The Synthesis of Alisamycin, Nisamycin, LL-C10037α and Novel Epoxyquinol and Epoxyquinone Analogues of Manumycin A

Richard J. K. Taylor,[a]* Lilian Alcaraz[a‡] Isabelle Kapfer-Eyer,[a] Gregor Macdonald,[a§] Xudong Wei,[a] Norman Lewis[b]
[a] Department of Chemistry, University of York, Heslington, York YO1 5DD, UK
E-mail: rjkt1@york.ac.uk
[b] SmithKline Beecham Pharmaceuticals, Leigh, Tonbridge, Kent TN11 9AN, UK

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Dedicated to Professor Sandy McKillop to mark his retirement from the University of East Anglia, Norwich and the many achievements, both in research and teaching, during his career there.

Abstract: Versatile synthetic routes are described for the preparation of a range of epoxyquinol and epoxyquinone analogues of the antitumour antibiotic manumycin A lacking the lower side chain, and these procedures have also been applied to prepare the bioactive natural product LL-C10037α. The extension of this methodology to provide a general synthetic route to the manumycin family of antibiotics is discussed and exemplified by the first total synthesis of alisamycin and *ent*-alisamycin. This route includes the novel, stereoselective organometallic addition of the Corey–Wollenberg reagent (*E*-2-tributylstannylethenyllithium) to the manumycin nucleus and palladium catalysed Stille coupling technology for the introduction of the polyunsaturated 2-amino-3-hydroxycyclopentenone derived amide. Similar methodology has also been employed to complete the first total synthesis of the antibiotic nisamycin.

Key words: LL-C10037α, alisamycin, nisamycin, manumycin analogues, Stille coupling

The manumycin family of antibiotics has grown steadily since the isolation of manumycin A (**1**) from *Streptomyces Parvalus* in 1963.[1,2] Other members (Figure 1) include manumycin B (**2**),[3] manumycin C (**3**),[3] manumycin E (**4**),[4] manumycin F (**5**),[4] manumycin G (**6**),[4] asukamycin (**7**),[5] alisamycin (**8**),[6–8] *ent*-alisamycin (**9**),[9] El-1625-2 (**10**),[9] El-1511-3 (**11**)[9] and El-1511-5 (**12**).[9] All of these compounds have the same *E*,*E*,*E*-trienyl lower side chains terminating in a 2-amino-3-hydroxycyclopentenone derived amide. U-56407 (**13**)[10] is reported to possess a *Z*,*Z*,*E*-trienyl lower side chain (although this stereochemical assignment must be treated with caution[5b]) whereas colabomycin (**14**)[11] is a higher vinylogue, nisamycin (**15**)[12] lacks the terminal amide linkage, and U-62162 (**16**)[13] has a saturated lower side chain. The upper side chains of the family members are more distinctive but all of these compounds are based on the epoxyaminocyclohexenone nucleus which is also found in the anti-tumour antibiotic LL-C10037α (**17**),[14] and the broad spectrum antibiotic MM-14201 (**18**).[15] Most remarkably, all diastereoisomers of the central nucleus are represented in the manumycin family. Thus, manumycin A (**1**), together with **2** and **10** have the *anti*-(4*R*, 5*R*, 6*S*) configuration whereas manumycin C (**3**) and **6**, **7**, **9** and **11–14** all have the isomeric *syn*-hydroxy epoxide (4*S*, 5*R*, 6*S*) configuration found in LL-C10037α (**17**). Manumycin F (**5**) is in the enantiomeric *anti*-series (4*R*, 5*S*, 6*R*); alisamycin (**8**) and nisamycin (**15**) are in the enantiomeric *syn* (4*R*, 5*S*, 6*R*) series along with MM 14201 (**18**). The related diols, manumycin D (**19**),[3,16] TMC-1 A (**20**),[16] TMC-1 B (**21**),[16] TMC-1 C (**22**),[16] and TMC-1 D (**23**)[16] (Figure 2) have also been isolated.

The manumycin natural products possess a range of bioactivities in addition to their anti-bacterial properties. These include antifungal activity and inhibitory activity against polymorphonuclear leukocyte elastase and interleukin-1β converting enzyme. Of greatest interest, however, is the discovery that the manumycins A–C act as selective inhibitors of *ras* farnesyltransferase and as such have potential in cancer chemotherapy.[17] It is noteworthy that the oxidative degradation products of the manumycins, epoxyquinones **24**–**26** (Figure 3), retain their anti-tumour activity indicating that the lower side chain is not too important in this regard. The dihydroxy manumycin analogues **19–23** were also shown to retain cytotoxicity but were ineffective antibiotics, indicating the importance of the epoxide group for antibacterial activity.[16]

There have been a number of studies by Floss, Gould, Zeeck and others[3b,5b,18] to elucidate the biosynthetic pathway leading to the manumycin family and related compounds. It has been established that the polyene side chains are of polyketide origin and that the C_5N unit which terminates the lower side chain is derived from 5-aminolevulinic acid. The biosynthesis of the *m*C_7N nucleus, however, proved surprising in that it is not shikimate derived but rather originates from 3-amino-4-hydroxybenzoic acid[18a] which in turn is constructed from succinate and glycerol.[3b]

Despite their promising biological properties and interesting biogenesis, synthetic approaches to the manumycins have not been reported (although Wipf et al. have prepared analogues lacking the lower side chain[19]). In designing a synthetic route to the manumycin antibiotics we adopted an approach which would also allow us to prepare a range of quinol **29** and quinone **30** analogues lacking the lower side chain for further structure-activity studies. Thus, as shown in Scheme 1, the protected amido quinone epoxide **28** was identified as a key intermediate for the synthesis of both novel manumycin analogues and the natural products themselves. We envisaged preparing **28** by acylation of **27** with the acid chloride corresponding to the upper side chain, the simplified target molecules then being obtained by straightforward functional group modification. It should be noted that the alternative sequence involving acylation before epoxidation, is not viable in these systems due to facile *N*-deacylation during epoxidation.[19,22]

Amides **28** were also seen as the cornerstone of the synthetic route to the manumycin family, as is shown in retrosynthetic form in Scheme 2.

Biographical Sketches

Richard Taylor gained his B. Sc. and Ph. D. from the University of Sheffield, carrying out his postgraduate research into steroid synthesis under the supervision of Dr. D. Neville Jones. He then carried out postdoctoral research with Dr. Ian Harrison at Syntex, Palo Alto and Professor Franz Sondheimer at University College, London. After academic jobs with the Open University (1975–79) and the University of East Anglia, Norwich (1979–1993) he moved to a Chair of Organic Chemistry at the University of York in 1993. Professor Taylor's research interests centre on the development of new organometallic and organosulfur based synthetic methodology and its application to the synthesis of compounds of biological importance. Natural product classes studied include steroids, prostaglandins, prostacyclins, thromboxanes, leukotrienes, insect pheromones, and a range of marine, fungal and plant metabolites.

Lilian Alcaraz was born in 1969 in France and received his Ph. D. degree in 1995 from the University of Strasbourg. His research was carried out on a novel synthetic approach to the total synthesis of Taxol as well as the development of new methodology using ylides under the direction of Dr. C. Mioskowski. In December 1995, Lilian joined the University of York as an ARC (France) Fellow and in 1996 was awarded a Marie-Curie (EC) postdoctoral fellowship. He is currently working as a research chemist for Astra Charnwood.

Isabelle Kapfer-Eyer was born in 1966 in France and received her Ph. D. degree in 1993 from the Université Louis Pasteur, Strasbourg. Her research was carried out in bio-organic chemistry under the direction of Professor M. Goeldner. In 1993, Isabelle joined the University of York as an EC TMR Fellow. In 1995 she took a teaching position (A. T. E. R.) in organic chemistry at the University of Strasbourg and is currently preparing for the agregation diploma in physical sciences.

Gregor Macdonald was born in Scotland in 1971 and received his B. Sc. from the University of Edinburgh in 1992. After two years with the Wellcome Foundation he joined the University of York to carry out his Ph. D. He was awarded the Kathryn Mary Stott Prize and a Pfizer Prize for his postgraduate research. He is currently working as a research chemist at SmithKline Beecham Pharmaceuticals.

Xudong Wei was born in 1965 in China and was awarded his Ph. D. degree in 1991 from Nanjing University. His research was carried out on new oxidative methodology and the addition reactions of iminoxy radicals under the supervision of Professor Hongwen Hu. Dr. Wei was appointed to a lectureship at Nanjing University in 1991 researching into heterocyclic chemistry. From 1994–1995 he carried out postdoctoral research with Professor Bernd Speiser at the University of Tübingen and in 1995–1996 was awarded a Royal Fellowship to study in York. Since then he has been supported by the University of York Innovation and Research Priming fund and the EPSRC.

Norman Lewis gained his B. Sc. and Ph. D. from the University of Bristol, under the supervision of Professor J. MacMillan. After carrying out postdoctoral research at the University of British Columbia (Professor J. Kutney) and the E. T. H., Zurich (Professor A. Eshenmoser), he joined Smith, Kline and French in 1982. He is now Associate Director in the the Synthetic Chemistry Department (part of Chemical Development) at SmithKline Beecham Pharmaceuticals, Tonbridge.

