Tetrahedron 67 (2011) 216–227

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Asymmetric syntheses of (+)-negamycin, (+)-3-*epi*-negamycin and sperabillin C via lithium amide conjugate addition

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ARTICLE INFO

Article history:
Received 16 August 2010
Received in revised form 6 October 2010
Accepted 25 October 2010
Available online 29 October 2010

Keywords:
Asymmetric synthesis
Lithium amide
(+)-Negamycin
(+)-3-*epi*-Negamycin
Sperabillin C

ABSTRACT

The chemo- and enantioselective reduction of ethyl 4-chloroacetoacetate and the diastereoselective conjugate addition of enantiopure lithium *N*-benzyl-*N*-(α-methylbenzyl)amide to an α,β-unsaturated ester have been used as the key steps in the total asymmetric syntheses of (+)-negamycin (in 13 steps and 24% overall yield), (+)-3-*epi*-negamycin (in 13 steps and 10% overall yield) and sperabillin C (in 17 steps and 13% overall yield) from commercially available starting materials.

1. Introduction

(+)-Negamycin **1** is a pseudopeptide antibiotic, which displays strong inhibitory activity against Gram-positive and Gram-negative bacteria, and exhibits low toxicity.[1] (+)-Negamycin **1** also exhibits genetic miscoding activity on bacterial ribosome systems[2] and is a specific inhibitor of protein synthesis in *Escherichia coli K*12.[3] Since Umezawa et al. first isolated (+)-negamycin **1** in 1970 from the culture filtrate of three strains related to *Streptomyces purpeofuscus*,[1] it has received a great deal of attention from the synthetic community.[4,5] The structure of (+)-negamycin **1** was initially elucidated via degradation studies[6] and was subsequently confirmed in 1972 by a total enantiospecific synthesis from D-galacturonic acid.[7] The sperabillin family of antibiotics **4**–**7**, which were isolated from the culture filtrates of *Pseudomonas fluoresens* YK-437,[8] are structurally related to (+)-negamycin **1** and are also active against Gram-positive and Gram-negative bacteria, including antibiotic resisitant strains.[8b] The structures of sperabillins A-D **4**–**7**, including their absolute configurations, were elucidiated by degradation studies[9] and by the total enantiospecific synthesis of sperabillin D **7**.[5a] Sperabillins A **4** and C **6** have the same core amino acid unit as (+)-negamycin **1**, whilst sperabillins B **5** and D **7** bear an additional C(6)-methyl substituent and consequently an additional stereogenic centre at C(6). We have previously reported the asymmetric synthesis of (*R*,*R*,*R*)-3,6-diamino-5-hydroxyheptanoic acid **3**,[10] the highly functionalised core fragment of sperabillins B **5** and D **7**, and subsequently the total asymmetric syntheses of both sperabillins B **5** and D **7** (Fig. 1).[11] Our strategy for the synthesis of these natural products employed the conjugate addition of an enantiopure lithium amide[12] to an α,β-unsaturated ester as one of the key steps. We have used this reaction in a series of natural product syntheses,[13] kinetic and parallel kinetic resolutions,[14] and for the synthesis of a range of β-amino acids and their derivatives.[15] It was also envisaged that this reaction could be employed for the total asymmetric syntheses of (+)-negamycin **1**, (+)-3-*epi*-negamycin **3** and sperabillin C **6**, and we report herein our full investigations within this area. Part of this work has been communicated previously.[4h]

2. Results and discussion

Retrosynthetic analysis of (+)-negamycin **1** proceeded via disconnection of the hydrazinoacetate component to give β-amino acid **9**. It was anticipated that β-amino acid **9** could be accessed via the intermediacy of a β-amino ester, such as **10**, which in turn could be synthesised via the conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*R*)-**11** to enantiopure *N*-Boc-*N*,*O*-acetonide protected α,β-unsaturated ester **12**.[12] Given that the δ-stereogenic centre within **12** is fairly remote from the site of reaction it was envisaged that the powerful stereocontrol exerted by the lithium amide reagent **11** would overwhelm any inherent stereofacial bias of the α,β-unsaturated ester **12** during the conjugate addition reaction[16,17] and thus allow the highly stereoselective preparation of the (3*R*)-stereocentre required for (+)-negamycin **1**. We have previously

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doi:10.1016/j.tet.2010.10.067

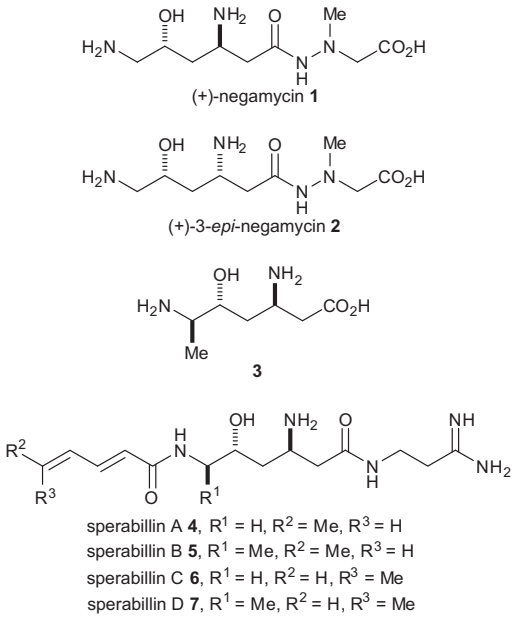


Fig. 1. The structures of (+)-negamycin **1**, (+)-3-*epi*-negamycin **2**, (*R*,*R*,*R*)-3,6-diamino-5-hydroxyheptanoic acid **3** and sperabillins A–D **4**–**7**.

shown that the use of a bulky ester moiety (usually a *tert*-butyl ester) effectively eliminates competing 1,2-addition in these systems;[12] however, it was anticipated that a *tert*-butyl ester would not be compatible with the proposed *N*-Boc-*N*,*O*-acetonide protecting group strategy as an orthogonal deprotection of β-amino ester **10** to give β-amino acid **9** would be required. 3-Pentyl α,β-unsaturated ester **12** was therefore selected in this case as it was anticipated that its steric bulk would suppress the potential for 1,2-addition of the lithium amide whilst also being susceptible to selective base-catalysed ester hydrolysis in the presence of the acid-labile protecting groups[18] (Fig. 2).

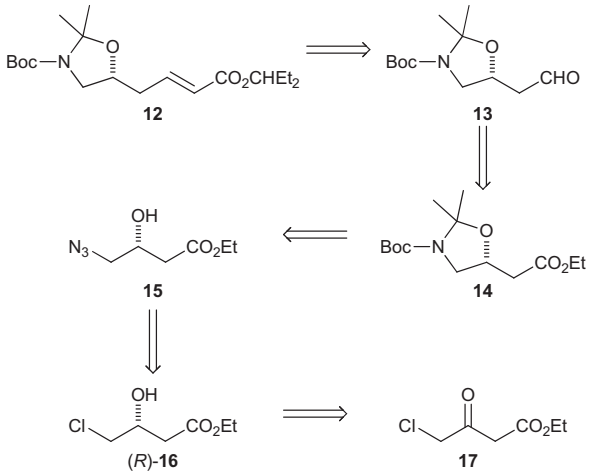


Fig. 3. Retrosynthetic analysis of enantiopure *N*-Boc-*N*,*O*-acetonide protected α,β-unsaturated ester **12**.

We also anticipated that this strategy would be equally applicable to the total asymmetric synthesis of (+)-3-*epi*-negamycin **2** since the very high stereocontrol of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*S*)-**11** was expected to dominate[16] any inherent stereocontrol of α,β-unsaturated ester **12** and therefore the conjugate addition of lithium amide (*S*)-**11** to **12** could be exploited as the key step for the generation of the (3*S*)-stereogenic centre within (+)-3-*epi*-negamycin **2** (Fig. 4).

2.1. Asymmetric synthesis of (+)-negamycin

The synthesis of α,β-unsaturated ester **12** began with the enantioselective reduction of commercially available ethyl 4-chloroacetoacetate **17**, which was achieved under 5 atmospheres of hydrogen in the presence of an [(*S*)-BINAP]Ru(II) complex to give γ-chloro-β-hydroxy ester (*R*)-**16** in 91% yield and 98:2 er.[20] Treat-

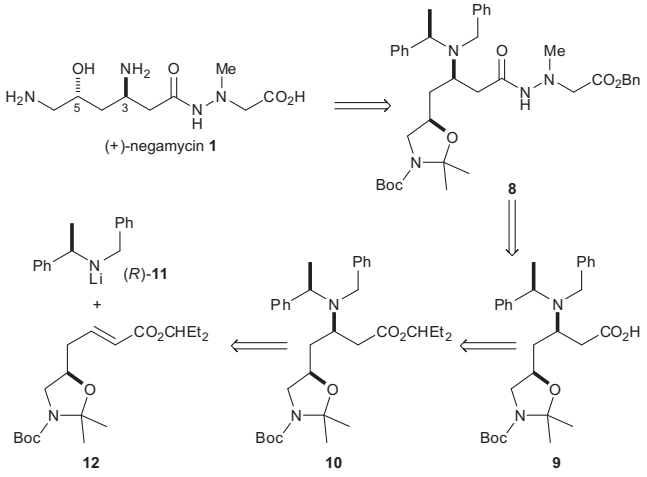


Fig. 2. Retrosynthetic analysis of (+)-negamycin **1**.

We proposed that α,β-unsaturated ester **12** could be obtained via Wittig reaction of 3-pentyl (triphenylphosphoranylidene)acetate with aldehyde **13**. In turn, **13** could be accessed via manipulation of alcohol (*R*)-**16**, which is known to be formed in high enantiomeric purity following catalytic hydrogenation of commercially available ethyl 4-chloroacetoacetate **17** in the presence of an [(*S*)-BINAP]Ru(II) complex[19] (Fig. 3).

ment of (*R*)-**16** with a large excess of NaI in acetone gave essentially quantitative conversion to γ-iodo-β-hydroxy ester **20**, which was treated with NaN_3 to give **15** in 95% isolated yield (two steps). Hydrogenolytic reduction of **15** in the presence of di-*tert*-butyl dicarbonate (Boc_2O) followed by acetonide formation gave **14** in 81% yield over the two steps. Attempted conversion of ester **14** into aldehyde **13** directly by treatment with diisobutylaluminum

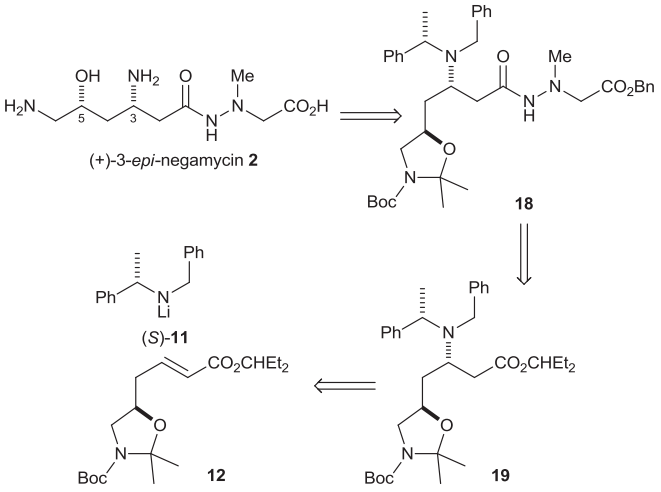
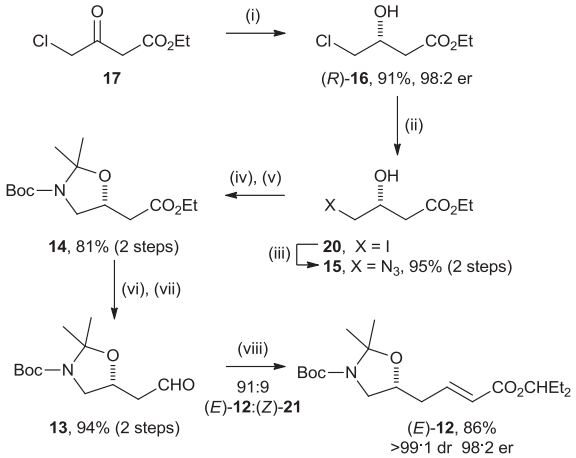


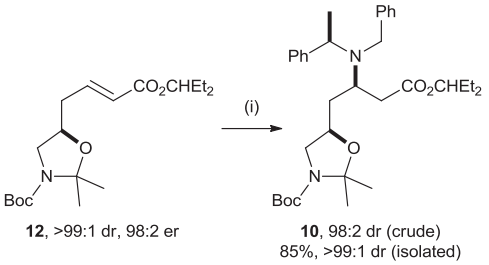
Fig. 4. Retrosynthetic analysis of (+)-3-*epi*-negamycin **2**.

hydride (DIBAL-H) at −78 °C was unsuccessful and therefore a reduction and re-oxidation protocol was employed. Thus, ester **14** was reduced with sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al®) and the resultant alcohol was oxidised under Swern conditions to give aldehyde **13** in 94% yield (two steps). Wittig reaction of **13** with 3-pentyl (triphenylphosphoranylidene) acetate in toluene at 70 °C gave quantitative conversion to a 91:9 mixture of (*E*)-**12** and (*Z*)-**21**, respectively. Subsequent chromatographic purification gave (*E*)-**12** in 86% yield and (*Z*)-**21** in 9% yield and >99:1 dr and 98:2 er[20] in each case (Scheme 1).



