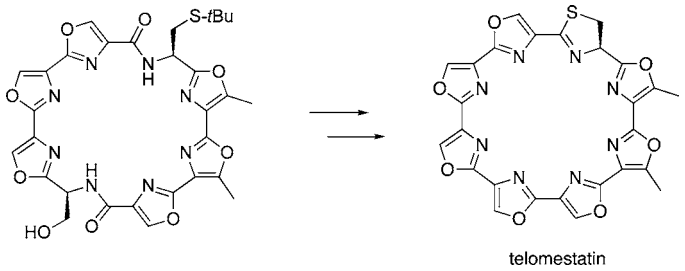
ABSTRACT



We have achieved a total synthesis of telomestatin, and its absolute configuration was determined to be (*R*). Coupling of cysteine-containing trisoxazole amine and serine-containing trisoxazole carboxylic acid, followed by macrocyclization, provided a 24-membered diamide. The seventh oxazole ring was formed by a Shin's procedure via dehydroamide. Cyclodehydration of a modified (*R*)-cysteine-(*S*-^{t}Bu) moiety using Kelly's method ($PPh_3(O)$–Tf_2O) with anisole furnished (*R*)-telomestatin, whose CD spectrum was in good agreement with that of the natural product.

Telomestatin (**1**), isolated from *Streptomyces anulatus* 3533-SV4, is a potent specific telomerase inhibitor (IC_{50} = 5.0 nM) because it acts on a human telomere sequence to stabilize the specific DNA structure called G-quadruplex without affecting DNA polymerases or reverse transcriptases.[1−3] The unique macrocyclic structure of telomestatin consists of the macrocyclic linkage of two methyloxazoles, five oxazoles, and one thiazoline ring. Although several synthetic approaches to telomestatin[4] and an oligo-oxazole ring system[5] have been reported, a total synthesis of telomestatin has been reported only in a patent.[6] We wish to report a total synthesis of telomestatin (**1**) and its complete stereochemical assignment.

As a thiazoline is labile for hydrolysis, the thiazoline ring in **1** would be formed at the final stage in the synthesis. We selected *N*-Boc-Cys-(*S*-^{t}Bu)-Thr-OMe (**2**) and 2,5-disubstituted oxazoles **3** and **4** as the constituent units (Figure 1). Oxidation of the secondary alcohol in dipeptide **2** with SO_3·

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(1) Shin-ya, K.; Wierzba, K.; Matsuo, K.; Ohtani, T.; Yamada, Y.; Furihata, K.; Hayakawa, Y.; Seto, H. *J. Am. Chem. Soc.* **2001**, *123*, 1262−1263.

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(5) (a) Chattopadhyay, S. K.; Kempson, J.; McNeil, A.; Pattenden, G.; Reader, M.; Rippon, D. E.; Waite, D. *Perkin Trans. 1* **2000**, 2415−2428. (b) Deeley, J.; Pattenden, G. *Chem. Commun.* **2005**, 797−799. (c) Atkins, J. M.; Vedejs, E. *Org. Lett.* **2005**, *7*, 3351−3354. (d) Riego, E.; Hernández, D.; Albericio, F.; Álvarez, M. *Synthesis* **2005**, 1907−1922. (e) Chattopadhyay, S. K.; Biswas, S.; Pal, B. K. *Synthesis* **2006**, 1289−1294.

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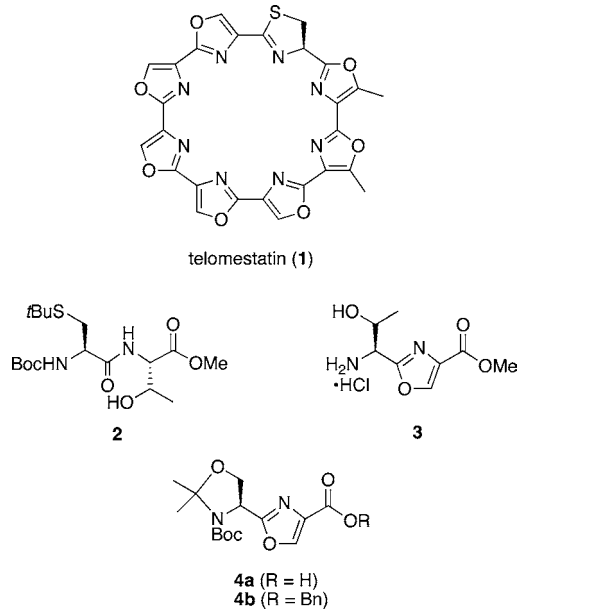
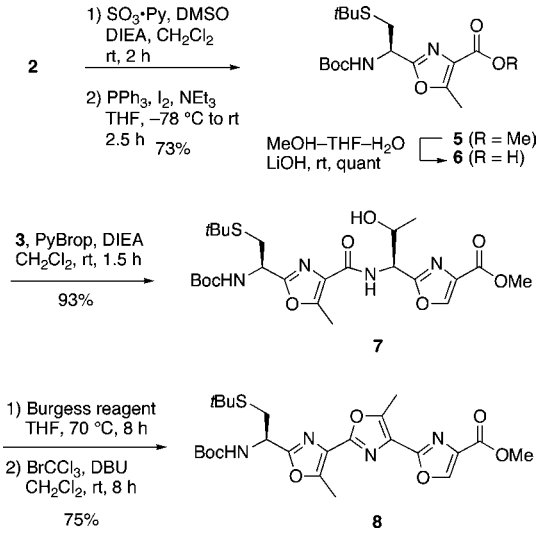


Figure 1. Structure of telomestatin (**1**) and synthetic units **2**−**4**.

