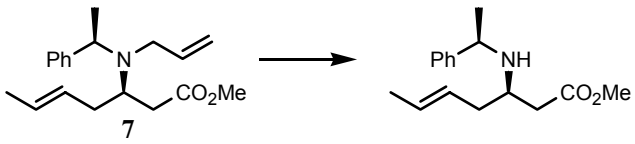
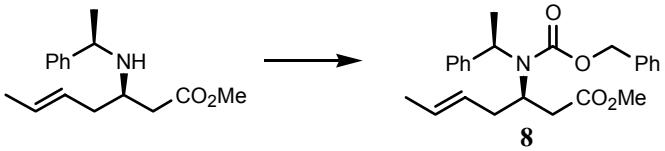
(3*R*,5*E*,α*R*)-Methyl 3-(*N*-[α-methybenzyl]amino)-hept-5-enoate



7

To a stirred solution of β-amino ester **7**[1] (18.9g, 62.8mmol) in MeCN/H_2O (4:1, 500mL) was added Wilkinson's catalyst (2.90g, 3.14mmol) and the mixture heated at reflux for 2h, with propanal being removed by azeotropic distillation. After cooling to rt, the solvent was removed *in vacuo*. Purification by column chromatography (50% ether in 40-60 petrol) afforded the title compound as a pale yellow oil (15.9mg, 97%).

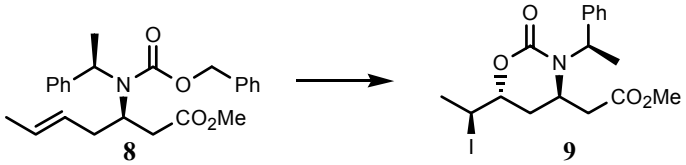
(3*R*,5*E*,α*R*)-Methyl 3-(*N*-[benzyloxycarbonyl]-*N*-[α-methybenzyl]amino)hept-5-enoate 8



8

To (3*R*,5*E*,α*R*)-methyl 3-(*N*-[α-methybenzyl]amino)-hept-5-enoate (27.9g, 107mmol) was added dibenzyl dicarbonate (61.2g, 214mmol, containing dibenzyl carbonate as an impurity) and the mixture stirred under high vacuum for 4 days. Purification by column chromatography (20% ether in 40-60 petrol) afforded an inseparable mixture of the title compound **8** and dibenzyl carbonate as a colourless oil (32.6g, 80:20 **8**:dibenzyl carbonate, 88% yield of **8**), which was used without further purification.

(4*R*,6*R*,1′*S*,α*R*)-3-(α-Methylbenzyl)-4-(methoxycarbonylmethyl)-6-(1′-iodoethyl)-1,3-oxazinan-2-one 9

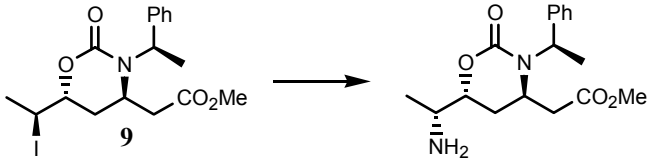


8 **9**

To a stirred solution of benzyl carbamate **8** (2.09g, 5.29mmol) in DCM (50mL) under N_2 at 0°C was added I_2 (5.37g, 21.2mmol). After stirring for 3h at 0°C, aq NaS_2O_3 (1M, 600mL) was added, and the mixture extracted with DCM (3×300mL). The

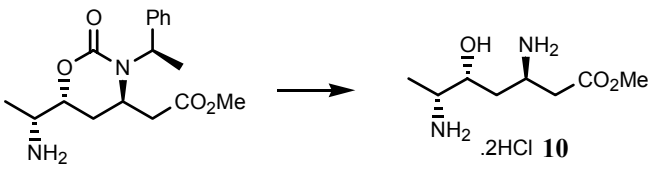
organic material was combined, dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. 400MHz ^{1}H NMR spectroscopic analysis showed the reaction to have occurred in 84% de. Purification *via* column chromatography (25% EtOAc in 40-60 petrol) and recrystallisation (hot EtOAc / hexane) afforded the title compound **9** as white needles (1.66g, >98% de, 77%).

