

Total asymmetric synthesis of sperabillins B and D†

Stephen G. Davies,* Richard J. Kelly and Anne J. Price Mortimer

Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford, UK OX1 3QY.

E-mail: steve.davies@chemistry.ox.ac.uk

Received (in Cambridge, UK) 22nd May 2003, Accepted 8th July 2003

First published as an Advance Article on the web 21st July 2003

A concise route to the core fragment of sperabillins B and D, methyl (3*R*,5*R*,6*R*)-3,6-diamino-5-hydroxyheptanoate, has been developed with a subsequent novel protection strategy allowing the total asymmetric synthesis of sperabillins B and D.

The sperabillin family of antibiotics **1–4**, isolated from the culture filtrates of *Pseudomonas fluorescens* YK-437,¹ are active *in vitro* and *in vivo* against Gram-positive and Gram-negative bacteria including antibiotic resistant strains.² Notably, their *in vivo* potencies are greater than expected from their *in vitro* activities. Sperabillin polymers have also been shown to have antitumour activity.³ The structures of the sperabillins **1–4**, including the absolute configurations, were elucidated by the degradation studies of Hida *et al.*⁴ and by the total enantioselective synthesis of sperabillin D **4** by Natsugari *et al.*⁵ Sperabillins A **1** and C **3** have the same core amino acid as the potent antibiotic negamycin,⁶ whilst sperabillins B **2** and D **4** (which are more active than A **1** and C **3** respectively)² bear an additional C-6 methyl substituent and consequently an additional stereogenic centre. We have previously reported the asymmetric synthesis of the highly functionalised (3*R*,5*R*,6*R*)-3,6-diamino-5-hydroxyheptanoic acid **5**,⁷ the common core fragment of sperabillins B **2** and D **4** (Fig. 1). Herein we describe an improved synthesis of the core fragment and its conversion *via* a novel protection strategy to both sperabillins B **2** and D **4**.

Analogously to our previous work,⁷ a strategy of stereoselectively introducing the C-3 amino group by lithium amide conjugate addition to a $\alpha,\beta,\delta,\epsilon$ -unsaturated acceptor, followed by installation of the other stereogenic centres *via* an iodocarbamation, was envisaged. A more efficient acceptor synthesis than that previously employed was necessary for a viable synthesis. Thus, the palladium catalysed co-dimerisation of butadiene and methyl acrylate⁸ was optimised to give methyl (2*E*,5*E*)-hepta-2,5-dienoate **6** in very good yield, with only a small amount (8%) of Diels–Alder product being generated (Scheme 1).

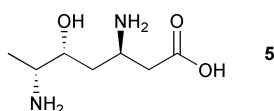
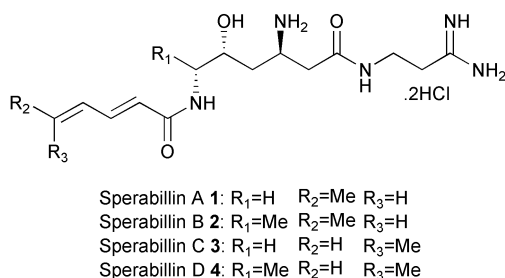
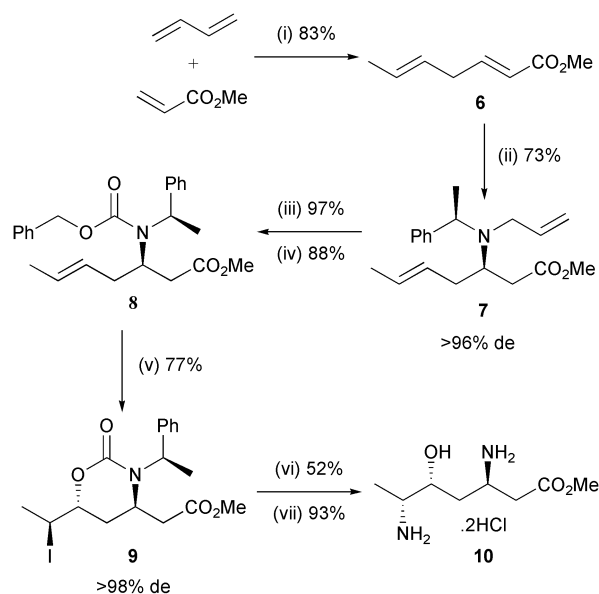


