# Synthetic ansamycins prepared by a ring-expanding Claisen rearrangement. Synthesis and biological evaluation of ring and conformational analogues of the Hsp90 molecular chaperone inhibitor geldanamycin†

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A series of ansa-quinones has been prepared by chemical synthesis, and evaluated by biological techniques. Thus, 19-membered ansa-lactams, simplified analogues of the naturally occurring Hsp90 molecular chaperone inhibitor geldanamycin, were obtained by concise routes, the key steps being the combination of a ring-closing metathesis to give a 17-membered ring followed by Claisen rearrangement to effect ring expansion. The methodology was also used to prepare an "unnatural" 18-membered ring analogue. In ATPase enzyme assays, the synthetic ansa-quinones were weak inhibitors of Hsp90.

## Introduction

The ATP-dependent molecular chaperone heat shock protein 90 (Hsp90) is one of the most abundant proteins in eukaryotic cells. It plays a major role in regulating the stabilization, activation and degradation of a range of so-called client proteins,[1–3] including several key proteins involved in cell cycle regulation and signal transduction. These client proteins also include a number of known over-expressed or mutant oncogenic proteins such as C-RAF, B-RAF, ERBB2, AKT, telomerase and p53, many of which are associated with the six hallmarks of cancer.[4,5] Consequently, inhibition of Hsp90 will disrupt multiple cancer causing pathways simultaneously. Not surprisingly, therefore, Hsp90 has become an attractive target for novel cancer therapeutic agents, and has been the subject of several recent reviews.[4,6–14]

Most inhibitors of Hsp90 block the ATP-binding site, a conserved pocket in the *N*-terminal domain,[15–18] and it is disruption of ATP binding (and subsequent hydrolysis) that leads to proteasomal degradation of client proteins.[19] Known inhibitors include the natural products geldanamycin **1a** and radicicol **2**, both of which have been co-crystallized with the yeast protein and their bound structures determined by X-ray crystallography,[17] and in solution by NMR spectroscopy.[20] In view of the intense interest in Hsp90, several synthetic inhibitors have been developed. Many of these are ATP mimics and are based on the purine framework as exemplified by PU3 **3a** and PU24FC1 **3b**, and the related aryl- and heteroaryl-sulfanyl compound PU-H58 **4**.[21–29] However, other families of inhibitors are now emerging, in particular the 3-(2,4-dihydroxyphenyl)pyrazoles,[30] as in CCT018159 **5a**,[31,32] G3130 **5b**,[33] and VER-49009 **5c**,[34,35] whilst another group contains the 1-aryl-2-naphthol moiety as in compound **6**[36] (Fig. 1). Of the above Hsp90 inhibitors, radicicol **2** (also known as monorden), is the most potent *in vitro*,[37] although it has little or no activity *in vivo*.[38,39]

Geldanamycin **1a**, a member of the ansamycin class of antibiotics, was isolated from *Streptomyces hygroscopicus* var. *geldanus* in 1970,[40] and its structure determined by Rinehart and co-workers.[41] The ansamycins as a class display a range of biological activities, and a number of analogues of geldanamycin derived from the natural product have been synthesized and evaluated.[42,43] Although initial studies focused on geldanamycin's ability to lower cellular levels of the oncogene *erbB-2*, it was the report in 1994 that geldanamycin was a potent inhibitor of Hsp90 that sparked interest in this natural product,[44] and following this discovery, a number of geldanamycin analogues have been evaluated as Hsp90 inhibitors. For the most part, these are semi-synthetic derivatives derived by functionalization of the natural product, primarily at the 17-position,[45–48] and include linked geldanamycin dimers designed to modulate Hsp90 dimerization.[49] Variations on the 7-carbamate are also known.[50] Conjugates with steroids,[51,52] a kinase inhibitor,[53] and the monoclonal antibody Herceptin™[54] have also been investigated, as have a small range of "unnatural" analogues derived by genetic engineering of the *Streptomyces hygroscopicus* strain.[55,56] Finally, given the *in vitro* potency of radicicol as an inhibitor of Hsp90, a number of compounds incorporating features of both geldanamycin and radicicol have been prepared and evaluated. These chimeric structures are known as radamide, radester and radanamycin.[57–60]

As a result of these efforts, a derivative of geldanamycin, 17-allylamino-17-desmethoxygeldanamycin (17-AAG) **1b**, is the first-in-class inhibitor of Hsp90 to enter phase II clinical trial.[61–64] The fact that the (more soluble) derivative 17-DMAG **1c** is also undergoing evaluation,[65] coupled with recent studies on the time-dependent binding of geldanamycin to Hsp90,[66] and the suggestion that it may be the hydroquinone form of 17-AAG that is more active,[67–70] highlights the intense interest in this class of compound.[71]

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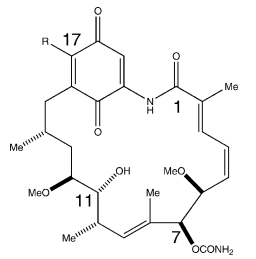
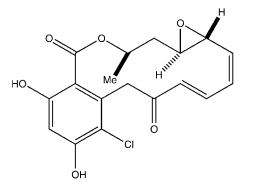
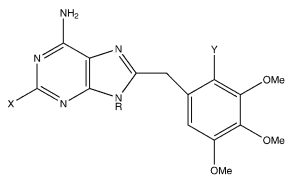


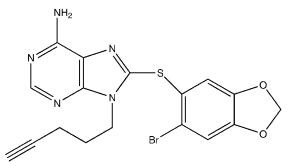
**1a** geldanamycin; R = OMe
**1b** 17AAG; R = $NHCH_2CH{=}CH_2$
**1c** 17DMAG; R = $NHCH_2CH_2NMe_2$



**2** radicicol



**3a** PU3; X = Y= H, R = $C_4H_9$
**3b** PU24FCl; X = F, Y = Cl, R = $(CH_2)_3C{\equiv}CH$



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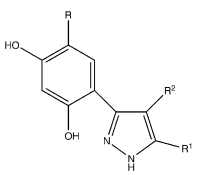
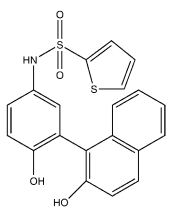


**5a** CCT018159; R = Et, $R^1$ = Me, $R^2$ = 2,3-dihydrobenzodioxin-6-yl
**5b** G3130; R = Et, $R^1$ = H, $R^2$ = imidazol-4-yl
**5c** VER-49009; R = Cl, $R^1$ = CONHEt, $R^2$ = 4-MeO-$C_6H_4$



**6**

**Fig. 1** Structures of Hsp90 inhibitors.

Whilst the success to date with 17-AAG validates the potential of geldanamycin analogues as potential chemotherapeutic agents, the range of semi-synthetic analogues that can be readily accessed by chemical manipulation of natural material is severely limited. Likewise, although the total synthesis of geldanamycin has been achieved by Andrus *et al.*,[72,73] the molecule is too complex to contemplate a drug development programme based around the total synthesis of novel derivatives. However, the *de novo* synthesis of simpler derivatives is a realistic proposition. Therefore in continuation of our interest in analogues of natural products as Hsp90 inhibitors,[74] we undertook the design and chemical synthesis of a series of ansa-quinones as simple analogues of geldanamycin, and their biological evaluation. The results of this integrated chemistry–biology approach are described herein.

## Results and discussion

The starting point for our work was a consideration of the detailed structure of geldanamycin **1a** bound in the ATP-pocket in the *N*-terminal domain of yeast Hsp90,[17] and of 17-DMAG **1c** in the corresponding binding site in the human protein.[75] The important features of the binding to the yeast protein are shown in Fig. 2(c), which shows the key role played by the C-7 carbamate that is involved in hydrogen-bonding interactions with Gly83, Thr171, Asp79 and Leu34. The C-11 hydroxyl group forms a hydrogen bond to Lys44 whilst the quinone oxygen interacts with Lys98. The macrocyclic amide bond is involved in hydrogen-bonding interactions with Gly123 and Phe124, but, critically, appears to have to undergo *trans* to *cis* isomerization to allow the antibiotic to adopt the tightly folded conformation within the protein.[76]

It is clear from the above analysis that any simplified analogues of geldanamycin should retain the key structural features adumbrated above, *i.e.* the ansa-quinone macrolactam motif with appropriately positioned hydroxyl and carbamate groups on the periphery. These criteria could be met by a much simpler compound, which lacks the five methyl and methoxy groups which adorn the natural ansa-chain, and is therefore much more amenable to synthesis. Such a compound **7b** (Fig. 2(b)), which is simplified further by removal of the C-11 hydroxyl and C-14 methyl groups, was shown by molecular modelling to be able to adopt the required folded conformation whilst retaining all the remaining hydrogen-bonds (Fig. 2(d)). The conformation of analogue **7b** is slightly rigidified by the presence of the *trans*-alkene bond at C13–C14. Although the simplified analogue **7b** retains the 19-membered ring ansa-quinone structure of the natural product with the key carbamate functionality at C-7, the corresponding compounds with the carbamate at C-8, and with an "unnatural" 18-membered ring should also bind to the enzyme. The synthesis of a range of such simplified geldanamycin derivatives is described herein.[77,78]

The ansamycin antibiotics are usually synthesized by a route that involves formation of the amide bond to access the macrocycle, and until recently alternative approaches were rarely considered. However, the advent of reliable catalysts for ring closing metathesis (RCM) has rendered this reaction highly suitable for macrocycle construction,[79] and the method has recently been used by others for the synthesis of geldanamycin analogues.[80–83] However, the novel feature of our route is the combination of the RCM reaction (to form a 17-membered macrocycle) with the Claisen rearrangement (which results in ring expansion to the 19-membered ansa-ring). Preliminary studies have demonstrated the feasibility of such a new use of the Claisen rearrangement.[77]

In order to establish the required methodology, the synthesis of two very simple ansa-quinones **16a** and **16b** was carried

