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Synthesis of an L-proline modified mimetic of the A83586C antitumour cyclodepsipeptide†

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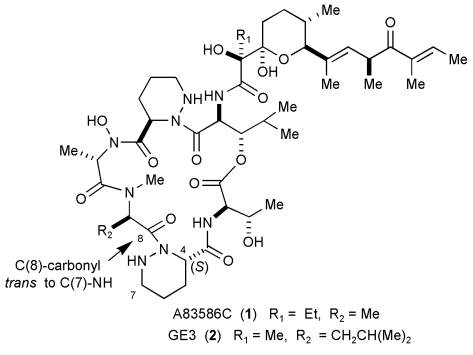
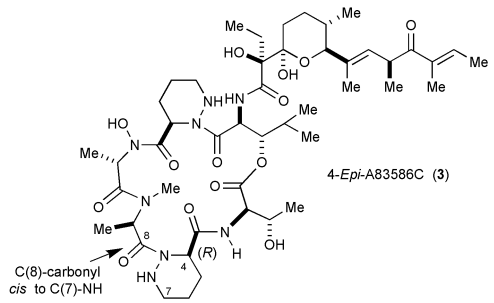
A mimetic of the A83586C cyclodepsipeptide has been synthesised *via* a three-segment coupling protocol involving dipeptides 9, 8 and 7; in contrast to our previous synthesis of A83586C, where the HATU-mediated macrolactamisation proceeded in 25% yield, the corresponding macro-lactamisation of *seco*-amino acid 18 occurred in *ca.* 78% yield.

A83586C[1] and GE3[2] are exciting new anticancer agents with a mechanism of action thought to involve the selective inhibition of deregulated E2F transcription factors within cancer cells.[2]

Some time ago, we reported the first asymmetric total synthesis of A83586C[3] and its 4-*epi*-analogue.[4] 4-*Epi*-A83586C has a (3*R*)-piperazic acid component replacing the (3*S*)-Piz unit. While this modification does actually serve to improve the yield of macrolactamisation from 25 to 70%,[3,4] it has a seriously detrimental effect on antitumour potency; the 4-*epi*-analogue being much less active as an antitumour drug.[5] High-field NMR studies on 4-*epi*-A83586C[4] suggest that its C(8)-carbonyl assumes a *cis*-orientation relative to the C(7)-piperazine-NH, which is opposite to A83586C, where a *trans*-relationship is believed to exist between these two groupings.[1] The combined experimental data suggests that significant conformational perturbations to this region are not well tolerated.

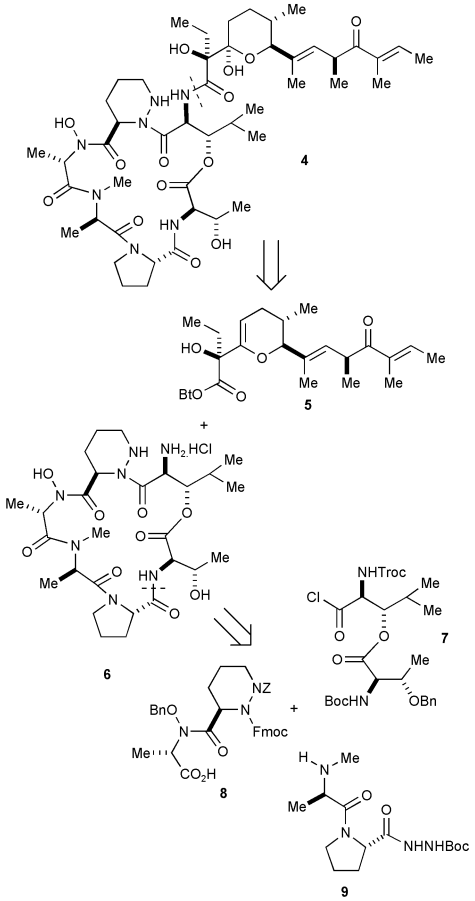




As part of an ongoing programme aimed at identifying a more readily synthesised analogue of A83586C that has similar conformational properties and improved potency, we selected the L-proline-modified congener **4** as a candidate for study. Our choice of an L-proline replacement for the (3*S*)-piperazic acid unit was guided by two factors. First, cyclisation at an activated proline residue is usually free of racemisation risk, and second, (3*S*)-piperazic acid has previously functioned as a very effective mimic of L-proline in ACE-inhibitory drugs such as cilazapril.[6] It seemed logical, therefore, to reverse the roles for the situation at hand.

We anticipated obtaining **4** from the chemoselective union of **5**[3] with **6**. A [2 + 2 + 2]-fragment condensation was envisaged for constructing the linear hexadepsipeptide precursor of **6**; the key ring-closure would be effected through the L-pro and D-Thr termini (Scheme 1).

Dipeptide **14** (Scheme 2) was prepared from *N*(Z)-L-proline (**10**) by amidation with *tert*-butyl carbazate,[7] hydrogenolytic removal of the Z-group from **11** with a Pd/C catalyst, and silver cyanide mediated coupling[8] of **12** with **13**. Fmoc[9] cleavage of **14** with Et_2NH in acetonitrile subsequently procured amine **9**. The coupling of dipeptides **9** and **8**[3] proceeded smoothly when mediated by BOP-Cl[10] and Et_3N at low temperature for 1.5 h; tetrapeptide **15** was isolated in 89% yield after chromatography. Fmoc-deprotection and subsequent reaction of **16** with acid chloride **7**[3] under silver cyanide-assisted conditions[8] furnished the desired depsipeptide **17** in 73% yield. The Boc-protected



Scheme 1 Retrosynthetic strategy for the L-proline modified A83586C congener (**4**).

