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Convergent synthesis of a 24-membered macrocyclic hexaoxazole derivative related to the novel telomerase inhibitor telomestatin

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Abstract—An efficient construction of a 24-membered macrocyclic hexaoxazole derivative pertinent to the synthesis of analogues of the important natural product telomestatin was developed, which featured a convergent union of two trisoxazole units.
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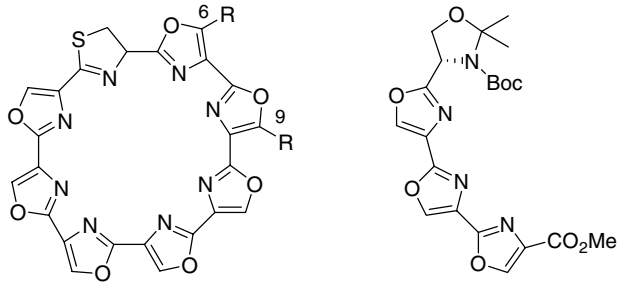
Telomestatin **1** (Fig. 1), isolated[1] from the *Streptomyces anulatus* 3533-SV4, is an intriguing member of the expanding family[2,3] of oxazole and thiazole containing bio-active natural products. It has been demonstrated that telomestatin specifically inhibits telomerase without affecting other enzymes like DNA-polymerase and reverse transcriptase, possibly through interacting[4] with the G-quadruplex structure of telomers. The combination of the unprecedented and unique chemical structure with unusual and useful level of biological activity has rendered telomestatin an attracting synthetic target[5] as well as a candidate for the design and synthesis of analogues with relevance to anti-cancer drug development.[6] We became interested in the synthesis and biological evaluation of 6,9-demethyltelomestatin (**2**) as a possible analogue of telomestatin. We have recently reported[7] a linear synthesis of the doubly functionalised trisoxazole derivative **3**. Herein, we wish to report a convergent synthesis of **3** as well as its utility in the construction of a macrocyclic hexaoxazole derivative as a possible precursor of **2**.



1, R = Me
2, R = H

3

Figure 1.

Thus, the doubly functionalised monooxazole derivative **4**[7] was treated with trifluoroacetic acid to liberate amino alcohol **6** as its TFA salt (Scheme 1). The peptide bond formation between **6** and carboxylic acid **5** previously prepared[7] by us, proceeded well to provide β-hydroxyamide **7** as a colourless solid, with a mp of 104 °C. Cyclodehydration of the latter with diethylaminosulfur trifluoride (DAST) to the corresponding oxazoline **8** (not isolated) followed by its oxidation under Williams's protocol,[8] as developed[9] by Pattenden and co-workers for the oxidation of oxazolines containing oxazole rings at C-2 and C-4, led to the one-pot synthesis of trisoxazole derivative **3** in an overall yield of 47% over three steps from **4**. This convergent synthesis[10] of **3** has advantages over our reported linear synthesis in terms of the reduced number of steps and overall yield.

The doubly functionalised trisoxazole derivative **3** was then separately deprotected at its two termini to liberate carboxylic acid **9** and amino alcohol **10** (Scheme 2). As delineated[7] before, we then attempted convergent union of these two trisoxazole units for the construction of the