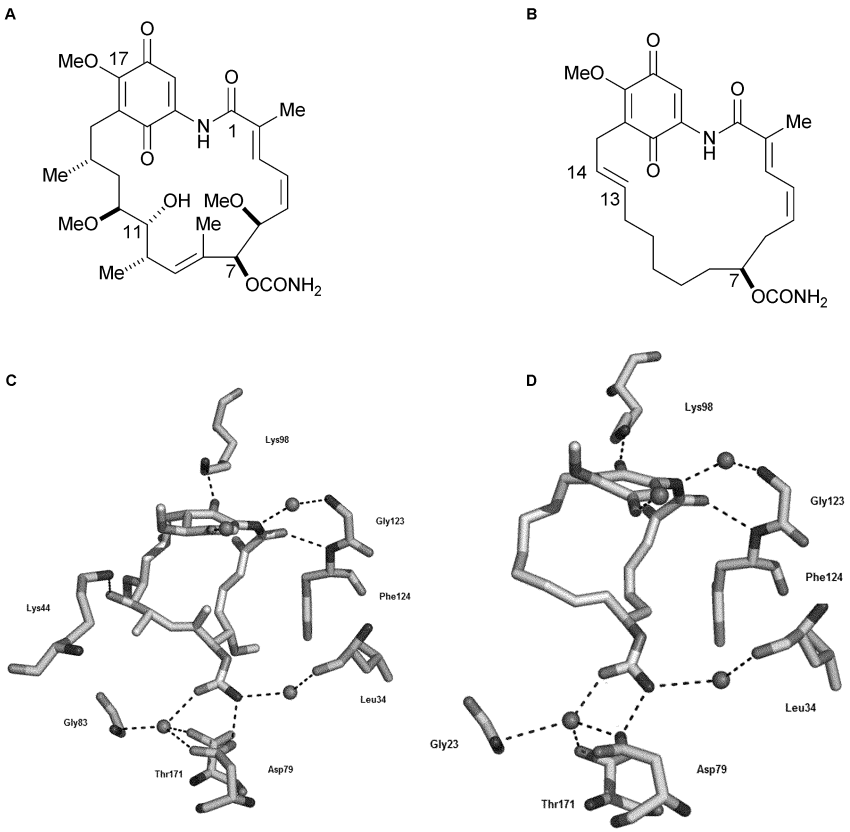


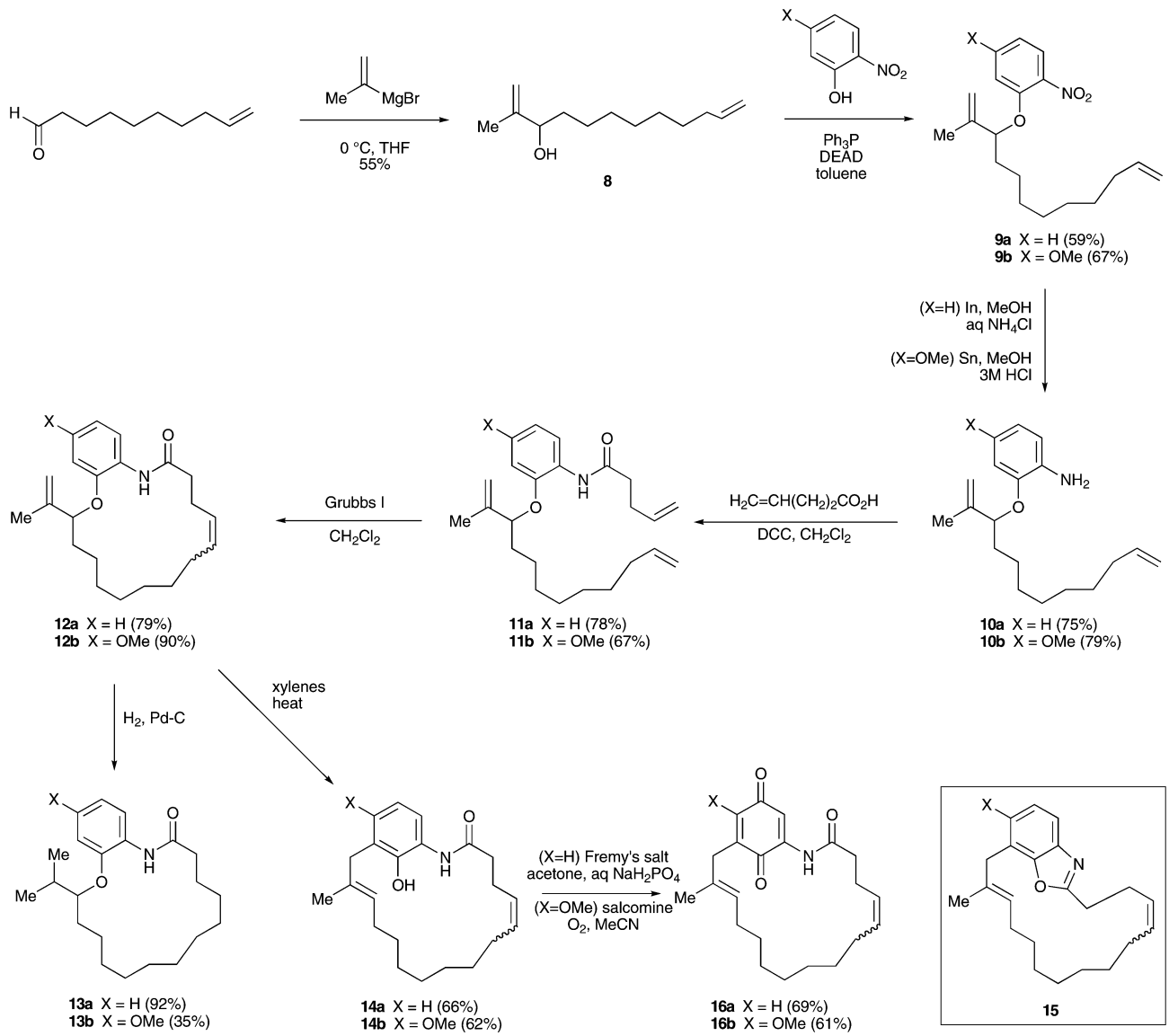

**Fig. 2** (a) Structure of geldanamycin **1a**; (b) structure of the simplified analogue **7b**; (c) geldanamycin bound in ATP-site of yeast Hsp90 (from X-ray crystal structure PDB ID 1A4H[15]†); (d) molecular modelling derived structure of analogue **7b** bound in ATP-site of yeast Hsp90.

out initially (Scheme 1). Thus 2-methyldodeca-1,11-dien-3-ol **8**, prepared by addition of isopropenylmagnesium bromide to 9-decenal, underwent Mitsunobu reaction with 2-nitrophenol to give **9a**. Reduction of the nitro group with indium metal,[84] followed by DCC-mediated coupling to 4-pentenoic acid gave the RCM–Claisen substrate **11a**. Treatment of triene **11a** with Grubbs' catalyst [benzylidene bis(tricyclohexylphosphine) dichlororuthenium] gave the 17-membered macrocycle **12a** in good yield, with reaction occurring at the less hindered terminal $CH{=}CH_2$ bond. Unfortunately, however, the macrolactam **12a** was formed as a 1 : 1 mixture of *cis*-and *trans*-isomers at the 4,5-double bond. Hydrogenation gave a single characterizable tetrahydro derivative **13a** in excellent yield.

The Claisen rearrangement of allyl ether **12a** was effected by heating in boiling xylenes (bp 138–141 °C) and gave the ring expanded 19-membered ansa-lactam **14a** in 66% yield as a mixture of isomers. As far as we are aware this transformation of an *n*-membered 1,2-bridged macrocycle into an ansa-bridged (*n* + 2)-membered ring represents a new use for the Claisen rearrangement. Since the Claisen rearrangement itself can result in a mixture of isomers at the newly formed 13,14-double bond, the reaction was carried out in the presence of sodium carbonate, conditions which are reported to favour the formation of the (*E*)-alkene.[85] However, due to the complexity of the $^1$H NMR spectrum of **14a**, we were unable to determine precisely the number of isomers present, although it appeared to be a mixture of two major components (2.5 : 1). If the Claisen rearrangement was conducted at a higher temperature in 1,2-dichlorobenzene (bp 179–180 °C), then an additional complication ensued, namely the formation of benzoxazoles **15** by cyclodehydration of the phenolic amide. Finally oxidation of the phenol **14a** using Fremy's salt (potassium nitrosodisulfonate) gave the ansa-quinone **16a** (as a mixture of alkene isomers). The synthetic sequence was repeated starting from 5-methoxy-2-nitrophenol to give the 17-methoxy-ansa-quinone **16b** as shown in Scheme 1.

Unsurprisingly, the ansa-quinones **16** lacking the critical carbamate functionality at C-7 showed no activity as inhibitors of Hsp90 (data given later), and therefore our RCM–Claisen methodology was adapted for the synthesis of quinones bearing a carbamate at appropriate positions on the ansa-chain (Schemes 2 and 3). The synthesis was initially carried out in the racemic series, and started from the known 7,7-dimethoxyheptanal **17**, obtained by ozonolysis of cycloheptene under Schreiber's conditions.[86,87] Addition of allylmagnesium chloride was followed by protection of the resulting alcohol as its *tert*-butyldiphenylsilyl ether **19a**. Deprotection of the dimethyl acetal gave the corresponding aldehyde that was immediately reacted with isopropenylmagnesium bromide to give the methyl substituted 12-carbon chain **20a** as a mixture of diastereomers. No attempt was made to separate the diastereomers since the second stereocentre is eventually lost in the Claisen rearrangement. Mitsunobu reaction of alcohol **20a** with 5-methoxy-2-nitrophenol gave the nitrophenyl ether **21a**, reduction of which with indium–acetic acid in THF gave the aniline **22a**.

Initially the aniline **22a** was coupled to (*E*)-2-methyl-2,4-pentadienoic acid, prepared by Wittig reaction of acrolein with (carboethoxyethylidene)triphenylphosphorane followed by ester




**Scheme 1**

hydrolysis,[88,89] using DCC, but this proved unsatisfactory and therefore the corresponding acid chloride was used to obtain the desired amide **23a**. Ring-closing metathesis of **23a** resulted in formation of the desired 17-membered lactam **24a** in good yield, but as a mixture of isomers. The aromatic Claisen rearrangement of allyl aryl ethers is ideally suited to microwave conditions, and reaction times are shortened dramatically.[90–100] Therefore, heating lactam **24a** in xylene under microwave irradiation effected the Claisen rearrangement to give the ring-expanded ansa-lactam **25a**. Deprotection of the silyl ether with fluoride gave the 7-hydroxy ansa-lactam **26a** which after crystallization was obtained as a single (*E*,*Z*,*E*)-isomer at the 2,3-, 4,5- and 13,14-double bonds respectively, the structure being confirmed by X-ray crystallography (Fig. 3).‡ Two points are noteworthy: firstly the deprotection of the silyl ether was surprisingly difficult and probably reflects the hindered nature of the 7-position as a consequence of the folded

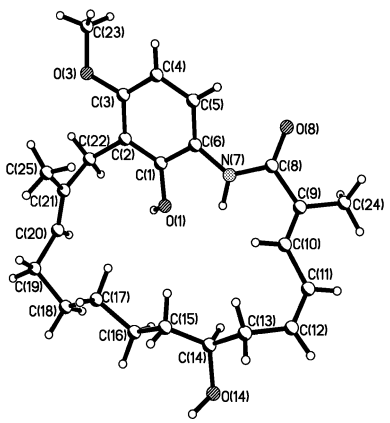
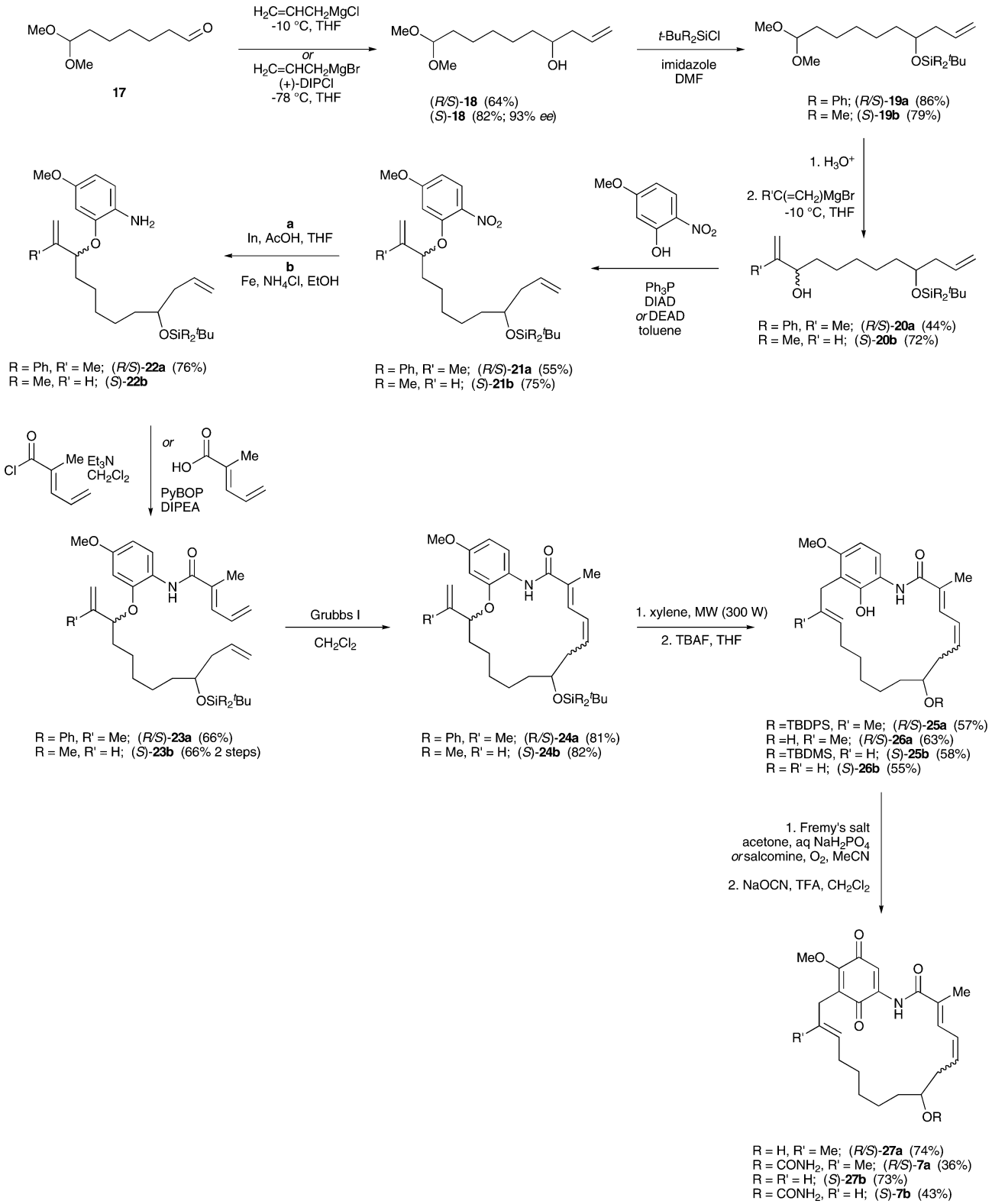



**Fig. 3** X-Ray crystal structure of ansa-lactam **26a**.

‡ CCDC reference numbers 624769. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b615378j

conformation of the ansa-chain. Secondly, notwithstanding the fact that the ansa-lactam **26a** could be obtained as single isomer,