† Electronic supplementary information (ESI) available: characterisation data. See http://www.rsc.org/suppdata/cc/b2/b204018b/

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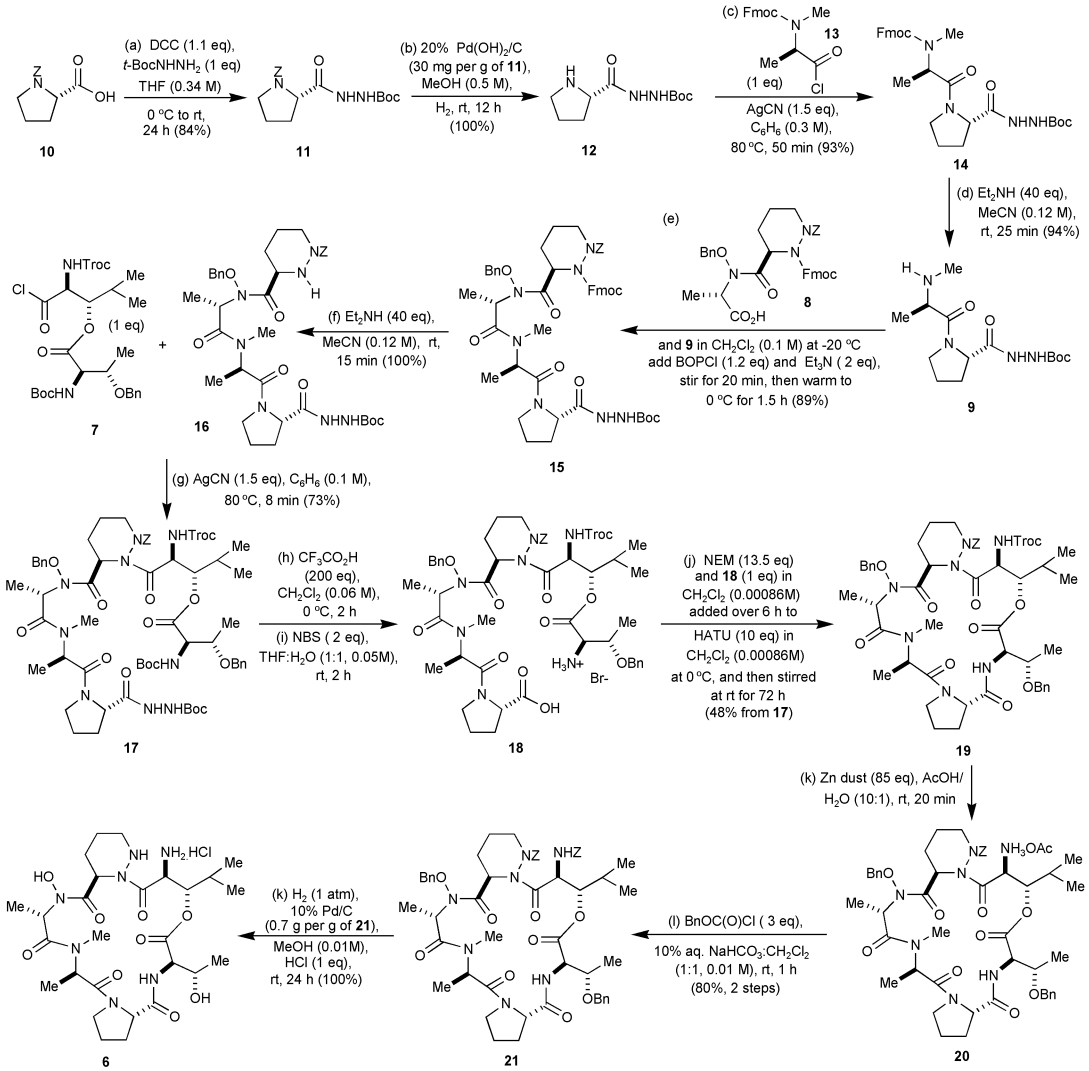

Scheme 2 Synthetic route to the L-proline modified mimetic **6**.

acyl-hydrazide of the L-proline residue in **17** was next converted to the corresponding acid by successive treatment with TFA (to remove the Boc groups) and *N*-bromosuccinimide in aqueous THF. The latter reaction is thought to create a hydrolytically-labile acyl diazene.[11] The macrolactamisation of *seco*-aminoacid **18** proceeded smoothly when HATU[12] was used to activate the proline residue under high-dilution conditions. The desired macrolactam **19** was isolated in 48% overall yield for the three steps from **17**. The Troc group of **19** was now detached with Zn in aqueous AcOH[13] and compound **20** acylated with ZCl to obtain **21**. This protocol enabled **21** to be obtained highly pure by flash chromatography prior to it being hydrogenated over Pd on C in methanolic HCl. The latter process worked efficiently, compound **6** being recovered in essentially quantitative yield.

Future work will attempt to chemoselectively couple **6** to the pyran activated ester **5**[3] to obtain **4**. It is envisaged that the solution conformation and antitumour activity of **4** will then be determined to see how they compare with A83586C. Attempts will also be made to exploit cyclodepsipeptide **6** for high-throughput parallel synthesis work aimed to identifying simplified new anticancer drugs that act by an E2F inhibitory mechanism.

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