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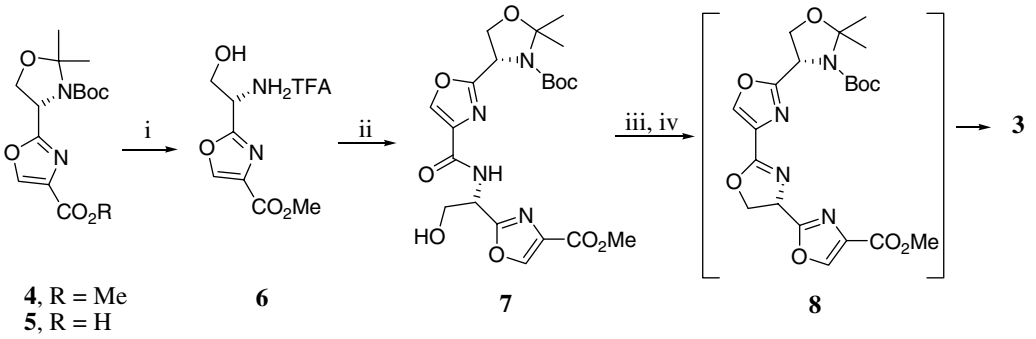
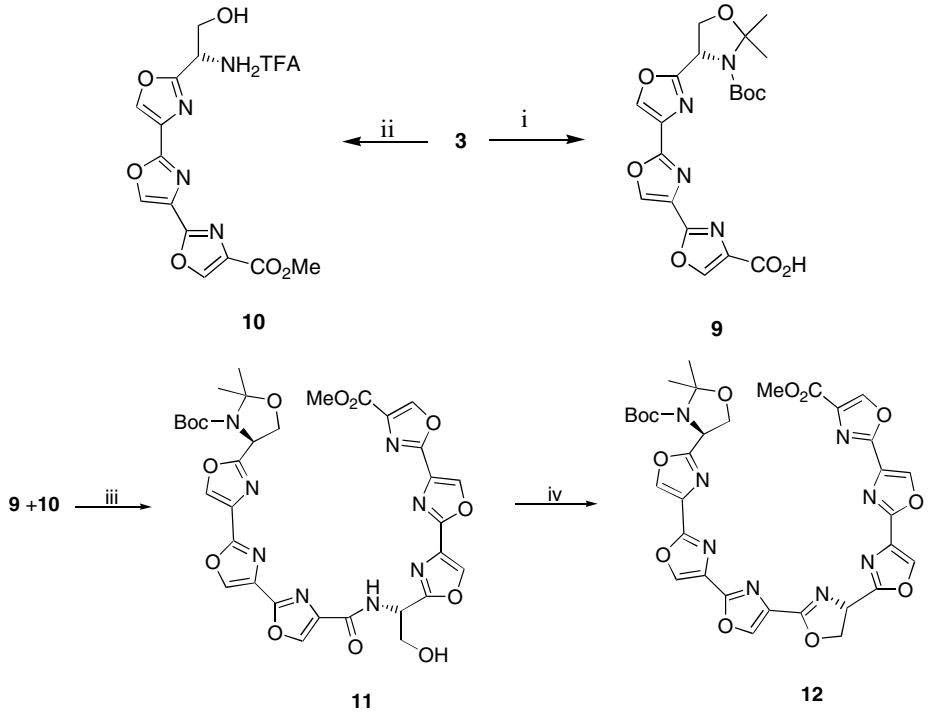


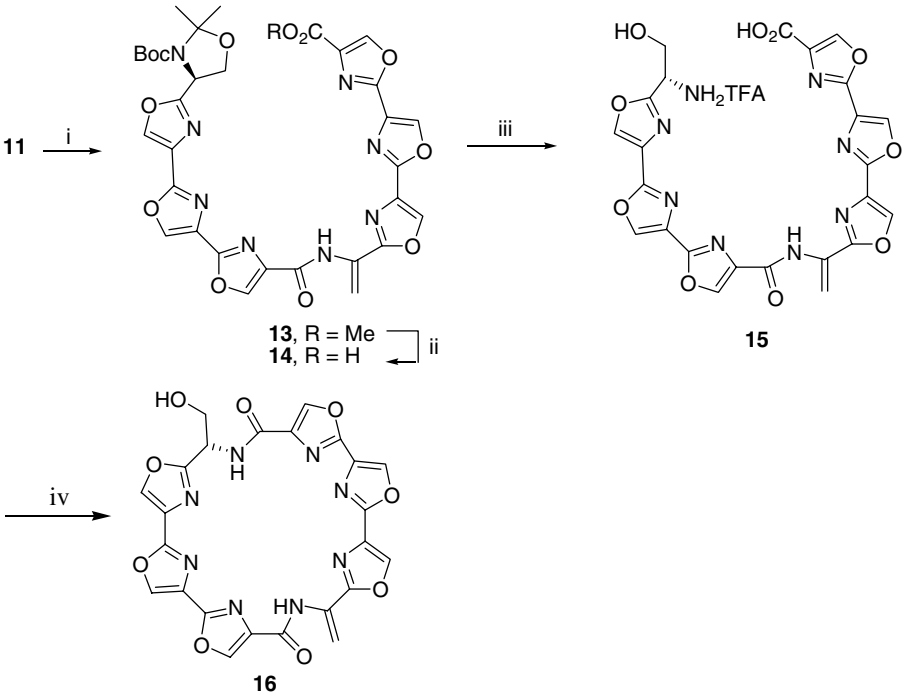
Scheme 1. Reagents and conditions: (i) TFA (50%) in CH_2Cl_2, 0 °C, 1.5 h; (ii) **5**, DCC, HOBt, NMM, *N*,*N*-DMF, 0 °C to rt, 18 h, 73% over two steps; (iii) DAST, K_2CO_3, CH_2Cl_2, −78 °C, 1.5 h; (iv) $BrCCl_3$, DBU, CH_2Cl_2, 0–5 °C, 10 h, 64% over two steps.



Scheme 2. Reagents and conditions: (i) LiOH, THF–H_2O, rt, 4 h, 95%; (ii) TFA (50%) in CH_2Cl_2, 0 °C, 1.5 h; (iii) EDC, HOBt, NMM, *N*,*N*-DMF, 0 °C to rt, 18 h, 74% over two steps; (iv) DAST, K_2CO_3, CH_2Cl_2, −78 °C, 1.5 h, 72%.

seventh oxazole ring through the projected cyclodehydration–oxidation sequence on the β-hydroxy amide **11** formed by the peptide bond formation between **9** and **10**. Thus, the treatment of **11** with DAST smoothly led to the formation of the trisoxazole–oxazoline–trisoxazole derivative **12** in a good yield. However, the attempted oxidation of the oxazoline ring in the latter compound to the corresponding oxazole under a range of conditions (NiO_2,[11] MnO_2,[12] $BrCCl_3$/DBU,[8,9] etc.) proved to be unsuccessful. This led us to consider alternative options.