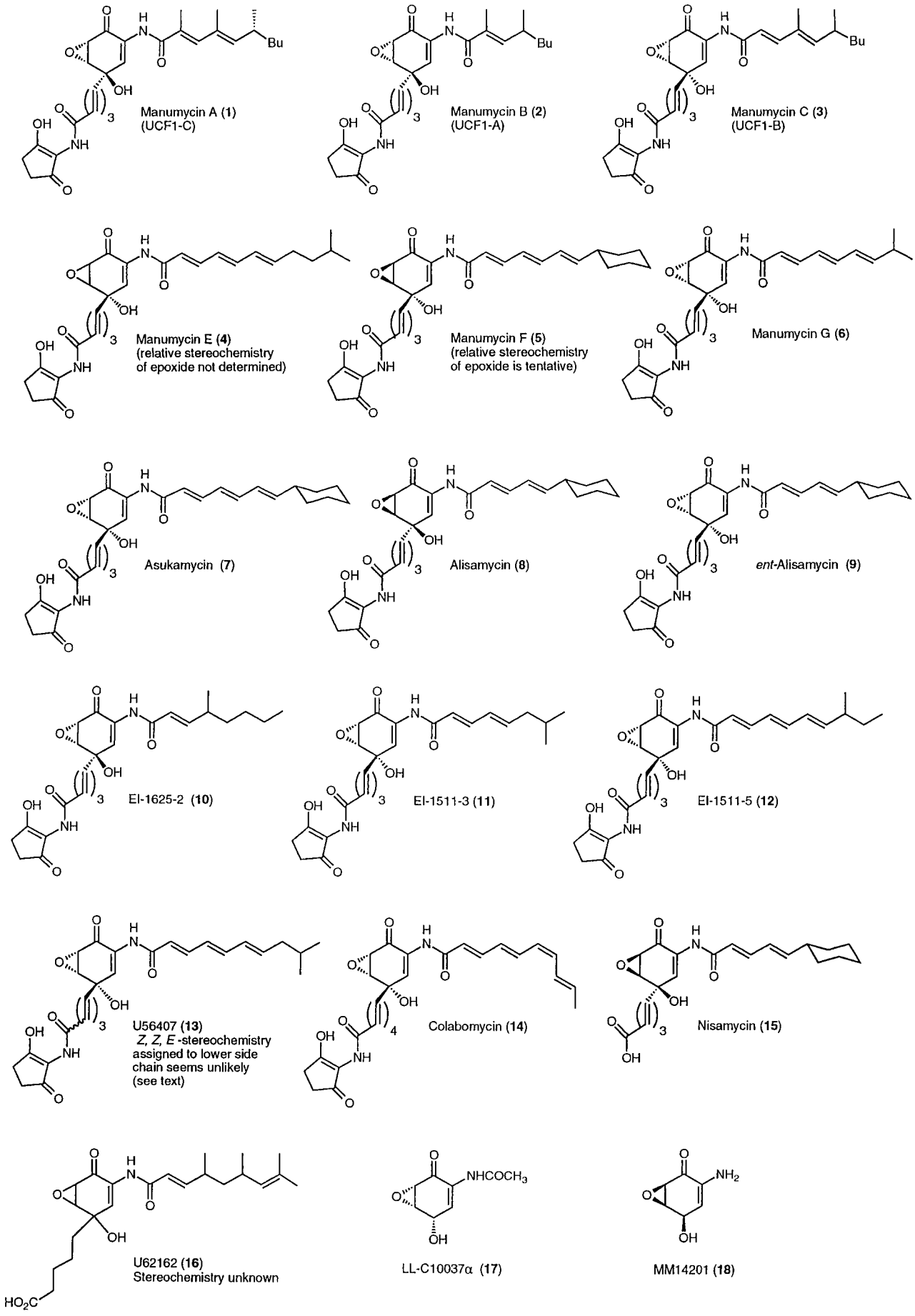


Figure 1

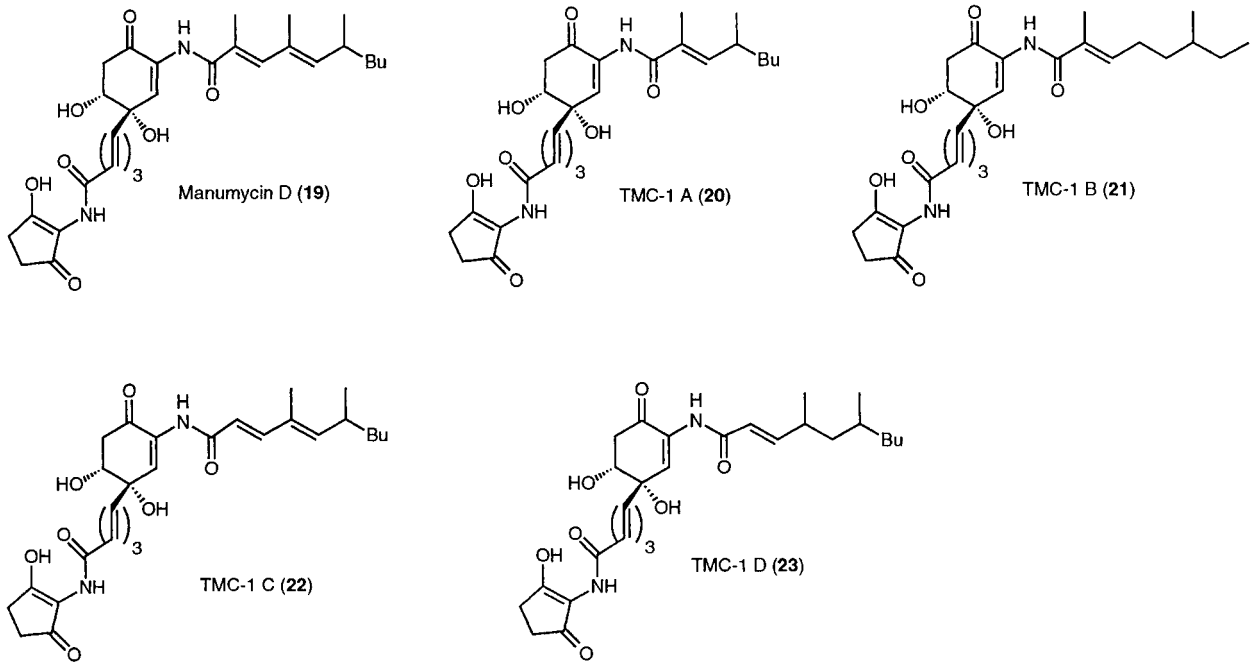


Figure 2

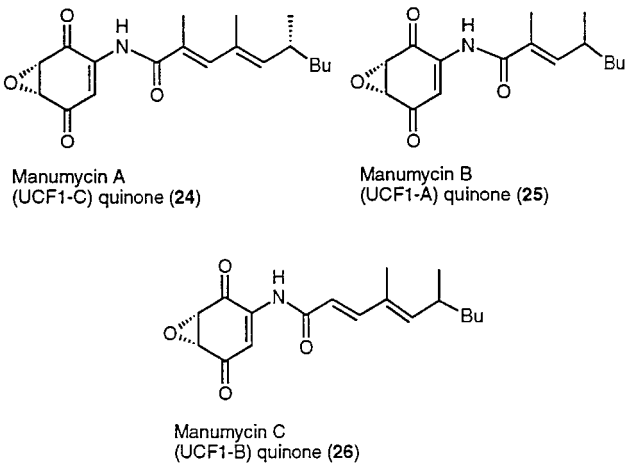


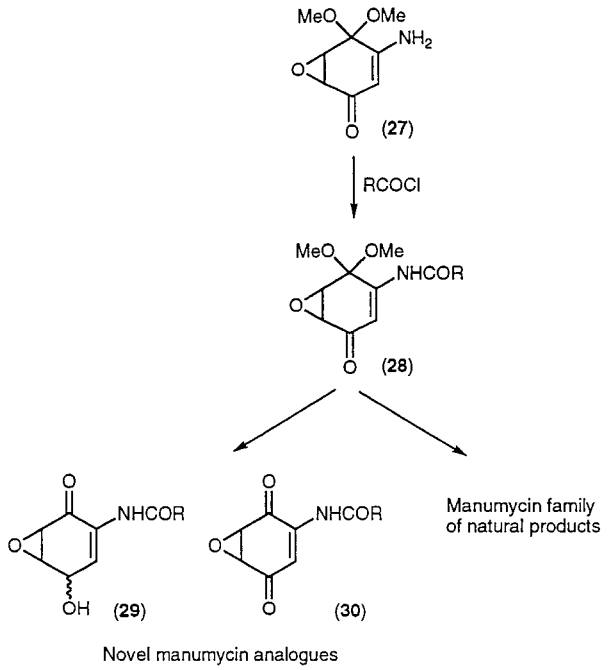
Figure 3

Thus, we planned to use organometallic elaboration of **28** with vinyllithium reagent **31**[20] to give the vinylstannane **32**. This organometallic addition was obviously the crucial (and most speculative) step in the sequence and is discussed in more detail later. The use of the Stille coupling between vinylstannane **32** and bromodienamide **33**[21] was central to the end-game of this succinct synthetic approach (see later).

Results and Discussion

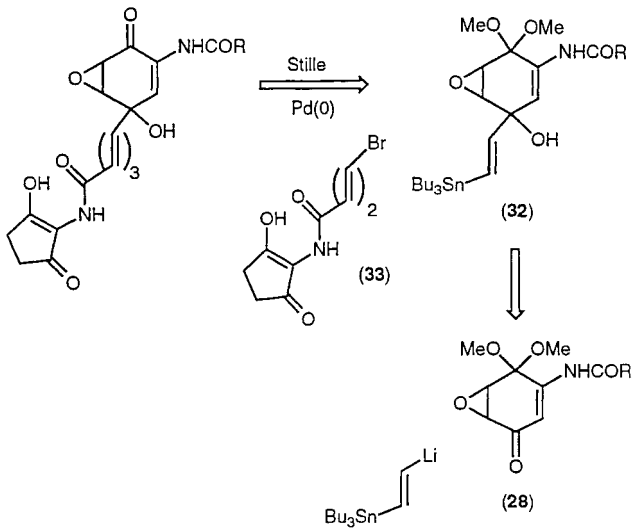
(a) *Preparation and Elaboration of Amine* **27**[22]

The preparation of the key epoxycyclohexenylamine **27** was achieved using methodology based on that employed in our synthesis of the diepoxycyclohexanone antibiotic aranorosin[23] and the marine antitumour natural product

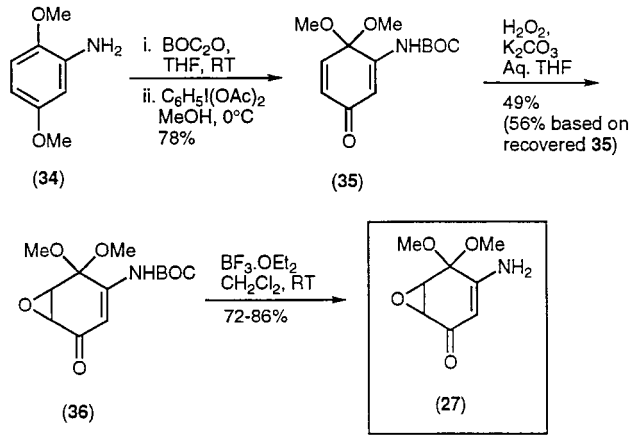


Scheme 1

bromoxone[24] (and to that employed by Wipf and Kim[19] in their synthesis of LL-C10037α). The BOC derivative of 2,5-dimethoxyaniline (**34**) was oxidised using $PhI(OAc)_2$[19,23–25] to give monoacetal **35** in 78% yield (Scheme 3). Several epoxidation methods were investigated for the conversion of **35** into monoepoxide **36**. On a small scale (0.4 mmol) sodium perborate[26] gave the best results (36% + 45% recovery of starting material) but the efficiency diminished as the reaction was scaled up. On a larger scale the preferred procedure involved the use of



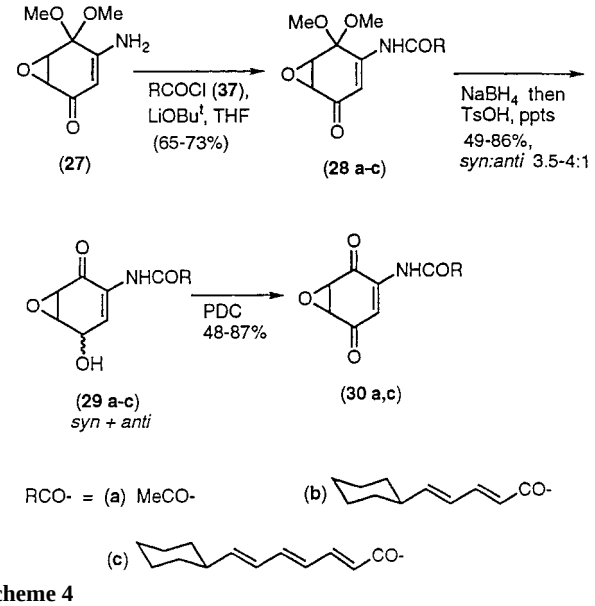
Scheme 2



Scheme 3

H_2O_2/K_2CO_3 in aqueous THF (methoxy conjugate addition adducts were observed when methanol was employed as solvent).

In order to obtain the key amine intermediate **27** from **36** selective removal of the BOC group in the presence of the methyl acetal was required. This was efficiently achieved using boron trifluoride–diethyl ether complex and activated molecular sieves in dichloromethane at room temperature. This novel and mild procedure, which was developed for this transformation, has also proved to be more widely applicable.[27] To our delight, amine **27** proved to be a stable, crystalline solid (mp 156–157 °C) which could be stored at –20 °C for several weeks without noticeable decomposition. It is a vinylogous amide and therefore, not surprisingly, proved to be rather unreactive to standard acylation conditions. Acetylation was achieved in good yield (79%; 84% based on recovered starting material) with excess acetic anhydride and DMAP in THF but the transformation did not give reproducible yields, and did not proceed at all when acetyl chloride was employed. The requirement for an excess of an acid anhydride seemed to limit the value of this route for the preparation of manumycin analogues and therefore other acylating conditions were explored (Scheme 4). It was eventually found that acylation to give amides **28** could be carried out using a number of acid chlorides **37**[28a] providing lithium *tert*-butoxide in THF was employed as the base.[28b] Reduction of ketones **28** was achieved with sodium borohydride and then acetal hydrolysis carried out using tosic acid and pyridinium *p*-toluenesulfonate (PPTS)[19] to give separable mixtures of the *syn*- and *anti*-hydroxy epoxides **29**. Compound *syn*-**29a** is the anti-tumour agent LL-C10037α **17** and its NMR characteristics were entirely consistent with published data.[14,19] This new route[22] to (±)-LL-C10037α is only 7 steps long and, although unoptimised, proceeds in ca. 10% overall yield. It also reduces the number of protection-deprotection steps compared to the published procedure (9 steps, *ca.* 7% overall yield).[19] Amides **29b** and **29c** are analogues of alisamycin (**8**) and asukamycin (**7**), respectively, lacking the lower side chains.



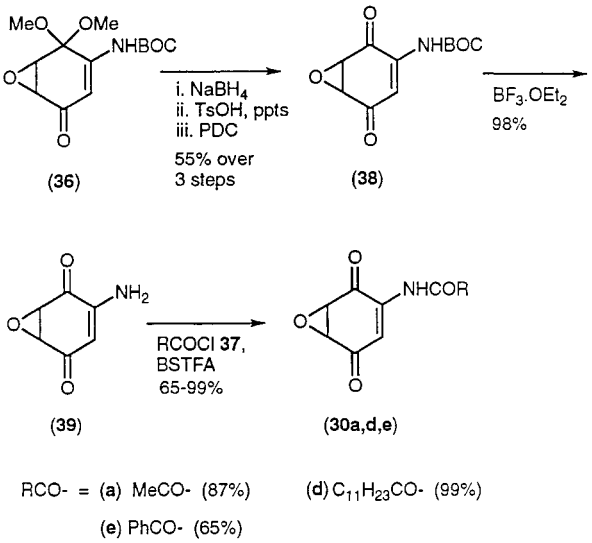
Scheme 4

We also extended this chemistry to produce the manumycin quinone analogues **30** lacking the C-4 polyene chain (Scheme 4). Thus PDC oxidation of alcohols **29** produced the known epoxyquinones **30a**[14b,29] and **30c**[5a] in fair to excellent yields.

(b) Alternative Routes to Epoxyquinones 30

The route to epoxyquinones **30** shown in Scheme 4 is rather long and other routes were investigated as shown in Schemes 5 and 6.[30,31] Thus, we first attempted to prepare amine **39** which, on acylation, would lead directly to a range of quinones. The direct hydrolysis of **36** to give **38** or **39** was not successful but an efficient indirect route to prepare **38** was developed (Scheme 5). Once again, the use of boron trifluoride–diethyl ether[27] gave efficient removal of the BOC group, amine **39** being obtained as a crystalline material (mp 133–134 °C dec.) which proved to

be stable when stored at –20 °C. Unfortunately, amine **39** was very unreactive towards acylation using a range of conditions (including *tert*-BuOLi, THF). It was eventually found that acylation could be accomplished using acid chlorides in the presence of bis(trimethylsilyl)trifluoromethylacetamide (BSTFA) as a chloride scavenger.[32] Even with these optimum conditions, however, the acylation yields were satisfactory only with saturated acid chlorides. With benzoyl chloride, the yield was reduced and no acylation at all was observed with polyunsaturated systems such as **37c**.

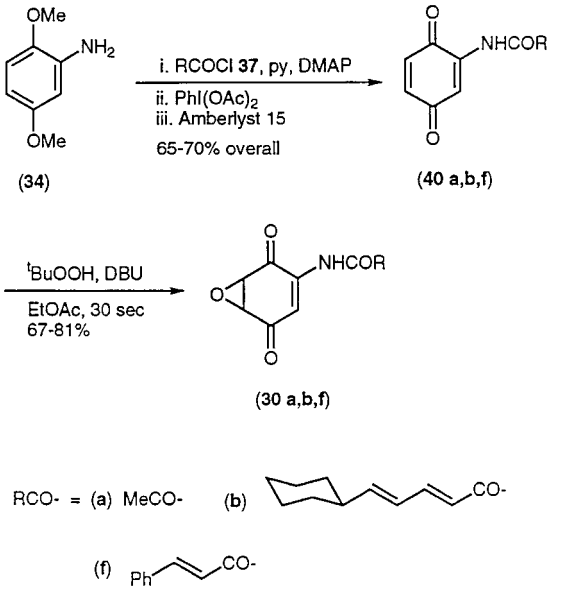


Scheme 5

The routes to epoxyquinones shown in Scheme 5 is still lengthy and is limited to more reactive acid chlorides. We therefore developed the third route shown in Scheme 6. In this procedure 2,5-dimethoxyaniline (**34**) is acylated in the first step and then hypervalent iodine oxidation followed by acetal removal gives the amidoquinones **40**. Monoepoxidation of dienones **40** was attempted using hydrogen peroxide and *tert*-butyl hydroperoxide with a range of bases (Na_2CO_3, NaOH, triton B, triethylamine, pyridine *etc.*) but it was eventually discovered that the best procedure utilised *tert*-butyl hydroperoxide with DBU as base.[33] Epoxides **30** were found to be very sensitive towards basic conditions and thus, for optimum yields, it was important to minimise the reaction time. This was not a problem given the susceptibility of **40** towards epoxidation: reaction times of 30 seconds gave yields of 67–81%. For these high yields of epoxides **30** it was essential to remove the DBU and excess peroxide immediately after the completion of the reaction. This was achieved by washing the reaction mixture with saturated aqueous iron(II) sulfate in place of the metasulfite procedure[33] normally employed.