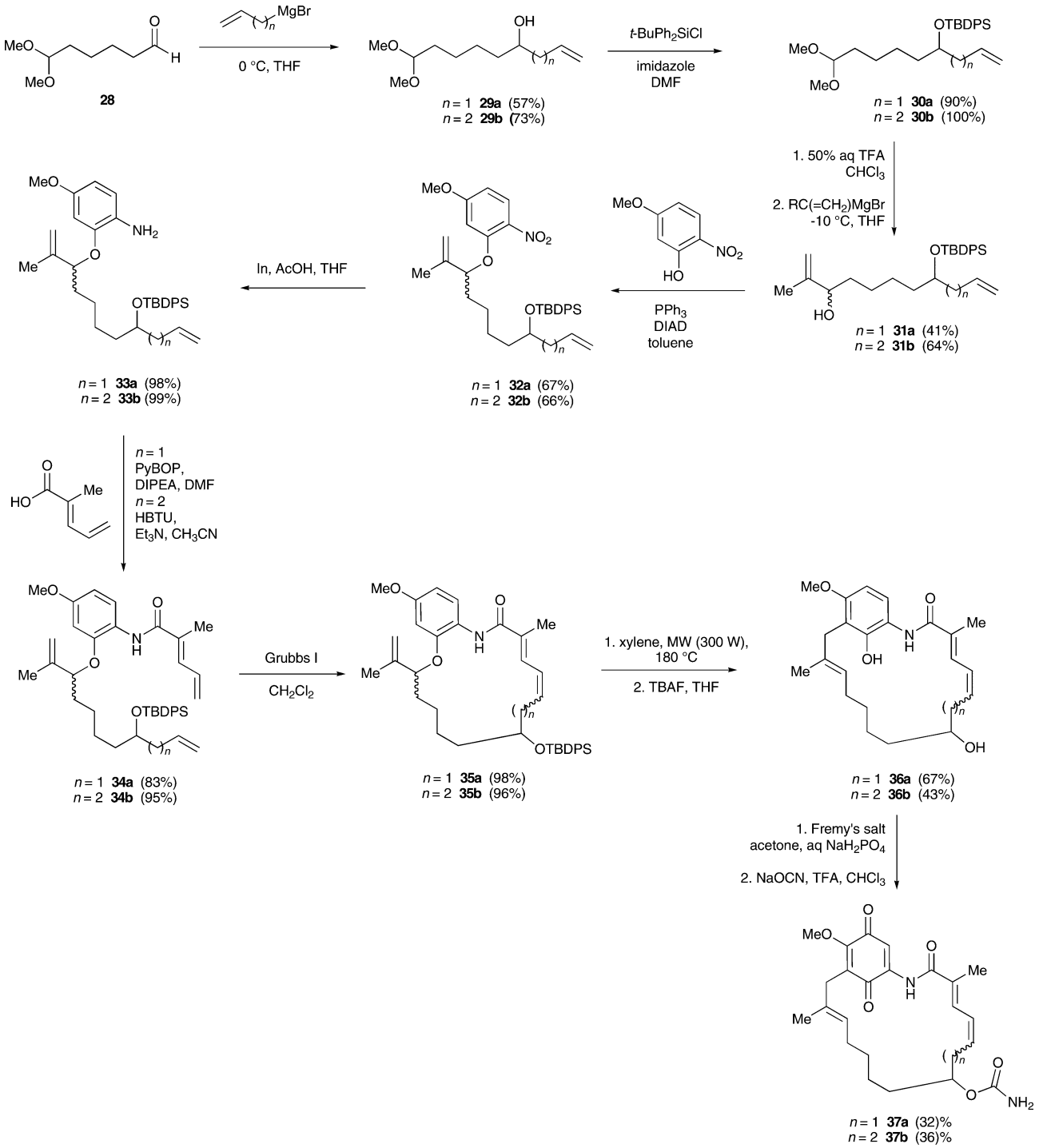



**Scheme 2**

the facile (*E*/*Z*)-isomerization of, presumably, the 13,14-double bond was a constant problem.

Indeed following oxidation of the phenol **26a** with Fremy's salt the ansa-quinone **27a** was obtained as a *ca.* 6 : 1 mixture of isomers. Finally, the C-7 carbamate was introduced by reaction of the alcohol **27a** with sodium cyanate and trifluoroacetic acid (TFA) in dichloromethane[101] to give the ansa-quinone carbamate **7a** (Scheme 2).

With a route to the C-7 substituted ansa-quinone successfully established, the sequence was repeated to obtain chiral




**Scheme 3**

non-racemic material. Thus 7,7-dimethoxyheptanal **17** was subjected to Brown's chiral allylation methodology[102,103] to give the (*S*)-homoallylic alcohol (*S*)-**18** in good yield. Analysis of the corresponding benzoate ester by HPLC on a chiral stationary phase established the enantiomeric excess of (*S*)-**18** as 93%. Protection of the alcohol with the more labile *tert*-butyldimethylsilyl group, deprotection of the acetal, and addition of vinylmagnesium bromide gave the 12-carbon side chain **20b** as a mixture of diastereomers. The methyl group at the eventual 14-position was omitted in this series of compounds in an attempt to prevent the facile isomerization of the 13,14-double bond. Mitsunobu reaction, nitro reduction and coupling to 2-methyl-2,4-pentadienoic acid proceeded as before, albeit with some minor modifications, to give the RCM-substrate **23b**. Cyclization of **23b** mediated by Grubbs' catalyst gave the 17-membered lactam **24b** as a mixture of diastereomers, Claisen rearrangement of which, again under microwave irradiation, gave the ansa-lactam **25b** as a single isomer. Deprotection, oxidation and installation of the carbamate then

gave the desired ansa-quinone carbamate **7b** (Scheme 2). The assignment of *E*,*Z*-geometry to the 2,3- and 4,5-alkenes was confirmed by NOE experiments.

Although the ansa-quinones **7** are simplified analogues of geldanamycin they still share the 19-membered ring structure of the natural product with a carbamate positioned at C-7 on the ansa-chain. However, our synthetic route is sufficiently flexible to allow the preparation of "unnatural" analogues. Therefore the ansa-quinones **37a** containing an 18-membered ring, and **37b** containing a 19-membered ring but with the carbamate at C-8 on the ansa-chain were also prepared starting from 6,6-dimethoxyhexanal **28**[104] as shown in Scheme 3. The chemistry proceeded as before, although again problems of isomerization of the alkene resulting from Claisen rearrangement were encountered.

The novel compounds were evaluated in the malachite green assay for Hsp90 ATPase activity,[105] and for their ability to inhibit the growth of HCT116 human colon cancer cells using the colorimetric sulforhodamine B (SRB) assay;[106] the results are shown in Table 1. It is immediately apparent that these "stripped down" analogues of geldanamycin exhibit only weak activity as inhibitors of Hsp90, notwithstanding the fact that molecular modelling suggested that such compounds should bind to the enzyme's ATP-site. Presumably the structures have been simplified too much, with the loss of the C-11 hydroxyl hydrogen bond being most likely responsible for their poor potency as Hsp90 inhibitors. Interestingly, inhibition of cell growth was seen at 25–40 μM, presumably due to alternative mechanisms.

In summary, a versatile route to simplified analogues of the naturally occurring ansa-quinone geldanamycin has been developed. The route involves a ring-closing metathesis to give a 17-membered ring followed by Claisen rearrangement to effect ring expansion. Biological evaluation of these novel analogues showed that they were poor inhibitors of Hsp90. Studies involving the synthesis of further geldanamycin analogues, in particular those containing a C-11 hydroxyl group, are in progress.

## Experimental section

### Chemistry

**General.** Commercially available reagents and solvents were used throughout without further purification. Indium powder was ~100 mesh purchased from Aldrich. 'Light petroleum' refers to the fraction that boils between 40 °C and 60 °C. Microwave reactions were carried out in a CEM Discover™ 300 W microwave. Analytical thin layer chromatography was carried out using aluminium backed plates coated with Merck Kieselgel 60 GF254. Developed plates were visualized under ultra-violet light (254 nm) and/or potassium permanganate, ethanolic anisaldehyde, or ninhydrin dip. Flash chromatography was carried out using Merck Kieselgel 60 H silica. Fully characterized compounds were chromatographically homogeneous.

IR spectra were recorded on a Nicolet Magna 550 spectrometer with internal calibration. Spectra were recorded as potassium bromide discs, as solutions in $CHCl_3$, or as films between sodium chloride plates. NMR spectra were recorded on a Bruker AM 300 or Bruker Advance DRX 400 spectrometer at the frequencies stated. Chemical shifts are recorded in ppm and *J* values in Hz. Chemical shift values are referenced against residual chloroform at 7.27 ppm ($\delta_H$) and 77.1 ppm ($\delta_C$), and are accurate to ±0.01 ppm and ±0.10 ppm respectively. In reporting the NMR data for mixtures of diastereoisomers, signals arising from the major and minor isomers are reported separately if possible; in the $^1$H NMR, the integration of signals is consistent within each isomer, *e.g.* a methyl group is reported as 3 H for *both isomers* even though the peaks are unequal in area when the ratio of isomers is >1 : 1. In the $^{13}$C NMR spectra, signals corresponding to CH, $CH_2$, or $CH_3$ groups are assigned from DEPT. Mass spectra (CI and EI) were obtained from EPSRC national mass spectrometry centre, Swansea or on an Agilent 6890 series GC and Micromass GCT.

**Lactam 24a.** *N*-[2-(9-*tert*-Butyldiphenylsiloxy-2-methyl-dodeca-1,11-dien-3-yloxy)-2-methoxyphenyl]-2-methylpenta-2,4-dienamide **23a** (0.35 g, 0.53 mmol) in anhydrous dichloromethane (100 mL) was slowly added to a solution of Grubbs' catalyst (0.13 g, 0.16 mmol, 30 mol%) in anhydrous dichloromethane (952 mL) under reflux. The mixture was heated under reflux for 24 h then concentrated *in vacuo.* The crude product was purified twice by flash chromatography on silica, eluting with ethyl acetate and light petroleum (1 : 9) to give the *title compound* as a colourless sticky solid (0.27 g, 81%) as a mixture of three isomers (Found: $MH^+$, 638.3663. $C_{40}H_{51}NO_4Si$ + H requires 638.3665); $\nu_{max}$ (film)/cm$^{-1}$ 3426, 3063, 2935, 2853, 1665, 1593, 1516, 1484, 1048; $\delta_H$ (400 MHz; $CDCl_3$) *mixture of isomers* 8.34–8.27 (1 H, m, ArH), 8.02 (1 H, s, NH), 8.00 (1 H, s, NH), 7.73–7.71 (4 H, m, ArH), 7.47–7.38 (6 H, m, ArH), 6.90 (1 H, d, *J* 11.1, CMe=C*H*CH=CH), 6.87 (1 H, d, *J*, 10.8, CMe=C*H*CH=CH), 6.52–6.39 (2 H, m, ArH), 6.32 (1 H, t, *J* 11.1, CMe=CHC*H*=CH), 6.25–6.17 (1 H, m, CMe=CHCH=C*H*), 6.07–5.97 (1 H, m, CMe=CHCH=C*H*), 5.89–5.84 (1 H, m, CMe=CHCH=C*H*), 5.69–5.62 (1 H, m, CMe=CHCH=C*H*), 4.98 (2 H, s, MeC=C$H_2$), 4.97 (2 H, s, MeC=C$H_2$), 4.92 (2 H, s, MeC=C$H_2$), 4.90 (2 H, s, MeC=C$H_2$), 4.55–4.45 (1 H, m, ArOC*H*), 3.97–3.91 (1 H, m, C*H*OTBDPS), 3.77 (3 H, s, OMe), 3.76 (3 H, s, OMe), 2.69–2.22 (2 H, m, $CH_2$), 2.09 (3 H, s, Me), 2.07 (3 H, s, Me), 2.02 (3 H, s, Me), 2.01 (3 H, s, Me), 1.74 (3 H, s, Me), 1.68–1.42 (8 H, m, 4 × $CH_2$), 1.11 (9 H, s, *t*-Bu), 1.10 (9 H, s, *t*-Bu), 1.09 (9 H, s, *t*-Bu); $\delta_C$ (100 MHz; $CDCl_3$) *mixture of isomers* 168.6 (C), 168.23 (C), 168.2 (C), 156.0 (C), 155.9 (C), 155.63 (C), 155.6 (C), 148.1 (C), 148.0 (C), 147.4 (C), 143.9 (C), 143.6 (C), 143.1 (C), 142.3 (C), 138.1 (CH), 137.8 (CH), 135.94 (CH), 135.9 (CH), 135.87 (CH), 135.2 (C), 134.9 (C), 134.4 (C), 134.32 (C), 134.3 (C), 134.25 (C), 134.2 (C), 133.2 (CH), 132.9 (C), 132.85 (C), 132.7 (CH), 132.2 (CH), 132.1 (CH), 129.7 (CH), 129.68 (CH), 129.6 (CH), 127.64 (CH), 127.61 (CH), 127.6 (CH), 126.9 (CH), 126.8 (CH), 125.7 (CH), 125.5 (CH), 125.3 (CH), 125.2 (CH), 122.4 (C), 122.3 (C), 121.7 (C), 121.6 (C), 120.4 (CH), 120.2 (CH), 118.7 (CH), 118.6 (CH), 112.6 ($CH_2$), 112.5 ($CH_2$), 112.2 ($CH_2$), 112.1 ($CH_2$), 103.9 (CH), 103.8 (CH), 103.7 (CH), 103.68 (CH), 101.2 (CH), 101.0 (CH), 100.8 (CH), 100.77 (CH), 82.3 (CH), 82.2 (CH), 81.9 (CH), 81.4 (CH), 72.8 (CH), 72.6 (CH), 72.1 (CH), 71.8 (CH), 55.4 (Me), 55.42 (Me), 41.9 ($CH_2$), 41.7 ($CH_2$), 37.6 ($CH_2$), 36.9 ($CH_2$), 35.7 ($CH_2$), 35.2 ($CH_2$), 34.9 ($CH_2$), 34.4 ($CH_2$), 34.3 ($CH_2$), 34.26 ($CH_2$), 33.5 ($CH_2$), 29.4 ($CH_2$), 29.1 ($CH_2$), 28.5 ($CH_2$), 28.1 ($CH_2$), 27.2 ($CH_2$), 27.1 (CH), 26.9 (CH), 26.0 ($CH_2$), 25.5 ($CH_2$), 25.4 ($CH_2$), 25.1 ($CH_2$), 24.9 ($CH_2$), 24.7 ($CH_2$), 24.4 ($CH_2$), 24.1 ($CH_2$), 22.7 (Me), 19.4 (C), 19.39 (C), 19.3 (C), 19.2 (C), 18.9 (Me), 18.5 (Me), 18.3 (Me), 18.2

