Asymmetric total synthesis of antitumour antibiotic A83586C

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The first asymmetric total synthesis of antitumour antibiotic A83586C has been accomplished.

A83586C **1** is a highly ornate hexadepsipeptide isolated from the fermentation broths of *Streptomyces karnatakensis* by Smitka *et al.*[1] It shows pronounced antimicrobial activity *in vitro* against Gram-positive strains of bacteria, and can combat the growth of a CCRF-CEM human T-cell leukaemia line (IC_{50} = 0.0135 μg ml^{-1}). From a synthetic standpoint, A83586C **1** presents a formidable challenge owing to its ominous expanse of diverse functionality, which looks set to overwhelm most protecting group endgames conceived for its total synthesis. In light of this, we thought it prudent to dispense with protecting groups for the final stages, and some time ago, we synthesised the C(1)–C(47) sequence **2** *via* a chemoselective union between **3** and **4** (Scheme 1).[2] Unfortunately, difficulties later arose not only in the macrolactonisation of **2**, but also its *seco*-acid. This led us to consider new ways of completing this synthetic venture. One plan that looked particularly worthwhile featured a coupling between **6** and **3** to obtain **5** and a subsequent glycal hydration at C(30) to produce **1**. We now report the first total synthesis of A83586C based on this strategy.

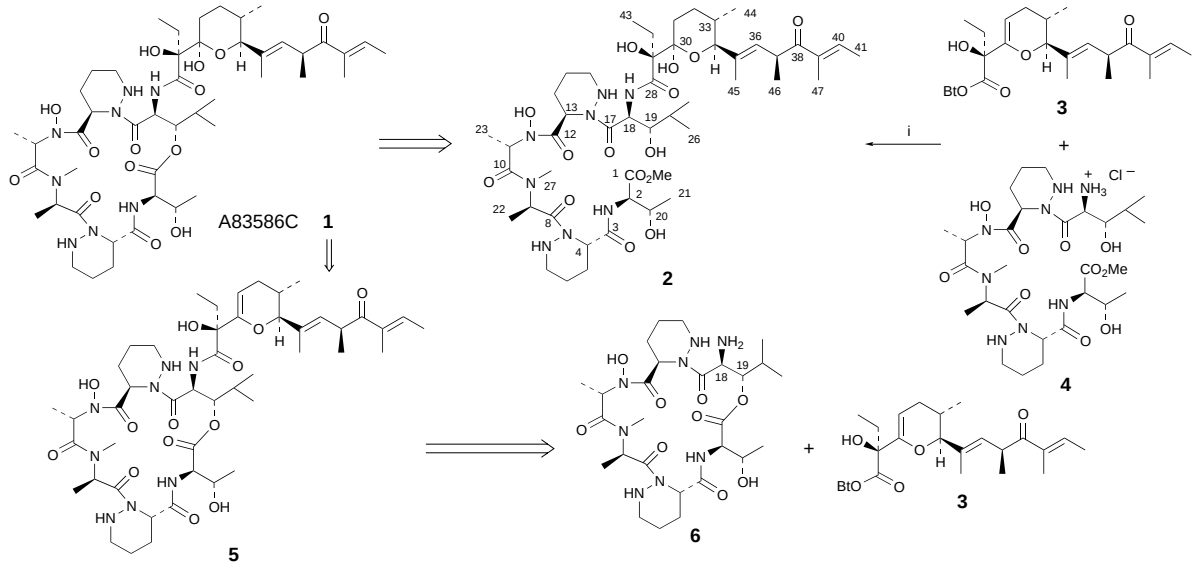
Initial attention focused on constructing **11** and **16** (Scheme 2). Tetrapeptide **11** was assembled in eight steps from known dipeptide **7**.[3] Our first manoeuvres replaced the Ph_2CH ester[4] group in **7** with a Boc-NHNH group,[5] to prevent diketopiperazine formation occurring when the Fmoc group was removed with Et_2NH. Fortunately, this tactic worked very well, **8** being isolated uneventfully after Fmoc deprotection. Compound **8** coupled readily to acid **9**[3,6] in CH_2Cl_2 at 0 °C after sequential treatment with Et_3N and bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl);[7] **10** was obtained in 75% yield. The Boc group was cleaved from **10** with TFA, and the acyl hydrazine oxidised with *N*-bromosuccinimide (NBS) in aqueous THF.[8] Without further purification, the crude acid was esterified with Ph_2CN_2[4] and the Fmoc group excised to deliver **11**.