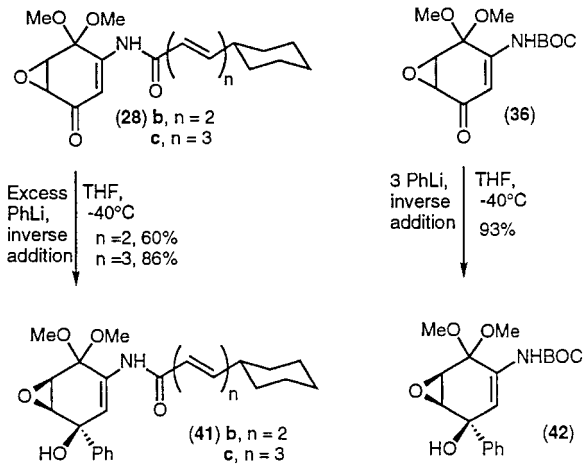
(c) Organometallic Addition Reactions

As shown in Scheme 2, the proposed synthetic route to the manumycin natural products involved elaboration of ke-



Scheme 6

tones **28** by organometallic addition to C-4. This approach appeared to be fraught with potential problems, particularly concerning the regio and stereoselectivity of the addition reaction. The likely low reactivity of the C-4 carbonyl group, which is a vinylogous imide, and which would presumably be further deactivated by deprotonation of the amide substituent, was a particular concern. In view of this, we first carried out the model studies as shown in Scheme 7. To our delight, reaction of amides **28b** and **28c** with phenyllithium in THF, gave good yields of adducts **41** as single diastereoisomers with no other byproducts observed. The *syn*-stereochemistry of compounds **41** was assigned on steric grounds and by analogy with the reduction reactions shown in Scheme 5 where the *syn*-isomer predominates.[34a] In view of the importance of this stereochemical assignment, however, we felt that more concrete evidence was required. Unfortunately, high field NMR spectroscopy did not provide an unambiguous answer and we therefore sought a crystalline adduct. Suit-

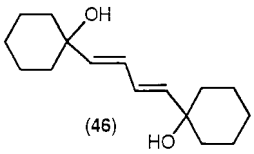


Scheme 7

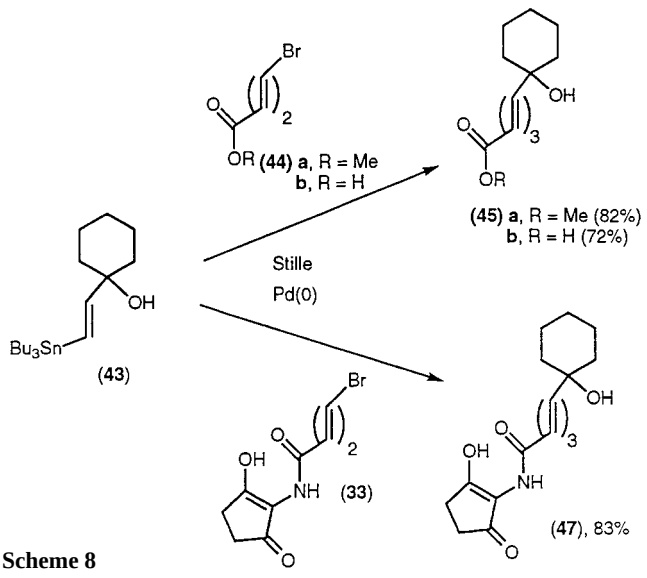
able crystals were obtained from adduct **42** produced by phenyllithium addition to the *N*-BOC analogue **36**, and X-ray crystallography[34b] confirmed the *syn*-hydroxy epoxide relationship [which is present in alisamycin (**8**) and other members of the manumycin family].

(d) Construction of the Manumycin Lower Side Chain

As mentioned earlier (Scheme 2) we planned to elaborate the lower manumycin side chain via a palladium-catalysed Stille coupling procedure.[21,35,36] Model studies, shown in Scheme 8, were carried out to establish the viability of this approach with cyclohexane carbinol vinylstannane **43**[37] and bromodienes **44**[21,38] as substrates. A range of palladium catalysts were investigated, initially with ester **44a**, and although adduct **45a** was isolated it was discovered that dimerisation of the vinylstannane occurred to a significant extent to produce **46** unless the reaction solvent was rigorously degassed.[39]



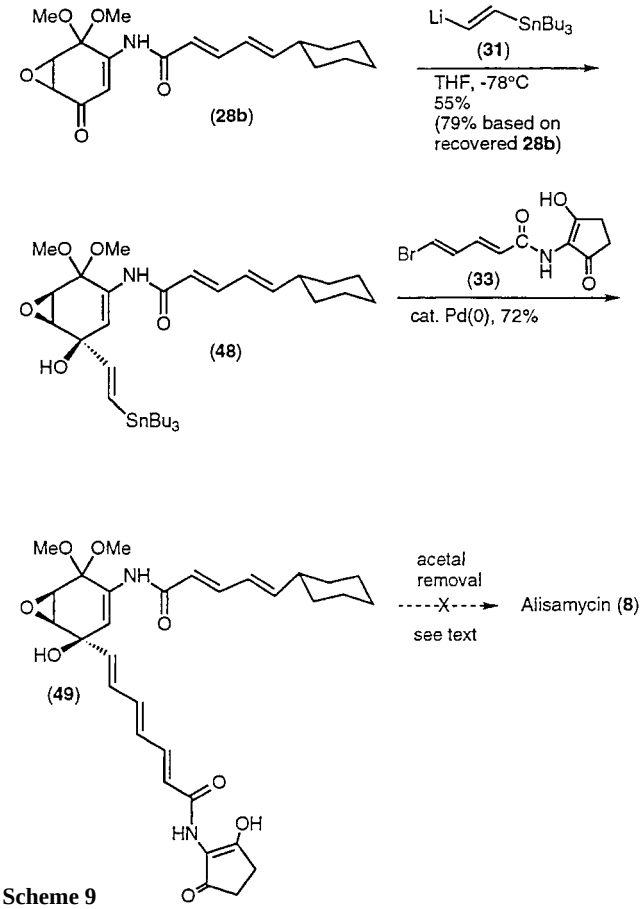
Using 5% PdCl2(MeCN)$_2$ under these conditions, **44a** gave trienyl ester **45a** in 82% yield. Acid **44b** also underwent efficient coupling, although the first formed product (tentatively assumed to be the stannyl ester[40]) had to be treated with fluoride and then hydrolysed to provide adduct **45b**. In this case, the optimum procedure utilised the palladium(0) catalyst generated from $PdCl_2(PPh_3)_2$ and DIBAL-H using Negishi's procedure.[36] We then attempted the direct introduction of the fully functionalised lower side chain unit **33** (previously described by us[21]), and found that coupling again proceeded in good yield using $PdCl_2(MeCN)_2$ providing that the solvent was efficiently deoxygenated. Unfortunately, using these conditions, adduct **47** was contaminated by minor impurities. We discovered that these impurities could be avoided by use of the Negishi catalyst[36] with adduct **47** being obtained in an excellent 83% yield. The *E*,*E*,*E*-stereochemistry of adducts **45** and **47** were established by high field NMR studies.



Scheme 8

(e) Initial Approach to Alisamycin

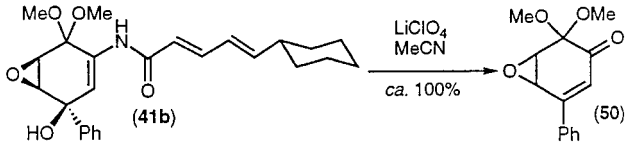
We were now in a position to attempt the first synthesis of a member of the manumycin family of antibiotics. Alisamycin (**8**) was chosen to illustrate the methodology. Alisamycin[6–9] is a potent antibiotic (MIC 1.6 mg/mL against *staphylococcus aureus*) which also possesses weak antifungal and cytotoxic activity.[6] Its structure was established by Chatterjee et al.[7] using a combination of mass spectrometry, IR, UV and NMR spectroscopy, and the absolute configuration was revealed as 4*R*, 5*S*, 6*R* using the exciton chirality method together with CD studies of degradation products.[8] The enantiomer **9** also occurs naturally.[9] The first synthetic approach to racemic alisamycin is shown in Scheme 9.[41]



Scheme 9

Thus, treatment of protected quinone **28b** with *E*-2-tributylstannylethenyllithium (**31**), generated from the corresponding bis-stannane,[20] introduced an embryonic C-4 side chain giving **48** in 55% yield (79% based on recovered starting material). Stille coupling of vinylstannyl reagent **48** with bromodienamide **33**[21] proceeded efficiently using $PdCl_2(PPh_3)_2$/DIBAL-H in DMF/THF at room tem-

perature to give **49** in 72% yield. All that was required to complete the synthesis of alisamycin was to deprotect the acetal functionality of **49**. Unfortunately, using a number of procedures,[31,42,43] either little reaction occurred or, under more forcing conditions, decomposition was observed. Similar problems were encountered when attempting to deprotect the phenyl analogue **41b** (Scheme 10): the only product that could be isolated was ketone **50** resulting from enamide hydrolysis (with lithium perchlorate in MeCN[43] **50** was formed in almost quantitative yield).



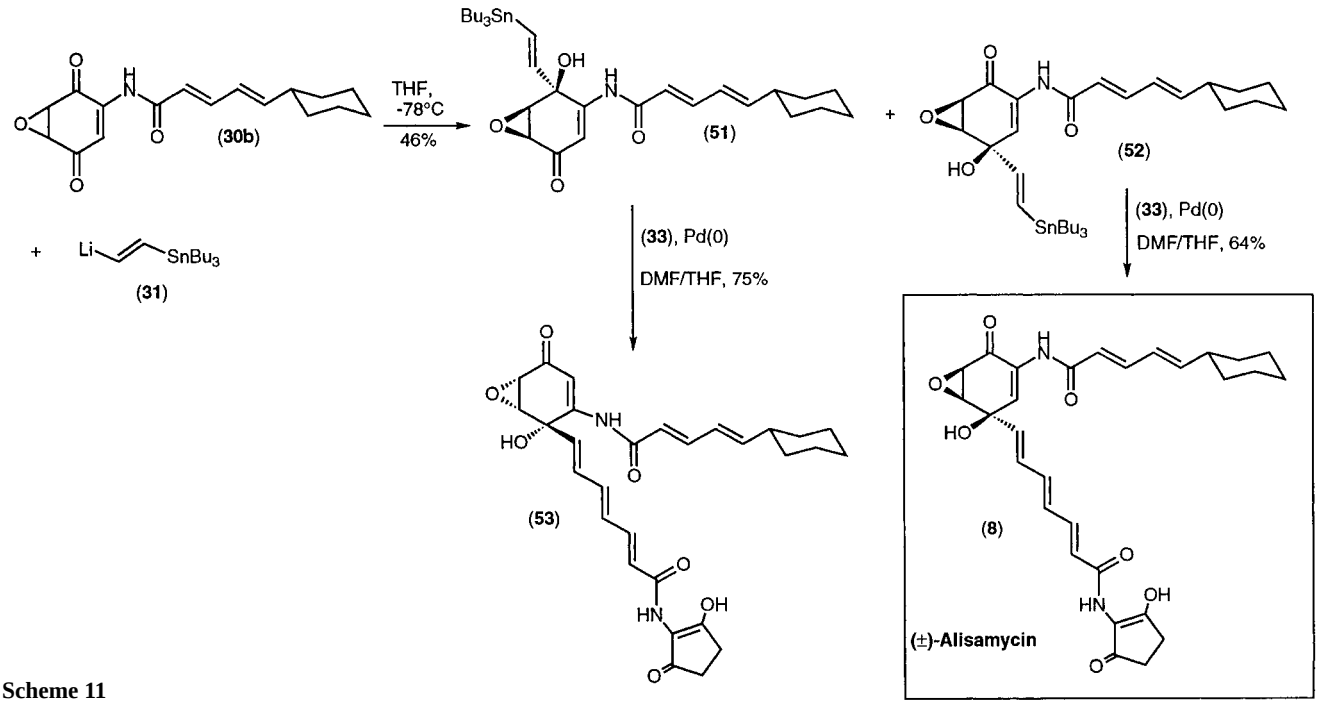
Scheme 10

*(f) Successful Synthesis of Alisamycin and Nisamycin via Organometallic Additions to Ouinone **30b***

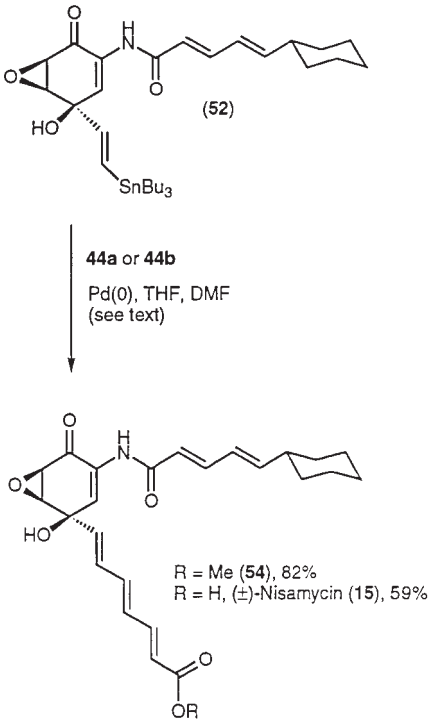
We therefore turned to a more direct (and even more speculative) synthetic approach (Scheme 11). In this procedure, organometallic addition was carried out using the unprotected epoxyquinone **30b**. Treatment with *E*-2-tributylstannylethenyllithium (**31**) gave two major products **51** and **52** (46%, 1:1.3), resulting from attack at each of the ring carbonyl groups. The stereochemical assignments were again made on the basis of steric considerations and, in the case of **52**, this was confirmed by conversion into alisamycin and nisamycin.