**Table 1** Inhibition of yeast Hsp90 by novel ansa-quinones

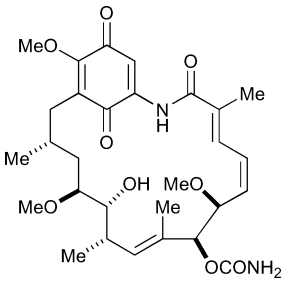
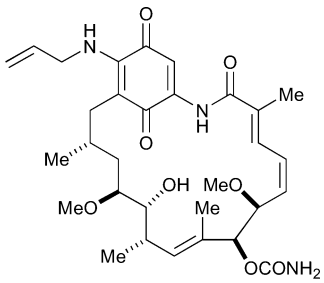
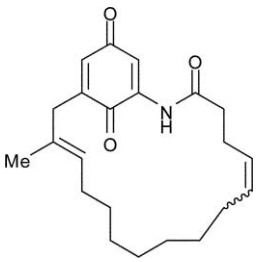
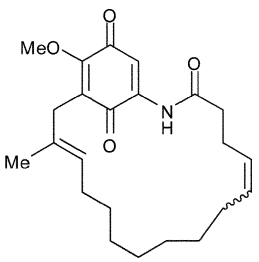
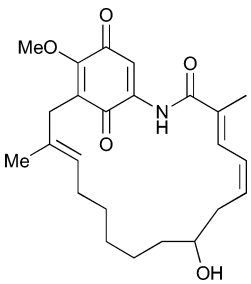
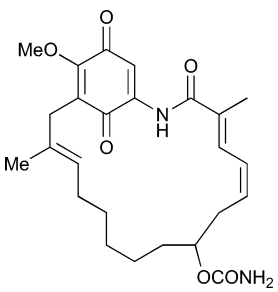
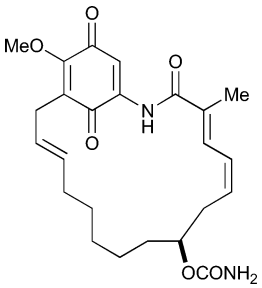
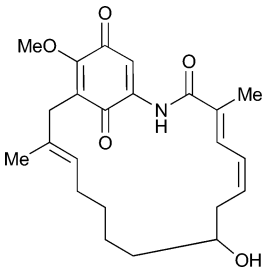
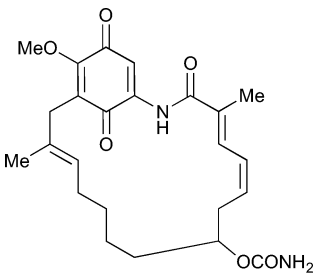
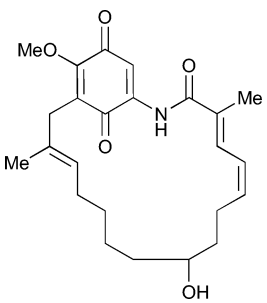
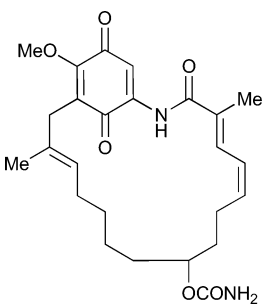
| Compound | Structure | ATPase assay $IC_{50}/\mu M$ | SRB assay $IC_{50}/\mu M$[a] |
|---|---|---|---|
| Geldanamycin **1a** |  | >4.8 | >0.067 |
| 17-AAG **1b** |  | >8.7 | >0.099 |
| **16a** |  | >100 | 26 |
| **16b** |  | >100 | 28 |
| **27a** |  | >100 | 32 |
| **7a** |  | >50 | 32 |

**Table 1** (cont.)

| Compound | Structure | ATPase assay $IC_{50}/\mu M$ | SRB assay $IC_{50}/\mu M$[a] |
|---|---|---|---|
| **7b** |  | >100 | 40 |
| **36a** |  | >100 | nd |
| **37a** |  | >100 | nd |
| **36b** |  | >100 | nd |
| **37b** |  | >100 | nd |

[a] nd = not determined.

(Me), 13.5 (Me), 13.49 (Me), 13.4 (Me), 13.3 (Me), 11.5 (Me); *m/z* (CI) 638 ($MH^+$, 93%), 620 (20), 580 (25), 560 (47), 422 (28), 382 (100), 297 (24), 239 (37), 199 (57), 179 (53).

**Claisen rearrangement of lactam 24a to ansa-lactam 25a.** Lactam **24a** (0.395 g, 0.620 mmol) was dissolved in xylene (4 mL) in a sealed tube. The mixture was heated at 150 °C for 40 min in a microwave reactor (300 W). The crude product was purified by flash chromatography on silica, eluting with ethyl acetate and light petroleum (3 : 7) to give the *title compound* as a colourless sticky oil (0.225 g, 57%) (Found: $MH^+$, 638.3675. $C_{40}H_{51}NO_4Si$ + H requires 638.3665); $\nu_{max}$ (film)/$cm^{-1}$ 3421, 2935, 2863, 1650, 1583, 1521, 1491; $\delta_H$ (300 MHz; $CDCl_3$) 8.20 (1 H, d, *J* 8.9, ArH), 8.08 (1 H, s, NH), 7.73–7.69 (4 H, m, ArH), 7.44–7.37 (6 H, m, ArH), 6.83 (1 H, d, *J* 11.1, CMe=C*H*CH=CH), 6.52–6.49 (2 H, m, ArH, OH), 6.25 (1 H, t, *J* 11.0, CMe=CHC*H*=CH), 5.73 (1 H, q, *J* 8.3, CMe=CHCH=C*H*), 5.59 (1 H, t, *J* 6.2, $ArCH_2CMe=CHCH_2$), 3.84–3.77 (1 H, m, C*H*OTBDPS), 3.81 (3 H, s, OMe), 3.52 (2 H, q, *J* 15.4, $ArCH_2$), 2.52–2.25 (2 H, m, $CH_2$), 2.11–2.00 (5 H, m, Me, $CH_2$), 1.59 (3 H, s, Me), 1.55–1.44 (2 H, m, $CH_2$), 1.34–1.26 (4 H, m, 2 × $CH_2$), 1.08 (11 H, br, *t*-Bu, $CH_2$); OH not observed; $\delta_C$ (75 MHz; $CDCl_3$) 168.5 (C), 154.0 (C), 145.9 (C), 136.8 (C), 134.8 (C), 134.6 (C), 134.5 (CH), 129.9 (CH), 128.7 (CH), 127.9 (CH), 127.87 (CH), 126.4 (CH), 125.6 (CH), 121.7 (C), 117.7 (CH), 112.8 (C), 103.1 (CH), 73.8 (CH), 56.4 (Me), 38.5 ($CH_2$), 36.6 ($CH_2$), 34.6 ($CH_2$), 30.1 ($CH_2$), 29.0 ($CH_2$), 27.7 ($CH_2$), 27.5 (Me), 26.3 ($CH_2$), 19.9 (C), 16.0 (Me), 13.3 (Me); *m/z* (CI) 638 ($MH^+$, 88%), 620 (37), 580 (32), 560 (53), 382 (100), 199 (32), 179 (23).

**Ansa-lactam 26a.** Ansa-lactam **25a** (0.126 g, 0.200 mmol) was dissolved in anhydrous THF (3 mL) and tetra-*n*-butylammonium fluoride (1 M in THF; 0.50 mL, 0.50 mmol) was added. The mixture was stirred under an atmosphere of nitrogen at room temperature for 24 h, then quenched by the addition of saturated ammonium chloride solution (3 mL). The mixture was then extracted with ethyl acetate (3 × 10 mL), th extracts combined, washed with water (3 × 10 mL), brine (10 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo.* The crude product was purified by flash chromatography on silica, eluting with ethyl acetate and light petroleum (1 : 4) to give the *title compound* as a colourless solid (0.050 g, 63%); mp 185–187 °C (Found: $MH^+$, 400.2485. $C_{24}H_{33}NO_4$ + H requires 400.2488); $\nu_{max}$ (KBr)/$cm^{-1}$ 3406, 2929, 2856, 1652, 1645, 1616, 1558, 1539, 1520, 1507; $\delta_H$ (400 MHz; $CDCl_3$) 8.22 (1 H, d, *J* 9.0, ArH), 8.17 (1 H, br, NH), 6.99 (1 H, d, *J* 11.4, CMe=C*H*CH=CH), 6.57 (1 H, s, ArO*H*), 6.50 (1 H, d, *J* 9.0, ArH), 6.48 (1 H, t, *J* 11.6, CMe=CHC*H*=CH), 6.44 (1 H, br, OH), 5.95 (1 H, q, *J* 8.3, CMe=CHCH=C*H*), 5.65 (1 H, t, *J* 7.1, $ArCH_2CMe=CH$), 3.81 (3 H, s, OMe), 3.53 (2 H, q, *J* 15.4, $ArCH_2$), 2.53–2.52 (1 H, m, C*H*OH), 2.15–2.14 (2 H, m, $CH_2$), 2.03 (3 H, s, Me), 1.58 (3 H, s, Me), 1.57–1.26 (10 H, m, 5 × $CH_2$); $\delta_C$ (100 MHz; $CDCl_3$) 167.9 (C), 153.7 (C), 145.6 (C), 136.6 (C), 134.9 (C), 132.8 (CH), 128.6 (CH), 126.8 (CH), 125.8 (CH), 121.2 (C), 117.4 (CH), 112.4 (C), 102.8 (CH), 71.8 (CH), 56.0 (Me), 38.0 ($CH_2$), 36.3 ($CH_2$), 34.4 ($CH_2$), 29.4 ($CH_2$), 29.1 ($CH_2$), 27.6 ($CH_2$), 25.7 ($CH_2$), 15.5 (Me), 12.9 (Me); *m/z* (CI) 400 ($MH^+$, 100%), 382 (18).

*Crystal data for* ***26a****.* $C_{24}H_{33}NO_4$, $M = 399.51$, triclinic, space group $P\bar{1}$, $a = 8.8832(12)$, $b = 10.3813(15)$, $c = 12.0879(17)$ Å, $\alpha = 81.631(2)$, $\beta = 81.670(2)$, $\gamma = 78.225(2)°$, $U = 1072.0(3)$ Å$^3$, $F(000) = 432$, $Z = 2$, $D_c = 1.238$ Mg m$^{-3}$, $\mu = 0.083$ mm$^{-1}$(Mo–K$\alpha$, $\lambda = 0.71073$ Å). The data were collected at $T = 125(2)$ K, 6794 reflections were measured on a Bruker SMART CCD diffractometer equipped with an Oxford Cryostream low-temperature device (ω-scan, 0.3°/frame) yielding 3816 unique data ($R_{merg} = 0.0133$). Conventional $R = 0.0681$ for 3131 reflections with $I \geq 2\sigma$, GOF = 1.032. Final $wR2 = 0.0834$ for all data (278 refined parameters). The hydroxy hydrogen atoms were refined subject to a tight distance constraint. (O–H −0.980(1) Å). The largest peak in the residual map is 1.515 *e* Å$^{-3}$, near C(15).‡