The synthesis of **16** was achieved from (2*S*,3*S*)-hydroxyleucine.[9] After Troc protection of the amino group,[6] a selective *O*-allylation was performed with $NaHCO_3$ and allyl bromide in DMF;[10] **13** was isolated in 92% yield. A range of coupling conditions were examined for establishing the O(19)–C(1) ester bond between **13** and **14**.[11] Success finally came using DCC and DMAP in CH_2Cl_2, but 5–10% epimerisation was always encountered at the α-carbon atom of the threonine unit. Notwithstanding this, **15** was usually prepared in 83–88% yield. The next two steps involved removal of the allyl ester group from **15** using palladium(0) catalysis,[12] and acid chloride formation with excess oxalyl chloride in benzene.

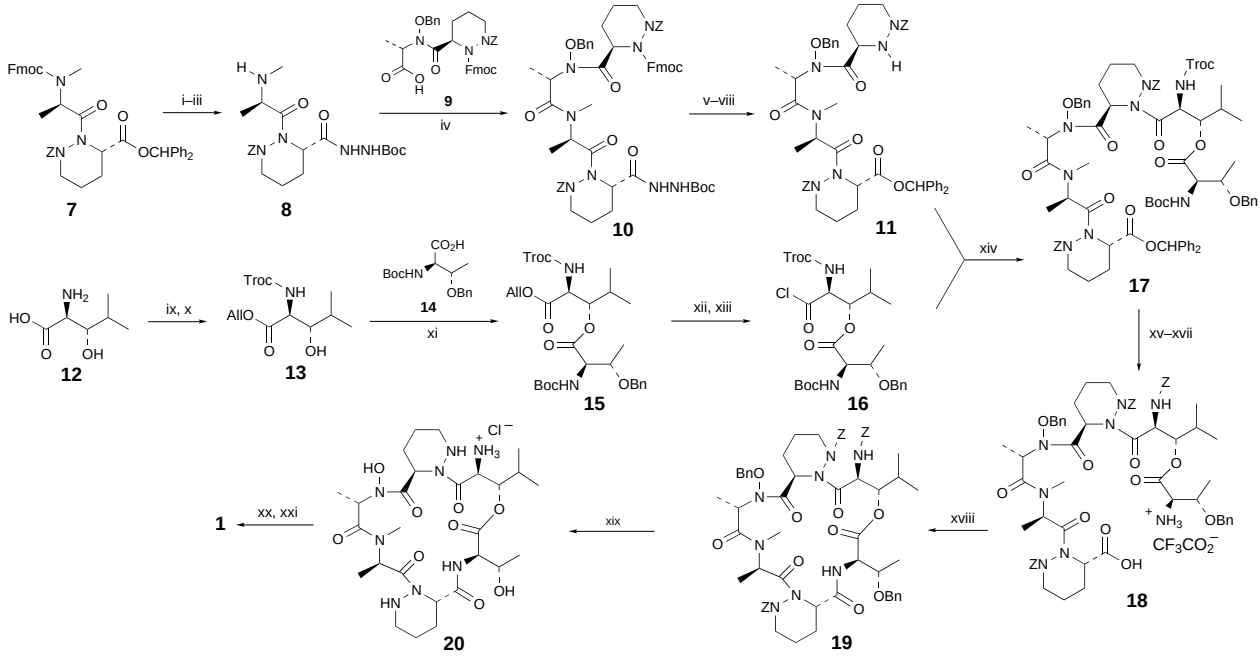
To our delight, [4 + 2]-fragment condensation between **11** and **16** was complete after 2 min when conducted in benzene at 60 °C in the presence of AgCN;[6] **17** was formed in yields of 73–86%.

Our next goal was to convert **17** into **18** and then macrolactamise at the (3*S*)-piperazic acid and D-threonine residues. The Troc group in **17** was substituted with a *Z* group by reacting **17** with excess zinc in acetic acid,[6] and acylating the crude amine with BnO_2CCl. TFA was then used to simultaneously deprotect the Boc and Ph_2CH ester groups to give **18** in 78% overall yield for the three steps.

