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Asymmetric Synthesis of the C(1)-C(47) Backbone of Antitumour Antibiotic A83586C

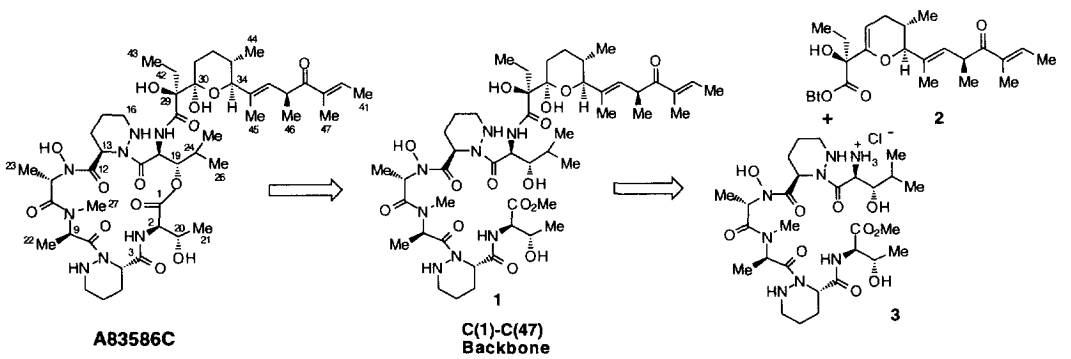
Karl J. Hale,* Jiaqiang Cai, and Vern M. Delisser

The Christopher Ingold Laboratories, Department of Chemistry,
University College London,
20 Gordon Street, London WC1H 0AJ, UK.

Abstract: Protected pentapeptide **9** has been converted to hexapeptide **3** and this chemoselectively coupled to activated ester **2** to give **1** after glycal hydration during SiO_2 flash chromatography.

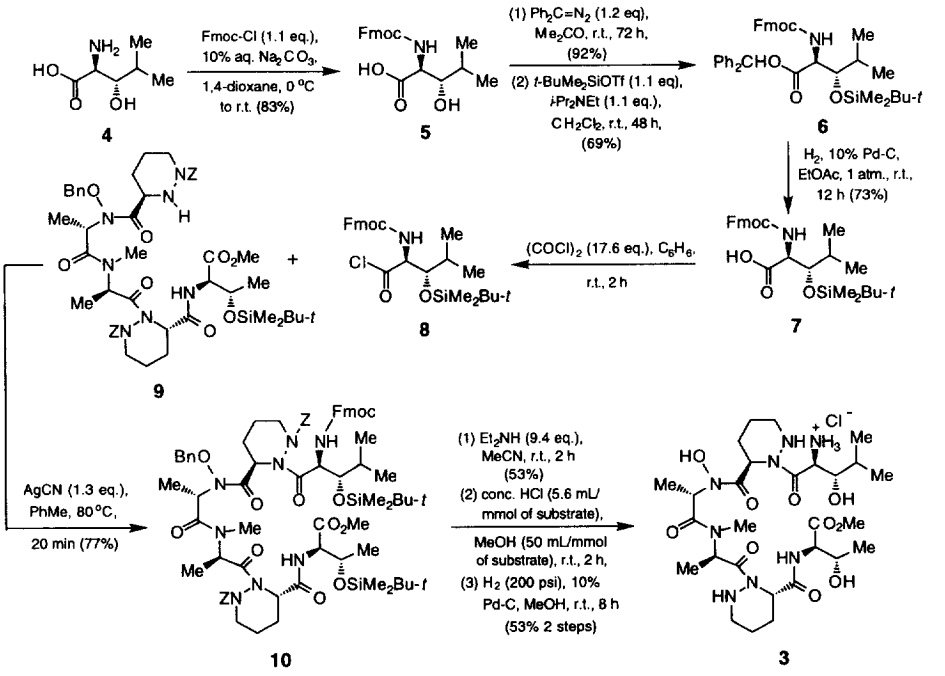
The diverse array of reactive functionality present within the structure of antitumour antibiotic A83586C[1a] conspires to make it a difficult and challenging target for total synthesis. One design element which requires particularly careful consideration is protecting group strategy. Conceptually, an approach which utilises protecting groups solely for the purpose of assembling highly functionalised pyran and linear hexapeptide fragments, but which dispenses with them prior to fragment coupling, could prove advantageous. Besides avoiding risky deprotection and oxidation steps for the final stages, the enhanced opportunities for intramolecular hydrogen bonding in the coupled product could be expected to facilitate macrolactonisation. One retrosynthetic analysis which encompasses this thinking is depicted in Scheme 1. It has as its centrepiece, a union between activated ester **2** and linear hexapeptide **3**, followed by glycal hydration. This would create **1**, a molecule embodying the entire C(1)-C(47) sequence of A83586C. In this communication, we describe our progress towards implementing this synthetic plan.

