Synthesis of the penta-oxazole core of telomestatin in a convergent approach to poly-oxazole macrocycles

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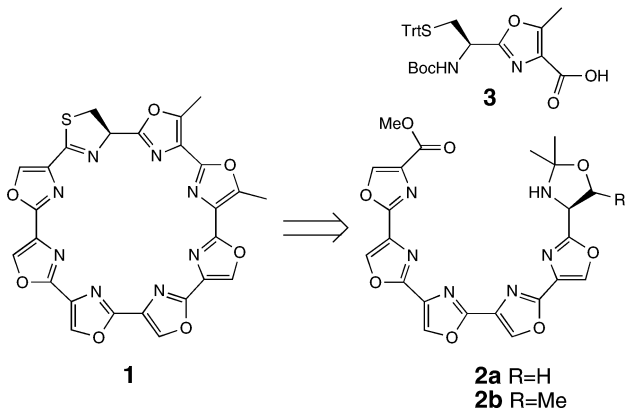
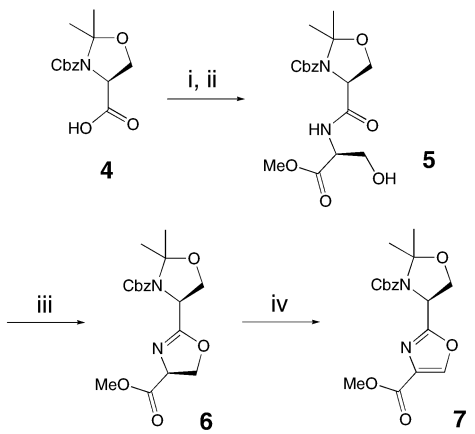
A protocol for the construction of poly-oxazoles with consecutive 2,4′-linkages is described, and has afforded an efficient route to a penta-oxazole which demarcates a route to telomestatin and related macrocyclic poly-oxazole systems.

Telomestatin (**1**), the most potent inhibitor of telomerase function known (IC_{50} = 5 nM), was recently isolated from *Streptomyces anulatus* 3533-SV4.[1] Telomestatin is also a specific inhibitor of telomerase function, and does not inhibit DNA polymerases or reverse transcriptases such as *Taq* polymerase or HIV-RT.[1] The mode of inhibition is considered to involve stabilisation of human DNA G-quadruplex structures or facilitation of their formation.[2] The synthesis of telomestatin requires the assembly of seven oxazole rings, each with a consecutive 2,4′-linkage. Whereas both linear[3] and convergent[4] routes to such tris-oxazoles have been reported, the synthesis of poly-oxazoles, especially with terminal substituents appropriate to natural product synthesis, remains a challenge.[5] Here, we report the synthesis of the penta-oxazole core **2a** of telomestatin whose methyl derivative **2b** could be an advanced intermediate in its total synthesis, by subsequent condensation with a suitably substituted oxazole such as **3**.



The biosynthesis of telomestatin (**1**), although not yet elucidated, can be interpreted as a formal assembly of one cysteine, five serine and two threonine sub-units. From a synthetic viewpoint, condensation of pairs of amino acid residues to give 2,4-disubstituted oxazoles such as **7**, followed by convergent condensation to give tetra-serine building blocks such as **12**, appeared to offer a practical and flexible strategy. Accordingly, an efficient route to di-serine building blocks (Scheme 1) was developed based upon the Williams–Wipf cyclisation–dehydrogenation protocol using (dimethylamino)sulfur trifluoride (DAST) followed by treatment with $BrCCl_3$ and DBU.[6] *N*-Cbz-L-Ser (prepared from L-serine and benzyl chloroformate in aqueous 2 M NaOH) was protected using dimethoxypropane in the presence of *p*-TsOH as catalyst to give acid **4** (57% over two steps) which, as its mixed anhydride, was reacted with the hydrochloride salt of L-Ser-OMe to give the di-serine derivative **5**. This was cyclised using DAST at −78 °C to give the oxazoline **6**, which with $BrCCl_3$–DBU afforded the oxazole **7**.



Scheme 1 *Reagents and conditions*: i, *t*-BuOCOCl, Et_3N, CH_2Cl_2; ii, L-serine methyl ester hydrochloride, −30 °C, 2.5 h, 95% over two steps; iii, DAST, CH_2Cl_2, −78 °C, 2.5 h, 85%; iv, $BrCCl_3$, DBU, CH_2Cl_2, −10 °C to 20 °C, 17 h, 92%.