(4*R*,6*S*,1′*R*,α*R*)-3-(α-Methylbenzyl)-4-(methoxycarbonylmethyl)-6-(1′-aminoethyl)-1,3-oxazinan-2-one



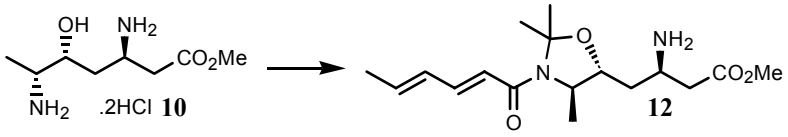
To a solution of the iodide **9** (3.27g, 7.53mmol) in DMF/H_2O (25:1, 62.5mL) was added NaN_3 (2.45g, 37.7mmol) and the mixture heated to 110°C for 5h. The reaction mixture was allowed to cool, H_2O (400mL) added and the organic material extracted with ether (3×250mL). The combined organic extracts were washed with brine (300mL), filtered, and the solvent removed *in vacuo*. The residue was dissolved in degassed MeOH (60mL) and 10% Pd on C (100mg) was added, and the resulting mixture was stirred under 1atm of H_2 for 40h. The reaction mixture was filtered through Celite®, eluting with further MeOH (100mL) and the solvent removed *in vacuo*. Purification *via* column chromatography (9% MeOH in DCM then 17% MeOH in DCM) afforded the title compound as a white solid (1.24g, 52% over 2 steps).

(3*R*,5*R*,6*R*)-Methyl 3,6-diamino-5-hydroxyheptanoate dihydrochloride 10



(4*R*,6*S*,1′*R*,α*R*)-3-(α-Methylbenzyl)-4-(methoxycarbonylmethyl)-6-(1′-aminoethyl)-1,3-oxazinan-2-one (1.52g, 4.75mmol) was dissolved in aq HCl (5M, 50mL) and the mixture heated to reflux for 24h. The mixture was allowed to cool to rt then diluted with H_2O (200mL), washed with DCM (4×200mL) and the aqueous layer concentrated *in vacuo*. The residue was dissolved in MeOH (50mL) and cooled to 0°C. Thionyl chloride (2.54g, 1.56mL, 21.4mmol) was added drop-wise. The mixture was heated at reflux for 18h, allowed to cool, and the volatile material removed *in vacuo* to afford the title compound **10** as a colourless foam (1.07g, 93% over 2 steps): $[\alpha]_D^{21}$ +2.6 (*c* 0.71, MeOH); ν_{max}/cm^{-1} (KBr disc) 3418 (s, br), 3014 (s, br), 1727 (s); δ_H (400MHz, CD_3OD) 1.34 (3H, d, *J*=6.6, CHC*H*$_3$), 1.88 (1H, m, CHC*H*HCH), 2.03 (1H, m, CHCH*H*CH), 2.85, 2.93 (2H, ABX system, AB part J_{AB}=17.5, J_{AX}=7.2, J_{BX}=5.5, C*H*$_2$C=O), 3.27 (1H, m, CH_3CHNH_2), 3.77 (1H, s, OC*H*$_3$), 3.82-3.88 (2H, m, C*H*OH and CH_2CHCH_2); δ_c (100MHz, CD_3OD) 16.3 (*C*H$_3$CH), 37.0 (CH*C*H$_2$CH), 38.1 (*C*H$_2$C=O), 47.5 (CH_2CHCH_2), 53.2 (O*C*H$_3$), 53.7 (CH_3CH), 70.3 (*C*HOH), 172.7 (*C*=O); *m/z* (APCI$^+$) 191 (MH^+, 100%), 174 ($(M-OH)^+$, 28), 159 (20), 124 (13); Expected MH^+ 191.1396, Found 191.1393.