Scheme 1



Our route to linear hexapeptide **3** commenced with known[2] pentapeptide **9** and is outlined in Scheme 2. Since we were aware that activated esters and mixed anhydrides of protected amino acids are insufficiently reactive to allow peptide coupling to *N*-2 of *N*-1 acylated piperazic acid derivatives, we selected amino-acid

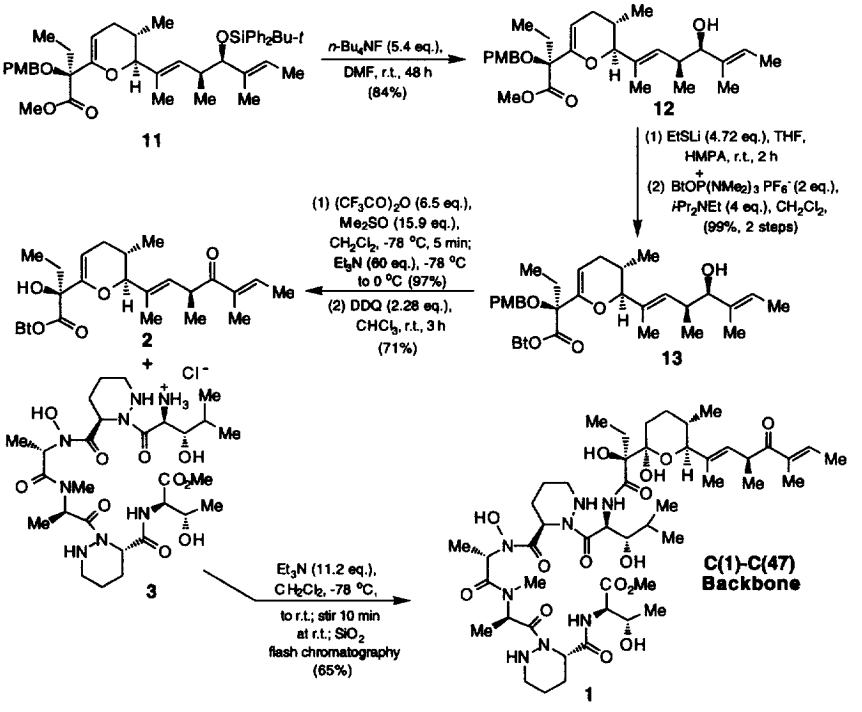
Scheme 2



chloride **8** as our initial sub-target. (*2S,3S*)-3-Hydroxyleucine **4** [3] was selectively protected with Fmoc-Cl in 1,4-dioxane and 10% aqueous sodium carbonate to give **5**, and the acid group masked as a diphenylmethyl ester.[4] The β-hydroxyl was then *O*-silylated in 69% yield by treatment with *tert*-butyldimethylsilyl triflate and Hunig's base in dichloromethane. The diphenylmethyl group was removed from **6** by hydrogenation in EtOAc in the presence of a 10% palladium on carbon catalyst. The resulting acid **7** was then converted to acid chloride **8** by reaction with excess oxalyl chloride in benzene. After removing excess chlorinating reagent *in vacuo*, the crude acid chloride was coupled to pentapeptide **9** in toluene at 80 °C in the presence of silver cyanide,[5] with hexapeptide **10** being obtained in 77% yield. Our next task was to remove virtually all of the protecting groups from **10** to give **3**. The best sequence involved cleavage of the Fmoc group[6] from **10** with Et_2NH in acetonitrile, removal of the *O*-silyl protecting groups with conc. HCl in methanol, and exhaustive hydrogenation of the hydrochloride salt in methanol in the presence of a 10% palladium on carbon catalyst. Hexapeptide **3** was purified by flash chromatography with 10:1 CH_2Cl_2/MeOH and isolated in 53% yield.