Oxazole **7** was the common precursor of the di-serine building blocks **8** and **9** (Scheme 2), which in a convergent strategy afforded the advanced intermediates **11**, **12** and **13** derived from four serine sub-units. Acid-catalysed hydrolysis of the *N*,*O*-acetal of **7** followed by hydrogenolysis of the Cbz group afforded the amino alcohol **8**. Alkaline hydrolysis of ester **7** afforded the acid **9**, which acylated **8** giving **10** without difficulty when performed at −62 °C in DMF using benzyltriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP) in the presence of $(i\text{-Pr})_2NEt$ and 1-hydroxybenzotriazole (HOBt). Cyclisation of amide **10** with DAST at −78 °C afforded oxazoline **11**, which underwent dehydrogenation with $BrCCl_3$–DBU to give the oxazole **12**. Alkaline hydrolysis of oxazole **12** afforded the acid **13**, which could also be used to acylate the amino group of **8** using the BOP procedure, at −62 °C for this condensation.

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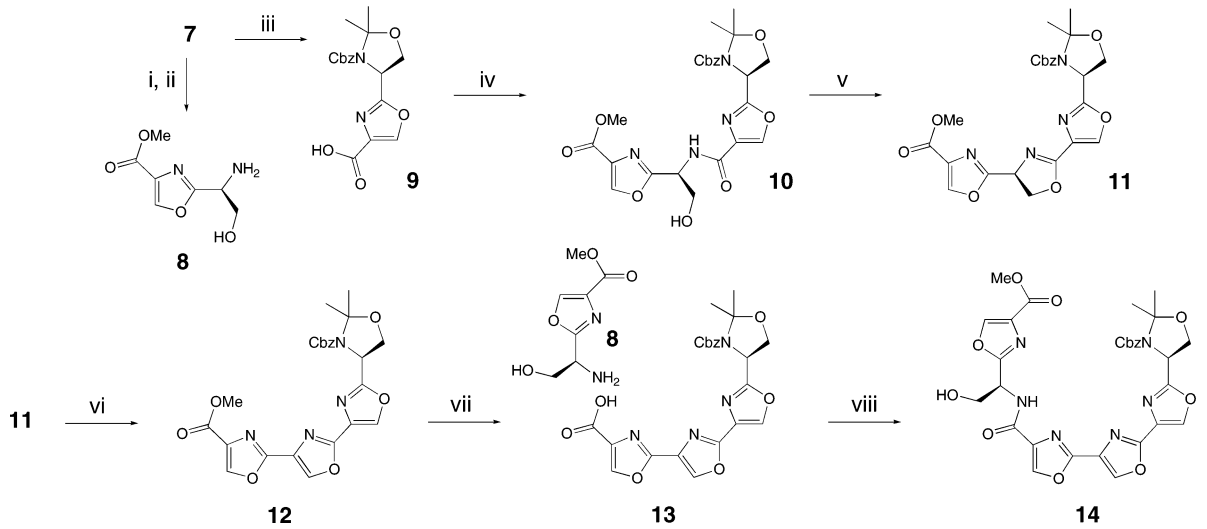
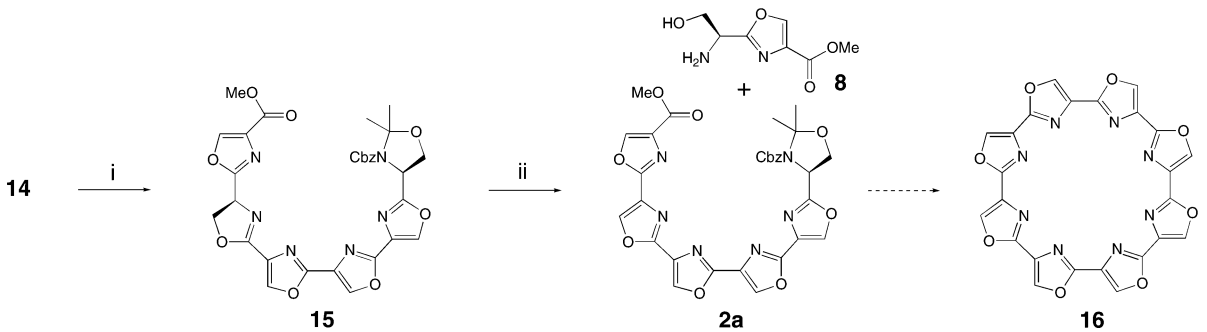