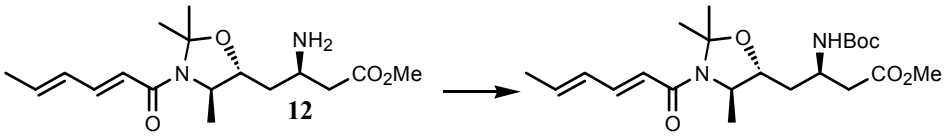
(3*R*,5*R*,6*R*,2′*E*,4′*E*)-Methyl 3-amino-5,6-(isopropylidene-5-oxy-6-[hex-2′,4′-dienoylamino])heptanoate 12



To a stirred solution of ester **10** (200mg, 0.760mmol) in acetone (15mL) under Ar was added Hunig's base (0.265mL, 1.52mmol) and powdered 3Å molecular sieves (800mg). The mixture was refluxed for 2h, cooled to 0°C, and further Hunig's base (0.15mL, 0.836mmol) added, followed by drop-wise addition of (*E*,*E*)-sorbyl chloride (109mg, 0.836mmol) as a solution in acetone (5mL). The mixture was stirred at 0°C for 1h and then at rt for 18h. The mixture was filtered, H_2O (10mL) added and the acetone removed *in vacuo*. Aq sat $NaHCO_3$ (20mL) was added and the organic

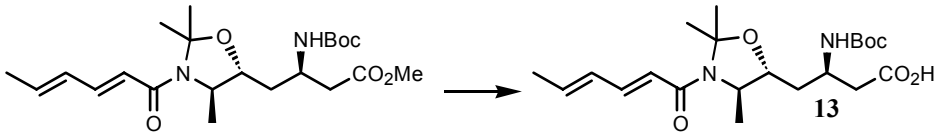
material extracted with EtOAc (3×50mL). The combined organic extracts were washed with brine (50mL), dried ($MgSO_4$), filtered and the volatile material removed *in vacuo*. Purification *via* column chromatography (EtOAc then 8% MeOH in EtOAc) and concentration of the more polar fraction afforded the title compound **12** as an orange oil (183mg, 74%).

(3*R*,5*R*,6*R*,2′*E*,4′*E*)-Methyl 3-(*tert*-butoxycarbonylamino)-5,6-(isopropylidene-5-oxy-6-[hex-2′,4′-dienoylamino])heptanoate



To a stirred solution of amine **12** (159mg, 0.49mmol) in MeOH (15mL) under N_2 was added $NaHCO_3$ (124mg, 1.47mmol) then Boc_2O (161mg, 0.74mmol). The mixture was stirred at rt for 72h, filtered and the volatile material removed *in vacuo*. The resulting oil was triturated with ether (20mL), filtered and the filtrate was concentrated *in vacuo*. Purification *via* column chromatography (40% EtOAc in pentane) afforded the title compound as a colourless oil (175mg, 84%).

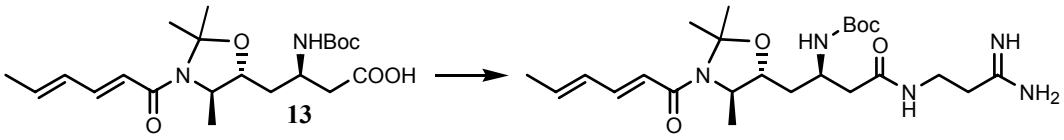
(3*R*,5*R*,6*R*,2′*E*,4′*E*)-3-(*tert*-Butoxycarbonylamino)-5,6-(isopropylidene-5-oxy-6-[hex-2′,4′-dienoylamino])heptanoic acid 13



To a stirred solution of (3*R*,5*R*,6*R*,2′*E*,4′*E*)-methyl 3-(*tert*-butoxycarbonylamino)-5,6-(isopropylidene-5-oxy-6-[hex-2′,4′-dienoylamino])heptanoate (175mg, 0.413mmol) in MeOH / THF (2:1, 15mL) at 0°C was added aq NaOH (1M, 1.65mL, 1.65mmol). The mixture was stirred at 0°C for 1h then at rt for 18h. The volatile material was removed *in vacuo*, the residue dissolved in H_2O (50mL) and washed with ether (50mL). The aqueous layer was acidified to pH 3 with aq $KHSO_4$ (0.5M) and extracted with EtOAc (3×50mL). The combined organic extracts were dried ($MgSO_4$), filtered and the