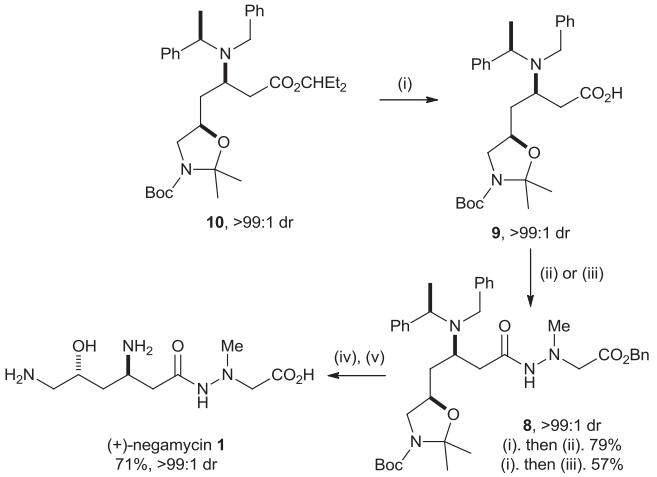
Scheme 1. Reagents and conditions: (i) H_2 (5 atm), Ru[(*S*)-BINAP]Cl_2, EtOH, 100 °C, 6 h; (ii) NaI, acetone, reflux, 2 days; (iii) NaN_3, MeCN/H_2O (5:1), 80 °C, 7 h; (iv) H_2 (1 atm), Pd/C, Boc_2O, EtOAc, 16 h; (v) (−)-CSA, $Me_2C(OMe)_2$/acetone (1:1), 70 °C, 2 h; (vi) Red-Al®, PhMe, 0 °C, 1 h; (vii) DMSO, $(COCl)_2$, $^iPr_2NEt$, CH_2Cl_2, −63 °C, 25 min; (viii) 3-pentyl (triphenylphosphoranylidene)acetate, PhMe, 70 °C, 4 h.

The conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*R*)-**11** to α,β-unsaturated ester (*E*)-**12** gave quantitative conversion to β-amino ester **10**. The rt ^1H NMR spectrum of the crude reaction mixture in $CDCl_3$ displayed extremely broad peaks (presumably due to the rotameric nature of the *N*-Boc group) and so an accurate determination of the reaction diastereoselectivity by peak integration of this spectrum was not possible. ^1H NMR spectroscopic analysis of this sample at 363 K in DMSO-d_6, however, gave sufficient resolution of peaks and it was found that **10** was produced in 98:2 dr. Considering the enantiomeric purity of (*E*)-**12** (98:2 er) it was reasoned that the major and minor diastereoisomeric products of the conjugate addition reaction differed in their configurations at C(5) and not at C(3): the conjugate addition of lithium amide (*R*)-**11** to α,β-unsaturated ester **12** is therefore completely diastereoselective. Purification of the crude reaction mixture gave **10** in 85% isolated yield and >99:1 dr (Scheme 2). The configuration of the newly formed C(3) stereogenic centre within the major diastereoisomer **10** was assigned as (*R*) by analogy to the transition state mnemonic developed by us for this class of lithium amide conjugate addition reaction,[21] and this was subsequently confirmed by the elaboration of **10** into (+)-negamycin **1** (vide infra).



Scheme 2. Reagents and conditions: (i) lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl) amide (*R*)-**11**, THF, −78 °C, 1 h then NH_4Cl (satd, aq).

LiOH-Mediated hydrolysis of the ester functionality within **10** proceeded to give the corresponding carboxylic acid **9**. Subsequent coupling of **9** with benzyl [*N*(1)-methylhydrazino]acetate **22** was achieved upon treatment with DCC or via conversion to the corresponding mixed anhydride, giving **8** in 79% yield (two steps) and 57% yield (two steps), respectively. Deprotection of **8** was achieved via treatment with TFA in THF/H_2O (to remove both the *N*-Boc and acetonide protecting groups) followed by catalytic hydrogenolysis, which gave (+)-negamycin **1** in quantitative conversion. Purification via ion-exchange chromatography (Amberlite CG-50) enabled isolation of (+)-negamycin **1** in 71% yield from **8** (Scheme 3). The spectroscopic data of our sample of (+)-negamycin **1** were in excellent agreement with those reported for the natural product by Umezawa et al.[1] {$[\alpha]_D^{20}$ +2.7 (*c* in H_2O); lit.[1] $[\alpha]_D^{29}$ +2.5 (*c* 2.0 in H_2O)} and with those reported for other synthetic samples[4] {e.g., lit.[4a] $[\alpha]_D^{20}$ +2.4 (*c* 1.5 in H_2O); lit.[4f] $[\alpha]_D^{20}$ +2.5 (*c* 1.4 in H_2O)}. The overall yield of (+)-negamycin **1** produced using this strategy was 24% (in 13 steps) from commercially available starting materials,

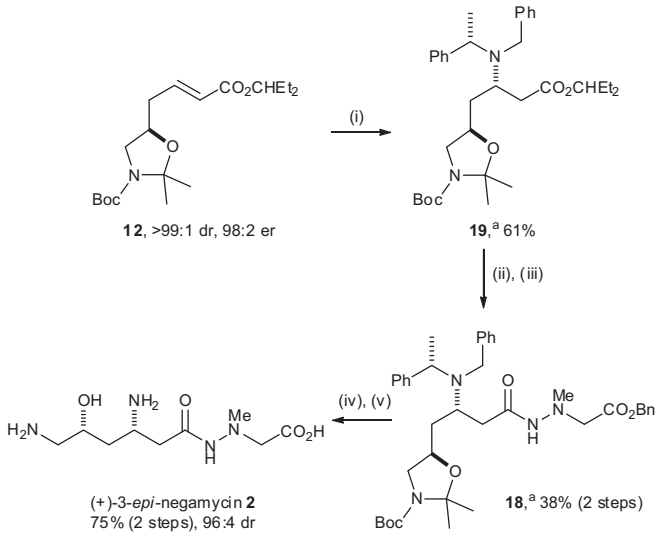


Scheme 3. Reagents and conditions: (i) LiOH, MeOH/THF/H_2O (3:1:1), reflux, 24 h; (ii) benzyl [*N*(1)-methylhydrazino]acetate **22**, DCC, HOBt, Et_3N, THF, 0 °C to rt, 5 h; (iii) Et_3N, $ClCO_2Et$, CH_2Cl_2, −15 °C, 5 min then 0 °C, 30 min; (iv) TFA, THF/H_2O (1:1), rt, 16 h; (v) H_2 (5 atm), $Pd(OH)_2$/C, AcOH (five drops), MeOH, rt, 22 h.

representing one of the most efficient syntheses of (+)-negamycin **1** reported to date.

2.2. Asymmetric synthesis of (+)-3-*epi*-negamycin

The synthesis of (+)-3-*epi*-negamycin **2**[22] via the conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*S*)-**11** to α,β-unsaturated ester **12** was next investigated. Treatment of **12** with (*S*)-**11** gave quantitative conversion to a mixture of β-amino esters. Peak integration of the ^{1}H NMR spectrum of the crude reaction mixture (obtained at 363 K in DMSO-d_6) revealed that a major diastereoisomeric product **19** accounted for ~95% of the product distribution.[23] Unfortunately, attempts to enrich the diastereoisomeric purity of **19** by column chromatography were unsuccessful and **19** was isolated in 61% yield and ~95% diastereoisomeric purity.[23] The configuration of the C(3) stereogenic centre within **19** was initially assigned as (*S*) on the assumption that the conjugate addition reaction proceeds under the dominant stereocontrol of the lithium amide reagent (*S*)-**11**,[21] and this was subsequently confirmed by the conversion of **19** into (+)-3-*epi*-negamycin **2**. Hydrolysis of **19** under basic conditions gave the corresponding carboxylic acid, which was coupled with benzyl [*N*(1)-methylhydrazino]acetate **22** to give **18** in 38% yield (two steps) and ~95% diastereoisomeric purity.[23] Removal of the *N*-Boc and acetonide protecting groups within **18**, followed by hydrogenolysis completed the synthesis of (+)-3-*epi*-negamycin **2** in 96:4 dr and 75% yield over the final two steps (10% overall yield in 13 steps from **17**) (Scheme 4).

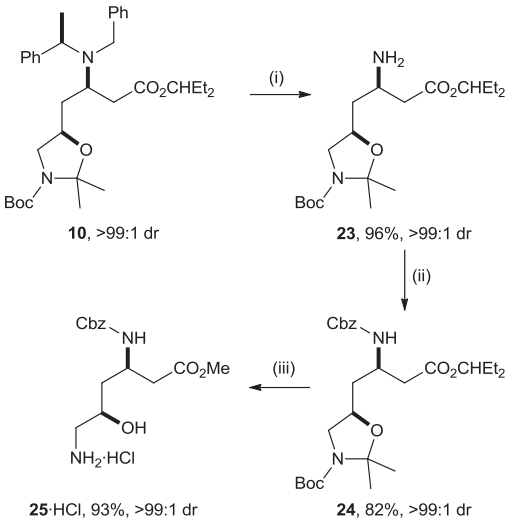


Scheme 4. Reagents and conditions: (i) lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*S*)-**11**, THF, −78 °C, 1 h then NH_4Cl (satd, aq); (ii) LiOH, MeOH/THF/H_2O (3:1:1), reflux, 24 h; (iii) benzyl [*N*(1)-methylhydrazino]acetate **22**, DCC, HOBt, Et_3N, THF, 0 °C to rt, 5 h; (iv) TFA, THF/H_2O (1:1), rt, 16 h; (v) H_2 (5 atm), $Pd(OH)_2$/C, AcOH (five drops), MeOH, rt, 20 h. [a]compounds **18** and **19** were isolated in ~95% diastereoisomeric purity].