Fig. 1

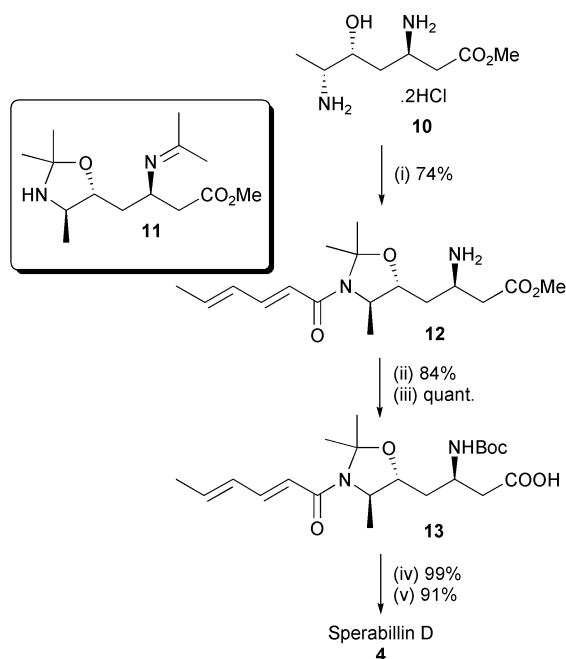
† Electronic supplementary information (ESI) available: experimental details. See <http://www.rsc.org/suppdata/cc/b3/b305740b/>

Conjugate addition of lithium (*R*)-*N*-allyl-*N*- α -methylbenzylamide⁹ to **6** generated the β -amino acid derivative **7** as a single diastereomer (>96% de).¹⁰ Replacement of the allyl protecting group with benzyloxycarbonyl gave alkene **8**, and subsequent iodocarbamation generated oxazin-2-one **9** in 84% de, which was improved to >98% de on recrystallisation. Azide displacement of the iodide with inversion of configuration followed by reduction installed the C-6 amino group. Global deprotection using concentrated aqueous acid gave, after re-esterification, the methyl ester of the core fragment **10** in 19.3% overall yield on a multigram scale.

In order to achieve selective amide formation on the C-6 amine group a simple protection strategy was envisaged. Treatment of the methyl ester **10** with acetone under dehydrative conditions was anticipated to generate the corresponding bis-imine which would be expected to cyclise exclusively to the *cis*-1,2 disubstituted 5-ring oxazolidine **11** rather than the alternative *trans*-1,3-disubstituted oxazinane. Consistent with this notion, sequential treatment of **10** with acetone/molecular sieves and sorbyl chloride/Hunig's base gave, after chromatography, the desired C-6 amine coupled derivative **12** (Scheme 2). *N*-Boc protection of the C-3 amine of **12** followed by ester hydrolysis under basic conditions gave the fully protected free acid **13**. Finally the amidine bearing side chain was introduced by coupling with 3-aminopropionamide¹¹ using DCC and

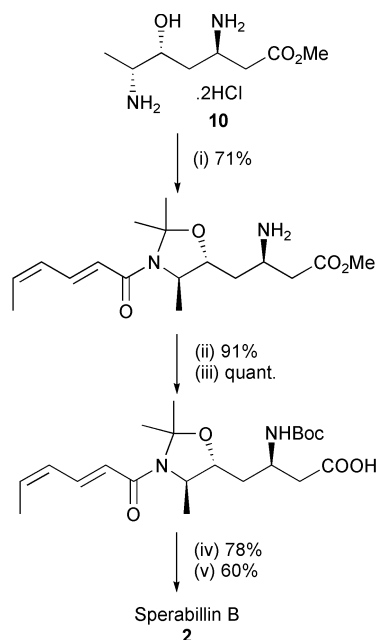


Scheme 1 Reagents and conditions: (i) Pd₂(dba)₃ (1.55 mmol, 0.2 mol%), HBF₄ etherate (6.20 mmol), PBU₃ (3.10 mmol), 80 °C, neat, sealed tube, 5 h; (ii) lithium (*R*)-*N*-allyl-*N*- α -methylbenzylamide (184 mmol, 1.3 eq), THF (400 mL), -78 °C, 2 h; (iii) Wilkinson's catalyst (3.14 mmol, 5 mol%), MeCN/H₂O (4 : 1, 500 mL), reflux, 2 h; (iv) Cbz₂O (214 mmol, 2 eq), vacuum, neat, 4 days; (v) I₂ (21.2 mmol, 5 eq), DCM (50 mL), 0 °C, 5 h; (vi) (a) NaN₃ (37.7 mmol, 5 eq), DMF/H₂O (25 : 1, 62.5 mL), 110 °C, 5 h; (b) H₂ (1 atm), Pd/C (0.094 mmol, 0.1 mol%), MeOH (60 mL), 18 h; (vii) (a) 5 M HCl (50 mL, excess), 100 °C, 24 h; (b) MeOH (50 mL), SOCl₂ (21.4 mmol, 4.5 eq), reflux, 18 h.