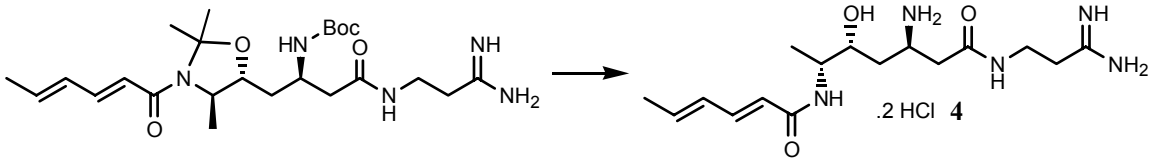
solvent removed *in vacuo* to afford the title compound **13** as a colourless oil (170mg, quant), which was used without further purification.

(3*R*,5*R*,6*R*,2″*E*,4″*E*)-3′-Amidinopropionyl 3-(*tert*-butoxycarbonylamino)-5,6-(isopropylidene-5-oxy-6-[hex-2″,4″-dienoylamino])heptanamide



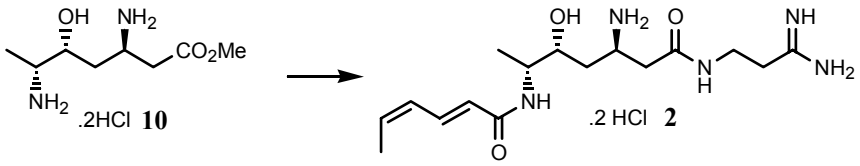
To a stirred solution of acid **13** (24mg, 0.059mmol) in THF (2mL) and 3Å molecular sieves (100mg) under Ar, was added DCC (16mg, 0.080mmol) and HOBT (10mg, 0.071mmol) and the mixture stirred for 3h. The resulting suspension was filtered, the precipitate washed with further THF (2×10mL) and to the combined filtrate and washings was added 3-aminopropionamidine dihydrobromide (15mg, 0.059mmol) and $NaHCO_3$ (10mg, 0.12mmol), both as a solution in H_2O (2mL). The resulting mixture was stirred for 48h and the solvent removed *in vacuo*. Purification *via* column chromatography (3% MeOH in DCM then 20% MeOH in DCM) and concentration of the more polar fraction afforded the title compound as a *ca* 5:1 mixture of its hydrobromide and HOBT salts. This mixture was dissolved in DCM/MeOH (10:1, 10mL), MP carbonate resin (120mg, 2.55mmol g^{-1}, 0.31mmol) added and the mixture stirred for 48h. After removal of the resin by filtration, and washing with DCM (2×10mL), the solvent was removed from the combined filtrate and washings *in vacuo* to afford the title compound as a pale yellow oil (28mg, 99%).

Sperabillin D 4



To a stirred solution of (3*R*,5*R*,6*R*,2″*E*,4″*E*)-3′-Amidinopropionyl 3-(*tert*-butoxycarbonylamino)-5,6-(isopropylidene-5-oxy-6-[hex-2″,4″-dienoylamino])heptanamide (28mg) in DCM (1mL), under Ar, was added TFA (1mL) drop-wise. The resulting mixture was stirred for 30min and the volatile material removed *in vacuo*. The crude material was passed through a column of Amberlite IRA-402 (H_2O) and the volatile material removed *in vacuo* to afford Sperabillin D **4** as a pale yellow foam (22mg, 91%, 94% purity by HPLC): $[\alpha]_D^{25}$ +27.4 (*c* 0.22, H_2O), lit[2] $[\alpha]_D^{25}$ +30.4 (*c* 0.50, H_2O); ν_{max}/cm^{-1} (KBr disc) 3387 (s), 1686 (m), 1654 (s), 1627 (m), 1612 (m), 1550 (m); δ_H (500MHz, D_2O) 0.96 (3H, d, *J* 7.0, C*H*$_3$CHN), 1.47-1.62 (2H, m, CHC*H*$_2$CH), 1.61 (3H, d, *J* 6.0, C*H*$_3$CH=CH), 2.43 (2H, t, *J* 6.9, C*H*$_2$C=N), 2.49 (2H, d, *J* 6.6, C*H*$_2$C=O), 3.27-3.37 (2H, m, NC*H*$_2$), 3.60-3.65 (2H, m, C*H*OH and CH$_2$C*H*CH$_2$), 3.77 (1H, dq, *J* 7.0, 3.5, CH$_3$C*H*N), 5.75 (1H, d, *J* 15.2, CH=C*H*C=O), 5.99-6.10 (2H, m, CH$_3$C*H*=C*H*), 6.90 (1H, dd, *J* 15.2, 9.9, C*H*=CHC=O); δ_C (125MHz, D_2O) 18.4 (*C*H$_3$CHN), 20.3 (*C*H$_3$CH=CH), 34.9 (*C*H$_2$C=N), 37.0 (CH*C*H$_2$CH), 38.8 (*C*H$_2$N), 39.5 (*C*H$_2$C=O), 48.8 (*C*HNH$_2$), 51.8 (*C*HNH), 72.0 (*C*HOH), 122.6 (CH=*C*HC=O), 131.6 (CH$_3$CH=*C*H), 142.7 (CH$_3$*C*H=CH), 144.9 (*C*H=CHC=O), 171.1, 171.3 (*C*=N and CH=CH*C*=O), 174.2 (CH$_2$*C*=O).