The ^{1}H and ^{13}C NMR spectroscopic data obtained for (+)-3-*epi*-negamycin **2** were in good agreement with those reported for other samples of this compound.[4e,g,5e] However, there are some discrepancies between the specific rotation data for *epi*-negamycin **2** reported in the literature. The specific rotation for our sample of (+)-3-*epi*-negamycin **2** {$[\alpha]_D^{22}$ +8.5 (*c* 0.7 in H_2O)} was consistent with the values for its enantiomer (−)-5-*epi*-negamycin **2** reported by Hegedus et al.[4g] {$[\alpha]_D^{25}$ −9.4 (*c* 0.5 in H_2O)} and the group of I.C.I. Pharma[5e] {$[\alpha]_D^{23}$ −9.9 (*c* 3.5 in H_2O)} although none of these date are in agreement with that reported for 3-*epi*-negamycin **2** by Kibayashi et al.[4e] {$[\alpha]_D^{20}$ −3.2 (*c* 4.4 in H_2O)}, which therefore appears anomalous.[24]

2.3. Asymmetric synthesis of sperabillin C

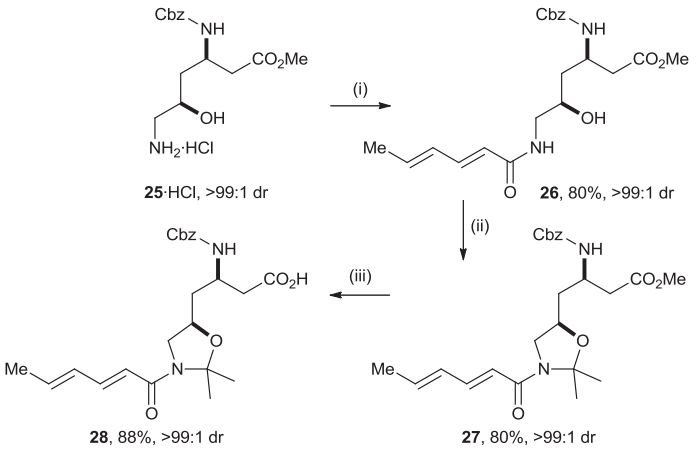
Given the similar structures of (+)-negamycin **1** and sperabillin C **6** it was envisaged that β-amino ester **10** could be easily elaborated into sperabillin C **6**: this would require only protecting group manipulation and two amide bond forming reactions. Removal of the *N*-benzyl and *N*-α-methylbenzyl protecting groups within **10** was achieved by catalytic hydrogenolysis with Pearlman's catalyst under 6 atm of hydrogen to give primary β-amino ester **23** in 96% yield. Subsequent treatment of **23** with benzyl chloroformate (CbzCl) gave **24** in 82% yield. Treatment of **24** with a solution of HCl in MeOH resulted in cleavage of the *N*-Boc and acetonide protecting groups as well as promoting in situ transesterification to give the corresponding methyl ester, which was isolated as its hydrochloride salt **25**·HCl in 93% yield (Scheme 5).



Scheme 5. Reagents and conditions: (i) H_2 (6 atm), $Pd(OH)_2$/C, AcOH (five drops), MeOH, rt, 20 h; (ii) CbzCl, $NaHCO_3$, CH_2Cl_2, rt, 45 min; (iii) HCl, MeOH, 0 °C, 30 min.

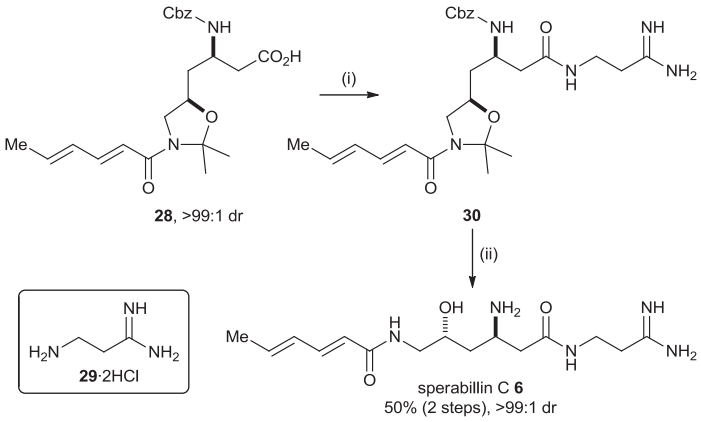
Using an analogous procedure to that described by Natsugari et al.[5a] for the transformation of the 6-methyl substituted congener of *N*-Cbz protected β-amino ester **25** into sperabillin D **7**, the hydrochloride salt **25**·HCl was treated with sorbyl chloride in the presence of Et_3N to give **26** in 80% yield as a single diastereoisomer. Protection of both the C(5)-hydroxyl and C(6)-amide groups within **26** was achieved by treatment with dimethoxypropane in acetone giving **27** in 80% yield, which was found to be prone to polymerisation when left to stand at rt and therefore was used immediately in the next step. Thus, ester **27** was hydrolysed by treatment with NaOH in THF/MeOH to give carboxylic acid **28** in 88% yield (Scheme 6).

By analogy to the method reported by Natsugari et al.,[5a,25] the coupling of carboxylic acid **28** with 2-amidinoethylamine **29**[26] was achieved upon treatment with DCC. This was immediately followed by treatment of **30** with TMSI in MeCN for 3.5 h, which gave sperabillin C **6** in 50% isolated yield (two steps) after sequential purification on Amberlite XAD-II resin then Amberlite 402 resin (Scheme 7). The spectroscopic data of our synthetic sample of **6** were in excellent agreement with those reported by Hida et al.[9] for a sample isolated from the natural source {$[\alpha]_D^{25}$ −10.2 (*c* 0.3 in H_2O); lit.[9] $[\alpha]_D^{25}$ −11.0 (*c* 0.7 in H_2O)} and other



Scheme 6. Reagents and conditions: (i) sorbyl chloride, Et_3N, CH_2Cl_2, 0 °C, 1 h; (ii) TsOH, $Me_2C(OMe)_2$/acetone (1:1), rt, 26 h; (iii) NaOH, MeOH/THF (2:1), 0 °C to rt, 4 h.

synthetic samples {lit.[25] $[\alpha]_D^{25}$ −10.1 (*c* 0.5 in H_2O); lit.[5d] $[\alpha]_D$ −10.2 (*c* 0.4 in H_2O)}. The overall yield of sperabillin C **6** produced using this strategy was 13% (in 17 steps) from commercially available starting materials.



Scheme 7. Reagents and conditions: (i) **29**·2HCl, DCC, HOBt, THF, rt, 2 h; (ii) TMSI, MeCN, rt, 3.5 h.

3. Conclusion

In conclusion, the chemo- and enantio-selective reduction of commercially available ethyl 4-chloroacetoacetate and the diastereoselective conjugate addition of enantiopure lithium *N*-benzyl-*N*-(α-methylbenzyl)amide to a chiral α,β-unsaturated ester have been used as the key steps for the introduction of stereochemistry at the C(3) and C(5) positions in the total asymmetric syntheses of (+)-negamycin, (+)-3-*epi*-negamycin and sperabillin C. The overall yields from ethyl 4-chloroacetoacetate were: (+)-negamycin, 24% over 13 steps; (+)-3-*epi*-negamycin, 10% over 13 steps; and sperabillin C, 13% over 17 steps.

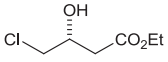
4. Experimental

4.1. General experimental

All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen or argon atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs et al.[27] Water was purified by a Millipore Elix® UV-10 system. 1,2-Dichlorobenzene, MeCN and DMSO were distilled from CaH_2 before use. All other reagents were used as supplied (analytical or HPLC grade) without prior purification. Reactions performed at −63 °C were cooled by means of a chloroform/dry ice bath. Reactions performed at −15 °C were cooled by means of a ethylene glycol/dry ice bath. Organic layers were dried over $MgSO_4$. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), iodine, 1% aq $KMnO_4$, or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed on Kieselgel 60 silica.

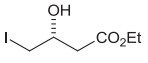
Elemental analyses were recorded by the microanalysis service of the Inorganic Chemistry Laboratory, University of Oxford, U.K. Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated. The field was locked by external referencing to the relevant deuteron resonance. The ^{13}C NMR spectra of many *N*-Boc protected compounds contained peaks that were doubled due to the presence of rotamers; the chemical shifts of these peaks are reported in *italics*. Low-resolution mass spectra were recorded on either a VG MassLab 20–250 or a Micromass Platform 1 spectrometer. Accurate mass measurements were run on either a Bruker MicroTOF, which was internally calibrated with polyalanine, or a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m×0.25 mm) using amyl acetate as a lock mass.

4.1.1. Ethyl (*R*)-3-hydroxy-4-chlorobutanoate ***16***.



Ru[(*S*)-BINAP]Cl_2[28] (270 mg, 145 mmol) was suspended in 1,2-dichlorobenzene (3 mL) and the resultant mixture was thoroughly degassed and heated at 160 °C for 10 min, during which time the initially purple suspension became dark brown. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. The brown solid residue was dried under high vacuum to give $RuCl_2$[(*S*)-BINAP]. A solution of ethyl 4-chloroacetoacetate (6.23 g, 37.9 mmol) in EtOH (7 mL) was then treated with $RuCl_2$[(*S*)-BINAP] (180 mg) and the resultant mixture was stirred under hydrogen (5 atm) at 100 °C for 6 h. Purification via reduced pressure distillation gave **16** as a colourless oil (5.74 g, 91%, 98:2 er[20]);[19] bp 85–87 °C (3 mmHg); $[\alpha]_D^{21}$ +20.7 (*c* 7.3 in $CHCl_3$); {lit.[19] for 97% ee $[\alpha]_D^{21}$ +20.9 (*c* 7.7 in $CHCl_3$)}; δ_H (200 MHz, $CDCl_3$) 1.28 (3H, t, *J* 7.2, OCH_2CH_3), 2.60–2.66 (2H, m, C(2)H_2), 3.21 (1H, br s, O*H*), 3.61 (2H, d, *J* 4.9, C(4)H_2), 4.12–4.32 (1H, m, C(3)*H*), 4.19 (2H, q, *J* 7.2, OCH_2CH_3).

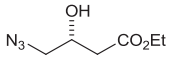
4.1.2. Ethyl (*R*)-3-hydroxy-4-iodobutanoate ***20***.



NaI (27.0 g, 180 mmol) was added to a stirred solution of **16** (15.0 g, 90.0 mmol) in acetone (100 mL) and the resultant mixture was heated at reflux for 2 days. The reaction mixture was then allowed to cool to rt, diluted with Et_2O (150 mL) and filtered. The filtrate was then passed through a short column of silica gel (eluent Et_2O) and concentrated *in vacuo* to give **20** as a pale yellow oil (22.9 g, 99%);[29] $[\alpha]_D^{20}$ +10.0 (*c* 3.0 in EtOH); {lit.[29] for enantiomer

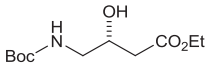
$[\alpha]_D^{20}$ −10.9 (*c* 3.0 in EtOH)}; δ_H (200 MHz, $CDCl_3$) 1.30 (3H, t, *J* 7.1, OCH_2CH_3), 2.65–2.69 (2H, m, C(2)H_2), 3.20 (1H, d, *J* 5.0, O*H*), 3.31–3.36 (2H, m, C(4)H_2), 3.99–4.05 (1H, m, C(3)*H*), 4.21 (2H, q, *J* 7.0, OCH_2CH_3).

*4.1.3. Ethyl (R)-3-hydroxy-4-azidobutanoate **15**.*



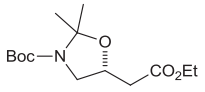
NaN_3 (20.2 g, 310 mmol) was added to a stirred solution of **20** (20.0 g, 77.5 mmol) in MeCN/H_2O (5:1, 200 mL) and the resultant mixture was heated at 80 °C for 7 h. The reaction mixture was then concentrated *in vacuo* and the residue was diluted with brine (500 mL). The resultant mixture was extracted with Et_2O (3×100 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give **15** as a pale yellow oil (12.9 g, 96%);[29] $[\alpha]_D^{20}$ +7.1 (*c* 4.1 in MeOH); {lit.[29] $[\alpha]_D^{20}$ +7.4 (*c* 4.1 in MeOH)}; δ_H (200 MHz, $CDCl_3$) 1.28 (3H, t, *J* 7.0, OCH_2CH_3), 2.42–2.66 (2H, m, C(2)H_2), 3.23 (1H, d, *J* 5.0, O*H*), 3.33–3.38 (2H, m, C(4)H_2), 4.20 (2H, q, *J* 7.0, OCH_2CH_3), 4.06–4.28 (1H, m, C(3)*H*).