A significant number of peptide coupling reagents were evaluated for instigating the desired macrolactamisation of **18** to **19**, the majority of which performed poorly. Success was eventually attained with *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*-tetramethyluronium hexafluorophosphate (HATU)[13] and *N*-ethylmorpholine (NEM) in CH_2Cl_2 under conditions of very



Scheme 1 *Reagents and conditions*: i, Et_3N, CH_2Cl_2, −78 to 25 °C, SiO_2, 65%



Scheme 2 *Reagents and conditions*: i, TFA–CH_2Cl_2 (10 : 1), PhOH (2 equiv.), 25 °C; ii, $BocNHNH_2$ (2 equiv.), DCC (2 equiv.), 1-hydroxybenzotriazole hydrate (HOBT) (2 equiv), THF (*ca.* 0.33 M), 0 to 25 °C, 93% (2 steps); iii, Et_2NH–MeCN (1 : 1) (*ca.* 0.55 M); iv, CH_2Cl_2 (*ca.* 0.15 M), add Et_3N (2.3 equiv.) at −10 °C, stir 5 min, then add BOP-Cl (1.2 equiv.), warm to 0 °C, 4 h, 75% (2 steps); v, TFA–CH_2Cl_2 (1 : 1) (*ca.* 0.2 M), 0 °C; vi, NBS (2 equiv.), THF–H_2O (1 : 1) (*ca.* 0.04 M), 0 to 25 °C; vii, Ph_2CN_2 (1.9 equiv.), Me_2CO (*ca.* 0.16 M), 25 °C, 12 h, 68% (3 steps); viii, Et_2NH–MeCN (1 : 1) (*ca.* 0.24 M), 25 °C, 40 min; ix, Troc-Cl (1.05 equiv.), NaOH (2 equiv.), THF, H_2O, 25 °C, 90%; x, $NaHCO_3$ (4.3 equiv.), allyl bromide (6.2 equiv.), DMF (*ca.* 0.31 M), 25 °C, 92%; xi, DCC (1.2 equiv.), DMAP (1.25 equiv.), CH_2Cl_2 (*ca.* 0.322 M), 0 to 25 °C, 83–88%; xii, morpholine (6.5 equiv.), $(Ph_3P)_4Pd$ (5.9 mol%), THF (*ca.* 0.22 M), 0 to 25 °C, 59%; xiii, $(COCl)_2$ (20 equiv.), C_6H_6 (*ca.* 0.4 M), 25 °C, 2.5 h; xiv, AgCN (1.3 equiv.), C_6H_6 (*ca.* 0.12 M), 60 °C for 2 min, 73–86% (for viii, xiii, xiv); xv, Zn (70 equiv.), AcOH–H_2O (10 : 1) (*ca.* 0.0685 M), 25 °C, 3 h; xvi, ZCl (3 equiv.), 10% aq. $NaHCO_3$, CH_2Cl_2, 25 °C, 2 h, 78% (2 steps); xvii, TFA–CH_2Cl_2 (2 : 1) (*ca.* 0.06 M), PhOH (2.2 equiv.), 0 °C, 1 h, 100%; xviii, HATU (10 equiv.), CH_2Cl_2 (500 ml), 0 °C, then slow addition of **18** (1.4 g) and NEM (13.5 equiv.) in CH_2Cl_2 (500 ml) over 3 h, then 0 °C, 2 h, then 25 °C, 30 h, 25%; xix, 10% Pd–C (= weight of **19** used), MeOH (*ca.* 0.01 M), HCl (1 equiv.), H_2 (1 atm.), 25 °C, 24 h; xx, **3** (1 equiv.), CH_2Cl_2 (*ca.* 0.03 M), −78 °C, add Et_3N (9.3 equiv.), warm to 25 °C, stir 10 min, 31% (from **19**); xxi, $CDCl_3$ (wet), 72 h, 0 °C, 100%

high dilution. This produced **19** in a reproducible 25% yield after flash chromatography. Compound **19** was then deprotected by catalytic hydrogenolysis over palladium on carbon. We deliberately conducted this hydrogenation in methanolic HCl, so as to minimise the occurrence of O(19) to N(18) acyl rearrangement during this lengthy reaction. Without further purification, crude **20** was suspended in CH_2Cl_2 along with **3**.[2] After cooling to −78 °C, Et_3N was added, and the reaction warmed to room temperature where it was stirred for 10 min. A rapid coupling ensued to deliver **5** in 31% yield after chromatographic purification. Upon standing in undried $CDCl_3$ (Aldrich) for 72 h, **5** readily hydrated to give A83586C in quantitative yield. The ^1H and ^{13}C NMR spectra of synthetic A83586C in $CDCl_3$ were identical in every respect with the spectra of authentic A83586C. In addition, synthetic A83586C also gave rise to an $(M + Na)^{+\cdot}$ ion at *m*/*z* 999.5360 in its high resolution FAB mass spectrum;† the calculated value for $C_{47}H_{76}N_8O_{14}Na$ is 999.5379.

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† All new compounds reported in this synthetic route gave satisfactory 400 MHz ^1H and 100 MHz ^{13}C NMR and IR spectra, as well as HRMS and/or microanalyses within 0.4%.

Footnotes and References

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