Sperabillin B 2



Sperabillin B **2** was prepared from ester **10** by a route analogous to that used for preparing sperabillin D **4**, but using (2*E*,4*Z*)-hexadienoyl chloride (>95% pure). Sperabillin B **2** was afforded in 30% over 5 steps from **10**. Data for sperabillin B **2**: $[\alpha]_D^{22}$ +48.3 (*c* 0.24, H_2O), lit[2] $[\alpha]_D$ +56.0 (*c* 1.0, H_2O); ν_{max}/cm^{-1} (KBr disc) 3269 (m), 3068 (m), 1692 (s), 1654 (s), 1618 (s), 1609 (s), 1546 (s); δ_H (500MHz, D_2O) 1.10 (3H, d, *J* 6.7, C*H*$_3$CHN), 1.61-1.74 (2H, m, CHC*H*$_2$CH), 1.77 (3H, d, *J* 7.3, C*H*$_3$CH=CH), 2.53-2.60 (2H, m, C*H*$_2$C=N), 2.62 (2H, d, *J* 6.7, C*H*$_2$C=O) 3.41-3.49 (2H, m, C*H*$_2$N) 3.72-3.78 (2H, m, CH$_2$C*H*CH$_2$ and C*H*O), 3.92 (1H, qd, *J* 6.7, 3.8, CH$_3$C*H*NH), 5.91 (1H, dq, *J* 10.7, 7.3, CH$_3$C*H*=CH), 5.97 (1H, d, *J* 15.2, CH=C*H*C=O), 6.12 (1H, app t, *J* 11.2, CH$_3$CH=C*H*), 7.45 (1H, dd, *J* 15.2, 11.7, C*H*=CHC=O); δ_C (125MHz, D_2O) 13.6 (*C*H$_3$CH=CH), 16.4 (*C*H$_3$CHN), 35.0 (*C*H$_2$C=N), 36.6 (*C*H$_2$N and CH*C*H$_2$CH), 37.5 (*C*H$_2$C=O), 46.7 (CH$_2$*C*HCH$_2$), 49.8 (CH$_3$*C*HN), 70.0 (*C*HO), 122.8 (CH=*C*HC=O), 127.1 (CH$_3$CH=*C*H), 136.9 (CH$_3$*C*H=CH), 137.0 (*C*H=CHC=O), 169.2, 172.2 (*C*=NH, CH$_2$*C*=O and CH=CH*C*=O).

References

1. S. G. Davies, K. Iwamoto, C. A. P. Smethurst, A. D. Smith and H. Rodriguez-Solla, *Syn. Lett.*, 2002, **7**, 1146.
2. T. Hida, S. Tsubotani, Y. Funabashi, H. Ono and S. Harada, *Bull. Chem. Soc. Japan*, 1993, **66**, 863.