*4.1.4. Ethyl (R)-3-hydroxy-4-(N-tert-butoxycarbonylamino)butanoate **31**.*



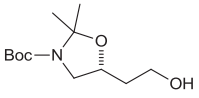
Boc_2O (13.5 g, 61.9 mmol) and **15** (8.88 g, 51.3 mmol) were added to a suspension of Pd/C (10% wt, 2.40 g) in EtOAc (100 mL) and the resultant mixture was stirred vigorously under hydrogen (1 atm) for 16 h. The reaction mixture was then filtered through Celite (eluent EtOAc) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/CH_2Cl_2/Et_2O, 1:1:1) gave **31** as a colourless oil (11.2 g, 88%); $C_{11}H_{21}NO_5$ requires C, 53.4; H, 8.6; N, 5.7%; found C, 53.2; H, 8.8; N, 5.7%; $[\alpha]_D^{20}$ +6.6 (*c* 1.1 in $CHCl_3$); ν_{max} (film) 3650, 3100, 2480, 2440, 1735 (C=O), 1700 (C=O), 1520, 1370, 1170; δ_H (200 MHz, $CDCl_3$) 1.27 (3H, t, *J* 7.2, OCH_2CH_3), 1.45 (9H, s, CMe_3), 2.60 (2H, d, *J* 6.3, C(2)H_2), 3.05–3.18 (1H, m, C(4)H_A), 3.28–3.33 (1H, m, C(4)H_B), 3.53 (1H, br s, N*H*), 4.07–4.23 (1H, m, C(3)*H*), 4.17 (2H, q, *J* 7.2, OCH_2CH_3), 5.00 (1H, br s, O*H*); δ_C (50 MHz, $CDCl_3$) 14.0 (OCH_2CH_3), 28.2 (CMe_3), 38.6 (*C*(2)), 45.4 (*C*(4)), 60.8 (OCH_2CH_3), 67.7 (*C*(3)), 79.6 (*C*Me$_3$), 156.8 (NCO), 172.8 (*C*(1)); *m*/*z* (CI^+) 248 ($[M+H]^+$, 65%), 192 (100%).

*4.1.5. Ethyl (R)-[2′,2′-dimethyl-N(3′)-tert-butoxycarbonyl-1′,3′-oxazolidin-5′-yl]ethanoate **14**.*



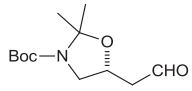
(−)-CSA (500 mg, 2.15 mmol) was added to a stirred solution of **31** (13.9 g, 56.3 mmol) in 2,2-dimethoxypropane/acetone (1:1, 200 mL) and the resultant mixture was heated at 70 °C for 2 h. The reaction mixture was then allowed to cool to rt, Et_3N (1.0 mL) was added and the resultant mixture was concentrated *in vacuo*. Purification via flash column chromatography (eluent CH_2Cl_2/Et_2O, 2:1) gave **14** as a pale yellow oil (14.9 g, 92%); $C_{14}H_{25}NO_5$ requires C, 58.5; H, 8.8; N, 4.9%; found C, 58.45; H, 8.8; N, 4.8%; $[\alpha]_D^{20}$ −26.8 (*c* 2.7 in $CHCl_3$); ν_{max} (film) 2480, 2440, 1730 (C=O), 1695 (C=O), 1395, 1260, 1195, 1055, 870, 770; δ_H (200 MHz, $CDCl_3$) 1.27 (3H, t, *J* 7.1, OCH_2CH_3), 1.47 (9H, s, CMe_3), 1.50 (3H, s, C(2′)Me_A), 1.55 (3H, s, C(2′)Me_B), 2.56 (1H, dd, *J* 15.9, 7.0, C(2)H_A), 2.68–2.72 (1H, m, C(2)H_B), 3.11–3.16 (1H, m, C(4′)H_A), 3.78–3.82 (1H, m, C(4′)H_B), 4.17 (2H, q, *J* 7.1, OCH_2CH_3), 4.41–4.45 (1H, m, C(5′)*H*); δ_C (50 MHz, $CDCl_3$) 14.0 (OCH_2CH_3), *24.0, 25.2, 26.2, 27.4* (C(2′)Me_2), 28.3 (CMe_3), 38.4 (*C*(2)), 50.6 (*C*(4′)), 60.7 (OCH_2CH_3), 70.0 (*C*(5′)), *79.6, 80.1* (*C*Me$_3$), *93.2, 93.6* (*C*(2′)), 152.2 (NCO), 170.6 (*C*(1)); *m*/*z* (CI^+) 288 ($[M+H]^+$, 28%), 188 (100%).

*4.1.6. (R)-2-[2′,2′-Dimethyl-N(3′)-tert-butoxycarbonyl-1′,3′-oxazolidin-5′-yl]ethanol **32**.*



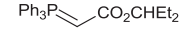
Red-Al® (3.4 M in PhMe, 3.2 mL, 11 mmol) was added to a stirred solution of **14** (790 mg, 2.75 mmol) in PhMe (30 mL) and the resultant mixture was stirred at 0 °C for 1 h. H_2O (2 mL) was added, the reaction mixture was allowed to warm to rt and the resultant mixture was diluted with H_2O (25 mL) and stirred for 30 min. The mixture was then filtered through Celite (eluent Et_2O) and the aqueous layer was extracted with Et_2O (3×30 mL). The combined organic extracts were dried and concentrated *in vacuo* to give **32** as a viscous, colourless oil (591 mg, 86%); $C_{12}H_{23}NO_4$ requires C, 58.75; H, 9.45; N, 5.7%; found C, 58.85; H, 9.5; N, 5.7%; $[\alpha]_D^{25}$ −22.4 (*c* 2.1 in $CHCl_3$); ν_{max} (film) 3600, 3100, 2980, 2940, 2880, 1700 (C=O), 1480, 1260, 1175, 1150, 1100, 1060; δ_H (200 MHz, $CDCl_3$) 1.46 (9H, s, CMe_3), 1.49 (3H, s, C(2′)Me_A), 1.57 (3H, s, C(2′)Me_B), 1.82–1.87 (2H, m, C(2)H_2), 2.30 (1H, br s, O*H*), 3.13 (1H, dd, *J* 9.5, 9.5, C(4′)H_A), 3.40–3.82 (1H, m, C(4′)H_B), 3.77 (2H, t, *J* 6.3, C(1)H_2), 4.20–4.26 (1H, m, C(5′)*H*); δ_C (50 MHz, $CDCl_3$) *24.1, 25.0, 26.1, 27.1* (C(2′)Me_2), 28.3 (CMe_3), 35.3 (*C*(2)), 50.8 (*C*(4′)), 59.6 (*C*(1)), 72.2 (*C*(5′)), *79.6, 80.2* (*C*Me$_3$), *93.1, 93.5* (*C*(2′)), *152.1, 152.5* (NCO); *m*/*z* (CI^+) 246 ($[M+H]^+$, 15%), 146 (100%).

*4.1.7. (R)-[2′,2′-Dimethyl-N(3′)-tert-butoxycarbonyl-1′,3′-oxazolidin-5′-yl]ethanal **13**.*



DMSO (6.47 g, 76.9 mmol) was added to a stirred solution of $(COCl)_2$ (4.47 g, 35.2 mmol) in CH_2Cl_2 (100 mL) at −63 °C. The reaction mixture was stirred for 10 min then a solution of **32** (7.85 g, 32.0 mmol) in CH_2Cl_2 (50 mL) was added and the resultant mixture was stirred at −63 °C for 15 min. A solution of $^iPr_2NEt$ (10.3 g, 79.8 mmol) in CH_2Cl_2 (10 mL) was then added and the reaction mixture was allowed to warm to rt before H_2O (100 mL) was added. The resultant mixture was extracted with CH_2Cl_2 (2×50 mL) and the combined organic extracts were dried and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 and the resultant solution was filtered through a short plug of silica gel (eluent CH_2Cl_2). The filtrate was concentrated *in vacuo* to give **13** as a pale yellow oil, which was used immediately without further purification (7.48 g, 96%); δ_H (200 MHz, $CDCl_3$) 1.47 (9H, s, CMe_3), 1.51 (3H, s, C(2′)Me_A), 1.55 (3H, s, C(2′)Me_B), 2.70 (1H, dd, *J* 15.8, 6.0, C(2)H_A), 2.80–2.95 (1H, m, C(2)H_B), 2.90–3.20 (1H, m, C(4′)H_A), 3.70–3.90 (1H, m, C(4′)H_B), 4.47–5.52 (1H, m, C(5′)*H*), 9.82 (1H, s, C(1)*H*); δ_C (50 MHz, $CDCl_3$) *24.2, 25.1, 26.1, 27.1* (C(2′)Me_2), 28.3 (CMe_3), 47.0 (*C*(2)), 50.6 (*C*(4′)), 68.5 (*C*(5′)), 80.0 (*C*Me$_3$), 93.3 (*C*(2′)), 151.7 (NCO), 199.3 (*C*(1)); *m*/*z* (CI^+) 244 ($[M+H]^+$, 10%), 144 (100%).

*4.1.8. 3-Pentyl (triphenylphosphoranylidene)ethanoate **33**.*



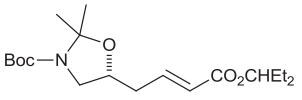
Step 1: Concd aq H_2SO_4 (0.2 mL) was added to a solution of bromoacetic acid (10.8 g, 77 mmol) and 3-pentanol (8.8 g,

100 mmol) in C_6H_6 (180 mL) and the resultant mixture was heated at reflux in a Dean–Stark apparatus until the evolution of H_2O ceased (~5 h). The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. H_2O (50 mL) was added to the residue and the resultant mixture was extracted with Et_2O (2×20 mL). The combined organic extracts were washed with 1% aq $NaHCO_3$ (30 mL), then dried. Distillation of the resultant solution gave 3-pentyl bromoacetate **34** as a colourless oil (13.6 g, 84%); $C_7H_{13}BrO_2$ requires C, 40.2; H, 6.3%; found C, 40.2; H, 6.45%; bp 65–67 °C (3 mmHg); ν_{max} (film) 2970, 2880, 1730 (C=O), 1460, 1280, 1170, 1105; δ_H (200 MHz, $CDCl_3$) 0.92 (6H, t, *J* 7.3, OCH(CH_2CH_3)$_2$), 1.62 (4H, dq, *J* 7.3, 6.3, OCH(CH_2CH_3)$_2$), 3.82 (2H, s, CH_2Br), 4.83 (1H, quintet, *J* 6.3, OC*H*Et$_2$); *m*/*z* (CI^+) 228 ([M(^{81}Br)+NH_4]$^+$, 100%), 226 ([M(^{79}Br)+NH_4]$^+$, 100%).

Step 2: PPh_3 (10.4 g, 39.8 mmol) was added to a stirred solution of **34** (9.36 g, 39.8 mmol) in PhMe (40 mL) and the resultant mixture was stirred at rt for 16 h. Fine crystals precipitated from the mixture and were subsequently washed with PhMe then dried under high vacuum to give 2-[2-oxo-2-(3′-pentyl)ethyl]triphenylphosphonium bromide **35** as a colourless oil (17.3 g, 92%); $C_{25}H_{28}BrO_2P$ requires C, 63.7; H, 6.0%; found C, 63.4; H, 6.0%; ν_{max} (KBr) 3560, 3410, 2970, 2760, 1725 (C=O), 1440, 1260, 1150, 1110; δ_H (200 MHz, $CDCl_3$) 0.71 (6H, t, *J* 7.0, OCH(CH_2CH_3)$_2$), 1.41 (4H, dq, *J* 7.0, 6.3, OCH(CH_2CH_3)$_2$), 4.62 (1H, quintet, *J* 6.3, OC*H*Et$_2$), 5.58–5.63 (2H, m, C(2)H_2), 7.27–7.97 (15H, m, *Ph*); *m*/*z* (CI^+) 391 ([M−Br]$^+$, 7%), 279 (100%).