Activated ester **2** was prepared from known[7] methyl ester **11** as shown in Scheme 3. The first step entailed *O*-desilyation with tetra-*n*-butylammonium fluoride in DMF at room temperature which proceeded in 84% yield. The methyl ester was then detached from **12** {$[\alpha]_D$ +46.6 ° (*c* 0.8, CH_2Cl_2)} with lithium ethanethiolate[8] in THF and HMPA, and the crude acid converted to its benzotriazole (Bt) ester **13** by reaction with *i*-Pr_2NEt and BOP[9] in CH_2Cl_2. After Swern oxidation with trifluoroacetic anhydride and DMSO, the product ketone was isolated in 97% yield. The *p*-methoxybenzyl group was then excised from O(29) by exposure to 2.28 equivalents of DDQ[10] in chloroform for 3 h. It proved essential to remove all the DDQ residues from the deprotected product **2**, by rapid flash chromatography with 4:1 petrol/EtOAc, prior to performing the coupling with **3**. If this purification step was omitted, a serious decomposition reaction would always ensue whenever this reaction was attempted. Fortunately, when purified **2** was used, the desired regio-

Scheme 3



selective acylation proceeded cleanly to give **1** in 65% isolated yield *after* SiO_2 flash chromatography. Significantly, unmasking of the tertiary hydroxyl group at C(29) greatly facilitated glycal hydration at the flash chromatography stage, removing any need to develop a separate reaction for this purpose. Amazingly, the 400 MHz ^1H NMR spectrum of **1** in $CDCl_3$ indicated the presence of only one rotameric form (See Fig. 1). Moreover, the amide NH protons of the β-hydroxyleucine and D-threonine residues resonated at δ 7.89 and 7.15 respectively. According to Gellman[11] and Gung,[12] such chemical shifts are highly characteristic of amide

Fig. 1. 400 MHz ^1H NMR spectrum of **1** (*c* 8 mg in 0.7 ml $CDCl_3$)