Adducts **51** and **52** were separated by chromatography and individually coupled to bromodienamide **33** using $PdCl_2(PPh_3)_2$/DIBAL-H as before. The use of **52** produced alisamycin **8** in 64% yield, the structure being confirmed by comparison of IR, MS, ^1H and ^{13}C NMR data with authentic spectra.[44] The NMR data for the epoxycyclohexenone nucleus was particularly informative [found δ_H: H-3, 7.41 (d, J = 2.5 Hz), H-5, 3.72 (dd, J = 3.5, 2.5 Hz), H-6, 3.67 (d, J = 3.5 Hz); δ_C: C-3, 126.0, C-5, 57.4, C-6, 53.0; authentic[7] δ_H: H-3, 7.40 (d, J = 2.6 Hz), H-5, 3.70 (dd, J = 3.6, 2.6 Hz), H-6, 3.65 (d, J = 3.6 Hz); δ_C: C-3, 126.3, C-5, 57.4, C-6, 52.9]. It should be noted that although this produces racemic **8**, this is in fact a mixture of two natural products, alisamycin and *ent*-alisamycin. The novel regioisomer **53** of alisamycin was also prepared by homologation of **51** in 75% yield.

This methodology was also employed to prepare nisamycin (**15**), and its methyl ester **54**, as shown in Scheme 12. Thus, vinylstannane **52**, used to prepare alisamycin, was coupled with bromodiene **44a** to produce the methyl ester of nisamycin **54** in 82% yield. All attempts to convert ester **54** into acid **15** were unsuccessful, however. Acid **15** was therefore prepared, albeit in moderate yield, by the direct coupling reaction between vinylstannane **52** and bromodiene **44b**. This reaction again produces the stannyl ester derivative **54** (R = $SnBu_3$) which is converted into the acid by treatment with KF followed by neutralisation with phosphate buffer.[40] Adduct **15** is (±)-nisamycin, the only member of the manumycin family to lack the terminal C_5N unit. This is the first synthesis of nisamycin, an antibiotic which also possesses antifungal and cytotoxic properties, and which has proved useful for the preparation of manumycin analogues containing novel amide linkages.[12] Synthetic nisamycin **15** was fully characterised and gave NMR data fully consistent with those published [δ_H: 7.41 (d, 1 H, J = 2.5 Hz, H-3), 3.72 (dd, 1 H, J = 4.0, 2.5 Hz, H-5), 3.66 (d, 1 H, J = 4.0 Hz, H-6); δ_C: 126.3 (C-3), 57.4 (C-5), 52.9 (C-6). Lit.[12a] values, δ_H: 7.41



Scheme 11



Scheme 12

(d, 1 H, *J* = 2.1 Hz), 3.70 (dd, 1 H, *J* = 4.0, 2.1 Hz), 3.63 (d, 1 H, *J* = 4.0 Hz); δ_C: 126.9, 57.3, 52.8].

(g) Summary and Future Work

We have devised new chemistry for the preparation of a range of manumycin analogues of increasing complexity and utilised these procedures to prepare the natural products LL-C10037α, alisamycin and nisamycin, the last two for the first time. The novel organometallic methodology for Southern side-chain introduction and elaboration is applicable to all of the manumycin family. We are currently optimising the synthetic route to the nucleus in enantiomerically pure form and will then apply this methodology to other members of this group of natural products.[45]

The EPSRC and SmithKline Beecham are acknowledged for a CASE studentship (G. M.), and ARC (France), the EC and the EPSRC for fellowships (L. A., I. K. and X. W.). We also thank Drs. T. A. Dransfield and G. K. Barlow for their expert assistance with MS and NMR studies, respectively, and Dr. H. Kogler for copies of spectra of authentic alisamycin.

NMR spectra were recorded on Jeol GX-270 or Bruker AMX 500 instruments. TMS or $CDCl_3/CHCl_3$ was used as the internal standard. Carbon spectra were verified using DEPT experiments. Mps were recorded on an Electrothermal IA9100 digital melting point apparatus and are uncorrected. IR spectra were recorded on an ATI Mattson Genesis FTIR spectrometer. Low resolution electron impact (EI) mass spectra were recorded on a Kratos MS 25 spectrometer. Chemical ionisation (CI), fast atom bombardment (FAB) and HRMS were recorded on a Micromass Autospec spectrometer. Elemental analyses were carried out at the University of East Anglia, Norwich. Chromatography is medium pressure flash column chromatography and was performed using ICN silica gel (32–63) or Matrex silica gel 60 (70–200) using the eluant specified. Preparative TLC was carried out using pre-prepared plates (Merck silica gel 60 F-254, 5715). PE is petroleum ether (bp 40–60 °C). Where necessary Et_2O and THF were distilled from Na/benzophenone ketyl, and CH_2Cl_2 from CaH, immediately before use. H_2O is distilled water. Except where specified, all reagents were purchased from commercial sources and were used without further purification. All synthetic compounds are racemic.

3-*tert*-Butoxycarbonylamino-4,4-dimethoxycyclohexa-2,5-dien-1-one (35):
To a stirred solution of *N-tert*-butylcarbonyl-2,5-dimethoxyaniline[46] (10.0 g, 0.041 mol) in anhyd MeOH (100 mL) at 0°C under N_2 was added $PhI(OAc)_2$ (15.9 g, 0.049 mol) portionwise over 1 h. The mixture was stirred at 0 °C for 6 h before being diluted with CH_2Cl_2 (200 mL)/H_2O (100 mL) and then neutralised using aq $NaHCO_3$. The organic layers were separated and washed with H_2O (60 mL) and brine (60 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a brown oil. Column chromatography (Et_2O/PE, 3:7 and then 1:1) gave **35** as an off-white solid, yield: 8.35 g (78%); R_f 0.30 (Et_2O/PE, 1:1); mp 130–l31 °C.
IR (CCl_4): ν = 3415, 2986, 1743, 1672, 1502, 1232, 1153 cm^{-1}.
^1H NMR (270 MHz, $CDCl_3$): δ = 7.01 (d, 1 H, *J* = 1.9 Hz, H-2), 6.85 (br s, 1 H, NH), 6.53 (d, 1 H, *J* = 10.2 Hz, H-5), 6.41 (dd, 1 H, *J* ≃ 10.2, 1.9 Hz, H-6), 3.27 (s, 6 H, 2 × OMe), 1.51 (s, 9 H, ^{t}Bu).
^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 185.3, 151.3, 148.2, 138.0, 133.1, 111.0, 94.1, 82.1, 51.3, 27.9.
MS (CI): *m/z* (%) = 270 (MH^+, 100).
HRMS (CI): Calc for $C_{13}H_{20}NO_5$: 270.1342. Found: 270.1338.
Anal: Calc C, 57.98; H, 7.11; N, 5.20. Found: C, 58.21; H, 7.13; N, 5.07.

3-*tert*-Butoxycarbonylamino-4,4-dimethoxy-5,6-epoxycyclohex-2-en-1-one (36):
To a stirred solution of dienone **35** (2.7 g, 10.03 mmol) and H_2O_2 (29% soln., 34 mL, 301.2 mmol) in THF (50 mL) was added aq K_2CO_3 (0.8 *M*, 12.5 mL, 10.0 mmol) dropwise at 0 °C. After stirring at r.t. for 6 d, the mixture was diluted with EtOAc (50 mL) and brine (10 mL) added. The aqueous layer was then extracted with EtOAc (6 × 50 mL). The combined organic layers were dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a brown oil. Column chromatography (CH_2Cl_2/EtOAc, 95:5) gave the title compound **36** as a white solid; yield: 1.4 g (49%); R_f 0.40 (CH_2Cl_2/EtOAc, 95:5); mp 144–145 °C.
IR (CCl_4): ν = 3416, 2980, 1747, 1679, 1630, 1500, 1153 cm^{-1}.
^1H NMR (270 MHz, $CDCl_3$): δ = 7.05 (br s, 1 H, NH), 6.77 (d, 1 H, *J* = 2.2 Hz, H-2), 3.82 (d, 1 H, *J* = 4.1 Hz, H-5), 3.65 (s, 3 H, OMe), 3.51 (dd, 1 H, *J* = 4.1, 2.2 Hz, H-6), 3.31 (s, 3 H, OMe), 1.50 (s, 9 H, ^{t}Bu).
^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 192.3, 151.1, 146.6, 106.1, 95.5, 82.5, 52.1, 51.5, 51.4, 50.6, 28.1.
MS (CI): *m/z* (%) = 286 (MH^+, 100).
HRMS (CI): Calc for $C_{13}H_{20}NO_6$: 286.1291. Found: 286.1290.
Anal: Calc C, 54.73; H, 6.71; N, 4.91. Found: C, 54.87; H, 6.78; N, 4.81.
Unreacted starting material **35** (350 mg, 13%) was also recovered from this reaction.

3-Amino-4,4-dimethoxy-5,6-epoxycyclohex-2-en-1-one (27):
To a stirred solution of BOC compound **36** (291 mg, 1.02 mmol) and powdered activated 4 Å molecular sieves (625 mg) in anhyd CH_2Cl_2 (15 mL) was added $BF_3{\cdot}Et_2O$ (0.19 mL, 1.53 mmol) in CH_2Cl_2 (5 mL) dropwise at 0 °C over 30 min. The reaction was left to stir at r.t. for 20 h. On completion, the solvent was evaporated under reduced pressure to give a brown oil. Column chromatography (EtOAc/MeOH, 95:5) gave **27** as a white solid; yield: 136 mg (72%); R_f 0.30 (EtOAc); mp 156–157 °C.
IR ($CDCl_3$): ν = 3401, 2944, 2854, 1621, 1255 cm^{-1}.

^{1}H NMR [270 MHz, $(CD_3)_2CO$] : δ = 6.42 (br s, 2 H, NH_2), 5.00 (d, 1 H, *J* = 2.0 Hz, H-2), 3.84 (d, 1 H, *J* = 4.0 Hz, H-5), 3.56 (s, 3 H, OMe), 3.35 (s, 3 H, OMe), 3.24 (dd, 1 H, *J* = 4.0, 2.0 Hz, H-6).
^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 190.6, 156.9, 96.3, 95.7, 52.8, 51.3, 51.7, 50.2.
MS (CI): *m/z* (%) = 186 (MH^+, 100).
HRMS (CI): Calc for $C_8H_{12}NO_4$: 186.0766. Found: 186.0769.

Preparation of Amides (28); General Procedure:
A solution of lithium *tert*-butoxide (1.0 M solution in THF, 1.1 equiv.) was added dropwise over 15 min to a stirred solution of amine **27** (1 equiv.) in anhyd THF at 0 °C under N_2.After stirring at 0 °C for 30 min, a solution of the acid chloride **37**[28a] (1.2 equiv.) in THF was added dropwise over 1 h. The reaction was allowed to warm and then stirred at r.t. until acylation was complete. The THF was evaporated under reduced pressure and EtOAc and H_2O were added. The two layers were separated and the aqueous layer extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a dark oily residue. Column chromatography (EtOAc/PE, 1:1) gave the desired compound, usually as an off-white solid which could be recrystallised from CH_2Cl_2/PE.

3-Acetamido-4,4-dimethoxy-5,6-epoxycyclohex-2-en-1-one (**28a**):
White solid; yield: 65%; R_f 0.45 (EtOAc); mp 107–108 °C.
IR (CCl_4): ν = 3415, 2956, 2927, 2854, 1722, 1680, 1498, 1223, 1120, 1064 cm^{-1}.
^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.66 (br s, 1 H, NH), 7.15 (d, 1 H, *J* = 2.0 Hz, H-2), 3.82 (d, 1 H, *J* = 4.3 Hz, H-5), 3.66 (s, 3 H, OMe), 3.53 (dd, 1 H, *J* = 4.3, 2.0 Hz, H-6), 3.30 (s, 3 H, OMe), 2.19 (s, 3 H, Me).
^{13}C NMR (67.5 MHz, CD_3COCD_3): δ = 193.7, 170.9, 147.7, 108.3, 96.3, 52.6, 52.3, 51.4, 50.4, 24.9.
MS (CI): *m/z* (%) = 245 (MNH_4^+, 35), 228 (MH^+, 100).
HRMS (CI): Calc for $C_{10}H_{14}NO_5$: 228.0872. Found: 228.0873.

3-(5-Cyclohexylpenta-2E,4E-dienamido)-4,4-dimethoxy-5,6-epoxy-cyclohex-2-en-1-one (**28b**):
White solid; yield: 73%; R_f 0.37 (EtOAc/PE, 1:1); mp 135–136 °C.
IR (CH_2Cl_2): ν = 3406, 3051, 2983, 2854, 1701, 1674, 1633, 1548, 1500, 1340, 1261, 1120 cm^{-1}.
^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.71 (s, 1 H, NH), 7.28 (dd, 1 H, *J* = 14.8, 9.7 Hz, H-3′), 7.22 (d, 1 H, *J* = 1.9 Hz, H-2), 6.19–6.06 (m, 2 H, H-4′ and H-5′), 5.88 (d, 1 H, *J* = 14.8 Hz, H-2′), 3.82 (d, 1 H, *J* = 4.1 Hz, H-5), 3.64 (s, 3 H, OMe), 3.51 (dd, 1 H, *J* = 4.1, 1.9 Hz, H-6), 3.28 (s, 3 H, OMe), 2.09 (m, 1 H, cy-H), 1.70–1.03 (m, 10 H, cy).
^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 192.7, 164.9, 151.6, 145.2, 125.3, 120.7, 145.6, 108.6, 95.4, 52.0, 51.4, 51.2, 50.6, 41.1, 32.1, 25.9, 25.4.
MS (CI): *m/z* (%) = 348 (MH^+, 96), 316 (100).
HRMS: Calc for $C_{19}H_{26}NO_5$: 348.1811. Found: 348.1812.