Step 3: Phenolphthalein (1.0 M in EtOH, two drops) was added to a suspension of **35** (1.56 g, 33 mmol) in H_2O/PhMe (1:1, 50 mL) in a separating funnel. NaOH (2.0 M, aq) was added in small portions to the suspension with vigorous shaking until the aqueous layer turned pink. The aqueous layer was then extracted with PhMe (2×25 mL) and the combined organic extracts were dried and concentrated *in vacuo*. The residue was dried at 50 °C under high vacuum for 1 h to give **33** as a viscous, colourless oil (1.30 g, quant); $C_{25}H_{27}O_2P$ requires C, 76.9; H, 7.0%; found C, 76.7; H, 6.8%; ν_{max} (film) 3060, 2960, 2940, 2880, 1625, 1435, 1380, 1320, 1110; δ_H (200 MHz, $CDCl_3$) 0.72 (6H, br s, OCH(CH_2CH_3)$_2$), 1.34 (4H, br s, OCH(CH_2CH_3)$_2$), 2.87 (1H, br s, C(2)*H*), 4.64 (1H, quintet, *J* 6.3, OC*H*Et$_2$), 7.21–7.73 (15H, m, *Ph*); *m*/*z* (CI^+) 391 ([M+H]$^+$, 100%), 303 (65%).

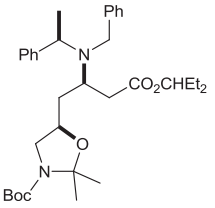
4.1.9. 3″-Pentyl (R,E)-4-[2′,2′-dimethyl-N(3′)-tert-butoxycarbonyl-1′,3′-oxazolidin-5′-yl]but-2-enoate ***12****.*



(*E*)-**12**

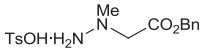
A solution of **13** (6.43 g, 26.5 mmol) and **33** (16.5 g, 42.3 mmol) in PhMe (300 mL) was stirred at 70 °C for 4 h then concentrated *in vacuo*. 30–40 °C Petrol was added to the residue and the resultant mixture was filtered. The filtrate was concentrated *in vacuo* to give a 91:9 mixture of (*E*)-**12** and (*Z*)-**21**. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 3:2) gave (*Z*)-**21** as a colourless oil (840 mg, 9%, >99:1 dr); $C_{19}H_{33}NO_5$ requires C, 64.2; H, 9.4; N, 3.9%; found C, 64.4; H, 9.3; N, 4.2%; $[\alpha]_D^{20}$ −12.7 (*c* 2.2 in $CHCl_3$); ν_{max} (film) 2970, 2940, 2880, 1700 (C=O), 1645, 1390, 1180; δ_H (200 MHz, $CDCl_3$) 0.89 (6H, t, *J* 7.4, OCH(CH_2CH_3)$_2$), 1.01–1.70 (10H, m, C(2′)*Me*$_2$, OCH(CH_2CH_3)$_2$), 1.47 (9H, s, C*Me*$_3$), 3.00 (2H, m, C(4)H_2), 3.06–3.13 (1H, m, C(4′)H_A), 3.64–3.69 (1H, m, C(4′)H_B), 4.18–4.25 (1H, m, C(5′)*H*), 4.77–4.81 (1H, m, OC*H*Et$_2$), 5.92 (1H, d, *J* 11.5, C(2)*H*), 6.25–6.34 (1H, m, C(3)*H*); δ_C (50 MHz, $CDCl_3$) 9.5 (OCH(CH_2CH_3)$_2$), *24.2, 25.2, 26.3, 27.1* (C(2′)*Me*$_2$), 28.3 (C*Me*$_3$), 28.3 (OCH(CH_2CH_3)$_2$), 32.0 (*C*(4)), 50.1 (*C*(4′)), 72.7 (*C*(5′)), 76.3 (OCHEt$_2$), 79.3, 79.9 (*C*Me$_3$), 93.1, 93.4 (*C*(2′)), 122.3 (*C*(2)), 143.7 (*C*(3)), 152.0 (NCO), 165.9 (*C*(1)); *m*/*z* (CI^+) 356 ([M+H]$^+$, 25%), 256 (100%). Further elution gave (*E*)-**12** as a colourless oil (8.11 g, 86%, >99:1 dr); $C_{19}H_{33}NO_5$ requires C, 64.2; H, 9.4; N, 3.9%; found C, 64.3; H, 9.2; N, 3.85%; $[\alpha]_D^{20}$ −17.9 (*c* 2.1 in $CHCl_3$); ν_{max} (film) 2970, 2930, 2880, 1705 (C=O), 1660, 1390, 1265, 1170, 1105, 1145; δ_H (200 MHz, $CDCl_3$) 0.88 (6H, t, *J* 6.7, OCH(CH_2CH_3)$_2$), 1.40–1.70 (10H, m, C(2′)*Me*$_2$, OCH(CH_2CH_3)$_2$), 1.47 (9H, s, C*Me*$_3$), 2.4–2.53 (2H, m, C(4)H_2), 3.10 (1H, br s, C(4′)H_A), 3.70 (1H, br s, C(4′)H_B), 4.15–4.21 (1H, m, C(5′)*H*), 4.82 (1H, quintet, *J* 6.0, OC*H*Et$_2$), 5.93 (1H, d, *J* 15.7, C(2)*H*), 6.91 (1H, dt, *J* 15.7, 5.7, C(3)*H*); δ_C (50 MHz, $CDCl_3$) 9.5 (OCH(CH_2CH_3)$_2$), 24.2, 25.2, 26.2, 27.1 (C(2′)*Me*$_2$), 26.4 (OCH(CH_2CH_3)$_2$), 28.3 (C*Me*$_3$), 35.6 (*C*(4)), 50.3 (*C*(4′)), 71.9 (*C*(5′)), 76.6 (OCHEt$_2$), 80.1 (*C*Me$_3$), 93.2 (*C*(2′)), 124.3 (*C*(2)), 142.8 (*C*(3)), 152.1 (NCO), 165.9 (*C*(1)); *m*/*z* (CI^+) 373 ([M+NH_4]$^+$, 5%), 356 ([M+H]$^+$, 4%), 256 (100%).

4.1.10. 3″-Pentyl (R,R,R)-3-[N-benzyl-N-(α-methylbenzyl)amino]-4-[2′,2′-dimethyl-N(3′)-tert-butoxycarbonyl-1′,3′-oxazolidin-5′-yl]butanoate ***10****.*



BuLi (1.6 M in hexanes, 9.9 mL, 15.8 mmol) was added to a stirred solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (3.36 g, 15.9 mmol) in THF (25 mL) at −78 °C and the resulting pink solution was stirred at −78 °C for 30 min. A solution of **12** (3.77 g, 10.6 mmol) in THF (5 mL) was then added dropwise and the resultant mixture was stirred at −78 °C for 1 h. Satd aq NH_4Cl (4 mL) was then added and the mixture was allowed to warm to rt. The reaction mixture was poured into brine (150 mL) and extracted with Et_2O (3×50 mL). The combined organic extracts were dried and concentrated *in vacuo* to give **10** in 98:2 dr. Purification via flash chromatography (eluent 30–40 °C petrol/Et_2O, 10:3) gave **10** as a viscous, colourless oil (5.11 g, 85%, >99:1 dr); $C_{34}H_{50}N_2O_5$ requires C, 72.05; H, 8.9; N, 4.9%; found C, 72.25; H, 8.5; N, 5.0%; $[\alpha]_D^{21}$ −23.9 (*c* 2.0 in $CHCl_3$); ν_{max} (film) 2970, 2930, 1730 (C=O), 1700 (C=O), 1600, 1495, 1455, 1245; δ_H (500 MHz, DMSO-d_6, 363 K) 0.81 (6H, t, *J* 7.4, OCH(CH_2CH_3)$_2$), 1.34 (3H, d, *J* 6.9, C(α)*Me*), 1.44 (15H, s, C*Me*$_3$, C(2′)*Me*$_2$), 1.46–1.57 (4H, m, OCH(CH_2CH_3)$_2$), 1.76 (1H, dd, *J* 9.4, 3.7, C(4)H_A), 1.79 (1H, dd, *J* 9.4, 4.2, C(4)H_B), 2.11 (2H, m, C(2)H_2), 2.89 (1H, dd, *J* 9.5, 9.5, C(4′)H_A), 3.50–3.55 (1H, m, C(3)*H*), 3.54 (1H, dd, *J* 9.8, 5.8, C(4′)H_B), 3.57 (1H, d, *J* 15.1, NCH_AH$_B$Ph), 3.85 (1H, d, *J* 15.1, NCH$_A$$H_B$Ph), 3.91 (1H, q, *J* 6.9, C(α)*H*), 4.23–4.28 (1H, m, C(5′)*H*), 4.56–4.61 (1H, m, OC*H*Et$_2$), 7.41–7.21 (10H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 9.6 (OCH(CH_2CH_3)$_2$), 19.7 (C(α)*Me*), *24.3, 25.2, 26.3, 27.3* (C(2′)*Me*$_2$), 26.3 (OCH(CH_2CH_3)$_2$), 28.5 (C*Me*$_3$), 37.0 (*C*(2)), 37.0 (*C*(4)), 37.1, 49.8 (*C*(3), NCH_2Ph), *50.9, 51.2* (*C*(4′)), 57.5 (*C*(α)), *70.3, 70.7* (*C*(5′)), 76.5 (OCHEt$_2$), *79.0, 79.9* (*C*Me$_3$), 92.9 (*C*(2′)), 126.8, 127.3, 128.4 (*o,m,p-Ph*), 140.9 (*i-Ph*), *151.8, 152.5* (NCO), 172.1 (*C*(1)); *m*/*z* (CI^+) 567 ([M+H]$^+$, 100%).

4.1.11. Benzyl N(1)-methylhydrazinylethanoate·TsOH ***22****·TsOH.*

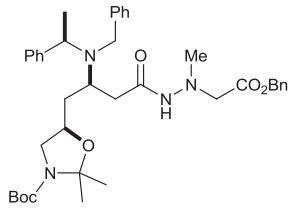


Step 1: Chloroacetic acid (4.5 g, 47.6 mmol) was added to a solution of methylhydrazine (12.0 g, 260 mmol) in H_2O (80 mL) and the

resultant mixture was allowed to stand at rt for 5 days. Excess methylhydrazine was removed by reduced pressure distillation. The residue was dissolved in H_2O (80 mL) and purified by ion-exchange chromatography (Dowex 50WX8-200, eluent 1.0 M NH_4OH). EtOH (50 mL) was added to the residue and the resultant mixture was allowed to stand at −20 °C for 16 h. The crystals that formed were filtered off and dried under high vacuum to give *N*(1)-methylhydrazinylacetic acid **36** as a white solid (2.57 g, 52%);[30] mp 151–152 °C; {lit.[30] mp 153–154 °C}; δ_H (200 MHz, D_2O) 2.90 (3H, s, N*Me*), 3.70 (2H, s, C(2)H_2).

Step 2: TsOH (8.36 g, 44.2 mmol) was added to a stirred solution of **36** (2.00 g, 19.2 mmol) and BnOH (20 mL) in C_6H_6 (80 mL) and the resultant mixture was heated at reflux for 6 h using a Dean–Stark apparatus. The reaction mixture was then allowed to cool to rt, poured into Et_2O (500 mL), and the white precipitate that formed was collected by filtration. Purification via recrystallisation (MeOH/Et_2O) gave **22**·TsOH as a white powder (3.80 g, 54%);[31] mp 93–94 °C; {lit.[31] mp 96–99 °C}; δ_H (200 MHz, D_2O) 2.10 (3H, s, Ar*Me*), 2.60 (3H, s, N*Me*), 3.67 (2H, s, C(2)H_2), 4.98 (2H, s, OCH_2Ph), 7.06 (2H, d, *J* 8.2, *Ar*), 7.41 (2H, d, *J* 8.2, *Ar*), 7.12–7.25 (5H, m, *Ph*).