**Oxidation of ansa-lactam 26a to ansa-quinone 27a.** Ansa-lactam **26a** (0.052 g, 0.130 mmol) was dissolved in acetone (30 mL) and Fremy's salt (0.140 g, 0.520 mmol) in sodium dihydrogen phosphate buffer (15 mL) was added. The mixture was stirred for 2 h, then diluted with ethyl acetate (60 mL) and washed with water (2 × 20 mL), brine (20 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo.* The crude product was purified by flash chromatography on silica, eluting with ethyl acetate and light petroleum (1 : 4) to give the *title compound* as an orange oil (0.040 g, 74%) as a mixture of isomers (Found: $MH^+$, 414.2294. $C_{24}H_{31}NO_5$ + H requires 414.2280); $\nu_{max}$ (film)/$cm^{-1}$ 3360, 2925, 2853, 1680, 1650, 1598, 1511; $\delta_H$ (300 MHz; $CDCl_3$) *major isomer* 8.73 (1 H, br, NH), 7.25 (1 H, s, quinone-H), 7.04 (1 H, d, *J* 11.3, CMe=C*H*CH=CH), 6.45 (1 H, t, *J* 11.0, CMe=CHC*H*=CH), 6.06 (1 H, q, *J* 9.4, CMe=CHCH=C*H*), 5.23 (1 H, td, *J* 7.4, 1.1, $ArCH_2CMe=CH$), 4.10 (3 H, s, OMe), 3.85–3.76 (1 H, m, C*H*OH), 3.15 (2 H, s, $ArCH_2$), 2.52–2.44 (1 H, m, C*H*OH), 2.40–2.25 (1 H, m, C*H*OH), 2.03–1.97 (5 H, m, Me, $CH_2$), 1.63–1.55 (7 H, m, Me, 2 × $CH_2$), 1.43–1.20 (4 H, m, 2 × $CH_2$); OH not observed; *minor isomer* 8.89 (1 H, br, NH), 7.26 (1 H, s, quinone-H), 7.04 (1 H, d, *J* 11.3, CMe=C*H*CH=CH), 6.45 (1 H, t, *J* 11.0, CMe=CHC*H*=CH), 6.06 (1 H, q, *J* 9.4, CMe=CHCH=C*H*), 5.09 (1 H, t, *J* 5.5, $ArCH_2CMe=CH$), 4.13 (3 H, s, OMe), 3.85–3.76 (1 H, m, C*H*OH), 3.15 (2 H, s, $ArCH_2$), 2.52–2.44 (1 H, m, C*H*OH), 2.40–2.25 (1 H, m, C*H*OH), 2.03–1.97 (5 H, m, Me, $CH_2$), 1.63–1.55 (7 H, m, Me, 2 × $CH_2$), 1.43–1.20 (4 H, m, 2 × $CH_2$); OH not observed; $\delta_C$ (100 MHz; $CDCl_3$) *major isomer* 184.2 (C), 183.1 (C), 168.7 (C), 156.7 (C), 138.3 (C), 135.8 (CH), 132.4 (C), 130.6 (C), 129.4 (CH), 127.9 (CH), 126.1 (C), 126.0 (CH), 111.4 (CH), 71.9 (CH), 61.7 (Me), 38.2 ($CH_2$), 35.9 ($CH_2$), 33.3 ($CH_2$), 29.5 ($CH_2$), 28.9 ($CH_2$), 27.6 ($CH_2$), 25.6 ($CH_2$), 15.8 (Me), 12.5 (Me); *minor isomer* 184.2 (C), 183.1 (C), 168.7 (C), 156.7 (C), 138.3 (C), 135.9 (CH), 132.4 (C), 130.6 (C), 129.0 (CH), 128.8 (CH), 126.1 (C), 126.0 (CH), 111.3 (CH), 71.89 (CH), 61.7 (Me), 37.5 ($CH_2$), 35.6 ($CH_2$), 33.3 ($CH_2$), 29.4 ($CH_2$), 28.5 ($CH_2$), 27.1 ($CH_2$), 24.6 ($CH_2$), 24.4 (Me), 12.5 (Me); *m/z* (CI) 414 ($MH^+$, 5%), 285 (13), 257 (12), 111 (16), 107 (19), 101 (20), 91 (63), 85 (31), 69 (23), 57 (26).

**Ansa-quinone carbamate 7a.** Ansa-quinone **27a** (0.040 g, 0.097 mmol) was dissolved in dichloromethane (6 mL). Sodium cyanate (0.151 g, 2.33 mmol) and TFA (0.180 mL, 0.266 g, 2.33 mmol) were then added at 0 °C. The mixture was then stirred slowly at room temperature for 17 h, before quenching with sodium hydrogen carbonate solution (5%; 10 mL). The mixture was then extracted with ethyl acetate (3 × 20 mL), the extracts combined and washed with brine (20 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo.* The crude product was purified by flash chromatography on silica, eluting with ethyl acetate and light

petroleum (2 : 3) to give the *title compound* as a sticky, orange oil (0.016 g, 36%) as a mixture of isomers (5 : 2) (Found: $MH^+$, 457.2354. $C_{25}H_{32}N_2O_6$ + H requires 457.2338); $\nu_{max}$ (film)/cm$^{-1}$ 3473, 3359, 2925, 2858, 1733, 1716, 1695, 1653, 1597, 1557, 1506; $\delta_H$ (400 MHz; $CDCl_3$) *major isomer* 8.66 (1 H, s, NH), 7.28 (1 H, d, *J* 1.3, quinone-H), 7.07 (1 H, d, *J* 11.4, CMe=C*H*CH=CH), 6.42 (1 H, t, *J* 10.8, CMe=CHC*H*=CH), 5.99–5.92 (1 H, m, CMe=CH CH=C*H*), 5.28 (1 H, t, *J* 7.2, $ArCH_2CMe=CH$), 4.99–4.94 (2 H, m, $OCONH_2$), 4.15 (3 H, s, OMe), 3.28–3.14 (2 H, m, $ArCH_2$), 2.70–2.61 (1 H, m, $CHOCONH_2$), 2.27–2.23 (2 H, m, $CH_2CHOCONH_2$), 2.04–1.98 (5 H, m, Me, $CH_2$), 1.82–1.76 (2 H, m, $CH_2$), 1.72–1.66 (2 H, m, $CH_2$), 1.57 (3 H, s, Me), 1.55–1.45 (2 H, m, $CH_2$), 1.36–1.25 (2 H, m, $CH_2$); *minor isomer* 8.89 (1 H, s, NH), 7.27 (1 H, d, *J* 1.3, quinone-H), 7.10 (1 H, d, *J* 13.2, Me=C*H*CH=CH), 6.45 (1 H, t, *J* 10.8, CMe=CHC*H*=CH), 5.13 (1 H, t, *J* 6.7, $ArCH_2CMe=CH$), 4.16 (3 H, s, OMe), 2.56–2.51 (1 H, m, $CHOCONH_2$), 2.38–2.34 (2 H, m, $CH_2CHOCONH_2$), 1.63 (3 H, s, Me); $\delta_C$ (100 MHz; $CDCl_3$) *major isomer* 184.1 (C), 183.6 (C), 169.0 (C), 157.0 (C), 156.9 (C), 138.2 (C), 134.7 (CH), 132.8 (C), 130.4 (C), 129.6 (CH), 128.0 (CH), 126.09 (CH), 125.66 (C), 111.3 (CH), 74.1 (CH), 61.8 (Me), 34.2 ($CH_2$), 33.2 ($CH_2$), 32.99 ($CH_2$), 30.0 ($CH_2$), 29.7 ($CH_2$), 28.0 ($CH_2$), 25.2 ($CH_2$), 15.8 (Me), 12.5 (Me); *minor isomer* 184.4 (C), 183.57 (C), 168.2 (C), 156.8 (2 × C), 138.0 (C), 134.5 (CH), 132.5 (C), 130.2 (C), 129.1 (CH), 128.8 (CH), 126.1 (CH), 125.7 (C), 111.3 (CH), 74.5 (CH), 61.6 (Me), 33.7 ($CH_2$), 33.0 ($CH_2$), 29.5 ($CH_2$), 28.6 ($CH_2$), 27.6 ($CH_2$), 25.6 ($CH_2$), 24.7 ($CH_2$), 23.6 (Me), 61.6 (Me); 1 C unobserved; *m*/*z* (CI) 457 ($MH^+$, 59%), 416 (100), 398 (80).

**Lactam 24b.** (3*R*,9*S*)- and (3*S*,9*S*)-*N*-[2-(9-(*tert*-Butyldimethylsiloxydodeca-1,11-dien-3-yloxy)-4-methoxyphenyl]-2-methylpenta-2,4-dienamide **23b** (200 mg, 0.379 mmol) was dissolved in dichloromethane (76 mL) and Grubbs' catalyst (62 mg, 0.076 mmol, 20 mol%) was added. The solution was stirred at reflux for 3 h and then the solvent was removed. Flash chromatography using ether and light petroleum (1 : 9) gave the *title compound* as a brown oil (156 mg, 82%); $[\alpha]_D^{32}$ −63 (*c* 0.63, $CHCl_3$); $\nu_{max}$ ($CHCl_3$)/cm$^{-1}$3430, 3020, 2930, 1655, 1522; $\delta_H$ (300 MHz; $CDCl_3$) *mixture of isomers* 8.24–8.17 (1 H, m, ArH), 7.89 (1 H, s, NH), 6.82–6.57 (1 H, m, CMe=C*H*CH=CH), 6.41–6.30 (3 H, m, ArH, CMe=CHC*H*=CH), 5.84–5.73 (2 H, m, C*H*=$CH_2$, CMe=CHCH=C*H*), 5.21–5.12 (2 H, m, $CH_2$=CHCH(O)), 4.70–4.56 (1 H, m, CH=C$H_2$), 3.80–3.72 (1 H, m, C*H*OTBS), 3.69 and 3.68 (3 H, 2 × s, OMe), 2.61–2.40 (1 H, m, $CH_2$CHOTBS), 2.45–2.08 (1 H, m, $CH_2$CHOTBS), 1.99 and 1.95 (3 H, 2 × s, Me), 1.76–1.15 (10 H, m, 5 × $CH_2$), 0.83 (9 H, s, *t*-Bu), 0.00 (6 H, s, Me); $\delta_C$ (75 MHz; $CDCl_3$) *mixture of isomers* 169.0 (C), 168.9 (C), 168.6 (C), 156.3 (C), 148.3 (C), 147.7 (C), 138.3 (CH), 137.9 (CH), 137.7 (CH), 137.4 (CH), 135.5 (C), 135.1 (C), 133.7 (CH), 133.2 (CH), 132.5 (CH), 127.3 (CH), 126.1 (CH), 125.8 (CH), 122.8 (C), 122.1 (C), 122.0 (C), 120.8 (CH), 117.4 ($CH_2$), 117.2 ($CH_2$), 116.8 ($CH_2$), 116.7 ($CH_2$), 104.1 (CH), 101.9 (CH), 101.7 (CH), 101.4 (CH), 79.7 (CH), 79.2 (CH), 72.4 (CH), 72.1 (CH), 71.5 (CH), 71.3 (CH), 55.8 (Me), 42.5 ($CH_2$), 42.2 ($CH_2$), 36.6 ($CH_2$), 35.8 ($CH_2$), 35.7 ($CH_2$), 35.6 ($CH_2$), 35.4 ($CH_2$), 35.3 ($CH_2$), 30.1 ($CH_2$), 28.3 ($CH_2$), 27.8 ($CH_2$), 26.2 (Me), 24.7 ($CH_2$), 24.5 ($CH_2$), 24.4 ($CH_2$), 24.1 ($CH_2$), 18.5 (C), 13.8 (Me), −4.1 (Me).

**Claisen rearrangement of lactam 24b to ansa-lactam 25b.** Lactam **24b** (59 mg, 0.12 mmol) was dissolved in xylenes (2.5 mL) and was subjected to microwave irradiation at 300 W and 180 °C for 50 min. After solvent evaporation, flash chromatography using ether and light petroleum (3 : 17) gave the *title compound* as a yellow oil (34 mg, 58%); $[\alpha]_D^{32}$ +2.15 (*c* 1.86, $CHCl_3$) (Found: $MH^+$, 500.3174. $C_{29}H_{45}NO_4Si$ + H requires 500.3196); $\nu_{max}$ ($CHCl_3$)/cm$^{-1}$ 3426, 3019, 2930, 1656, 1524, 1265; $\delta_H$ (300 MHz; $CDCl_3$) 8.13 (1 H, d, *J* 9.0, ArH), 8.11 (1 H, br s, NH), 6.90 (1 H, d, *J* 12.0, CMe=C*H*CH=CH), 6.43 (1 H, d, *J* 9.0, ArH), 6.33 (1 H, t, *J* 12.0, CMe=CHC*H*=CH), 6.31 (1 H, s, OH), 5.86–5.75 (2 H, m, CMe=CHCH=C*H*$CH_2$, $ArCH_2CH=CH$), 5.67–5.61 (1 H, m, $ArCH_2CH$=CH), 3.75 (3 H, s, OMe), 3.74–3.70 (1 H, m, C*H*OTBS), 3.51 (1 H, dd, *J* 15.0, 6.0, ArCH*H*CH=CH), 3.43 (1 H, dd, *J* 15.0, 6.0, ArC*H*HCH=CH), 2.45–2.24 (2 H, m, $CH(OTBS)CH_2$), 2.20–2.06 (2 H, m, $ArCH_2CH=CHCH_2$), 1.98 (3 H, s, Me),1.48–1.17 (8 H, m, 4 × $CH_2$), 0.84 (9 H, s, *t*-Bu), 0.00 (6 H, s, Me); $\delta_C$ (75 MHz; $CDCl_3$) 168.6 (C), 153.4 (C), 145.7 (C), 135.5 (CH), 134.9 (C), 134.6 (CH), 129.8 (CH), 126.7 (CH), 125.8 (CH), 121.9 (C), 117.8 (CH), 113.1 (C), 103.2 (CH), 72.8 (CH), 56.3 (Me), 38.8 ($CH_2$), 37.1 ($CH_2$), 32.5 ($CH_2$), 29.9 ($CH_2$), 29.1 ($CH_2$), 27.6 ($CH_2$), 26.36 ($CH_2$), 26.31 (Me), 18.5 (C), 13.3 (Me), −3.8 (Me).