3-(7-Cyclohexylhepta-2E,4E,6E-trienamido)-4,4-dimethoxy-5,6-epoxycyclohex-2-en-1-one (**28c**):
White solid; yield: 67%; R_f 0.35 (EtOAc/PE, 1:1); mp 151–153 °C.
IR (CH_2Cl_2): ν = 3392, 3051, 2987, 1694, 1668, 1606, 1550, 1498, 1265, 1157, 1120 cm^{-1}.
^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.81 (s, 1 H, NH), 7.36 (dd, 1 H, *J* = 14.9, 11.6 Hz, H-3′), 7.27 (d, 1 H, *J* = 2.0 Hz, H-2), 6.60 (dd, 1 H, *J* = 14.9, 10.6 Hz, H-5′), 6.24 (dd, 1 H, *J* = 11.6, 14.9 Hz, H-4′), 6.13 (dd, 1 H, *J* = 10.6, 15.2 Hz, H-6′), 5.97 (d, 1 H, *J* = 14.9 Hz, H-2′), 5.95 (dd, 1 H, *J* = 15.2, 6.8 Hz, H-7′), 3.86 (d, 1 H, *J* = 4.0 Hz, H-5), 3.67 (s, 3 H, OMe), 3.54 (dd, 1 H, *J* = 4.0, 2.0 Hz, H-6), 3.32 (s, 3 H, OMe), 2.10–2.05 (m, 1 H, cy-H), 1.77–1.06 (m, 10 H, cy).
^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 192.9, 165.0, 147.1, 144.7, 143.0, 127.3, 127.3, 121.3, 145.8, 108.6, 95.4, 52.1, 51.5, 51.3, 50,61, 41.1, 32.4, 26.0, 25.8.
MS (CI): *m/z* (%) = 374 (MH^+, 53), 342 (100).
HRMS (CI): Calc for $C_{21}H_{28}NO_5$: 374.1968. Found: 374.1964.

Preparation of SecondaryAlcohols (29); General Procedure:
To a stirred solution of amide **28** in MeOH was added $NaBH_4$ (1 equiv.) at 0 °C under N_2. After stirring for ca. 1 h at 0 °C, the reaction was warmed to r.t. at which point H_2O was added followed by sufficient sat. NH_4Cl to give a neutral solution. The MeOH was evaporated under reduced pressure and the residue extracted with EtOAc. The organic layer was dried (Na_2SO_4) and the solvent evaporated under reduced pressure to give a quantative yield of product as a mixture of the two diastereomers. The crude material was dissolved in acetone/H_2O (8:1) and *p*-toluenesulphonic acid (0.15 equiv.) and pyridinium *p*-toluenesulphonate (0.9 equiv.) added at 0 °C under N_2. The mixture was stirred at r.t. until the reaction was complete (3.5–7 d). Volatiles were then removed under reduced pressure and H_2O added. Extraction with EtOAc, drying of the combined organic layers (Na_2SO_4) and removal of the solvent under reduced pressure gave the crude product. Column chromatography or preparative TLC (EtOAc/PE) gave the *syn* and *anti*-diastereomers as white solids.

2-(Acetamido)-5,6-epoxy-4-hydroxy-cyclohex-2-en-1-one (**29a**):
Anti-isomer [(±)-5-epi-LL-C10037α] as colourless needles; yield: 12%; R_f 0.25 (EtOAc/DCM, 1:1); mp 148–149 °C (from CH_2Cl_2/Et_2O) (lit.[19] mp 154 °C dec.).
IR ($CHCl_3$): ν = 3687, 3595, 3392, 3039, 1682, 1516, 1375, 1026 cm^{-1}.
^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.70 (br s, 1H, NH), 7.61 (dd, 1H, *J* = 5.3, 2.4 Hz, H-3), 4.90 (dddd, 1H, *J* = 7.0, 5.3, 1.3, 1.2 Hz, H-4), 3.85 (ddd, 1H, *J* = 3.5, 2.4, 1.3 Hz, H-5), 3.62 (dd, 1H, *J* = 3.5, 1.2 Hz, H-6), 2.51 (d, 1H, *J* = 7.0 Hz, OH), 2.14 (3H, Me).
^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 188.7, 169.6, 130.3, 122.9, 63.1, 57.3, 52.2, 24.7.
MS (CI): *m/z* (%) = 201 (MNH_4^+, 47), 184 (MH^+, 100).
HRMS (CI): Calc for $C_8H_{10}NO_4$: 184.0610. Found: 184.0614.

Syn-isomer [(±)-LL-C10037α **17**] as a colourless powder; yield: 37%; R_f 0.20 (EtOAc/CH_2Cl_2, 1:1); mp 168–170 °C dec. (from acetone/Et_2O) (lit.[19] mp 167 °C dec.).
IR ($CHCl_3$): ν = 3687, 3597, 3394, 3033, 1684, 1516, 1373, 1032 cm^{-1}.
^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.56 (br s, 1H, NH), 7.44 (dd, 1H, *J* = 3.0, 2.2 Hz, H-3), 4.85 (ddd, 1H, *J* = 10.5, 3.2, 3.0 Hz, H-4), 3.88 (ddd, 1H, *J* = 3.9, 3.2, 2.2 Hz, H-5), 3.60 (d, 1H, *J* = 3.9 Hz, H-6), 2.25 (d, 1H, *J* = 10.5 Hz, OH), 2.14 (3H, Me).
^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 188.4, 169.2, 128.4, 124.5, 64.5, 54.1, 52.6, 24.6.
MS (CI): *m/z* (%) = 201 (MNH_4^+, 100), 184 (MH^+, 34).
HRMS (CI): Calc for $C_8H_{10}NO_4$: 184.0610. Found: 184.0611.

2-(5-Cyclohexylpenta-2E,4E-dienamido)-5,6-epoxy-4-hydroxy-cyclohex-2-en-1-one (**29b**):
Anti isomer as a white solid; yield: 19%; R_f 0.36 (EtOAc/PE, 1:2); mp 184–185 °C.
IR (CH_2Cl_2): ν = 3944, 3691, 3062, 2989, 1676, 1632, 1550, 1514, 1422, 1265, 1155, 1024 cm^{-1}.
^{1}H NMR (500 MHz, CD_3COCD_3): δ = 8.32 (s, 1 H, NH), 7.66 (dd, 1 H, *J* = 4.4, 2.3 Hz, H-3), 7.20 (dd, 1 H, *J* = 14.9, 10.6 Hz, H-3,), 6.33 (d, 1 H, *J* = 14.9 Hz, H-2′), 6.21 (dd, 1 H, *J* = 10.6, 15.3 Hz, H-4′), 6.13 (dd, 1 H, *J* = 15.3, 6.8 Hz, H-5′), 4.80 (m, 1 H, H-4), 3.83 (ddd, 1 H, *J* = 3.7, 2.3, 0.9 Hz, H-5), 3.58 (dd, 1 H, *J* = 3.7, 0.9 Hz, H-6), 2.83 (br s, 1 H, OH), 2.10–2.04 (m, 1 H, cy-H) and 1.76–1.12 (m, 10 H, cy).
^{13}C NMR (67.5 MHz, CD_3COCD_3): δ = 190.4, 166.1, 150.0, 143.7, 127.2, 125.1, 131.8, 123.8, 63.7, 58.7, 53.6, 42.1, 33.3, 26.9, 26.7.
MS (CI): *m/z* (%) = 304 (MH^+, 100).
HRMS (CI): Calc for $C_{17}H_{22}NO_4$: 304.1549. Found: 304.1553.

Syn isomer as a white solid; yield: 67%; mp 177–178 °C; R_f 0.22 (EtOAc/PE, 1:2).
IR (CH_2Cl_2): ν = 3328, 2924, 1652, 1548, 1371, 1252, 1108, 1066, 1005 cm^{-1}.
^1H NMR (500 MHz, CD_3COCD_3): δ = 8.23 (s, 1 H, NH), 7.49 (dd, 1 H, *J* = 2.8, 2.7 Hz, H-3), 7.19 (dd, 1 H, *J* = 14.9, 10.7 Hz, H-3′), 6.31 (d, 1 H, *J* = 14.9 Hz, H-2′), 6.20 (dd, 1 H, *J* = 15.3, 10.7 Hz, H-4′), 6.12 (dd, 1 H, *J* = 15.3, 6.8 Hz, H-5′), 4.93 (ddd, 1 H, *J* = 7.6, 2.9, 2.8 Hz, H-4), 3.85 (ddd, 1 H, *J* = 4.1, 2.9, 2.7 Hz, H-5), 3.51 (d, 1 H, *J* = 4.1 Hz, H-6), 2.81 (m, 1 H, OH), 2.14–2.06 (m, 1 H, cy-H), 1.76–1.11 (m, 10 H, cy).
^{13}C NMR (67.5 MHz, CD_3COCD_3): δ = 190.4, 165.8, 149.9, 143.4, 127.6, 127.2, 129.8, 123.8, 65.3, 55.1, 53.3, 42.1, 33.3, 26.9, 26.7.
MS (Cl): *m/z* (%) = 304 (MH^+, 100).
HRMS (CI): Calc for $C_{17}H_{22}NO_4$: 304.1549. Found: 304.1553.
Anal: Calc C, 67.31; H, 6.98; N, 4.62. Found: 66.90; H, 6.84; N, 4.59.

2-(7-Cyclohexylhepta-2E,4E,6E-trienamido)-5,6-epoxy-4-hydroxycyclohex-2-en-1-one (**29c**):
Anti isomer as a white solid; yield: 16%; R_f 0.39 (EtOAc/PE, 1:2); mp 180–182 °C.
IR (CH_2Cl_2): ν = 3944, 3693, 3062, 2985, 1673, 1606, 1423, 1273, 1155, 987 cm^{-1}.
^1H NMR (500 MHz, CD_3COCD_3): δ = 8.33 (s, 1 H, NH), 7.67 (dd, 1 H, *J* = 3.9, 2.4 Hz, H-3), 7.26 (dd, 1 H, *J* = 14.9, 11.3 Hz, H-3′), 6.63 (dd, 1 H, *J* = 14.9, 10.7 Hz, H-5′), 6.38 (d, 1 H, *J* = 14.9 Hz, H-2′), 6.32 (dd, 1 H, *J* = 14.9, 11.3 Hz, H-4′), 6.18 (dd, 1 H, *J* = 15.3, 10.7 Hz, H-6′), 5.92 (dd, *J* = 15.3, 7.1 Hz, H-7′), 4.80 (m, 1 H, H-4), 3.83 (br dd, 1 H, *J* = 3.7, 2.4 Hz, H-5), 3.58 (d, 1 H, *J* = 3.7 Hz, H-6), 2.80–2.77 (m, 1 H, OH), 2.11–2.06 (m, 1 H, cy-H) and 1.75–1.11 (m, 10 H, cy).
^{13}C NMR (125 MHz, CD_3COCD_3): δ = 190.1, 165.2, 145.9, 142.8, 141.8, 129.3, 128.6, 124.4, 129.1, 124.1, 63.5, 58.4, 53.2, 41.8, 33.2, 26.7, 26.5.
MS (CI): *m/z* (%) = 330 (MH^+, 100).
HRMS (CI): Calc for $C_{19}H_{24}NO_4$: 330.1705. Found: 330.1697.

Syn isomer as a white solid; yield: 64%; mp 175–176 °C; R_f 0.22 (EtOAc/PE, 1:2).
IR (CH_2Cl_2): ν = 3944, 3693, 3052, 2987, 1674, 1608, 1516, 1423, 1263, 1157, 987 cm^{-1}.
^{1} H NMR (500 MHz, CD_3COCD_3): δ = 8.23 (s, 1 H, NH), 7.49 (dd, 1 H, *J* = 2.9, 2.7 Hz, H-3), 7.25 (dd, 1 H, *J* = 14.9, 11.4 Hz, H-3′), 6.63 (dd, 1 H, *J* = 14.9, 10.7 Hz, H-5′), 6.35 (d, 1 H, *J* =14.9 Hz, H-2′), 6.32 (dd, 1 H, *J* = 14.9, 11.4 Hz, H-4′), 6.18 (dd, 1 H, *J* = 15.3, 10.7 Hz, H-6′), 5.91 (dd, 1 H, *J* = 15.3, 7.0 Hz, H-7′), 4.92 (ddd, 1 H, *J* = 7.5, 3.0, 2.9 Hz, H-4), 3.85 (ddd, 1 H, *J* = 4.1, 3.0, 2.7 Hz, H-5), 3.50 (d, 1 H, *J* = 4.1 Hz, H-6), 2.79 (m, 1 H, OH), 2.07 (m, 1 H, cy-H), 1.75–1.11 (m, 10 H, cy).
^{13}C NMR (67.5 MHz, CD_3 $COCD_3$): δ = 190.2, 165.7, 145.9, 142.8, 141.7, 129.26, 128.7, 127.4, 129.6, 124.3, 65.2, 54.9, 53.2, 41.9, 33.3, 26.8, 26.6.
MS (CI): *m/z* (%) = 330 (MH^+, 100).
HRMS (CI): Calc for $C_{19}H_{24}NO_4$: 330.1705. Found: 330.1697.

Oxidation of Secondary Alcohols 29; General Procedure:
To a stirred solution of alcohol **29** (1 equiv.) in CH_2Cl_2 under N_2 at 0 °C was added PDC (1.5–2.0 equiv.) in one portion. After stirring at r.t. overnight (athough the reactions were often finished earlier), the inorganics were removed by filtration and the solvent evaporated under reduced pressure. The resulting brown oil was purified by column chromatography (EtOAc/PE).

2-Acetamido-5,6-epoxy-1,4-benzoquinone (**30a**):
As a pale yellow solid from **29a** (*syn*); yield: 87%; R_f 0.60 (EtOAc/DCM, 1:1); mp (from EtOAc/PE) 169–170 °C (dec.).
IR (CCl_4): ν = 3386, 1728, 1699, 1685, 1610, 1502, 1315, 1213, 758 cm^{-1}.
^1H NMR (270 MHz, $CDCl_3$): δ = 7.88 (br s, 1 H, NH), 7.52 (d, 1 H, *J* = 2.3 Hz, H-3), 3.92 (d, 1 H, *J* = 3.6 Hz, H-6), 3.84 (dd, 1 H, *J* = 3.6, 2.3 Hz, H-5), 2.23 (s, 3 H, Me).
^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 191.1, 188.0, 169.3, 138.5, 115.4, 53.8, 52.4, 24.9.
MS (CI): *m/z* (%) = 199 (MNH_4^+, 18), 182 (MH^+, 80).
HRMS (CI): Calc for $C_8H_8NO_4$: 182.0453. Found: 182.0456.
The ^1H NMR data was entirely consistent with published[14b] values. See also preparation by two other procedures described later.