Scheme 2 *Reagents and conditions*: i, MeOH, *p*-TsOH, reflux 2.5 h; ii, H_2, 10% Pd/C, 92% over two steps; iii, LiOH, THF–H_2O (8 : 1), 50 °C, 17 h, 83%; iv, BOP, $(i\text{-Pr})_2$NEt, HOBt, DMF, −30 °C, 77%; v, DAST, CH_2Cl_2, −78 °C, 2.5 h, 79%; vi, $BrCCl_3$ (2 equiv.), DBU (4 equiv.), CH_2Cl_2, −10 °C to 20 °C, 17 h, 72%; vii, LiOH, THF–H_2O (8 : 1), 60 °C, 17 h, 95%; viii, BOP, $(i\text{-Pr})_2$NEt, HOBt, DMF, −62 °C, 40%.



Scheme 3 *Reagents and conditions*: i, DAST, CH_2Cl_2, −78 °C, 2.5 h, 80%; ii, $BrCCl_3$ (22 equiv.), DBU (40 equiv.), CH_2Cl_2, −10 °C to 20 °C, 17 h, 68%.

The successive use of amines bearing unprotected hydroxymethyl groups is a notable feature of the strategy, and permits iterative assembly of polyoxazoles without the need for repeated protection and deprotection.

A further round of acylation–cyclisation–dehydrogenation was successful: coupling acid **13** with amine **8** using the BOP procedure at −62 °C gave the amide **14**, which cyclised with DAST to give the oxazoline **15** (Scheme 3). Again, the internal oxazoline ring could be dehydrogenated, and thus gave the penta-oxazole **2a**.[7] In addition to demarcating an approach to telomestatin (**1**), the penta-oxazole **2a** could also be reacted with oxazole **8**, using the protocol outlined, to furnish the C_8-symmetric octa-oxazole analogue **16**, which would provide a valuable comparison with the natural product **1**, especially in terms of their relative biological effects on telomerase. The strategy permits regioselective introduction of substituents at the 5-position of one or more oxazole rings (as required), and thus a variety of analogues with which to probe telomerase function. The synthetic route also provides several linked polyoxazole systems of increasing complexity, but derived from serine as the only amino acid.

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Notes and references

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7 **2a**: δ_H (DMSO-d_6, 313 K, 400 MHz) 8.99 (1H, s), 8.97 (1H, s), 8.90 (1H, s), 8.85 (1H, s), 8.78 (1H, s), 7.24 (5H, m), 5.30 (1H, dd, J = 6.5 and 2.5 Hz, C*H*CH_2), 5.14 (1H, d, J = 12.7 Hz, C*H*HPh), 5.02 (1H, d, J = 12.7 Hz, CH*H*Ph), 4.34 (1H, dd, J = 9.3 and 6.5 Hz, C*H*HCH), 4.16 (1H, dd, J = 9.3 and 2.7 Hz, CH*H*CH), 3.87 (3H, s, OCH_3), 1.70 (3H, s, CH_3), 1.57 (3H, s, CH_3) ppm; δ_C (DMSO-d_6, 353 K, 100 MHz) 163.4 (s), 160.1 (s), 155.1 (s), 155.0 (s), 154.9 (s), 154.3 (s), 151.0 (s), 144.3 (d), 140.1 (d), 140.05 (×2, d), 140.0 (d), 135.7 (s), 133.1 (s), 129.7 (s), 129.6 (s), 129.5 (s), 129.7 (s), 127.5 (d), 127.0 (d), 126.7 (d), 94.1 (NCO), 66.4 (CH_2OCO), 65.8 (OCH_2CH), 54.0 (OCH_2CH), 50.9 (OCH_3), 24.9 (CH_3), 23.6 (CH_3) ppm; *m*/*z* found: 651.1462; $C_{30}H_{24}N_6O_{10}$ (M + Na)$^+$ requires 651.1452.