**Ansa-lactam 26b.** Ansa-lactam **25b** (18 mg, 0.036 mmol) was dissolved in THF (1 mL) and tetra-*n*-butylammonium fluoride (1 M in THF; 180 μL, 0.18 mmol) was added and the solution was stirred at room temperature for 5.5 h. Solvent evaporation gave a brown oil which was subjected to flash chromatography using ether and light petroleum (3 : 1) which gave the *title compound* as an amorphous, off-white solid (7.7 mg, 55%); mp 173–178 °C; $[\alpha]_D^{32}$ +13 (*c* 0.77, $CHCl_3$) (Found: $MH^+$, 386.2297. $C_{23}H_{31}NO_4$ + H requires 386.2331); $\nu_{max}$ ($CHCl_3$)/cm$^{-1}$ 3428, 3020, 2929, 1646, 1524, 1266; $\delta_H$ (300 MHz; $CDCl_3$) 8.21 (1 H, d, *J* 9.0, ArH), 8.17 (1 H, br s, NH), 6.97 (1 H, d, *J* 9.0, CMe=C*H*CH=CH), 6.52–6.45 (2 H, m, ArH, CMe=CHC*H*=CH), 6.35 (1 H, s, OH), 5.94 (1 H, dt, *J* 9.0, 6.0, CMe=CHCH=C*H*), 5.83 (1 H, dt, *J* 18.0, 6.0, $ArCH_2CH=CH$), 5.62 (1 H, dt, *J* 18.0, 6.0, $ArCH_2CH$=CH), 3.80 (3 H, s, OMe), 3.80–3.76 (1 H, m, C*H*OH), 3.56 (1 H, dd, *J* 15.0, 6.0, $ArCH_2CH=CH$), 3.46 (1 H, dd, *J* 15.0, 6.0, $ArCH_2CH=CH$), 2.55–2.46 (1 H, m, $CH(OH)CH_2$), 2.33–2.27 (1 H, m, $CH(OH)CH_2$), 2.23–2.04 (3 H, m, $ArCH_2CH=CHCH_2$ and CHO*H*), 1.99 (3 H, s, Me), 1.70–1.12 (8 H, m, 4 × $CH_2$); $\delta_C$ (75 MHz; $CDCl_3$) 168.4 (C), 153.4 (C), 145.7 (C), 135.5 (CH), 135.3 (C), 133.0 (CH), 129.8 (CH), 127.3 (CH), 126.3 (CH), 121.8 (C), 117.8 (CH), 113.0 (C), 103.2 (CH), 72.0 (CH), 56.3 (Me), 38.4 ($CH_2$), 36.8 ($CH_2$), 32.8 ($CH_2$), 31.2 ($CH_2$), 29.6 ($CH_2$), 27.7 ($CH_2$), 26.1 ($CH_2$), 13.3 (Me).

**Ansa-quinone 27b.** Ansa-lactam **26b** (14 mg, 0.036 mmol) was dissolved in acetonitrile (2 mL) and salcomine (2.5 mg, 0.0072 mmol, 20 mol%) was added. The solution was rapidly stirred overnight open to the atmosphere. After solvent evaporation, flash chromatography using ether and light petroleum (1 : 1) gave the *title compound* as an amorphous, orange solid (11 mg, 73%); mp 48–56 °C; $[\alpha]_D^{32}$ +34 (*c* 1.0, $CHCl_3$) (Found: $MH^+$, 400.2139. $C_{23}H_{29}NO_5$ + H requires 400.2124); $\lambda_{max}$ ($CH_3CN$)/nm ($\varepsilon$/dm$^3$ mol$^{-1}$ cm$^{-1}$) 206 ($\varepsilon$ 13400), 295 ($\varepsilon$ 18200), 362 ($\varepsilon$ 2500); $\nu_{max}$ ($CHCl_3$)/cm$^{-1}$ 3018, 2929, 1689, 1652, 1498, 1220, 1206; $\delta_H$ (300 MHz; $CDCl_3$) 8.67 (1 H, s, NH), 7.20 (1 H, s, quinone-H), 6.99 (1 H, d, *J* 12.05, CMe=C*H*CH=CH), 6.40 (1 H, dd, *J* 12.0, 9.0, CMe=CHC*H*=CH), 6.00 (1 H, q, *J* 9.0, CMe=CHCH=C*H*),

5.41 (1 H, dt, *J* 15.0, 6.0, $ArCH_2CH$=CH), 5.19 (1 H, dt, *J* 15.0, 6.0, $ArCH_2CH$=C*H*), 4.03 (3 H, s, OMe), 3.77–3.70 (1 H, m, C*H*OH), 3.09 (2 H, d, *J* 6.0, $ArCH_2CH$=CH), 2.46–2.37 (1 H, m, CH(OH)$CH_2$), 2.32–2.22 (1 H, m, CH(OH)$CH_2$), 1.96 (2 H, d, *J* 6.0, $ArCH_2CH$=CH$CH_2$), 1.92 (3 H, s, Me), 1.60 (1 H, br s, OH), 1.54–1.48 (4 H, m, 2 × $CH_2$), 1.36–1.18 (4 H, m, 2 × $CH_2$); $\delta_C$ (75 MHz; $CDCl_3$) 184.6 (C), 183.5 (C), 169.2 (C), 156.6 (C), 138.7 (C), 136.1 (CH), 133.9 (CH), 132.9 (C), 129.9 (CH), 126.7 (C), 126.4 (CH), 125.8 (CH), 111.6 (CH), 72.3 (CH), 62.2 (Me), 38.6 ($CH_2$), 36.2 ($CH_2$), 32.7 ($CH_2$), 29.7 ($CH_2$), 29.0 ($CH_2$), 26.9 ($CH_2$), 26.0 ($CH_2$), 12.8 (Me); *m*/*z* (EI) 399 ($M^+$, 9%), 384 (100), 368 (17), 321 (5), 215 (17).

**Ansa-quinone carbamate 7b.** Ansa-quinone **27b** (10 mg, 0.025 mmol) was dissolved in dichloromethane (2.5 mL). Sodium cyanate (40 mg, 0.62 mmol) was added and the mixture was cooled to 0 °C. Trifluoroacetic acid (46 μL, 0.62 mmol) was added and the reaction mixture was stirred for 15 h at room temperature before dilution with dichloromethane (10 mL). The solution was neutralized by the addition of saturated sodium hydrogen carbonate (10 mL). The layers were separated and the aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organics were dried ($Na_2SO_4$) and the solvent was evaporated. Flash chromatography using ether and light petroleum (1 : 1) gave the *title compound* as an amorphous yellow solid (4.7 mg, 43%); mp 128–131 °C; $[\alpha]_D^{32}$ +60 (*c* 0.10, $CHCl_3$) (Found: $MH^+$, 443.2200. $C_{24}H_{30}N_2O_6$ + H requires 443.2182); $\lambda_{max}$ ($CH_3CN$)/nm ($\varepsilon$/dm$^3$ mol$^{-1}$ cm$^{-1}$) 261 ($\varepsilon$ 33088), 331 ($\varepsilon$ 5311); $\nu_{max}$ ($CHCl_3$)/cm$^{-1}$ 3697, 3604, 2927, 2855, 1722, 1649, 1601, 1385; $\delta_H$ (300 MHz; $CDCl_3$) 8.56 (1 H, s, NH), 7.20 (1 H, s, quinone-H), 6.99 (1 H, d, *J* 12.0, CMe=C*H*CH=CH), 6.35 (1 H, dd, *J* 12.0, 9.0, CMe=CHC*H*=CH), 5.89 (1 H, q, *J* 9.0, CMe=CHCH=C*H*), 5.40 (1 H, dt, *J* 15.0, 6.0, $ArCH_2CH$=CH), 5.30–5.15 (3 H, m, $ArCH_2CH$=C*H*, OCO$NH_2$), 4.92–4.86 (1 H, m, C*H*OCO$NH_2$), 4.08 (3 H, s, MeO), 3.20–3.14 (1 H, m, $ArCH_2CH$=CH), 2.97 (1 H, dd, *J* 15.0, 9.0, $ArCH_2CH$=CH), 2.65–2.53 (1 H, m, CH(OCO$NH_2$)$CH_2$), 2.20–2.12 (1 H, m, CH(OCO$NH_2$)$CH_2$), 1.97–1.91 (2 H, m, $ArCH_2CH$=CH$CH_2$), 1.91 (3 H, s, Me), 1.76–1.23 (8 H, m, 4 × $CH_2$); $\delta_C$ (75 MHz; $CDCl_3$) 184.3 (C), 183.9 (C), 169.4 (C), 156.8 (C), 156.5 (C), 138.6 (C), 135.0 (CH), 134.1 (CH), 133.3 (C), 130.1 (CH), 126.5 (CH), 126.2 (C), 125.4 (CH), 111.6 (CH), 74.4 (CH), 62.3 (Me), 34.4 ($CH_2$), 33.4 ($CH_2$), 33.1 ($CH_2$), 30.1 ($CH_2$), 29.8 ($CH_2$), 26.9 ($CH_2$), 25.6 ($CH_2$), 12.8 (Me).

**Lactam 35a.** *N*-[2-(8-*tert*-Butyldiphenylsiloxy-2-methylundeca-1,10-dien-3-yloxy)-4-methoxyphenyl]-2-methylpenta-2,4-dienamide **34a** (0.200 g, 0.30 mmol) in anhydrous dichloromethane (56 mL) was slowly added to a solution of Grubbs' catalyst (0.075 g, 0.09 mmol, 30 mol%), in anhydrous dichloromethane (550 mL) under reflux. The mixture was heated under reflux for 24 h then concentrated *in vacuo.* The crude product was purified by flash chromatography on silica, eluting with ethyl acetate and light petroleum (1 : 9) to give the *title compound* as a dark oil (0.188 g, 98%) as a 1 : 1 mixture of diastereoisomers (Found: $MH^+$, 624.3504. $C_{39}H_{49}NO_4Si$ + H requires 624.3509); $\nu_{max}$ (film)/cm$^{-1}$ 3431, 3070, 2932, 2856, 1659, 1615, 1522, 1110, 702; $\delta_H$ (300 MHz; $CDCl_3$) *mixture of isomers* 8.47–8.43 (1 H, 2 × d, *J* 8.8, ArH), 8.11 (0.5 H, s, NH), 7.99 (0.5 H, s, NH), 7.67–7.62 (4 H, m, ArH), 7.37–7.28 (6 H, m, ArH), 6.72 (1 H, t, *J* 11.3, CMe=C*H*CH=CH), 6.45 (1 H, dt, *J* 2.6 7.3, CMe=CHC*H*=CH), 6.38–6.23 (2 H, m, ArH), 5.93 (1 H, q, *J* 8.8, CMe=CHCH=C*H*), 4.93–4.83 (2 H, m, CMe=C$H_2$), 4.51–4.44 (1 H, m, ArOC*H*), 3.99–3.85 (1 H, m, C*H*OTBDPS), 3.75 (1.5 H, s, OMe), 3.74 (1.5 H, s, OMe), 2.60–2.03 (2 H, m, CH(OTBDPS)$CH_2$), 2.03 (3 H, s, Me), 1.70–0.82 (8 H, m, 4 × $CH_2$), 1.70 (1.5 H, s, Me), 1.67 (1.5 H, s, Me), 1.03 (9 H, s, *t*-Bu); $\delta_C$ (75 MHz; $CDCl_3$) *mixture of isomers* 167.5 (C), 167.1 (C), 155.71 (C), 155.67 (C), 147.64 (C), 147.61 (C), 142.9 (C), 142.4 (C), 135.99 (CH), 135.93 (CH), 134.9 (CH), 134.5 (C), 134.48 (CH), 134.41 (CH), 134.0 (CH), 133.7 (CH), 133.5 (C), 129.67 (CH), 129.62 (CH), 127.49 (CH), 127.40 (CH), 125.9 (CH), 125.5 (CH), 125.3 (CH), 124.7 (CH), 121.8 (C), 119.5 (CH), 112.1 ($CH_2$), 111.9 ($CH_2$), 103.6 (CH), 103.5 (CH), 100.6 (CH), 100.5 (CH), 81.7 (CH), 81.6 (CH), 73.0 (CH), 72.8 (CH), 55.4 (Me), 36.0 ($CH_2$), 35.7 ($CH_2$), 34.7 ($CH_2$), 34.06 ($CH_2$), 34.00 ($CH_2$), 33.6 ($CH_2$), 27.06 (Me), 27.04 (Me), 26.1 ($CH_2$), 25.1 ($CH_2$), 23.8 ($CH_2$), 22.9 ($CH_2$), 10.4 (C), 19.3 (C), 18.9 (Me), 18.6 (Me), 13.2 (Me), 13.0 (Me); *m*/*z* (CI) 624 ($MH^+$, 62%), 606 (100), 529 (17), 368 (64).