2-(7-Cyclohexylhept-2E,4E,6E-trienamido)-5,6-epoxy-1,4-benzoquinone (**30c**):
As a dark yellow oil from **29c** (*anti*); yield: 48%; R_f 0.72 (EtOAc/PE, 1:1).
IR ($CHCl_3$): ν = 3373, 3028, 2929, 2854, 1693, 1678, 1606, 1504, 1317, 1261, 1174, 1117, 1088, 1012, 723 cm^{-1}.
^1H NMR (270 MHz, $CDCl_3$): δ = 7.85 (br s, 1 H, NH), 7.63 (d, 1 H, *J* = 2.4 Hz, H-3), 7.39 (dd, 1 H, *J* = 14.9, 11.4 Hz, H-3′), 6.63 (dd, 1 H, *J* = 15.0, 10.3 Hz, H-5′), 6.31–6.09 (m, 2 H, H-4′ and H-6′), 5.95 (d, 1 H, *J* = 14.9, H-2′), 6.01–5.94 (m, 1 H, H-7′), 3.93 (d, 1 H, *J* = 3.6 Hz, H-6), 3.85 (dd, 1 H, *J* = 2.4, 3.6 Hz, H-5), 1.80–1.05 (m, 11 H, cy-H and cy).
^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 191.0, 188.2, 164.9, 147.6, 145.6, 143.7, 130.9, 128.8, 127.2, 120.4, 115.2, 53.9, 52.5, 41.1, 32.4, 26.0.
MS (EI): *m/z* (%) =327 (M^+, 13).
HRMS (EI): Calc for $C_{19}H_{21}NO_4$: 327.1471. Found: 327.1480.
The NMR data were consistent with published[5a] values. See also preparation described later.

2-tert-Butoxycarbonylamino-5,6-epoxy-1,4-benzoquinone (**38**):
Following the general procedure for the preparation of secondary alcohols and then the general procedure for the oxidation of secondary alcohols, oxo acetal **36** gave dione **38** which was purified by chromatography (EtOAc/CH_2Cl_2, 1:9) to give **38** as a light yellow oil; yield: 55% from **36**; R_f 0.72 (EtOAc/PE, 1:1).
IR (CCl_4): ν = 3390, 2983, 2935, 1747, 1703, 1680, 1612, 1502, 1317, 1236, 1215, 1151, 997 cm^{-1}.
^1H NMR (270 MHz, $CDCl_3$): δ = 7.26 (br s, 1 H, NH), 7.16 (d, 1 H, *J* = 2.3 Hz, H-3), 3.89 (d, 1 H, *J* = 3.6 Hz, H-6), 3.81 (dd, 1 H, *J* = 3.6, 2.3 Hz, H-5), 1.50 (s, 9H, ^{t}Bu).
^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 190.6, 187.7, 150.9, 139.8, 113.1, 83.1, 53.8, 52.5, 28.0.
MS (Cl): *m/z* (%) = 257 (MNH_4^+, 100), 240 (MH^+, 57).
HRMS (CI): Calc for $C_{11}H_{14}NO_5$: 240.0872. Found: 240.0872.

2-Amino-5,6-epoxy-1,4-benzoquinone (**39**):
Urethane **38** (221 mg, 0.92 mmol) was dissolved in anhyd CH_2Cl_2 (10 mL) under N_2 at 0 °C and powdered, activated 4Å molecular sieves (800 mg) were added followed by dropwise addition of a solution of $BF_3{\cdot}Et_2O$ (0.17 mL, 1.1 mmol), the temperature was allowed to rise slowly to r.t. and the mixture was stirred at r.t. for 20 h. Direct purification by chromatography (EtOAc/PE, 1:1 to pure EtOAc) afforded a yellow powder; yield: 126 mg (98%); R_f 0.30 (EtOAc/PE, 1:1) mp 133–134 °C (dec.).
IR (DCM): ν = 3685, 3504, 3392, 1710, 1655, 1620, 1404, 1344, 1010, 839 cm^{-1}.
^{1} H NMR (270 MHz, $CDCl_3$): δ = 5.56 (d, 1 H, *J* = 2.3 Hz, H-3), 4.89 (br s, 2 H, NH_2), 3.75 (d, 1 H, *J* = 3.6 Hz, H-6), 3.65 (dd, 1 H, *J* = 3.6, 2.3 Hz, H-5).
^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 189.6, 189.5, 147.1, 103.3, 54.3, 52.6.
MS (CI): *m/z* (%) = 157 (MNH_4^+, 48), 140 (MH^+, 100).
HRMS (Cl): Calc for $C_6H_9N_2O_3$: 157.0613. Found: 157.0619.

Preparation of Amides 30 by Acylation of 39; General Procedure:
Amine **39** (1 equiv.) was dissolved in anhyd CH_2Cl_2 and stirred under N_2 at 0 °C and BSTFA (5 equiv.) was added. Then, a solution

of the acid chloride (1.5 equiv.) in CH_2Cl_2 was added over 10 min. The resulting mixture was stirred at r.t. for up to 4 d until reaction was complete. Volatile material was removed under reduced pressure and the residue was purified by chromatography.

2-Acetamido-5,6-epoxy-1,4-benzoquinone (**30a**):
Yield: 65% (+ 25% recovered **39**): data as before.

2-Lauramido-5,6-epoxy-1,4-benzoquinone (**30d**):
As yellow needles; yield: 99%; R_f 0.40 (EtOAc/PE, 1:4); mp 108 °C (from CH_2Cl_2/PE).
IR (CCl_4): ν = 3384, 2927, 2856, 1699, 1682, 1610, 1500, 1315, 1213, 1174 cm^{-1}.
^1H NMR (270 MHz, $CDCl_3$): δ = 7.83 (br s, 1 H, NH), 7.55 (d, 1 H, *J* = 2.4 Hz, H-3), 3.92 (d, 1 H, *J* = 3.6 Hz, H-6), 3.84 (dd, 1 H, *J* = 3.6, 2.4 Hz, H-5), 2.44–2.32 (m, 2 H), 1.65–1.59 (m, 2 H), 1.26–1.18 (m, 16 H), 0.91–0.82 (m, 3 H).
^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 191.1, 188.2, 172.5, 138.5, 115.3, 53.8, 52.4, 37.9, 33.7, 31.9, 29.5, 29.4, 29.3, 29.2, 29.0, 24.9, 22.7, 14.1.
MS (EI): *m/z* (%) = 321 (M^+, 4), 43 (100).
HRMS (EI): Calc for $C_{18}H_{27}NO_4$: 321.1940. Found: 321.1939.

2-Benzamido-5,6-epoxy-1,4-benzoquinone (**30e**):
As yellow crystals; yield: 65%; R_f 0.25 (EtOAc/PE, 1:4); mp 111–112 °C (from CH_2Cl_2/PE);
IR (CCl_4): ν = 3390, 1694, 1682, 1601, 1510, 1490, 1350, 1311, 1238, 1215, 1172, 1063, 901, 881, 785, 704 cm^{-1}.
^1H NMR (270 MHz, $CDCl_3$): δ = 8.66 (br s, 1 H, NH), 7.86–7.83 (m, 2 H, ArH), 7.69 (d, 1 H, *J* = 2.3 Hz, H-3), 7.65–7.49 (m, 3 H, ArH), 3.98 (d, 1 H, *J* = 3.6 Hz, H-6), 3.87 (dd, 1 H, *J* = 3.6, 2.3 Hz, H-5).
^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 191.0, 188.2, 165.8, 138.8, 133.2, 132.8, 129.1, 127.3, 115.5, 53.8, 52.5.
MS (EI): *m/z* (%) = 243 (M^+, 1), 105 (100).
HRMS (EI): Calc for $C_{13}H_9NO_4$: 243.0532. Found: 243.0538.

Preparation of Amides 30 by Epoxidation of Quinones 40; General Procedure:

(a) Preparation of Quinones 40:

To a solution of 2,5-dimethoxyaniline (**34**) (1 equiv.), pyridine (1.1 equiv.) and a catalytic amount (*ca.* 5 mg/mmol amine) of DMAP in CH_2Cl_2 was added the corresponding acid chloride **37** (1.1 equiv.) in CH_2Cl_2 at 0 °C under N_2. The resulting solution was then stirred at r.t. for 12 h. The mixture was then poured into H_2O, and extracted with EtOAc. The organic layers were combined and washed with 2 M HCl and sat. aq $NaHCO_3$, and dried (Na_2SO_4). After the removal of the solvent, the dark residue was purified by column chromatography to give the corresponding amide which was used directly in the next step.

A solution of the amide (1 equiv.) in anhyd MeOH was stirred at 0 °C under N_2 and treated portionwise with iodobenzene diacetate (1.5 equiv.). The reaction was then stirred at 0 °C for 4 h. If starting material was still remaining (TLC), the reaction was warmed to r.t. for 1 h. On completion, the mixture was diluted with CH_2Cl_2 and H_2O and then neutralized with aq $NaHCO_3$. The reaction was extracted with CH_2Cl_2 and the organic layers combined, washed with H_2O and brine, and then treated with Amberlyst-15 (ca. 3.5 g/mmol) and several drops of H_2O. ln the case of **40a** the hydrolysis was carried out at r.t. for about 12 h, and in the case of **40b,f** the reaction was run at 35–40 °C for about 4 h and monitored by TLC. The Amberlyst-15 was then filtered off, the solvent evaporated and the residue was washed with a small amount of Et_2O to give the quinones **40** as dark yellow solids after filtration. The filtrates were concentrated and subjected to column chromatography to give additional product.

2-Acetamido-/,4-benzoquinone (**40a**):
As a dark solid; yield: 66%; mp 145–147 °C (Lit:[47] 146–148 °C with data in accord with the literature.[47]

2-(5-Cyclohexylpenta-2E,4E-dienamido)-1,4-benzoquinone (**40b**):
As an orange solid; yield: 70%; R_f 0.33 (EtOAc/PE, 1:3); mp 164–l65 °C.
IR ($CHCl_3$): ν = 3369, 2929, 2854, 1666, 1631, 1595, 1500, 1342, 1321, 1178, 1115, 1001, 893 cm^{-1}.
^1H NMR (270 MHz, $CDCl_3$): δ = 8.03 (s, 1 H, NH), 7.67 (d, 1 H, *J* = 2.3 Hz, H-3), 7.34 (dd, 1 H, *J* = 14.8, 10.2 Hz, H-3′), 6.81–6.72 (m, 2 H, H-4′ and H-5′), 6.24–6.16 (m, 2 H, H-5 and H-6), 5.95 (d, 1 H, *J* = 14.8 Hz, H-2′), 2.20–2.02 (m, 1 H, cy-H), 1.78–1.12 (m, 10 H, cy).
^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 187.9, 182.8, 164.9, 152.1, 145.7, 125.4, 120.3, 138.5, 138.3, 133.1, 114.5, 41.2, 32.1, 25.9, 25.8.
MS (EI): *m/z* (%) = 285 (M^+, 21), 202 (27), 163 (78).
HRMS (EI): Calc. for $C_{17}H_{19}NO_3$: 285.1365. Found: 285.1373.
The NMR data were consistent with published[12c] values.

2-(E-Cinnamido)-1,4-benzoquinone (**40f**):
As a dark solid; yield: 65%, R_f 0.30 (PE/EtOAc, 2:1); mp 204–205.5 °C (dec.).
IR (nujol): ν = 3326, 1693, 1663, 1645, 1625, 1597, 1500, 1345, 1140, 883, 721 cm^{-1}.
^1H NMR (270 MHz, $CDCl_3$): δ = 8.19 (br s, 1 H, NH), 7.77 (d, 1 H, *J* = 15.5 Hz, H-3′), 7.73 (d, 1 H, *J* = 2.2 Hz, H-3), 7.57 (m, 2 H, ArH), 7.45–7.40 (m, 3 H, ArH), 6.84–6.74 (m, 2 H, H-5,6), 6.59 (d, l H, *J* = 15.5 Hz, H-2′).
^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 187.8, 182.7, 164.5, 144.9, 138.5, 138.3, 133.9, 133.1, 130.8, 129.0, 128.3, 119.2, 114.9.
MS (EI): *m/z* (%) = 253 (M^+, 8), 131 (100).
HRMS (EI): Calc. for $C_{15}H_{11}NO_3$: 253.0739. Found: 253.0745.

(b) Epoxidation of Quinones 40:

To a solution of quinone **40** (0.2 mmol) in EtOAc (40 mL) in a 100 mL separating funnel was added *tert*-butyl hydroperoxide in nonane (5–6 M, 5 equiv.) containining DBU (1.0 equiv.). The mixture was shaken for 30 sec, washed with sat. aq iron(II) sulphate (3 × 30 mL), then brine (2 × 30 mL), and then dried (Na_2SO_4). After evaporation of the solvent, the residue was purified by column chromatography (EtOAc/PE, 1:4) to give epoxyquinones **30**:

2-Acetamido-5,6-epoxy-1,4-benzoquinone (**30a**):
Yield: 67%: data as before.

2-(5-Cyclohexylpenta-2E,4E-dienamido)-5, 6-epoxy-1,4-benzoquinone (**30b**):
As an off-white solid; yield: 8 l%; R_f 0.55 (PE/EtOAc, 1:1); mp 159–160 °C.
IR (CCl_4): ν = 3381, 2929, 2854, 1695, 1680, 1633, 1605, 1502, 1350, 1313, 1213, 1172, 1115, 999 cm^{-1}.
^1H NMR (270 MHz, $CDCl_3$): δ = 7.90 (br s, 1 H, NH), 7.61 (d, 1 H, *J* = 2.3 Hz, H-3), 7.36–7.17 (m, 1 H, vinyl), 6.23–6.09 (m, 2 H, vinyl), 5.93 (d, 1 H, *J* = 15.8 Hz, H-2′), 3.93 (d, 1 H, *J* = 3.6 Hz, H-6), 3.83 (dd, 1 H, *J* = 2.3, 3.6 Hz, H-5), 2.17–2.00 (m, 1 H, cy-H), 1.77–1.68 (m, 5 H, cy), 1.32–1.10 (m, 5 H, cy).
^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 191.0, 188.1, 165.0, 152.4, 146.1, 139.0, 125.3, 120.0, 115.2, 53.8, 52.5, 41.2, 32.1, 25.9, 25.7.
MS (EI): *m/z* (%)= 301 (M^+, 10), 163 (100).
HRMS (EI): Calc. for $C_{17}H_{19}NO_4$: 301.1314. Found: 301.1323.