*4.1.12. Benzyl (R,R,R)-N(1′)-methyl-N(2′)-{3″-[N-benzyl-N-(α-methylbenzyl)amino]-4″-[2‴,2‴-dimethyl-N(3‴)-tert-butoxycarbonyl-1‴,3‴-oxazolidin-5‴-yl]butanoyl}hydrazinylethanoate **8**.*

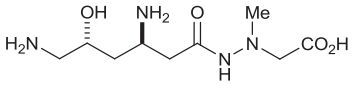


Step 1: LiOH·H_2O (2.27 g, 543 mmol) was added to a stirred solution of **10** (3.06 g, 5.43 mmol) in MeOH/THF/H_2O (3:1:1, 180 mL) and the resultant mixture was heated at reflux for 24 h. The reaction mixture was then allowed to cool to rt and diluted with H_2O (250 mL). HCl (1.0 M, aq) was then added until pH 5 was reached. The resultant mixture was extracted with Et_2O (2×50 mL), and the combined organic extracts were dried and concentrated *in vacuo* to give **9** as a white solid (>99:1 dr); $C_{29}H_{40}N_2O_5$ requires C, 70.1; H, 8.1; N, 5.6%; found C, 70.4; H, 8.1; N, 5.6%; $[\alpha]_D^{21}$ −25.4 (*c* 0.8 in $CHCl_3$); ν_{max} (KBr) 2980, 2935, 1700 (C=O), 1395, 1255, 1170, 1150; δ_H (200 MHz, $CDCl_3$) 1.49 (CMe_3), 1.84–1.91 (1H, m, C(4)H_A), 1.33–1.77 (10H, m, C(4)H_B, C(2′)Me_2, C(α)*Me*), 2.00–2.52 (2H, m, C(2)H_2), 3.02 (1H, dd, *J* 9.7, 9.7, C(4′)H_A), 3.50–3.55 (2H, m, C(3)*H*, C(4′)H_B), 3.68 (2H, s, NCH_2Ph), 4.03 (1H, q, *J* 6.9, C(α)*H*), 4.07–4.14 (1H, m, C(5′)*H*), 7.27–7.37 (10H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 18.6 (C(α)*Me*), *24.3, 26.4, 27.4, 28.5* (C(2′)Me_2), 28.7 (CMe_3), 35.9 (*C*(4)), 50.0 (NCH_2Ph), 51.3 (*C*(3)), 57.7 (*C*(α)), *52.0, 52.4* (*C*(4′)), 71.2 (*C*(5′)), *79.7, 80.3* (CMe_3), 93.6 (*C*(2′)), 127.6, 128.4, 128.8 (*o,m,p-Ph*), 138.8 (*i-Ph*), 141.2, 152.0 (NCO), 175.6 (*C*(1)); *m/z* (FAB$^+$) 497 ([M+H]$^+$, 26%), 105 (100%).

Step 2A: Et_3N (120 mg, 1.20 mmol) was added to a stirred solution of **9** (500 mg, 1.00 mmol), **22**·TsOH (366 mg, 1.00 mmol) and HOBt (135 mg, 1.00 mmol) in THF (50 mL) and the resultant mixture was cooled to 0 °C. A solution of DCC (227 mg, 1.00 mmol) in THF (10 mL) was then added and the resultant mixture was stirred at 0 °C for 15 min, then allowed to warm to rt and stirred at rt for another 5 h. The reaction mixture was then concentrated *in vacuo*. CH_2Cl_2 (30 mL) was added to the residue (which caused the formation of white precipitate) and the resultant solution was filtered. The filtrate was washed with satd aq $NaHCO_3$, dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent Et_2O) gave **8** as a white solid (558 mg, 79% from **10**, >99:1 dr);[32] $C_{39}H_{52}N_4O_6$ requires C, 69.6; H, 7.8; N, 8.3%; found C, 69.7; H, 7.9; N, 8.4%; $[\alpha]_D^{25}$ −9.8 (*c* 0.8 in $CHCl_3$); δ_C (50 MHz, $CDCl_3$) 19.6 (C(α)*Me*), *24.2, 25.2, 26.3, 27.3* (C(2‴)Me_2), 28.5 (CMe_3), 34.2, *36.2, 37.1* (*C*(2″), *C*(4″)), *43.8, 44.8* (N*Me*), 49.9, 50.1 (*C*(3″), NCH_2Ph), 51.1 (*C*(4‴)), *57.3, 57.6* (*C*(α)), *58.0, 58.7* (*C*(2)), 66.5 (OCH_2Ph), 70.7 (*C*(5‴)), *79.3, 79.8* (CMe_3), *92.9, 93.2* (*C*(2‴)), 126.6, 126.8, 127.1, 127.3, 128.2, 128.7 (*o,m,p-Ph*), 135.1, 140.7 (*i-Ph*), *151.9, 152.3* (NCO), *170.0, 170.5* (C(1″)), 175.1 (*C*(1)); *m/z* (FAB$^+$) 673 ([M+H]$^+$, 37%), 105 (100%).

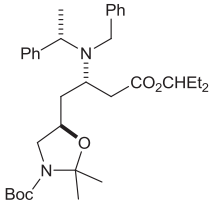
Step 2B: Ethyl chloroformate (0.06 mL, 0.60 mmol) was added to a stirred solution of **9** (300 mg, 0.60 mmol) and Et_3N (61 mg, 0.60 mmol) in CH_2Cl_2 (40 mL) at −15 °C and the resultant solution was stirred at −15 °C for 10 min. A solution of **22**·TsOH (220 mg, 0.60 mmol) and Et_3N (61 mg, 0.60 mmol) in CH_2Cl_2 (5 mL) was then added and the resultant mixture was stirred at −15 °C for 5 min, then allowed to warm to 0 °C and stirred for a further 30 min. The reaction mixture was then concentrated *in vacuo* and H_2O (50 mL) was added to the residue. The resultant mixture was extracted with Et_2O (3×30 mL) and the combined organic extracts were washed with satd aq $NaHCO_3$ (50 mL), dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent Et_2O) gave **8** as a white solid (286 mg, 57% from **10**, >99:1 dr).

*4.1.13. (R,R)-N(1′)-Methyl-N(2′)-(3″,6″-diamino-5″-hydroxyhexanoyl)hydrazinylethanoic acid [(+)-negamycin] **1**.*



A solution of **8** (1.29 g, 1.92 mmol) in TFA (3 mL) was stirred at 0 °C for 15 min, then allowed to warm to rt and stirred for a further 15 min. A mixture of THF/H_2O (1:1, 50 mL) was then added and stirring was continued at rt for 16 h. The reaction mixture was then poured into H_2O (100 mL) and satd aq $NaHCO_3$ was added until pH 9 was achieved. The aqueous layer was extracted with EtOAc (3×30 mL) and the combined organic extracts were dried and concentrated *in vacuo*. The residue was dissolved in MeOH (5 mL), then AcOH (five drops) and $Pd(OH)_2$/C (10% wt, 630 mg) were added and the resultant mixture was stirred under hydrogen (5 atm) at rt for 22 h. The reaction mixture was then filtered through a short plug of Celite (eluent MeOH) and the filtrate was concentrated *in vacuo*. Purification via ion-exchange chromatography (Amberlite CG-50 resin, eluent satd aq NH_4OH) gave (+)-negamycin **1** as a white solid (331 mg, 71%, >99:1 dr);[4] mp 104–110 °C (dec); {lit.[1] mp 110–120 °C (dec)}; $[\alpha]_D^{20}$ +2.7 (*c* 1.6 in H_2O); {lit.[1] $[\alpha]_D^{29}$ +2.5 (*c* 2.0 in H_2O)}; δ_H (200 MHz, D_2O) 1.46–1.70 (2H, m, C(4″)H_2), 2.33 (2H, d, *J* 7.2, C(2″)H_2), 2.58 (3H, s, N*Me*), 2.82 (1H, dd, *J* 13.2, 3.6, C(6″)H_A), 2.96 (1H, dd, *J* 13.2, 8.9, C(6″)H_B), 3.33 (2H, s, C(2)H_2), 3.37–3.42 (1H, m, C(3″)*H*), 3.92–3.97 (1H, m, C(5″)*H*); δ_C (50 MHz, D_2O) 40.3 (*C*(4″)), 41.8 (*C*(2″)), 44.6 (N*Me*), 45.7 (*C*(3″)), 45.9 (*C*(6″)), 61.7 (*C*(2)), 66.4 (*C*(5″)), 171.6 (*C*(1″)), 177.9 (*C*(1)).

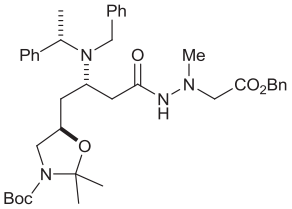
*4.1.14. 3″-Pentyl (3S,5R,αS)-3-[N-benzyl-N-(α-methylbenzyl)amino]-4-[2′,2′-dimethyl-N(3′)-tert-butoxycarbonyl-1′,3′-oxazolidin-5′-yl] butanoate **19**.*



BuLi (1.3 M in hexanes, 1.20 mL, 1.56 mmol) was added to a stirred solution of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine

(600 mg, 2.84 mmol) in THF (20 mL) at −78 °C and the resultant pink solution was stirred for 15 min. A solution of **12** (474 mg, 1.41 mmol) in THF (5 mL) at −78 °C was then added dropwise and the resultant mixture was stirred for 1 h at −78 °C. Satd aq NH_4Cl (2 mL) was then added and the reaction mixture was poured into brine (100 mL). The resultant mixture was extracted with Et_2O (3×30 mL), dried and concentrated *in vacuo* to give **19** in ∼95% diastereoisomeric purity. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 9:1; increased to 30–40 °C petrol/Et_2O, 4:1) gave **19** as a colourless oil (490 mg, 61%, ∼95% diastereoisomeric purity); $C_{34}H_{50}N_2O_5$ requires C, 72.05; H, 8.9; N, 4.9%; found C, 71.8; H, 9.0; N, 5.2%; $[\alpha]_D^{25}$ −13.5 (*c* 1.7 in $CHCl_3$); ν_{max} (film) 2980, 1730 (C=O), 1700 (C=O), 1600, 1495, 1455; δ_H (500 MHz, DMSO-d_6, 363 K) 0.80 (6H, t, *J* 7.5, OCH(CH_2CH_3)$_2$), 1.28 (3H, d, *J* 6.9, C(α)*Me*), 1.40–1.60 (4H, m, OCH(CH_2CH_3)$_2$), 1.42 (3H, s, C(2′)Me_A), 1.44 (9H, s, CMe_3), 1.45 (9H, s, C(2′)Me_B), 1.91–1.96 (2H, m, C(4)H_2), 2.18 (2H, dd, *J* 14.9, 3.3, C(2)H_A), 2.53 (2H, dd, *J* 14.9, 9.1, C(2)H_B), 2.79 (1H, dd, *J* 9.4, 9.4, C(4′)H_A), 3.17–3.24 (1H, m, C(3)*H*), 3.28–3.35 (1H, m, C(4′)H_B), 3.58 (2H, d, *J* 15.4, NCH_AH_BPh), 3.92 (2H, d, *J* 15.4, NCH_AH_BPh), 3.91.3.98 (1H, m, C(α)*H*), 4.20–4.26 (1H, m, C(5′)*H*), 4.60–4.63 (1H, m, OC*H*Et$_2$), 7.21–7.41 (10H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 9.6 (OCH(CH_2CH_3)$_2$), *20.4, 21.3* (C(α)*Me*), *24.2, 25.2, 26.3, 27.3* (C(2′)Me_2), 26.3 (OCH(CH_2CH_3)$_2$), 28.5 (CMe_3), *35.7, 36.5*, 37.2 (*C*(2), *C*(4)), 50.1, 50.8 (*C*(4′), NCH_2Ph), 51.8 (*C*(3)), *57.9, 58.9* (*C*(α)), 71.8 (*C*(5′)), 76.6 (OCHEt$_2$), *79.2, 79.9* (CMe_3), 92.9 (*C*(2′)), 126.7, 126.9, 127.3, 127.4, 128.1, 128.3 (*o,m,p-Ph*), 141.5, 143.2 (*i-Ph*), 152.2 (NCO), 172.1 (*C*(1)); *m/z* (CI^+) 567 ($[M+H]^+$, 100%).