**Claisen rearrangement of lactam 35a.** Lactam **35a** (0.370 g, 0.59 mmol) was dissolved in xylene (19.5 mL) in a sealed tube. The mixture was heated at 180 °C for 35 min in a microwave reactor (300 W). The solvent was then removed *in vacuo* and the crude product was purified by flash chromatography on silica, eluting with ethyl acetate and light petroleum (1 : 9) to give the *rearrangement product* as a yellow oil (0.312 g, 84%) (Found: $MH^+$, 624.3502. $C_{39}H_{49}NO_4Si$ + H requires 624.3509); $\nu_{max}$ (film)/cm$^{-1}$ 3427, 3071, 2931, 2857, 1665, 1590, 1523, 1110, 702; $\delta_H$ (300 MHz; $CDCl_3$) 8.15 (1 H, d, *J* 8.8, ArH), 8.13 (1 H, s, NH), 7.69–7.64 (4 H, m, ArH), 7.43–7.31 (6 H, m, ArH), 7.07 (1 H, d, *J* 10.9, CMe=C*H*CH=CH), 6.55 (1 H, s, OH), 6.49 (1 H, d, *J* 8.8, ArH), 6.26 (1 H, t, *J* 11.3, CMe=CHC*H*=CH), 5.89 (1 H, q, *J* 10.1, CMe=CHCH=C*H*), 5.45 (1 H, t, *J* 7.1, CMe=C*H*$CH_2$), 3.91–3.82 (1 H, m, C*H*OTBDPS), 3.80 (3 H, s, OMe), 3.50 (2 H, s, $ArCH_2$), 2.51–2.26 (2 H, m, CH(OTBDPS)$CH_2$), 2.12–0.80 (8 H, m, 4 × $CH_2$), 1.99 (3 H, s, Me), 1.53 (3 H, s, Me), 1.02 (9 H, s, *t*-Bu); $\delta_C$ (75 MHz; $CDCl_3$) 168.9 (C), 153.6 (C), 145.9 (C), 136.5 (C), 136.0 (CH), 135.3 (CH), 134.7 (C), 133.4 (C), 129.5 (CH), 128.3 (CH), 127.6 (CH), 127.3 (CH), 125.1 (CH), 121.2 (C), 117.7 (CH), 112.3 (C), 102.6 (CH), 73.7 (CH), 55.9 (Me), 38.8 ($CH_2$), 34.8 ($CH_2$), 34.1 ($CH_2$), 29.1 ($CH_2$), 28.0 ($CH_2$), 27.0 (Me), 23.9 ($CH_2$), 19.4 (C), 15.7 (Me), 12.4 (Me); some peaks are 'doubled' due to the presence of diastereomers; *m*/*z* (CI) 624 ($MH^+$, 100%), 546 (40), 368 (88), 350 (21).

**Ansa-lactam 36a.** The above ansa-lactam (0.187 g, 0.30 mmol) was dissolved in anhydrous THF (4.5 mL) and tetra-*n*-butylammonium fluoride (1 M in THF; 0.74 mL, 0.74 mmol) was added dropwise. The mixture was then stirred under reflux for 12 h, before being cooled to room temperature. The mixture was then acidified with saturated ammonium chloride solution extracted with ethyl acetate (3 × 15 mL), combined, washed with brine (30 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo.* The crude product was purified by flash chromatography on silica, eluting with ethyl acetate and light petroleum (4 : 1) to give the *title compound* as a colourless solid (0.093 g, 80%) as a 1 : 5 : 63 mixture of three diasteroisomers; mp 172–175 °C (from ethyl acetate and light petroleum) (Found: $MH^+$, 386.2325. $C_{23}H_{31}NO_4$ + H requires 386.2331); $\nu_{max}$ (KBr)/cm$^{-1}$ 3414, 2925, 2852, 1640,

1531; $\delta_H$ (300 MHz; $CDCl_3$) *mixture of isomers* 8.22 (1 H, s, NH), 8.02 (1 H, d, *J* 8.8, ArH), 7.15 (1 H, d, *J* 15.4, CMe=C*H*CH=CH), 6.69 (1 H, s, OH), 6.53–6.46 (2 H, m, ArH, CMe=CHC*H*=CH), 5.97 (1 H, q, *J* 13.8, CMe=CHCH=C*H*), 5.56 (1 H, t, *J* 7.8, CMe=C*H*$CH_2$), 3.80 (3 H, s, OMe), 3.80–3.73 (1 H, m, C*H*OH), 3.52 (2 H, s, Ar$CH_2$), 2.44–2.37 (2 H, m, CH(OH)$CH_2$), 2.03 (3 H, s, Me), 1.52 (3 H, s, Me), 2.22–1.23 (8 H, m, 4 × $CH_2$), 1.77 (1 H, br s, OH); $\delta_C$ (75 MHz; $CDCl_3$) *mixture of isomers* 168.7 (C), 153.7 (C), 145.9 (C), 136.9 (C), 134.5 (C), 133.7 (CH), 128.3 (CH), 127.0 (CH), 126.4 (CH), 121.2 (C), 117.6 (CH), 112.3 (C), 102.7 (CH), 71.7 (CH), 55.9 (Me), 38.1 ($CH_2$), 34.4 ($CH_2$), 34.2 ($CH_2$), 29.2 ($CH_2$), 27.7 ($CH_2$), 23.5 ($CH_2$), 15.7 (Me), 12.5 (Me); some peaks are 'doubled' due to the presence of diastereomers, but peaks due to minor isomer are very small; *m*/*z* (CI) 386 ($MH^+$, 100%), 350 (43).

**Oxidation of ansa-lactam 36a.** Ansa-lactam **36a** (0.093 g, 0.24 mmol) was dissolved in acetone (55 mL) and Fremy's salt (0.260 g, 0.96 mmol) in sodium dihydrogen phosphate buffer (28 mL) was added. The mixture was stirred for 2 h, then diluted with ethyl acetate (100 mL), and washed with water (2 × 30 mL), brine (30 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo.* The crude product was purified by flash chromatography on silica, eluting with ethyl acetate and light petroleum (1 : 4) to give the quinone as an orange oil (0.066 g, 70%) as a 1 : 10 mixture of diastereoisomers (Found: $MH^+$, 400.2134. $C_{23}H_{29}NO_5$ + H requires 400.2124); $\nu_{max}$ (film)/$cm^{-1}$ 3421, 3359, 2929, 2856, 1687, 1650, 1601, 1498, 703; $\delta_H$ (300 MHz; $CDCl_3$) *major isomer* 8.79 (1 H, s, NH), 7.25 (1 H, s, quinone-H), 7.10 (1 H, d, *J* 11.5, CMe=C*H*CH=CH), 6.49 (1 H, t, *J* 10.8, CMe=CHC*H*=CH), 6.11 (1 H, q, *J* 8.1, CMe=CHCH=C*H*), 5.27 (1 H, t, *J* 6.4, CMe=C*H*$CH_2$), 4.11 (3 H, s, OMe), 3.80–3.74 (1 H, m, C*H*OH), 3.21–3.14 (2 H, m, Ar$CH_2$), 2.43–2.10 (2 H, m, CH(OH)$CH_2$), 1.99 (3 H, s, Me), 1.69 (1 H, s, OH), 1.54 (3 H, s, Me), 2.07–0.88 (8 H, m, 4 × $CH_2$); *minor isomer* 8.43 (1 H, s, NH), 7.19 (1 H, s, ArH), 5.12–5.08 (1 H, m, CMe=C*H*$CH_2$), 4.14 (3 H, s, OMe); $\delta_C$ (75 MHz; $CDCl_3$) *mixture of isomers* 184.1 (C), 183.1 (C), 168.9 (C), 156.5 (C), 138.5 (C), 136.6 (CH), 132.0 (C), 130.7 (C), 129.9 (CH), 128.5 (CH), 125.9 (C), 125.6 (CH), 110.6 (CH), 72.0 (CH), 61.6 (Me), 38.8 ($CH_2$), 34.3 ($CH_2$), 33.1 ($CH_2$), 29.8 ($CH_2$), 27.3 (Me), 23.0 ($CH_2$), 15.7 (Me), 12.1 (Me); *m*/*z* (CI) 400 ($MH^+$, 100%), 384 (22), 368 (12).

**Ansa-quinone carbamate 37a.** The above ansa-quinone (0.038 g, 0.09 mmol) was dissolved in dichloromethane (6 mL). Sodium cyanate (0.154 g, 2.37 mmol) and trifluoroacetic acid (183 µl, 2.37 mmol) were then added at 0 °C. The mixture was stirred slowly at room temperature for 4.5 h, before the solution was diluted with dichloromethane (100 mL) and quenched with a sodium hydrogen carbonate solution (5%; 80 mL). The mixture was then extracted with ethyl acetate (3 × 100 mL), the extracts combined and washed with brine (100 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo.* The crude product was purified by flash chromatography on silica, eluting with ethyl acetate and light petroleum (3 : 7) to give the *title compound* as a orange oil (0.020 g, 47%) as a 1 : 2.2 : 3.4 : 12.8 mixture of four diastereoisomers (Found: $MH^+$, 443.2177. $C_{24}H_{30}N_2O_6$ + H requires 443.2182); $\nu_{max}$ (film)/$cm^{-1}$ 3478, 3361, 2925, 2855, 1693, 1651, 1600, 1503, 701; $\delta_H$ (300 MHz; $CDCl_3$) *major isomer* 8.74 (1 H, s, NH), 7.26 (1 H, s, quinone-H), 7.07 (1 H, d, *J* 11.5, CMe=C*H*CH=CH), 6.42 (1 H, t, *J* 10.9, CMe=CHC*H*=CH), 5.98 (1 H, q, *J* 10.2, CMe=CHCH=C*H*), 5.25 (1 H, t, *J* 6.4, CMe=C*H*$CH_2$), 5.02–4.63 (2 H, m, $OCONH_2$), 4.12 (3 H, s, OMe), 3.24–3.11 (2 H, m, Ar$CH_2$), 2.67–2.55 (1 H, m, C*H*O$CONH_2$), 2.42–2.28 (2 H, m, CH($OCONH_2$)$CH_2$), 1.96 (3 H, s, Me), 1.53 (3 H, s, Me), 2.11–0.82 (8 H, m, 4 × $CH_2$); *minor isomer* 8.40 (1 H, s, NH), 7.40 (1 H, s, ArH), 5.14 (1 H, t, *J* 7.3, CMe=C*H*$CH_2$), (3 H, s, OMe), 1.99 (3 H, s, Me), 1.57 (3 H, s, Me); $\delta_C$ (75 MHz; $CDCl_3$) *mixture of isomers; peaks due to major isomer reported* 184.1 (C), 183.6 (C), 168.9 (C), 156.65 (C), 156.60 (C), 138.6 (C), 135.2 (CH), 132.0 (C), 130.8 (CH) 130.1 (C), 128.5 (CH), 125.9 (C), 125.7 (CH), 110.5 (CH), 73.7 (CH), 61.7 (Me), 35.3 ($CH_2$), 33.0 ($CH_2$), 31.4 ($CH_2$), 29.7 ($CH_2$), 27.1 (Me), 22.3 ($CH_2$), 15.8 (Me), 12.1 ($CH_2$); *m*/*z* (CI) 443 ($MH^+$, 25%), 400 (83), 382 (100), 368 (18).

**Lactam 35b.** *N*-[2-(8-*tert*-Butyldiphenylsiloxy-2-methyldodeca-1,11-dien-3-yloxy)-4-methoxyphenyl]-2-methylpenta-2,4-dienamide **34b** (0.159 g, 0.24 mmol) in anhydrous dichloromethane (45 mL) was slowly added to a solution of Grubbs' catalyst (0.059 g, 0.07 mmol, 30 mol%), in anhydrous dichloromethane (425 mL) under reflux. The mixture was heated under reflux for 24 h then concentrated *in vacuo.* The crude product was purified by flash chromatography on silica, eluting with ethyl acetate and light petroleum (1 : 9) to give the *title compound* as a dark oil (0.147 g, 96%) as 1 : 1 mixture of diastereoisomers (Found: $MH^+$, 638.3655. $C_{40}H_{51}NO_4Si$ + H requires 638.3665); $\nu_{max}$ (film)/$cm^{-1}$ 3434, 3070, 2934, 2857, 1665, 1615, 1520, 1110, 702; $\delta_H$ (300 MHz; $CDCl_3$) *mixture of isomers* 8.40–8.29 (1 H, m, ArH), 8.02 (0.5 H, s, NH), 8.05 (0.5 H, s, NH), 7.67–7.65 (4 H, m, ArH), 7.41–7.32 (6 H, m, ArH), 6.48–6.45 (1 H, m, CMe=C*H*CH=CH), 6.44–6.38 (2 H, m, ArH), 6.26–6.22 (1 H, m, CMe=CHC*H*=CH), 5.80–5.45 (1 H, m, CMe=CHCH=C*H*), 4.95–4.93 (2 H, m, MeC=C$H_2$), 4.42–4.36 (1 H, m, ArOC*H*), 3.81–3.73 (1 H, m, C*H*OTBDPS), 3.74 (1.5 H, s, OMe), 3.73 (1.5 H, s, OMe), 2.18 (3 H, s, Me), 1.68 (1.5 H, s, Me), 1.67 (1.5 H, s, Me), 1.04 (9 H, s, *t*-Bu), 2.18–0.87 (12 H, 6 × $CH_2$); $\delta_C$ (75 MHz; $CDCl_3$) *mixture of isomers* 168.17 (C), 168.03 (C), 155.73 (C), 155.68 (C), 147.7 (C), 147.5 (C), 144.1 (C), 143.8 (C), 137.2 (CH), 137.0 (CH), 135.8 (CH), 134.45 (C), 134.39 (C), 129.52 (CH), 127.49 (CH), 124.86 (CH), 124.75 (C), 123.73 (CH), 123.60 (CH), 121.74 (C), 121.71 (C), 119.85 (CH), 119.75 (CH), 112.4 ($CH_2$), 112.2 ($CH_2$), 103.58 (CH), 103.54 (CH), 100.70 (CH), 100.62 (CH), 82.50 (CH), 82.44 (CH), 72.2 (CH), 71.4 (CH), 55.3 (Me), 35.9 ($CH_2$), 35.0 ($CH_2$), 34.8 ($CH_2$), 34.7 ($CH_2$), 27.00 (Me), 26.95 (Me), 26.1 ($CH_2$), 24.8 ($CH_2$), 24.5 ($CH_2$), 23.9 ($CH_2$), 22.8 ($CH_2$), 19.32 (C), 19.29 (CH), 17.9 (Me), 17.7 (Me), 13.29 (Me), 13.22 (Me); *m*/*z* (CI) 638 ($MH^+$, 77%), 620 (65), 386 (100), 300 (83).