2-(E-Cinnamido)-5,6-epoxy-1,4-benzoquinone (**30f**):
Yield: 68% as a white solid; R_f 0.27 (PE/EtOAc, 2:1); mp 183–185 °C (dec.).
IR (nujol): ν = 3349, 1672, 1627, 1610, 1505, 1173, 1140, 868, 665 cm^{-1}.
^1H NMR (270 MHz, $CDCl_3$): δ = 8.00 (br s, 1 H, NH), 7.76 (d, 1 H, *J* = 15.5 Hz, H-3′), 7.67 (d, 1 H, *J* = 2.4 Hz, H-3), 7.59–7.52 (m, 2 H, ArH), 7.44–7.38 (m, 3 H, ArH), 6.54 (d, 1 H, *J* = 15.5 Hz, H-2′), 3.95 (d, 1 H, *J* = 3.6 Hz, H-6), 3.86 (dd, 1 H, *J* = 2.4, 3.6 Hz, H-5).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 191.0, 188.2, 164.5, 145.3, 138.9, 133.75, 130.9, 129.0, 128.3, 118.8, 115.6, 53.9, 52.5.
MS (CI): *m/z* (%) = 287 (MNH_4^+, 35), 270 (MH^+, 100).
HRMS (CI): Calc. for $C_{15}H_{12}NO_4$: 270.0766. Found: 270.0770.

3-(7-Cyclohexylhepta-2*E*,4*E*,6*E*-trienamido)-4,4-dimethoxy-5,6-epoxy-1-phenylcyclohex-2-en-1-ol (41c); Typical Procedure:
To a stirred solution of PhLi (1.8 M in THF, 0.26 mL, 0.47 mmol) in THF (4 mL) at –40 °C under N_2 was added ketone **28c** (25 mg, 0.067 mmol) in THF (4 mL) dropwise over 3 h. After stirring at –40 °C for 30 min, the reaction was warmed to r.t., quenched with sat. NH_4Cl (50 mL) and extracted with EtOAc (5 × 40 mL). The combined organic layers were washed with H_2O (40 mL) and brine (40 mL), dried (Na_2SO_4) and the solvent evaporated under reduced pressure to give a yellow oil. Purification by column chromatography (EtOAc/PE, 1:1) gave **41c** as a colourless oil; yield: 26 mg (86%); R_f 0.40 (EtOAc/PE, 1:1).
IR ($CHCl_3$): ν = 3691, 3606, 3408, 3032, 2931, 2856, 1699, 1682, 1603, 1512, 1450, 1371, 1246, 1122, 1063, 780 cm^{-1}.
^{1}H NMR (270 MHz, CD_3COCD_3): δ = 8.11 (s, 1 H, NH), 7.67–7.64 (m, 2 H, ArH), 7.37–7.23 (m, 3 H, ArH), 7.17 (dd, 1 H, *J* = 14.9, 11.3 Hz, H-3′), 6.79 (1 H, d, *J* = 2.3 Hz, H-2), 6.58 (dd, 1 H, *J* = 15.2, 10.8 Hz, H-6′), 6.26 (d, 1 H, *J* = 14.9 Hz, H-2′), 6.26 (dd, 1 H, *J* = 15.2, 11.3 Hz, H-4′), 6.15 (dd, 1 H, *J* = 15.2, 10.8 Hz, H-5′), 5.88 (dd, 1 H, *J* = 15.2, 7.3 Hz, H-7′), 3.68 (d, 1 H, *J* = 4.3 Hz, H-5), 3.49 (s, 3 H, OMe), 3.32 (dd, 1 H, *J* = 4.3, 2.3 Hz, H-6), 3.34 (s, 3 H, OMe), 2.08 (s, 1 H, OH), 1.80–l.07 (m, 11 H, cy).
^{13}C NMR (125 MHz, CD_3COCD_3): δ = 165.0, 145.6, 142.0, 141.3, 129.4, 129.0, 128.7, 128.2, 127.2, 125.1, 96.3, 73.0, 53.2, 51.0, 50.6, 50.0, 41.9, 33.4, 26.7, 26.6.
MS (EI): *m/z* (%) = 451 (M^+, 14).
HRMS (EI): Calc for $C_{27}H_{33}NO_5$: 451.2359. Found: 451.2359.

3-(5-Cyclohexylpenta-2E,4E-dienamido)-4,4-dimethoxy-5,6-epoxy-1-phenylcyclohex-2-en-1-ol (**41b**):
In a similar manner, ketone **28b** was converted into **41b**, which was fully characterised, in 60% yield.

3-[(*tert*-Butoxycarbonyl)amido]-4,4-dimethoxy-5,6-epoxy-1-phenylcyclohex-2-en-1-ol (42):
To a stirred solution of PhLi (1.8 M in THF, 0.29 mL, 0.53 mmol) in THF (3 mL) at –40 °C under N_2 was added ketone **36** (50 mg, 0.18 mmol) in THF (2 mL), dropwise over 3 h. After stirring at –40 °C for 1 h, the reaction was warmed slowly to r.t., quenched with sat. NH_4Cl (30 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with H_2O (40 mL) and brine (40 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a pale yellow oil. Purification by column chromatography (EtOAc/PE, 1:3) gave **42** as a pale yellow solid; yield: 59 mg (93%); R_f 0.49 (Et_2O/PE, 1:1); mp 217–219 °C.
IR ($CHCl_3$): ν = 3577, 3425, 2981, 1725, 1504, 1450, 1369, 1346, 1242, 1159, 1124, 1063, 1041, 991, 947 cm^{-1}.
^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.19–6.81 (m, 5 H, ArH), 6.18 (s, 1 H, NH), 5.89 (br s, 1 H, H-2), 3.28 (d, 1 H, *J* = 4.3 Hz, H-5), 3.16 (s, 3 H, OMe), 3.08 (dd, 1 H, *J* = 4.3, 2.4 Hz, H-6), 2.95 (s, 3 H, OMe), 2.16 (s, 1 H, OH), 1.03 (s, 9 H, *t*-Bu).
^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 152.4, 141.7, 128.7, 128.4, 127.9, 127.7, 125.9, 113.8, 95.0, 72.9, 57.5, 50.9, 53.2, 49.9, 28.2.
MS (CI): *m/z* (%) = 381 (MNH_4^+, 7), 363 (15), 346 (100).
HRMS (CI): Calc for $C_{19}H_{29}N_2O_6$: 381.20262. Found: 381.2026.

Methyl 7-(1′-Hydroxycyclohexyl)hepta-2*E*,4*E*,6*E*-trienoate (45a):
A solution of stannane **43**[37] (50 mg, 0.12 mmol) in anhyd, degassed DMF (0.4 mL) followed by a solution of bromodiene **44a**[21,38] (21 mg, 0.11 mmol) in anhyd, degassed DMF (0.4 mL) were added to a solution of $PdCl_2(MeCN)_2$ (1.3 mg, 0.005 mmol) in anhyd, degassed DMF (0.2 mL) at r.t. under N_2. The reaction was stirred overnight at r.t., then the solvent was removed under reduced pressure and the crude product directly purified by column chromatography (PE/EtOAc, 3:2) to give ester **45a** as a colourless oil; yield: 21.3 mg (82%); R_f 0.50 (PE/EtOAc, 1:1).
IR (neat): ν = 3376, 2930, 2857, 1699, 1615, 1420, 1260, 1134, 1004 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32 (dd, 1 H, *J* = 15.3, 11.3 Hz, H-3), 6.56 (dd, 1 H, *J* = 10.8, 15.0 Hz, H-5), 6.39 (dd, 1 H, *J* = 10.8, 15.0 Hz, H-6), 6.32 (dd, 1 H, *J* = 11.3, 15.0 Hz, H-4), 6.03 (d, 1 H, *J* = 15.3 Hz, H-2), 5.88 (d, 1 H, *J* = 15.0 Hz, H-7), 3.75 (s, 3 H, OMe), 1.75–1.25 (m, 10 H, cy).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.5, 146.0, 144.6, 140.6, 129.6, 126.7, 120.3, 71.7, 51.5, 37.8, 25.4, 21.9.
MS (EI): *m/z* (%) = 236 (M^+, 65), 55 (100).
HRMS (EI): Calc for $C_{14}H_{20}O_3$: 236.1413. Found: 236.1410.

7-(1′-Hydroxycyclohexyl)hepta-2*E*,4*E*,6*E*-trienoic Acid (45b):
A solution of DIBAL-H (1.0 M in THF, 0.02 mL, 0.020 mmol) was added to a solution of $PdCl_2(PPh_3)_2$ (7.2 mg, 0.01 mmol) in THF (0.5 mL) at r.t. under N_2. After stirring for 10 min, a solution of stannane **43**[37] (85 mg, 0.21 mmol) in anhyd, degassed DMF (0.5 mL) followed by a solution of bromodiene **44b**[21,38] (33.8 mg, 0.19 mmol) in anhyd, degassed DMF (0.5 mL) were added to the solution of the pre-reduced catalyst at r.t. The reaction was stirred overnight at r.t., then treated with acetone (0.2 mL) and 1 M aq KF (0.2 mL). After stirring for 1 h, the mixture was filtered, washed with a 0.1 M solution of KH_2PO_4 (3 mL), extracted with EtOAc (3 × 3 mL) and the combined organic layers were dried ($MgSO_4$) and the solvent was removed. The crude product was purified by column chromatography (PE/EtOAc, 1:1) to give the ester **45b** as a white solid; yield: 30.4 mg (72%); R_f 0.17 (PE/EtOAc, 1:1); mp 96–98 C°.
IR (film): ν = 3406, 2933, 2856, 1685, 1615, 1419, 1268, 1134, 1006 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39 (dd, 1 H, *J* = 15.0, 11.5 Hz, H-3), 6.60 (dd, 1 H, *J* = 15.0, 10.5 Hz, H-5), 6.40 (dd, 1 H, *J* = 15.0, 10.5 Hz, H-6), 6.35 (dd, 1 H, *J* = 15.0, 11.5 Hz, H-4), 6.06 (d, 1 H, *J* = 15.0 Hz, H-2), 5.88 (d, *J* = 15.0 Hz, 1 H, H-7), 1.80–l.25 (m, 10 H, cy).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.7, 146.6 (2C), 141.5, 129.3, 126.5, 119.6, 71.7, 37.6, 25.3, 21.8.
MS (CI): *m/z* (%) = 240 (MNH_4^+, 10), 205 (100).
HRMS (CI): Calc for $C_{13}H_{22}NO_3$: 240.1600. Found: 240.1593.

***N*-(2″-Hydroxy-5″-oxocyclopent-1″-en-1″-yl)-7-(1′-hydroxycyclohexyl)hepta-2*E*,4*E*,6*E*-trienamide (47):**
Bromodiene **33**[21] (25 mg, 0.09 mmol) and stannane **43**[37] (46 mg, 0.11 mmol) were coupled using the same procedure described later for alisamycin. Purification by column chromatography (CH_2Cl_2/MeOH, 19:1) gave **47** as a yellow solid; yield: 24.3 mg (83%); R_f 0.13 (CH_2Cl_2/MeOH, 19:1); mp 132–133 °C.
IR ($CDCl_3$): ν = 3689, 3600, 3373, 3155, 2985, 2935, 1817, 1793, 1628, 1603, 1531, 1469, 1379, 1217, 1165, 1095 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$): δ = 13.64 (s, 1 H, enol-OH), 7.54 (s, 1 H, NH), 7.34 (dd, 1 H, *J* = 14.9, 11.4 Hz, H-3′), 6.61 (dd, 1 H, *J* = 14.5, 10.7 Hz, H-5′), 6.40 (dd, 1 H, *J* = 15.2, 10.7 Hz, H-6′), 6.32 (dd, 1 H, *J* = 14.5, 11.4 Hz, H-4′), 6.06 (d, 1 H, *J* = 15.2 Hz, H-7′), 5.99 (d, 1 H, *J* = 14.9 Hz, H-2′), 2.80–2.50 (m, 4 H, H-4″ and H-5″), 1.69–1.22 (m, 10 H, cy).
^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 197.3, 173.8, 167.1, 146.8, 144.4, 141.7, 129.1, 126.6, 119.8, 115.0, 71.7, 32.1, 25.6, 25.3, 21.9.
MS (EI): *m/z* (%) = 317 (M^+, 24), 299 (21), 188 (100).
HRMS (EI): Calc for C /z$H_{23}NO_4$: 317.1627. Found: 317.1629.

2-(5′-Cyclohexylpenta-2′*E*,4′*E*-dienamido)-4-(2″-*E*-tributylstannylethenyl)-4-hydroxy-5,6-epoxycyclohex-2-en-1-one (52) and Regioisomer (51):
BuLi (2.5 M in hexanes, 0.24 mL, 0.60 mmol) was added dropwise over 15 min to a stirred solution of *E*-1,2-bis(tributylstannyl)ethene[20]

(483 mg, 0.80 mmol) in THF (6 mL) under N_2. The reaction was stirred at –78 °C for 30 min and then at 0 °C for 90 min. The stirred solution of **31** was then re-cooled to –78 °C and epoxyquinone **30b** (60 mg, 0.20 mmol) in THF (2 mL) was added dropwise, under N_2 over 30 min. After stirring at –78 °C for 1 h, the reaction was quenched at this temperature with sat. NH_4Cl (10 mL) and extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with brine (25 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a yellow oil. Purification by column chromatography (EtOAc/PE, 3:7) gave **52** as a colourless oil; yield: 31 mg (26%); R_f 0.62 (EtOAc/PE, 3:7).
IR (film): ν = 3345, 2954, 2925, 2852, 1667, 1632, 1612, 1522, 1464, 1450, 1365, 1246, 997 cm^{-1}.
^1H NMR (500 MHz, $CDCl_3$): δ = 7.56 (br s, 1 H, NH), 7.40 (d, 1 H, *J* = 2.6 Hz, H-3), 7.23 (dd, 1 H, *J* = 10.0, 15.0 Hz, H-3′), 6.49 (d, 1 H, *J* = 19.3 Hz, H-7), 6.14–6.11 (m, 2 H, H-4′ and H-5′), 5.98 (d, 1 H, *J* = 19.3 Hz, H-8), 5.85 (d, 1 H, *J* = 15.0 Hz, H-2′), 3.67–3.63 (m, 2 H, H-5 and H-6), 2.15–2.05 (m, 1 H, cy-H), 1.77–0.93 (m, 37 H, cy + 3 × Bu).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 189.1, 164.9, 150.4, 145.5, 143.8, 133.5, 128.0, 127.4, 125.5, 121.2, 73.0, 57.7, 52.9, 41.1, 32.2, 29.0, 27.8, 26.0, 25.8, 13.6, 9.6.
MS (CI): *m/z* (%) = 620 [MH^+ (for ^{120}Sn), 7].
HRMS (CI): Calc for $C_{31}H_{50}NO_4{}^{116}Sn$: 616.2757. Found: 616.2767.