Scheme 2 Reagents and conditions: (i) acetone (15 mL), 3 Å molecular sieves, Hunig's base (1.52 mmol, 2 eq), reflux, 1 h then sorbyl chloride (0.863 mmol), Hunig's base (0.863 mmol), 0 °C to room temperature, 18 h; (ii) Boc₂O (0.74 mmol, 1.5 eq), NaHCO₃ (1.47 mmol), MeOH (15 mL), 72 h; (iii) NaOH (aq) (1.65 mmol, 4 eq), THF/MeOH (2 : 1, 15 mL), 18 h; (iv) DCC (0.08 mmol, 1.35 eq), HOBT (0.071 mmol), THF (2 mL), 3 Å molecular sieves, 3 h, then 3-aminopropionamide dihydrobromide (0.059 mmol), NaHCO₃ (0.12 mmol), THF/H₂O (10 : 1, 20 mL), 48 h; (v) TFA (1 mL, excess), DCM (1 mL), 30 min then Amberlite IRA-402 (Cl⁻ form).

HOBT. The purity of the highly polar amidine product was ensured by work-up with MP-carbonate scavenger resin.¹² Acidic global deprotection afforded sperabillin D 4,¹³ whose



Scheme 3 Reagents and conditions: (i) acetone (15 mL), 3 Å molecular sieves, Hunig's base (1.70 mmol, 2 eq), reflux, 1 h then (2*E*,4*Z*)-hexadienoyl chloride¹⁵ (0.933 mmol), Hunig's base (0.933 mmol), 0 °C to room temperature, 18 h; (ii) Boc₂O (0.681 mmol, 1.5 eq), NaHCO₃ (1.36 mmol), MeOH (15 mL), 72 h; (iii) NaOH (aq) (0.509 mmol, 4 eq), THF/MeOH (2 : 1, 4.5 mL), 5 h; (iv) DCC (0.115 mmol, 1.35 eq), HOBT (0.102 mmol), THF (2 mL), 3 Å molecular sieves, 3 h then 3-aminopropionamide dihydrobromide (0.085 mmol), NaHCO₃ (0.170 mmol), THF/H₂O (10 : 1, 20 mL), 48 h; (v) TFA (1 mL, excess), DCM (3 mL), 30 min then preparative reverse-phase HPLC then Amberlite IRA-402 (Cl⁻ form).

spectroscopic data were entirely consistent with the natural product, in 56% overall yield from **10**.

This straightforward procedure for the selective sequential C-6 NH₂ and C-1 CO₂H amide formation should be applicable to the rapid generation of libraries of analogues of sperabillins D **4** and B **2** and hence allow construction of detailed structure-activity relationships, as evidenced by its application to the first asymmetric synthesis of sperabillin B **2**¹⁴ (Scheme 3), whose spectroscopic data were entirely consistent with those of the natural product.

In conclusion, a concise route to the core β,ε-diamino-γ-hydroxy fragment **10** has been developed (in 19.3% yield from methyl acrylate) and a novel protection strategy utilised to complete the syntheses of the highly functionalised antibiotics sperabillins B **2** and D **4**. The first asymmetric total synthesis of sperabillin B **2** was achieved in 5.8% overall yield from methyl acrylate (30% from **10**). An efficient total synthesis of sperabillin D **4** has been achieved in 10.8% overall yield (56% from **10**).

Rhône-Poulenc Rôrer (R. J. K.) and EPSRC (A. J. P. M.) are gratefully acknowledged for funding.