**Claisen rearrangement of lactam 35b.** Lactam **35b** (0.156 g, 0.24 mmol) was dissolved in xylene (7 mL) in a sealed tube. The mixture was heated at 180 °C for 35 min in a microwave reactor (300 W). The solvent was then removed *in vacuo* and the crude product was purified by flash chromatography on silica, eluting with ethyl acetate and light petroleum (1 : 9) to give the *rearrangement product* as a red oil (0.085 g, 54%) as a mixture of diastereoisomers (Found: $MH^+$, 638.3672. $C_{40}H_{51}NO_4Si$ + H requires 638.3665); $\nu_{max}$ (film)/$cm^{-1}$ 3428, 3070, 2932, 2857, 1662, 1590, 1525, 1110, 703; $\delta_H$ (300 MHz; $CDCl_3$) *mixture of isomers* 8.20 (1 H, d, *J* 9.0, ArH), 8.15 (1 H, s, NH), 7.71–7.62 (4 H, m, ArH), 7.45–7.29 (6 H, m, ArH), 6.87 (1 H, d, *J* 11.3,

CMe=C*H*CH=CH), 6.48 (1 H, d, *J* 9.0, ArH), 6.44 (1 H, s, OH), 6.22 (1 H, t, *J* 11.1, CMe=CHC*H*=CH), 5.75 (1 H, q, *J* 10.3, CMe=CHCH=C*H*), 5.48 (1 H, t, *J* 6.8, CMe=C*H*$CH_2$), 3.79 (3 H, s, OMe), 3.66 (1 H, q, *J* 4.7, C*H*OTBDPS), 3.48–3.46 (2 H, m, ArC$H_2$), 2.25–0.82 (12 H, m, 6 × $CH_2$), 2.00 (3 H, s, Me), 1.55 (3 H, s, Me), 1.05 (9 H, s, *t*-Bu); $\delta_C$ (75 MHz; $CDCl_3$) *mixture of isomers* 167.9 (C), 153.4 (C), 145.4 (C), 137.0 (CH), 136.2 (CH), 135.8 (CH), 134.3 (C), 133.8 (C), 129.5 (CH), 128.1 (CH), 127.4 (CH), 125.9 (CH), 124.2 (CH), 121.3 (C), 117.1 (CH), 112.2 (C), 102.8 (CH), 73.6 (CH), 55.9 (Me), 37.3 ($CH_2$), 35.8 ($CH_2$), 34.1 ($CH_2$), 29.8 ($CH_2$), 27.8 ($CH_2$), 27.0 (Me), 24.2 ($CH_2$), 23.8 ($CH_2$), 19.3 (C), 15.7 (Me), 12.7 (Me); *m*/*z* (CI) 638 ($MH^+$, 56%), 620 (100), 542 (26), 382 (32).

**Ansa-lactam 36b.** The above ansa-lactam (0.168 g, 0.26 mmol) was dissolved in anhydrous THF (4 mL) and tetra-*n*-butylammonium fluoride (1 M in THF; 0.65 mL, 0.65 mmol) was added dropwise. The mixture was then stirred under reflux for 12 h, before being cooled to room temperature. The mixture was acidified with saturated ammonium chloride solution extracted with ethyl acetate (3 × 15 mL), the extracts combined, washed with brine (20 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo.* The crude product was purified by flash chromatography on silica, eluting with ethyl acetate and light petroleum (4 : 1) to give the *title compound* as a colourless solid (0.085 g, 80%) as a mixture of diastereoisomers; mp 194-196 °C (from ethyl acetate and light petroleum) (Found: $MH^+$, 400.2476. $C_{24}H_{33}NO_4$ + H requires 400.2488); $\nu_{max}$ (film)/$cm^{-1}$ 3468, 3401, 2925, 2853, 1652, 1590, 1525; $\delta_H$ (300 MHz; $CDCl_3$) *mixture of isomers* 8.20 (1 H, d, *J* 9.0, ArH), 8.17 (1 H, s, NH), 7.06 (1 H, d, *J* 11.3, CMe=C*H*CH=CH), 6.65 (1 H, s, OH), 6.49 (1 H, d, *J* 9.0, ArH), 6.33 (1 H, t, *J* 10.9, CMe=CHC*H*=CH), 5.93 (1 H, q, *J* 8.5, CMe=CHCH=C*H*), 5.62 (1 H, t, *J* 7.2, CMe=C*H*$CH_2$), 3.80 (3 H, s, OMe), 3.64–3.56 (1 H, m, C*H*OH), 3.52 (2 H, s, ArC$H_2$), 2.36–2.33 (2 H, m, $CH_2$), 2.17–2.15 (2 H, m, MeC=CHC$H_2$), 2.01 (3 H, s, Me), 1.59 (3 H, s, Me), 1.82 (1 H, s, OH), 1.70–0.85 (8 H, m, 4 × $CH_2$); $\delta_C$ (75 MHz; $CDCl_3$) *mixture of isomers* 168.0 (C), 153.6 (C), 145.5 (C), 136.8 (C), 133.6 (CH), 134.0 (C), 128.4 (CH), 126.1 (CH), 124.8 (CH), 121.1 (C), 117.5 (CH), 112.3 (C), 102.7 (CH), 72.4 (CH), 55.9 (Me), 38.0 ($CH_2$), 36.7 ($CH_2$), 34.3 ($CH_2$), 29.3 ($CH_2$), 27.4 ($CH_2$), 24.7 ($CH_2$), 24.5 ($CH_2$), 15.6 (Me), 12.8 (Me); *m*/*z* (CI) 400 ($MH^+$, 100%), 382 (45).

**Oxidation of ansa-lactam 36b.** Ansa-lactam **36b** (0.029 g, 0.07 mmol) was dissolved in acetone (16 mL) and Fremy's salt (0.063 g, 0.29 mmol) in sodium dihydrogen phosphate buffer (8 mL) was added. The mixture was stirred for 2 h, diluted with ethyl acetate (30 mL). The organic layer was washed with water (2 × 10 mL), brine (10 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo.* The crude product was purified by flash chromatography on silica, eluting with ethyl acetate and light petroleum (1 : 4) to give the quinone as an orange oil (0.019 g, 63%) as a 1 : 8.5 mixture of diastereoisomers (Found: $MH^+$, 414.2293. $C_{24}H_{31}NO_5$ + H requires 414.2293); $\nu_{max}$ (film)/$cm^{-1}$ 3362, 2928, 2855, 1684, 1651, 1600, 1504; $\delta_H$ (300 MHz; $CDCl_3$) *major isomer* 8.80 (1 H, s, NH), 7.38 (1 H, d, *J* 11.1, CMe=C*H*CH=CH), 7.35 (1 H, s, quinone-H), 6.32 (1 H, t, *J* 10.7, CMe=CHC*H*=CH), 6.05 (1 H, q, *J* 8.6, CMe=CHCH=C*H*), 5.25 (1 H, t, *J* 7.2, CMe=C*H*$CH_2$), 4.12 (3 H, s, OMe), 3.64–3.60 (1 H, m, C*H*OH), 3.19–3.13 (2 H, m, ArC$H_2$), 1.97 (3 H, s, Me), 1.52 (3 H, s, Me), 2.42–0.85 (13 H, m, OH, 6 × $CH_2$); *minor isomer* 8.84 (1 H, s, NH), 7.27 (1 H, d, *J* 11.3, CMe=C*H*CH=CH), 7.16 (1 H, s, quinone-H), 5.10 (1 H, t, *J* 6.8, CMe=C*H*$CH_2$), 4.18 (3 H, s, OMe); $\delta_C$ (75 MHz; $CDCl_3$) *mixture of isomers* 184.1 (C), 183.9 (C), 168.5 (C), 156.9 (C), 139.7 (C), 138.7 (CH), 134.7 (C), 131.4 (C), 129.9 (CH), 127.7 (CH), 125.8 (C), 124.6 (CH), 111.5 (CH), 70.6 (CH), 61.7 (Me), 37.1 ($CH_2$), 36.4 ($CH_2$), 33.4 ($CH_2$), 28.9 ($CH_2$), 27.1 ($CH_2$), 23.8 ($CH_2$), 23.6 ($CH_2$), 15.7 (Me), 12.3 (Me); *m*/*z* (CI) 414 ($MH^+$, 100%), 396 (54).

**Ansa-quinone carbamate 37b.** The above ansa-quinone (0.014 g, 0.038 mmol) was dissolved in dichloromethane (2.1 mL). Sodium cyanate (0.055 g, 0.84 mmol) and trifluoroacetic acid (0.096 g, 0.84 mmol) were then added at 0 °C. The mixture was stirred slowly at room temperature for 3 h, before quenching with sodium hydrogen carbonate solution (5%; 20 mL). The mixture was then extracted with ethyl acetate (3 × 30 mL), combined and washed with brine (50 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo.* The crude product was purified by flash chromatography on silica, eluting with ethyl acetate and light petroleum (1 : 4) to give the *title compound* as a orange oil (0.009 g, 58%) as a 1 : 6 mixture of diastereoisomers (Found: $MH^+$, 457.2329. $C_{25}H_{32}N_2O_6$ + H requires 457.2338); $\nu_{max}$ (film)/$cm^{-1}$ 3465, 3365, 2929, 2858, 1691, 1650, 1590, 1503; $\delta_H$ (300 MHz; $CDCl_3$) *major isomer* 8.81 (1 H, s, NH), 7.29 (1 H, s, quinone-H), 7.08–6.99 (1 H, m, CMe=C*H*CH=CH), 6.35–6.28 (1 H, m, CMe=CHC*H*=CH), 6.02–5.89 (1 H, m, CMe=CHCH=C*H*), 5.18–5.09 (1 H, m, CMe=C*H*$CH_2$), 4.59 (2 H, s, $CONH_2$), 4.12 (3 H, s, OMe), 3.24–3.12 (2 H, m, ArC$H_2$), 1.98 (3 H, s, Me), 2.42–2.20 (3 H, m, $CH_2$, C*H*($OCONH_2$)), 1.58 (3 H, s, Me), 2.05–0.85 (10 H, m, 5 × $CH_2$); *minor isomer* 8.91 (1 H, s, NH), 7.47 (1 H, s, quinone-H), 2.04 (3 H, s, Me), 1.58 (3 H, s, Me); $\delta_C$ (75 MHz; $CDCl_3$) *mixture of isomers* 184.1 (C), 183.9 (C), 168.5 (C), 156.9 (C), 139.7 (C), 138.7 (CH), 132.1 (C), 131.1 (C), 129.9 (CH), 128.3 (C), 127.7 (CH), 125.8 (C), 124.6 (CH), 111.5 (CH), 70.6 (CH), 61.7 (Me), 37.1 ($CH_2$), 36.4 ($CH_2$), 33.4 ($CH_2$), 28.9 ($CH_2$), 27.1 ($CH_2$), 23.8 ($CH_2$), 23.6 ($CH_2$), 15.7 (Me), 12.3 (Me); *m*/*z* (CI) 457 ($MH^+$, 16%), 416 (100), 398 (28), 285 (28).

## Molecular modelling

Molecular modelling was carried out in conjunction with Stephen Connelly (University of Exeter) using the Dock function in MOE (MOE 2004.03, Chemical Computing Group Inc, Cambridge, UK). In MOE-Dock, the configuration space includes all orientations and conformations of the ligand such that all of its atoms are inside the docking box.

## Biology

**Malachite green assay.** A colourimetric assay for the release of inorganic phosphate upon hydrolysis of ATP was used to determine the potency of Hsp90 inhibitors against the enzyme. It is based on the formation of phosphomolybdate complex and subsequent reaction with malachite green.[105]

**Growth inhibition assay.** The colorimetric sulforhodamine B assay (SRB) was used to measure growth inhibition studies as described previously.[106] The $IC_{50}$ was calculated as the drug concentration that inhibits cell growth by 50% compared with control growth.

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