The regioisomeric adduct **51** was also obtained as a colourless oil; yield: 24 mg (20%); R_f 0.38 (EtOAc/PE, 1:4).
IR (NaCl): ν = 3334, 2954, 2926, 2852, 1666, 1633, 1610, 1504, 1373, 1340, 1211, 998 cm^{-1}.
^1H NMR (500 MHz, $CDCl_3$): δ = 7.37 (br s, 1 H, NH), 7.34–7.24 (m, 1 H, H-3′), 7.12 (d, 1 H, *J* = 2.0 Hz, H-2), 6.67 (d, 1 H, *J* = 19.5 Hz, H-7), 6.20–6.08 (m, 2 H, H-4′ and H-5′), 5.86 (d, 1 H, *J* = 19.5 Hz, H-8), 5.80 (d, 1 H, *J* = 14.5 Hz, H-2′), 3.61–3.55 (m, 2 H, H-5 and H-6), 2.92 (br s, 1 H, OH), 2.17–2.05 (m, 1 H, cy-H, 1.80–1.05 (m, 28 H, cy + 9 × CH_2), 1.00–0.80 (m, 9 H, 3 × Me).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 193.0, 165.4, 151.6, 150.5, 145.2, 143.1, 135.0, 125.4, 120.6, 107.0, 74.2, 57.1, 54.4, 41.2, 32.2, 29.0, 27.1, 26.0, 25.8, 13.7, 9.7.
MS (Cl): *m/z* (%) = 620 [MH^+(for ^{120}Sn), 0].
HRMS (CI): Calc for $C_{31}H_{50}NO_4{}^{116}Sn$: 616.2757. Found: 616.2750.

(±)-*Alisamycin* (8) *and Regioisomer* (53):
A solution of DIBAL-H (1.0 M in THF, 0.051 mL, 0.051 mmol) was added to a solution of $PdCl_2(PPh_3)_2$ (18 mg, 0.026 mmol) in THF (4 mL) at r.t. under N_2. After stirring at r.t. for 5 min, 0.1 mL of this solution was removed and used immediately in the following coupling reaction. Solutions of vinylstannane **52** (10 mg, 0.016 mmol) in anhyd, degassed DMF (0.2 mL) and bromodiene **33**[21] (4.9 mg, 0.018 mmol) in anhyd, degassed DMF (0.2 mL) were added in rapid succession to a vigorously stirred solution of the pre-generated catalyst (*ca.* 0.65×10^{-3} mmol) in THF (0.1 mL) at r.t. under N_2. After stirring at r.t. for 12 h, the mixture was poured into H_2O (10 mL) and extracted with EtOAc (3×15 mL). The combined organic layers were dried (Na_2SO_4) and the solvent evaporated under reduced pressure to give a yellow residue. Preparative TLC (CH_2Cl_2/EtOAc, 4:6) gave **8** as a yellow waxy solid; yield: 5.4 mg (64%); R_f 0.22 (CH_2Cl_2/MeOH, 95:5); mp 186–188 °C [lit.[7] > 250 °C for (–)-**8**].
IR ($CHCl_3$): ν = 3311, 2960, 2925, 2852, 1666, 1599, 1514, 1369, 1259, 1095, 1012 cm^{-1}.
^1H NMR (500 MHz, $CDCl_3$): δ = 13.48 (br s, 1 H, enol-OH), 7.56 (br s, 1 H, NH), 7.45 (br s, 1 H, NH), 7.41 (d, 1 H, *J* = 2.5 Hz, H-3), 7.33 (dd, 1 H, *J* = 11.3, 14.8 Hz, H-11), 7.21 (dd, 1 H, *J* = 14.8, 10.5 Hz, H-3′), 6.58 (dd, 1 H, *J* = 14.8, 11.3 Hz, H-8), 6.58 (dd, 1 H, *J* = 11.3, 14.5 Hz, H-9), 6.42 (dd, 1 H, *J* = 14.8, 11.3 Hz, H-10), 6.12 (m, 2 H, H-4′ and H-5′), 6.04 (d, 1 H, J = 14.8 Hz, 12-H), 5.86 (d, 1 H, *J* = 14.5 Hz, H-6), 5.84 (d, 1 H, *J* = 15.0 Hz, H-2′), 3.72 (dd, 1 H, *J* = 2.5, 3.5 Hz, H-5), 3.67 (d, 1 H, *J* = 3.5 Hz, H-6), 2.65 (br s, 1 H, OH), 2.64–2.52 (m, 4 H, H-4″ and H-5″), 2.15–2.05 (m, 1 H, cy-H), 1.80–l.05 (m, 10 H, cy).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.1, 188.4, 173.5, 165.2, 165.0, 150.7, 144.1, 143.5, 139.5, 136.0, 131.6 (2 C), 128.1, 125.9, 125.4, 121.4, 121.0, 114.8, 71.2, 57.4, 53.0, 41.1, 32.2, 32.1, 26.0, 25.8, 25.6.
MS (FAB): *m/z* (%) = 543 (MNa^+, 37), 521 (MH^+, 100).
HRMS (FAB): Calc for $C_{29}H_{33}N_2O_7$: 521.2288. Found: 521.2294.
The NMR data were consistent with published[7,44] values.

Following the same procedure on the same scale, vinylstannane (**51**) gave the regioisomer (**53**) as a pale yellow solid; yield: 6.3 mg (75%); R_f 0.39 (CH_2Cl_2/MeOH, 9:1); mp = 233–236 °C (dec.).
IR ($CHCl_3$): ν = 3257, 2924, 2850, 1653, 1616, 1605, 1497, 1375, 1209, 1009 cm^{-1}.
^1H NMR (500 MHz, $CDCl_3$) δ = 13.50 (s, 1 H, enol-OH), 7.53 (br s, 1 H, NH), 7.42 (br s, 1 H, NH), 7.33 (dd, 1 H, *J* = 15.0, 11.5 Hz, H-11), 7.24 (dd, 1 H, *J* = 15.0, 10.0 Hz, H-3′), 7.12 (d, 1 H, *J* = 2.0 Hz, H-2), 6.64 (dd, 1 H, *J* = 14.5, 11.0 Hz, H-8), 6.57 (dd, 1 H, *J* = 14.5, 11.0 Hz, H-9), 6.46 (dd, 1 H, *J* = 14.5, 11.5 Hz, H-10), 6.20–6.12 (m, 2 H, H-4′ and H-5′), 6.08 (d, 1 H, *J* = 15.0 Hz, H-l2), 5.83 (d, 1 H, *J* = 14.5 Hz, H-7), 5.81 (d, 1 H, *J* = 15.0 Hz, H-2′), 3.66 (d, 1 H, *J* = 4.5 Hz, H-5), 3.59 (dd, 1 H, *J* = 4.5, 2.0 Hz, H-6), 3.27 (br s, 1 H, OH), 2.65–2.45 (m, 4 H, H-4″ and H-5″), 2.18–2.04 (m, 1 H, cy-H), 1.85–1.05 (m, 10 H, cy).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.4, 192.6, 174.1, 165.4, 165.2, 152.0, 150.1, 145.5, 143.1, 138.5, 134.2, 132.7, 132.6, 125.4, 122.2, 120.5, 114.9, 106.9, 72.6, 56.9, 54.3, 41.2, 32.2, 26.0, 25.8, 25.6.
MS (FAB^+): *m/z* (%) = 543 (MNa^+, 23), 521 (MH^+, 32).
HRMS (FAB^+): Calc for $C_{29}H_{33}N_2O_7$: 521.2288. Found: 521.2299.

Nisamycin Methyl Ester (54):
A solution of DIBAL-H (1.0 M in THF, 0.03 mL, 0.030 mmol) was added to a solution of $PdCl_2(PPh_3)_2$ (10.0 mg, 0.014 mmol) in THF (2.0 mL) at r.t. under N_2 and stirred for 10 min. To a portion (0.1 mL) of the pre-reduced catalyst at r.t. under N_2 was added a solution of stannane **52** (12 mg, 0.019 mmol) in anhyd, degassed DMF (0.2 mL) followed by a solution of bromodiene **44a** (4.5 mg, 0.023 mmol) in anhyd, degassed DMF (0.2 mL). The reaction was stirred overnight at r.t., diluted with EtOAc (5 mL), washed with H_2O (3 × 3 mL) and the organic layer dried ($MgSO_4$) and the solvent removed. The crude product was purified using preparative TLC (PE/EtOAc, 3:2) to give the ester **54** as a pale yellow oil; yield: 6.8 mg (82%); R_f 0.46 (PE/EtOAc, 3:2).
IR (film): ν = 3363, 2924, 2852, 1697, 1670, 1618, 1520, 1361, 1259, 1134, 1003 cm^{-1}.
^1H NMR (500 MHz, $CDCl_3$): δ = 7.56 (br s, 1 H, NH), 7.41 (d, 1 H, *J* = 2.5 Hz, H-3), 7.30 (dd, 1 H, *J* = 15.0, 11.0 Hz, H-11), 7.24 (dd, l H, *J* = 15.0, 10.5 Hz, H-3′), 6.62–6.50 (m, 2 H, H-8 and H-9), 6.41 (dd, 1 H, *J* = 15.0, 11.0 Hz, H- 10), 6.20–6.10 (m, 2 H, H-4′ and H-5′), 5.94 (d, 1 H, *J* = 15.0 Hz, H-2′), 5.85 (d, 1 H, *J* = 15.0 Hz, H-7), 5.84 (d, 1 H, *J* = 15.0 Hz, H-12), 3.76 (s, 3 H, OMe), 3.71 (dd, 1 H, *J* = 4.0, 2.5 Hz, H-5), 3.66 (d, 1 H, *J* = 4.0 Hz, H-6), 2.80 (br s, 1 H, OH), 2.18–2.08 (m, 1 H, H-6′), 1.80–1.05 (m, 10 H, cy).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 188.6, 167.3, 165.1, 150.8, 144.1, 143.8, 138.5, 135.5, 132.2, 131.7, 128.0, 126.3, 125.4, 121.9, 120.9, 71.1, 57.4, 52.9, 51.6, 41.1, 32.2, 26.0, 25.8.
MS (FAB^+): *m/z* (%) = 462 (MNa^+, 28), 176 (100).
HRMS (FAB^+): Calc for $C_{25}H_{29}NNaO_6$: 462.1893. Found: 462.1900.

(±)-*Nisamycin (15):*
A solution of DlBAL-H (1.0 M in THF, 0.028 mL, 0.028 mmol) was added to a solution of $PdCl_2(PPh_3)_2$ (10 mg, 0.014 mmol) in THF (1 mL) at r.t. under N_2 and the solution stirred for 10 min. To this solution of the pre-reduced catalyst at r.t. was added a solution of

stannane **52** (10 mg, 0.016 mmol) in anhyd, degassed DMF (0.2 mL) followed by a solution of bromodiene **44b** (3.5 mg, 0.019 mmol) in anhyd, degassed DMF (0.2 mL). The reaction was stirred for 24 h at r.t., and then treated with acetone (0.2 mL) and aq KF (1 M, 0.2 mL). After stirring for a further 1 h, the mixture was filtered, washed with KH_2PO_4 (0.1 M, 1 mL), extracted with EtOAc (3 × 3 mL), the combined organic layers were dried ($MgSO_4$) and the solvent removed. The crude product was purified by preparative TLC (CH_2Cl_2/MeOH, 95:5) to give the acid **15** as a pale yeiiow solid; yield: 4.0 mg (58%); R_f 0.27 (CH_2Cl_2/MeOH, 9:1); mp 107–l09 °C.
IR ($CHCl_3$): ν = 3360, 2954, 2926, 2852, 1680, 1614, 1520, 1367, 1261, 1128, 1005 cm^{-1}.
^1H NMR (500 MHz, $CDCl_3$): δ = 7.57 (br s, 1 H, NH), 7.41 (d, 1 H, *J* = 2.5 Hz, H-3), 7.36 (dd, 1 H, *J* = 15.0, 11.5 Hz, H-11), 7.24 (dd, 1 H, *J* = 15.0, 9.5 Hz, H-3′), 6.65–6.55 (m, 2 H, H-8 and H-9), 6.45 (dd, 1 H, *J* = 14.5, 11.5 Hz, H-10), 6.20–6.09 (m, 2 H, H-4′ and H-5′), 5.94 (d, 1 H, *J* = 15.0 Hz, H-2′), 5.87 (d, 1 H, *J* = 14.5 Hz, H-7), 5.85 (d, 1 H, *J* = 15.0 Hz, H- 12), 3.72 (dd, 1 H, *J* = 4.0, 2.5 Hz, H-5), 3.66 (d, 1 H, *J* = 4.0 Hz, H-6), 2.97 (br s, 1 H, OH), 2.17–2.08 (m, 1 H, H-6′), 1.90–1.05 (m, 10 H, cy).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 188.5, 170.6, 165.2, 150.9, 145.8, 144.2, 139.4, 136.1, 131.9, 131.5, 128.0, 126.3, 125.4, 121.1, 120.8, 71.2, 57.4, 52.9, 41.1, 32.2, 26.0, 25.8.
MS (FAB^+): *m/z* (%) = 426 (MH^+, 14), 93 (100).
HRMS (FAB^+): Calc for $C_{24}H_{28}NO_6$: 426.1917. Found: 426.1920.
The NMR data were consistent with published[12a] values.

‡ Present address: Medicinal Chemistry Department, Astra Charnwood, Bakewell Road, Loughborough LE11 5RH Leics, UK.
§ Present address: SmithKline Beecham Pharmaceuticals, Leigh, Tonbridge, Kent TN11 9AN, UK.

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