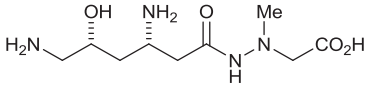
*4.1.15. Benzyl (3S,5R,αS)-N(1′)-methyl-N(2′)-{3″-[N-benzyl-N-(α-methylbenzyl)amino]-4″-[2‴,2‴-dimethyl-N(3‴)-tert-butoxycarbonyl-1‴,3‴-oxazolidin-5‴-yl]butanoyl}hydrazinylethanoate **18**.*



Step 1: LiOH·H_2O (380 mg, 9.10 mmol) was added to a solution of **19** (510 mg, 0.90 mmol, ∼95% diastereoisomeric purity) in MeOH/THF/H_2O (3:1:1, 40 mL) and the resultant mixture was heated at reflux for 24 h. The reaction mixture was then allowed to cool to rt and poured into H_2O (75 mL). aq HCl (1.0 M) was added until pH 6 was achieved then the mixture was extracted with Et_2O (3×30 mL). The combined organic extracts were dried and concentrated *in vacuo* to give **37** as a colourless oil (379 mg, 85%, ∼95% diastereoisomeric purity);[32] $C_{29}H_{40}N_2O_5$ requires C, 70.1; H, 8.1; N, 5.6%; found: C, 70.3; H, 8.0; N, 5.3%; $[\alpha]_D^{25}$ +13.4 (*c* 0.9 in $CHCl_3$); ν_{max} (KBr) 3700, 2200, 2980, 1700 (C=O), 1455, 1395, 1260, 1170, 1150; δ_C (50 MHz, $CDCl_3$) *18.1, 18.7* (C(α)*Me*), *24.2, 25.1* (C(2′)Me_A), *26.3, 27.3* (C(2′)Me_B), 28.4 (CMe_3), 35.1 (*C*(2), *C*(4)), 49.8, 51.1 (*C*(4′), NCH_2Ph), 52.1 (*C*(3)), 59.6 (*C*(α)), *70.6, 71.0* (*C*(4′)), *79.5, 80.2* (CMe_3), 93.2 (*C*(2′)), 127.2, 127.7, 128.4, 128.5, 128.7, 129.0 (*o,m,p-Ph*), *137.2, 137.9, 140.2, 140.8* (*i-Ph*), 151.8 (NCO), 174.4 (*C*(1)); *m/z* (CI) 497 ($[M+H]^+$, 78%), 212 (100%).

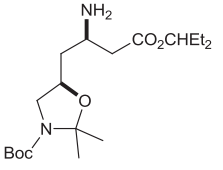
Step 2: Et_3N (78 mg, 0.78 mmol) was added to a stirred solution of **37** (382 mg, 0.77 mmol), HOBt (104 mg, 0.77 mL) and **22**·TsOH (282 mg, 0.77 mmol) in THF (30 mL) and the resultant mixture was cooled to 0 °C. A solution of DCC (174 mg, 0.84 mmol) in THF (5 mL) was then added. The reaction mixture was stirred at 0 °C for 15 min, allowed to warm to rt and stirred for a further 6 h then concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (40 mL), the white precipitate that formed was removed by filtration, and the filtrate was washed with satd aq $NaHCO_3$, then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent Et_2O/EtOAc, 9:1) gave **18** as a viscous, colourless oil (233 mg, 45%, ∼95% diastereoisomeric purity);[32] $C_{39}H_{52}N_4O_6$ requires C, 69.6; H, 7.8; N, 8.3%; found: C, 69.7; H, 7.9; N, 8.4%; $[\alpha]_D^{25}$ −19.5 (*c* 0.8 in $CHCl_3$); ν_{max} (KBr) 2980, 2935, 1745 (C=O), 1695 (C=O), 1395, 1180; δ_C (50 MHz, $CDCl_3$) 20.7 (C(α)*Me*), *24.2, 25.2* (C(2″)Me_A), *26.2, 27.3* (C(2″)Me_B), 28.5 (CMe_3), 36.8, 37.7 (*C*(2′), *C*(4′)), *43.8, 44.8* (N*Me*), 50.1, 50.9, 51.0 (*C*(3′)), *C*(4″), NCH_2Ph), 57.6 (*C*(α)), 58.2 (C(2)), 66.5 (OCH_2Ph), *71.7, 72.0* (*C*(5″)), *79.2, 80.0* (CMe_3), 93.2 (*C*(2″), 126.7, 126.8, 126.9, 127.4, 128.2, 128.7 (*o,m,p-Ph*), 135.1, 141.2 (*i-Ph*), 143.1, 151.9 (NCO), *169.7, 170.5* (*C*(1′)), 174.8 (*C*(1)); *m/z* (CI^+) 673 ($[M+H]^+$, 73%), 178 (100%).

*4.1.16. (3″S,5″R)-N(1′)-Methyl-N(2′)-(3″,6″-diamino-5″-hydroxyhexanoyl)hydrazinylethanoic acid [(+)-3-epi-negamycin] **2**.*



A solution of **18** (230 mg, 0.340 mmol, ∼95% diastereoisomeric purity) in TFA (2 mL) was stirred at 0 °C for 15 min, then allowed to warm to rt and stirred for a further 15 min. A mixture of THF/H_2O (1:1, 5 mL) was then added and stirring was continued at rt for 16 h. The reaction mixture was then poured into H_2O (40 mL) and satd aq $NaHCO_3$ was added until pH 9 was achieved. The aqueous layer was extracted with EtOAc (3×20 mL) and the combined organic extracts were dried and concentrated *in vacuo*. The residue was dissolved in MeOH (4 mL), then AcOH (five drops) and Pd(OH)$_2$/C (10% wt, 170 mg) were added and the resultant mixture was stirred under hydrogen (5 atm) at rt for 20 h. The reaction mixture was then filtered through a short plug of Celite (eluent MeOH) and the filtrate was concentrated *in vacuo*. Purification via ion-exchange chromatography (Amberlite CG-50 resin, eluent satd aq NH_4OH) gave (+)-3-*epi*-negamycin **2** as a white solid (63 mg. 75%, 96:4 dr);[4g] mp 145–168 °C (dec); $[\alpha]_D^{22}$ +8.5 (*c* 0.7 in H_2O); {lit.[4g] for enantiomer $[\alpha]_D^{25}$ −9.4 (*c* 0.5, H_2O); lit.[5e] for enantiomer $[\alpha]_D^{23}$ −9.9 (*c* 3.5 in H_2O)}; ν_{max} (KBr) 3700, 2000, 1650, 1580, 1400, 1315, 1130, 1045; δ_H (200 MHz, D_2O) 1.53–1.77 (2H, m, C(4)H_2), 2.31 (1H, dd, *J* 14.9, 5.6, C(2″)H_A), 2.42 (1H, dd, *J* 14.9, 7.5, C(2″)H_B), 2.58 (3H, s, N*Me*), 2.82 (1H, dd, *J* 13.2, 8.4, C(6″)H_A), 2.97 (1H, dd, *J* 13.2, 3.2, C(6″)H_B), 3.35 (2H, s, C(2)H_2), 3.46 (1H, m, C(6″)H_A), 3.91.3.96 (1H, m, C(4″)*H*); δ_C (50 MHz, D_2O) 39.4 (*C*(5″)), 40.2 (*C*(2″)), 44.6 (N*Me*), 45.7 (*C*(6″)), 46.5 (*C*(3)), 63.9 (C(2)), 67.5 (*C*(5)), 171.2 (*C*(1″)), 177.8 (*C*(1)).

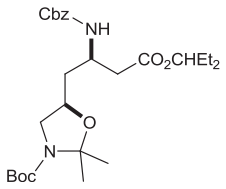
*4.1.17. 3″-Pentyl (R,R)-3-amino-4-[2′,2′-dimethyl-N(3′)-tert-butoxycarbonyl-1′,3′-oxazolidin-5′-yl]butanoate **23**.*



AcOH (five drops) and Pd(OH)$_2$/C (10% wt, 1.70 g) were added to a stirred solution of **10** (5.15 g, 9.70 mmol) in MeOH (10 mL). The resultant mixture was stirred under hydrogen (6 atm) for 20 h. Solid $NaHCO_3$ (4.00 g) was then added and the reaction mixture was filtered through Celite (eluent MeOH). The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (eluent EtOAc) to give **23** as a colourless oil (3.31 g, 96%, >99:1 dr); $C_{19}H_{36}N_2O_5$ requires C, 61.3; H, 9.7; N, 7.5%; found C, 61.1; H, 9.8; N, 7.8%; $[\alpha]_D^{25}$ −15.7 (*c* 0.6 in $CHCl_3$); ν_{max} (film)

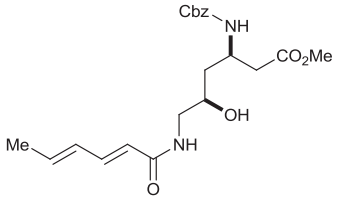
2970, 2940, 2880, 1730 (C═O), 1700 (C═O), 1460, 1395, 1315, 1260, 1175, 1110; δ_H (200 MHz, $CDCl_3$) 0.88 (6H, t, *J* 7.4, OCH(CH_2CH_3)$_2$), 1.47 (9H, s, CMe_3), 1.50–1.80 (14H, m, C(4)H_2, C(2′)Me_2, OCH(CH_2CH_3)$_2$, NH_2), 2.34 (1H, dd, *J* 15.7, 4.2, C(2)H_A), 2.51 (1H, dd, *J* 15.7, 8.6, C(2)H_B), 3.07 (1H, t, *J* 8.1, C(4′)H_A), 3.39–3.44 (1H, m, C(3)*H*), 3.69 (1H, m, C(4′)H_B), 4.22 (1H, m, C(5′)*H*), 4.79 (1H, quintet, *J* 6.0, OC*H*Et$_2$); δ_C (50 MHz, $CDCl_3$) 9.5 (OCH(CH_2CH_3)$_2$) 51.0 (*C*(4)), *24.2, 25.1, 26.3, 27.2* (C(2′)Me_2),26.3 (OCH(CH_2CH_3)$_2$), 28.3 (CMe_3), 40.5 (*C*(4′)), 43.2 (*C*(3)), *70.8, 71.1* (*C*(5′)), 76.7 (OCHEt$_2$), *79.3, 79.9* (*C*Me$_3$), *92.8, 93.3* (*C*(2′)), *151.7, 152.1* (NCO), 171.9 (*C*(1)); *m*/*z* (CI$^+$) 373 ([M+H]$^+$, 100%).

4.1.18. 3″-Pentyl (R,R)-3-(N-benzyloxycarbonylamino)-4-[N(3′)-tert-butoxycarbonyl-2′,2′-dimethyl-1′,3′-oxazolidin-5′-yl]butanoate ***24***.



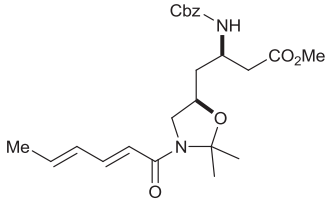
A solution of $NaHCO_3$ (790 mg, 9.40 mol) and NaCl (4.00 g) in H_2O (30 mL) was added to a solution of **23** (3.20 g, 8.60 mmol) in $CHCl_3$ (50 mL). A solution of benzyl chloroformate (1.54 g, 9.00 mmol) in CH_2Cl_2 (3 mL) was then added and the resultant mixture was stirred at rt for 45 min. The aqueous layer was extracted with Et_2O (2×30 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent Et_2O) gave **24** as a colourless oil (3.55 g, 82%, >99:1 dr); $C_{27}H_{42}N_2O_7$ requires C, 64.0; H, 8.4; N, 5.5%; found C, 64.1; H, 8.7; N, 5.5; $[\alpha]^{25}_{Hg365}$ −1.90 (*c* 0.6 in $CHCl_3$); νmax (film) 3320, 2980, 2940, 2880, 1730 (C═O), 1700 (C═O), 1530, 1390, 1175, 1105, 1055; δ_H (200 MHz, $CDCl_3$) 0.86 (6H, t, *J* 7.2, OCH(CH_2CH_3)$_2$), 1.40–1.65 (19H, m, C(2′)Me_2, OCH(CH_2CH_3)$_2$, CMe_3), 1.68–1.97 (2H, m, C(4)H_2), 2.58–2.69 (2H, m, C(2)H_2), 3.04 (1H, app t, *J* 9.6, C(4′)H_A), 3.60–3.69 (1H, m, C(4′)H_B), 4.08–4.21 (2H, m, C(3)*H*, C(5′)*H*), 4.77 (1H, quintet, *J* 6.1, OC*H*Et$_2$), 5.09 (2H, s, OCH_2Ph), 5.58 (1H, br s, N*H*), 7.27–7.36 (5H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 9.6 (OCH(CH_2CH_3)$_2$), *24.2, 25.1, 26.3, 27.2* (C(2′)Me_2), 26.3 (OCH(CH_2CH_3)$_2$), 28.4 (CMe_3), 37.0 (*C*(2), *C*(4)), 38.8, 46.1 (*C*(3)), 50.9 (*C*(4′)), 66.5 (OCH_2Ph), *70.9, 71.2* (*C*(5′)), 77.1 (OCHEt$_2$), *79.4, 80.0* (*C*Me$_3$), *93.1, 93.5* (*C*(2′)), 127.9, 128.1, 128.4 (*o,m,p-Ph*), 136.5 (*i-Ph*), *151.8, 152.1*, 155.6 (2×NCO), 171.3 (*C*(1)); *m*/*z* (CI$^+$) 507 ([M+H]$^+$, 7%), 299 (100%).