Py, followed by immediate cyclodehydration with PPh_3-I_2 in the presence of NEt_3, provided 2,4,5-trisubstituted oxazole **5** in 73% yield (Scheme 1).[7] Hydrolysis of ester **5** with LiOH,

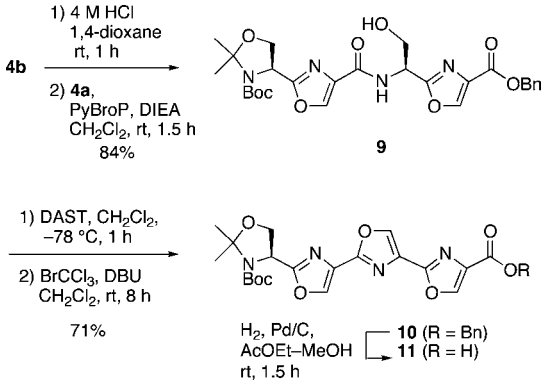
Scheme 1. Synthesis of Trisoxazole **8**



followed by coupling of the resulting acid **6** with amine **3**[4] using PyBroP[8]−DIEA, afforded bisoxazole amide **7**.[9] Cyclodehydration of **7** using the Burgess reagent ($Et_3NSO_2-NCO_2Me$),[10] followed by treatment with $BrCCl_3$−DBU[11] afforded Cys-containing trisoxazole **8** in 75% yield.

A trisoxazole unit **11** was prepared from the coupling between 2,5-disubstituted oxazole units **4a**[5a] and **4b** (Scheme 2). Acid cleavage of the *N*,*O*-acetonide and *N*-Boc groups

Scheme 2. Synthesis of Trisoxazole **11**



in **4b**, followed by condensation of the resultant amine with acid **4a**, provided bisoxazole amide **9** in 90% yield. Cyclodehydration of **9** with diethylaminosulfur trifluoride (DAST)[12] and oxazole formation with $BrCCl_3$−DBU afforded trisoxazole **10**,[13] in which hydrogenolysis of the benzyl ester furnished acid **11**.

Removal of the Boc group in **8** with 4 M HCl in dioxane afforded the corresponding ammonium salt without affecting the *S*-^{t}Bu group. Coupling of the resulting amine with acid **11** using PyBrop−DIEA provided hexaoxazole amide **12** in 85% yield (Scheme 3). Acid cleavage of the *N*,*O*-acetonide and *N*-Boc groups in **12**, followed by hydrolysis of the methyl ester with LiOH, afforded the cyclization precursor. Macrolactamization was performed using DPPA[14]−HOBt−DIEA in the presence of DMAP under high dilution conditions (3 mM) at room temperature for 3 days. Hexaoxazole-containing cyclic diamide **13** was isolated in 48% overall yield after silica gel column chromatography.

It was crucial to form the seventh oxazole ring in **16** from **13**. Attempts for direct cyclodehydration of **13** with DAST or the Burgess reagent did not afford the desired oxazoline rings except **14**. Oxidation of the primary alcohol in **13**, followed by cyclodehydration, did not proceed. Therefore, we investigated the formation of the seventh oxazole ring

(7) Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 3604−3606.

(8) PyBroP = bromo-trispyrrolidino-phosphonium hexafluorophosphate. (a) Coste, J.; Dufour, M.-N.; Pantaloni, A.; Castro, B. *Tetrahedron Lett.* **1990**, *31*, 669−672. (b) Coste, J.; Frérot, E.; Jouin, P.; Castro, B. *Tetrahedron Lett.* **1991**, *32*, 1967−1970.

(9) Several condensation reagents were investigated using the corresponding *S*-trityl derivative: PyBrop, 90%; HATU−HOAt, 78%; PyBop−HOBt, 69%; EDCI−HOBT, 53%.

(10) (a) Burgess, E. M.; Penton, H. R.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26−31. (b) Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 1575−1578. (c) Aguilar, E.; Meyers, A. I. *Tetrahedron Lett.* **1994**, *35*, 2477−2480.