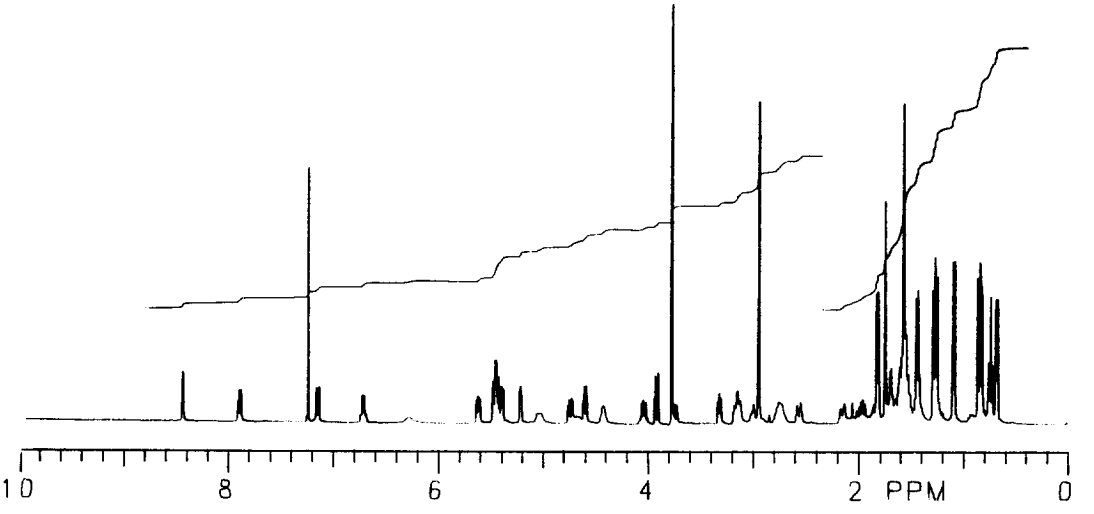
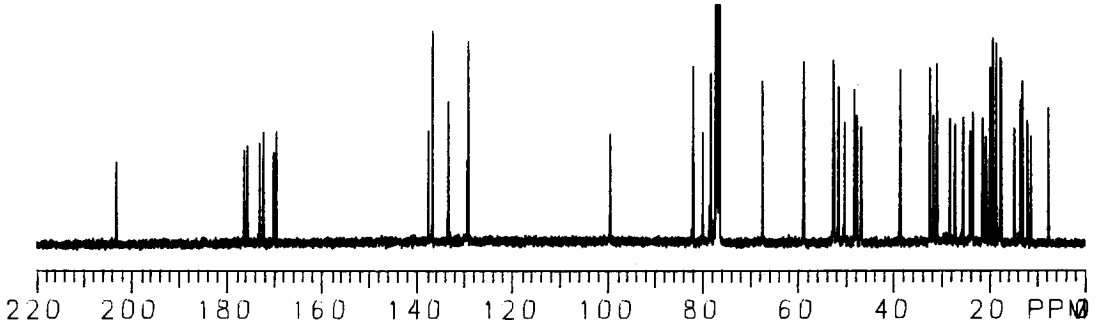


Fig. 2 100 MHz ^{13}C NMR spectrum of **1** (*c* 8 mg in 0.7 ml $CDCl_3$)



NH protons that are intramolecularly hydrogen bonded. A detailed analysis of the NMR and conformational properties of **1** will be the subject of a future publication. However, it suffices to say at present that the ^1H NMR spectrum of **1** is in full agreement with the proposed structure, as is the 100 MHz ^{13}C NMR spectrum in $CDCl_3$, which shows signals for 48 carbons (Fig. 2).[13] Further evidence for the structure of **1** comes from its high resolution FAB mass spectrum which exhibits an $(M+Na)^+$ ion at *m/e* 1031.5645 (Calcd. for $C_{48}H_{80}N_8O_{15}Na$ *m/e* 1031.5636). Surprisingly, prolonged storage of **1** at 4-5 °C for several months leads to its reversion to the glycal! If this occurs, compound **1** can be regenerated simply by storing the glycal in undried $CDCl_3$ (Aldrich 99.8%) for several days, or by subjecting it to SiO_2 flash chromatography with 40:1 CH_2Cl_2/MeOH as eluant, or by adding a very small quantity of conc. HCl to **1** in $CDCl_3$.

In conclusion, we have completed a viable asymmetric synthesis of the C(1)-C(47) backbone of A83586C and thereby demonstrated the feasibility of a chemoselective coupling strategy for linking unprotected pyran and hexapeptide sub-units in the Azinothricin family of antibiotics.[1] Further progress towards the total synthesis of A83586C and its analogues will be reported in due course.

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13. All new compounds gave satisfactory 400 MHz ^1H and 100 MHz ^{13}C NMR and IR spectral data as well as HRMS data. (**1**) is an amorphous solid: 100 MHz ^{13}C NMR ($CDCl_3$) at 25 °C δ 203.2, 176.4, 175.7, 173.2, 172.4, 172.2, 170.2, 169.7, 137.6, 136.8, 133.5, 129.3, 99.6, 82.1, 80.1, 78.5, 67.5, 59.0, 52.8, 52.7, 52.6, 51.7, 50.5, 48.4, 47.9, 46.9, 38.7, 32.5, 31.9, 31.0, 28.3, 27.3, 25.7, 24.1, 23.6, 21.6, 20.9, 20.0, 19.4, 18.7, 17.8, 17.7, 14.9, 13.6, 13.3, 12.1, 11.4, 7.7 ppm.

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