4.1.19. Methyl (R,R,E,E)-3-(N-benzyloxycarbonylamino)-5-hydroxy-6-[N-(2′,4′-hexadienoyl)amino]hexanoate ***26***.



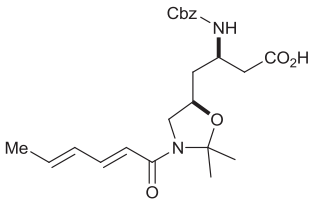
HCl gas was bubbled through a solution of **24** (3.29 g, 6.50 mmol) in MeOH (150 mL) at 0 °C for 1 min and the resultant mixture was stirred at 0 °C for 30 min then concentrated *in vacuo* to give **25**·HCl as a white solid (2.10 g, 93%, >99:1 dr). This residue was dissolved in CH_2Cl_2 (100 mL), treated with Et_3N (1.97 g, 19.5 mmol) and cooled to 0 °C. A solution of freshly distilled sorbyl chloride (1.19 g, 9.10 mmol) in CH_2Cl_2 (2 mL) was then added dropwise. After 1 h the reaction mixture was concentrated *in vacuo*. The residue was dissolved in EtOAc (100 mL) and the resultant solution was washed sequentially with brine (50 mL) and satd aq $NaHCO_3$ (50 mL), then dried and concentrated *in vacuo*. Purification via recrystallisation (30–40 °C petrol/Et_2O) gave **26** as a white solid (2.00 g, 80%, >99:1 dr); $C_{21}H_{28}N_2O_6$ requires C, 62.4; H, 6.9; N, 6.9%; found C, 62.4; H, 6.9; N, 6.75%; mp 100–109 °C; $[\alpha]^{25}_{Hg365}$ +6.67 (*c* 0.68 in $CHCl_3$); ν_{max} (KBr) 3320, 3073, 3030, 2960, 1735 (C═O), 1715, 1700 (C═O), 1660 (C═O), 1540, 1260, 965; δ_H (200 MHz, $CDCl_3$) 1.45–1.66 (2H, m, C(4)H_2), 1.67 (1H, s, O*H*), 1.85 (3H, d, *J* 5.3, C(6′)H_3), 2.55 (1H, dd, *J* 16.2, 5.0, C(2)H_A), 2.64 (1H, dd, *J* 16.2, 5.4, C(2)H_B), 3.13 (1H, dd, *J* 8.3, 4.5, C(6)H_A), 3.69 (3H, s, O*Me*), 3.60–3.80 (2H, m, C(3)*H*, C(6)H_B), 4.23 (1H, m, C(5)*H*), 4.31 (1H, d, *J* 3.0, N*H*), 5.07–5.14 (2H, m, OCH_2Ph), 5.76 (1H, s, N*H*), 5.81 (1H, d, *J* 15.2, C(2′)*H*), 5.88–6.25 (2H, m, C(4′)*H*), 7.14–7.30 (1H, m, C(3′)*H*), 7.28–7.38 (5H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 18.5 (*C*(6′)), 39.8, 39.6 (*C*(2), *C*(4)), 44.9, 44.8 (*C*(3), *C*(5)), 51.8 (*C*(6)), 67.3, 67.1 (O*Me*, OCH_2Ph), 121.4 (*C*(2′)), 128.5, 128.2, 128.0 (*o,m,p-Ph*), 129.6 (*C*(5′)), 136.1 (*i-Ph*), 137.9 (*C*(4′)), 141.3 (*C*(3′)), 157.3 (NCO), 166.8 (*C*(1′)), 171.9 (*C*(1)); *m*/*z* (CI$^+$) 405 ([M+H]$^+$, 93%), 222 (100%).

4.1.20. Methyl (R,R,E,E)-3-(N-benzyloxycarbonylamino)-4-[2′,2′-dimethyl-N(3′)-(2″,4″-hexadienoyl)- 1′,3′-oxazolidin-5′-yl]butanoate ***27***.



TsOH (10 mg) was added to a stirred solution of **26** (1.67 mg, 4.13 mmol) in acetone and 2,2-dimethoxypropane (1:1, 50 mL) and the resultant mixture was stirred at rt for 26 h. Et_3N (five drops) was added and the reaction mixture was concentrated *in vacuo* to give a pale yellow oil. Purification via filtration through a short plug of silica gel (eluent EtOAc) gave **27** as pale yellow oil, which was used immediately in the next step (1.47 g, 80%, >99:1 dr); δ_H (200 MHz, $CDCl_3$) 1.53 (3H, s, C(2′)Me_A), 1.64 (3H, s, C(2′)Me_B), 1.80–2.12 (2H, m, C(4)H_2), 1.83 (3H, d, *J* 5.3, C(6′)H_3), 2.69 (2H, m, C(2)H_2), 3.25 (1H, dd, *J* 9.5, 9.5, C(4′)H_A), 3.67 (3H, s, O*Me*), 3.52–3.82 (1H, m, C(3)*H*), 4.22 (2H, m, C(4′)H_B, C(5′)*H*), 5.00 (2H, m, OCH_2Ph), 5.56 (1H, d, *J* 9.5, N*H*), 5.95 (1H, d, *J* 14.2, C(2″)*H*), 6.00–6.26 (2H, m, C(4″)*H*, C(5″)*H*), 7.20–7.33 (1H, m, C(3″)*H*), 7.25–7.35 (5H, m, *Ph*).

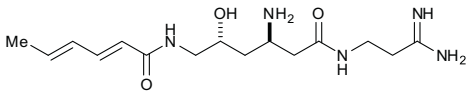
4.1.21. (R,R,E,E)-3-(N-Benzyloxycarbonylamino)-4-[N(3′)-(2″,4″-hexadienoyl)-2′,2′-dimethyl-1′,3′-oxazolidin-5′-yl]butanoic acid ***28***.



A solution of NaOH (460 mg, 11.5 mol) in H_2O (2 mL) was added to a solution of **27** (1.30 g, 2.87 mmol) in MeOH/THF (2:1, 40 mL) at 0 °C. The reaction mixture was then allowed to warm to rt and stirred for 4 h before being concentrated *in vacuo*. The residue was dissolved in H_2O (40 mL) and the resultant solution was acidified to pH 4 by the addition of aq $KHSO_4$ then extracted with EtOAc (3×30 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography

(eluent CH_2Cl_2/MeOH, 4:1) gave **28** as a white solid (1.11 g, 88%, >99:1 dr); $C_{23}H_{30}N_2O_6$ requires C, 64.2; H, 7.0; N, 6.5%; found C, 64.5; H, 6.85; N, 6.2%; $[\alpha]_D^{25}$ +17.2 (*c* 1.1 in $CHCl_3$); ν_{max} (KBr) 3700, 3200, 2980, 2940, 1740 (C=O), 1705 (C=O), 1650, 1625, 1595, 1425, 1245, 1150, 1060, 1000; δ_H (200 MHz, $CDCl_3$) 1.55 (3H, s, C(2′)Me_A), 1.63 (3H, s, C(2′)Me_B), 1.70–2.07 (2H, m, C(4)H_2), 1.84 (3H, d, *J* 4.9, C(6″)H_3), 2.62–2.69 (2H, m, C(2)H_2), 3.23 (1H, dd, *J* 8.8, 8.8, C(4′)H_A), 3.72 (1H, m, C(3)*H*), 4.19 (2H, m, C(4′)H_B, C(5′)*H*), 5.10 (2H, m, OCH_2Ph), 5.72 (1H, br s, N*H*), 5.93 (1H, d, *J* 14.8, C(2″)*H*), 6.00–6.23 (2H, m, C(4″)*H*, C(5″)*H*), 7.18–7.33 (1H, m, C(3″)*H*), 7.26–7.37 (5H, m, *Ph*); *m*/*z* (Cl^+) 431 ($[M+H]^+$, 36%), 373 (100%).

*4.1.22. 2′-Amidinoethyl (R,R,E,E)-3-amino-5-hydroxy-6-[N-(2″,4″-hexadienoyl)amino]butanamide [sperabillin C] **6**.*



Step 1: HOBt (320 mg, 2.37 mmol) and DCC (530 mg, 2.57 mmol) were added to a solution of **29**·2HCl[11b] (850 mg, 1.98 mmol) in THF (15 mL) and the resultant mixture was stirred at rt for 2 h. The reaction mixture was filtered then **28** (350 mg, 2.19 mmol) and satd aq $NaHCO_3$ (4.36 mmol, 2 mL) were added. The resultant mixture was stirred at rt for 31 h then concentrated *in vacuo*. The residue was dissolved in $CHCl_3$/EtOH (3:1, 50 mL), dried and concentrated *in vacuo* to give **30**.

Step 2: TMSI (1.1 mL, 7.9 mmol) was added to a suspension of **30** in MeCN (40 mL) at rt. The resultant solution was stirred for 3.5 h then concentrated *in vacuo*. The residue was dissolved in H_2O (20 mL), washed with Et_2O (10 mL) and concentrated *in vacuo*. Purification via ion-exchange chromatography (Amberlite XAD-II resin, eluent H_2O) gave sperabillin C **6** as a pale yellow solid (420 mg, 51% from **28**, >99:1 dr);[9] $[\alpha]_D^{25}$ −10.2 (*c* 0.3 in H_2O); {lit.[9] $[\alpha]_D^{25}$ −11 (*c* 0.7 in H_2O)}; νmax (KBr) 3700, 2650, 2650, 2050, 1655, 1635, 1540, 1435, 1160, 1090; δ_H (200 MHz, D_2O) 1.46–1.74 (2H, m, C(4)*H*), 1.57 (3H, d, *J* 5.3, C(6″)H_3), 2.46–2.53 (4H, m, C(2)H_2, C(2′)H_2), 2.97–3.34 (4H, m, C(6)H_2, C(1′)H_2), 3.71–3.75 (1H, m, C(5)*H*), 3.82–3.88 (1H, m, C(3)*H*), 5.72 (1H, d, *J* 15.9, C(2″)*H*), 6.00–6.04 (2H, m, C(4″)*H*, C(5″)*H*), 6.86 (1H, dd, *J* 9.5, 14.8, C(3″)*H*); δ_C (50 MHz, D_2O) 18.5 (*C*(6″)), 33.1 (*C*(2′)), 36.0 (*C*(4)), 37.0 (*C*(1′)), 37.6 (*C*(2)), 45.7 (*C*(6)), 47.0 (*C*(3)), 67.0 (*C*(5)), 121.0 (*C*(2″)), 130.1 (*C*(4″)), 141.2 (*C*(5″)), 143.4 (*C*(3″)), 170.6, 172.8, 175.4 (*C*(1), *C*(3′), *C*(1″)); *m*/*z* (FAB^+) 326 ($[M+H]^+$, 24%), 242 (100%).

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