Notes and references

- (a) S. Harada and H. Ono, *Eur. Pat. Appl.*, 1986, EP 206068; (b) N. Katayama, Y. Nozaki, S. Tsubotani, M. Kondo, S. Harada and H. Ono, *J. Antibiot.*, 1992, **45**, 10.
- N. Katayama, Y. Nozaki, S. Tsubotani, M. Kondo, S. Harada and H. Ono, *J. Antibiot.*, 1992, **45**, 10.
- T. Hida, S. Tsubotani, A. Hori, M. Murakami, H. Natsugari, Y. Kozai and S. Harada, *Chem. Pharm. Bull.*, 1993, **41**, 889.
- T. Hida, S. Tsubotani, Y. Funabashi, H. Ono and S. Harada, *Bull. Chem. Soc. Jpn.*, 1993, **66**, 863.
- S. Hashiguchi, A. Kawada and H. Natsugari, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2435.
- M. Hamada, T. Takeuchi, S. Kondo, Y. Ikeda, H. Naganawa, K. Maeda, Y. Okami and H. Umezawa, *J. Antibiot.*, 1970, **23**, 171.
- S. G. Davies and O. Ichihara, *Tetrahedron Lett.*, 1999, **40**, 9313.
- P. Grenouillet, D. Neibecker and I. Tkatchenko, *Fr. Demande*, 1987, FR 86-4644 19860327.
- S. G. Davies and D. R. Fenwick, *J. Chem. Soc., Chem. Commun.*, 1995, 1109.
- S. G. Davies, K. Iwamoto, C. A. P. Smethurst, A. D. Smith and H. Rodriguez-Solla, *Synlett*, 2002, **7**, 1146.
- G. Hilgetag, H. Paul, J. Günther and M. Witt, *Chem. Ber.*, 1964, 704.
- J. J. Weidner, J. J. Parlow and D. L. Flynn, *Tetrahedron Lett.*, 1999, **40**, 239.
- Sperabillin D **4**: [α]_D²⁵ +27.4 (c 0.22, H₂O), lit.⁴ [α]_D²⁵ +30.4 (c 0.50, H₂O); ν_{max}/cm⁻¹ (KBr disc) 3387 (s), 1686 (m), 1654 (s), 1627 (m), 1612 (m), 1550 (m); δ_H (500 MHz, D₂O) 0.96 (3H, d, *J* 7.0, CH₃CHN), 1.47–1.62 (2H, m, CHCH₂CH), 1.61 (3H, d, *J* 6.0, CH₃CH=CH), 2.43 (2H, t, *J* 6.9, CH₂C=N), 2.49 (2H, d, *J* 6.6, CH₂C=O), 3.27–3.37 (2H, m, NCH₂), 3.60–3.65 (2H, m, CHOH and CH₂CHCH₂), 3.77 (1H, dq, *J* 7.0, 3.5, CH₃CHN), 5.75 (1H, d, *J* 15.2, CH=CHC=O), 5.99–6.10 (2H, m, CH₃CH=CH), 6.90 (1H, dd, *J* 15.2, 9.9, CH=CHC=O); δ_C (125 MHz, D₂O) 18.4 (CH₃CHN), 20.3 (CH₃CH=CH), 34.9 (CH₂C=N), 37.0 (CHCH₂CH), 38.8 (CH₂N), 39.5 (CH₂C=O), 48.8 (CHNH₂), 51.8 (CHNH), 72.0 (CHOH), 122.6 (CH=CHC=O), 131.6 (CH₃CH=CH), 142.7 (CH₃CH=CH), 144.9 (CH=CHC=O), 171.1, 171.3 (C=N and CH=CHC=O), 174.2 (CH₂C=O).
- Sperabillin B **2**: [α]_D²² +48.3 (c 0.24, H₂O), lit.⁴ [α]_D²⁵ +56.0 (c 1.0, H₂O); ν_{max}/cm⁻¹ (KBr disc) 3269 (m), 3068 (m), 1692 (s), 1654 (s), 1618 (s), 1609 (s), 1546 (s); δ_H (500 MHz, D₂O) 1.10 (3H, d, *J* 6.7, CH₃CHN), 1.61–1.74 (2H, m, CHCH₂CH), 1.77 (3H, d, *J* 7.3, CH₃CH=CH), 2.53–2.60 (2H, m, CH₂C=N), 2.62 (2H, d, *J* 6.7, CH₂C=O) 3.41–3.49 (2H, m, CH₂N) 3.72–3.78 (2H, m, CH₂CHCH₂ and CHO), 3.92 (1H, qd, *J* 6.7, 3.8, CH₃CHNH), 5.91 (1H, dq, *J* 10.7, 7.3, CH₃CH=CH), 5.97 (1H, d, *J* 15.2, CH=CHC=O), 6.12 (1H, app t, *J* 11.2, CH₃CH=CH), 7.45 (1H, dd, *J* 15.2, 11.7, CH=CHC=O); δ_C (125 MHz, D₂O) 13.6 (CH₃CH=CH), 16.4 (CH₃CHN), 35.0 (CH₂C=N), 36.6 (CH₂N and CHCH₂CH), 37.5 (CH₂C=O), 46.7 (CH₂CHCH₂), 49.8 (CH₃CHN), 70.0 (CHO), 122.8 (CH=CHC=O), 127.1 (CH₃CH=CH), 136.9 (CH₃CH=CH), 137.0 (C H=CHC=O), 169.2, 172.2 (C=NH, CH₂C=O and CH=CHC=O).
- (2*E*,4*Z*)-Hexadienyl chloride was synthesised as >95 : 5 (2*E*,4*Z*) : (2*E*,4*E*) via Heck type coupling of *tert*-butyl acrylate and (*Z*)-1-bromo-1-propene.