We considered the construction of a dehydroamide unit within a macrocyclic polyoxazole scaffold as a possible surrogate of the seventh oxazole ring as well as a potential precursor of the latter in view of ample precedences of conversion of dehydroamides to oxazoles.[13] To this end, β-hydroxyamide **11** was transformed to the corresponding unsaturated amide **13** (Scheme 3) through a two-step one-pot mesylation–elimination sequence. Compound **13** was then subjected to sequential deprotection at its two termini employing hydrolysis of the methyl ester to the corresponding acid **14**, followed by its treatment with trifluoroacetic acid to convert the oxazolidine unit to the TFA salt of amino alcohol **15**. Macrolactamisation of **15** was attempted under a range of conditions. It proceeded best with *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU)[9,14] in a solvent mixture of *N*,*N*-DMF and CH_2Cl_2 under high dilution conditions (5 mM) at room temperature and the cyclic hexaoxazole derivative **16** was obtained[15] in a 36% overall yield (over two steps) after silica gel column chromatography as a colourless amorphous powder. The ^1H NMR spectrum of this macrocyclic diamide revealed the presence of two diagnostic amide protons, among others, as a sin-



Scheme 3. Reagents and conditions: (i) MsCl, DBU, CH_2Cl_2, 0 °C to rt, 18 h, 76%; (ii) LiOH, THF–H_2O (4:1), rt, 3 h, 91%; (iii) TFA (50%) in CH_2Cl_2, 0 °C, 1.5 h; (iv) HATU, DIPEA, DMF–CH_2Cl_2 (1:2) (5 mM), 0 °C to rt, 3 d, 36% over two steps.

glet and a doublet at δ 9.49 (broad singlet) and 8.34 (doublet, $J = 7.3$ Hz), respectively. However, its poor solubility in common solvents precluded recording its ^{13}C NMR spectrum. A high resolution mass measurement was in support of the molecular formula.

In short, we have developed a concise convergent synthesis of a doubly functionalised trisoxazole derivative and demonstrated its utility for the construction of a macrocyclic hexaoxazole ring system with built-in functionalities for the possible appendage of further oxazole/thiazole units.[16] Macrocyclic hexaoxazole derivatives have very recently been shown[17] to selectively bind to G-quadruplex DNA but not to duplex DNA, and also to exhibit cytotoxic activity against human lymphoblastoma and murine leukaemia. It remains to be seen whether compound **16** could be useful in this regard.

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15. Procedure for the conversion **14** → **16**: Compound **14** (60 mg, 0.082 mmol) was added in one portion to a 50% solution of trifluoroacetic acid in dichloromethane (3 ml) at 0 °C under nitrogen and the resulting mixture was stirred for 1.5 h at the same temperature. It was then concentrated in vacuo to leave **15** as a yellowish solid, which was used as such in the next step. The crude solid was dissolved in a mixture of dichloromethane (10 ml) and *N*,*N*-dimethylformamide (5 ml) and the resulting solution was cooled to 0 °C under nitrogen atmosphere. *N*,*N*-Diisopropylethylamine (50 μl, 0.28 mmol) was then added and after stirring for 15 min, HATU (47 mg, 0.124 mmol) was added. Stirring was continued for 1 h at the same temperature and then the reaction mixture was allowed to come to room temperature and stirred for 3 days. It was then concentrated in vacuo to leave a yellowish mass, which was dissolved in chloroform (25 ml). The organic extract was washed successively with aqueous citric acid (10%, 2 × 10 ml), saturated aqueous sodium bicarbonate solution (2 × 10 ml), water (10 ml) and brine (10 ml), and then dried (Na_2SO_4). It was then filtered and the filtrate was concentrated under reduced pressure to leave a crude solid, which was purified by chromatography over silica gel using a mixture of chloroform and methanol (19:1) as an eluent to afford product **16** as a colourless amorphous powder (16 mg, 36% over two steps). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.49 (1H, br s), 9.20 (1H, s), 9.16 (2H, s), 9.13 (1H, s), 9.07 (1H, s), 8.94 (1H, s), 8.34 (1H, d, $J = 7.3$ Hz), 6.74 (1H, s), 5.89 (1H, s), 5.34–5.32 (1H, m), 4.98 (1H, br s), 4.02–3.98 (2H, m). HRMS (TOF MS ES+): obsd 597.0529 (M+K); calcd 597.0521.
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