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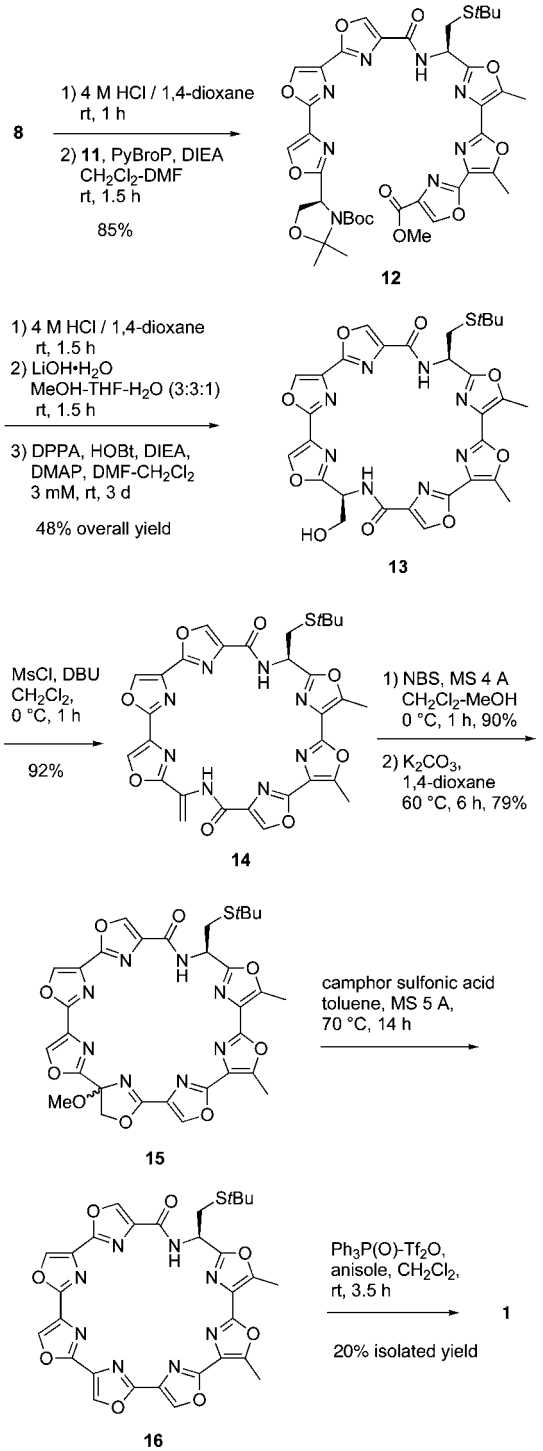
(12) (a) Burrell, G.; Evans, J. M.; Jones, G. E.; Stemp, G. *Tetrahedron Lett.* **1990**, *31*, 3649−3652. (b) Lafargue, P.; Guenot, P.; Lellouche, J.-P. *Heterocycles* **1995**, *41*, 947−958. (c) Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165−1168.

(13) Chattopadhyay et al. recently reported the synthesis of its methyl ester. See ref 5e.

(14) DPPA = diphenyl phosphorazidate. Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203−6205.

Scheme 3. Total Synthesis of Telomestatin (**1**)



via dehydroamide **14** according to the method reported by Shin et al.[4] Mesylation of **13** with DBU provided **14** in 92% yield. Treatment of **14** with NBS in CH_2Cl_2−MeOH in the presence of MS4A formed an α-methoxy-β-bromo cyclic peptide (90%).[15] Subsequent cyclization with K_2CO_3 afforded 4-methoxyoxazoline derivatives **15** as a 1:1 mixture of diastereomers (79%).[16]

Treatment of **15** with camphorsulfonic acid (5 equiv) in toluene at 70 °C in the presence of MS5A resulted in the elimination of MeOH leading to the desired cyclic hepta-oxazole **16**.[17] Finally, thiazoline formation was carried out by Kelly's method[18] with a modification. Cyclodehydration and deprotection of the *S*-^{t}Bu group in **16** were performed using $PPh_3(O)$−Tf_2O−anisole in CH_2Cl_2 at room temperature to provide (*R*)-telomestatin (**1**).[19] It was difficult, however, to purify **1** by either normal-phase or reversed-phase HPLC. The low isolated yield (20%) was due to the property of the product. The spectral data (NMR, UV, CD) of the synthetic (*R*)-**1** were in good agreement with those of the natural product. It was determined that the configuration of the cysteine residue in natural telomestatin was (*R*).

In conclusion, we have demonstrated the total synthesis of optically active telomestatin (**1**) by a convergent route: condensation of Cys-(*S*-^{t}Bu)-containing trisoxazole **8** and trisoxazole carboxylic acid **11**, macrolactamization, formation of the seventh oxazole ring, and construction of the thiazoline ring by a modified Kelly's method. On the basis of the synthesis, the absolute configuration of telomestatin was determined to be (*R*). Further study for the synthesis of its analogues and their biological evaluation is underway in our laboratories.

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Supporting Information Available: Experimental details, NMR spectra of **12**−**16**, and NMR, UV, and CD spectra of **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) In the absence of MS4A, the sulfide moiety was partially oxidized. The *S*-trityl derivative was decomposed under these reaction conditions.
(16) Cs_2CO_3 is usually selected for an oxazoline formation. However, the elimination of thiol was observed in this system.
(17) In the absence of MS5A, ring opening of the oxazoline by hydrolysis was observed.
(18) You, S.; Razavi, H.; Kelly, J. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 83−85.
(19) Without addition of anisole, the reaction was not complete.